Abstract Supplement to
Volume 22 No 5 July 2008

Journal of Psychopharmacology

Sage Science Press ISSN 0269 8811

Journal of Psychopharmacology

Commercial sales

For information on advertising, reprints and supplements please contact Matt Schlag, Commercial Sales Executive, SAGE, 1 Oliver's Yard, 55 City Road, London EC1Y 1SP, UK. Tel: +44(0)20 7324 8601; E-mail: matt.schlag@sagepub.co.uk

Aims and Scope

The *Journal of Psychopharmacology* is an international journal that publishes original research and review articles on both preclinical and clinical aspects of psychopharmacology. The major aim is to provide an interdisciplinary forum for studies on the effects of drugs on animal and human behaviour, and the mechanisms underlying these effects. All manuscripts are subject to peer review, and publication will normally be within six months of acceptance.

The *Journal of Psychopharmacology* (ISSN: 0269-8811) is published eight times a year (in January, March, May, June, July, August, September and November) by SAGE (Los Angeles, London, New Delhi and Singapore).

Annual Subscription (2008, 8 issues)
Individual Rate (print only) £78/$140
Combined Institutional Rate (print + electronic) £799/$1438.
Electronic only and print only subscriptions are available for institutions at a discounted rate. Note VAT may be applicable at the appropriate local rate. Visit www.sagepublications.com/subscriptioninfo.htm for more details.

To access your electronic subscription (institutional only) simply visit http://online.sagepub.com and activate your subscription. Abstracts, table of contents and contents alerts are available on this site free of charge for all.

Full rate subscriptions include the right for members of the subscribing institution to access the electronic content of the journal at no extra charge from SAGE. The content can be accessed online through a number of electronic journal intermediaries, who may charge for access. Full details available on our website: http://jop.sagepub.com

Student discounts, single issue rates and advertising details are available from SAGE, 1 Oliver's Yard, 55 City Road, London EC1Y 1SP,UK. Tel: + 44(0)207 324 8500; fax: +44(0)207 324 8600 [website: www. sagepublications.com]; and in North America from SAGE, 2455 Teller Road, Thousand Oaks, CA91320, USA.

Journal of Psychopharmacology is included in the following indexing and abstracting services: Biological Abstracts, BIOSIS database, CAB Abstracts Database, Chemical Abstracts, e-Psych PsychINFO, Current Contents/Life Sciences, Elsevier BIOBASE/Current Awareness in Biological Sciences, Embase, Excerpta Medica, Focus on: Psychopharmacology Index Medicus/ MEDLINE, IBSS (International Bibliography of the Social Sciences), Medical Documentation Research, Neuro-science Citation Index, Psychological Abstracts and WISE for medicine, Reference Update, Research Alert, Science Citation Index, SciSearch and Scopus.

Periodicals Postage Paid at Rahway, NJ. POSTMASTER. Send address corrections to *Journal of Psychopharmacology*, c/o Mercury Airfreight International Ltd, 365 Blair Road, Avenel, New Jersey 07001, USA.

Information for contributors is to be found on the inside back cover. Publishers: send books for review to the Editorial Manager.

SUPPLEMENT TO JOURNAL OF PSYCHOPHARMACOLOGY
VOLUME 22 NUMBER 5 2008

These papers were presented at the Summer Meeting of the

BRITISH ASSOCIATION FOR PSYCHOPHARMACOLOGY

20 – 23 July, Harrogate, UK

Indemnity:

BAP OFFICE
36 Cambridge Place, Hills Road
Cambridge CB2 1NS

Website: bap.org.uk

Supplement to Journal of Psychopharmacology

Abstract Book 2008

S1

HOW DO SCHIZOPHRENIA GENES WORK? OVERVIEW, CONCEPTS AND APPROACHES.

Harrison PJ. Psychiatry, Univ of Oxford, Warneford Hosp, Oxford OX3 7JX, paul.harrison@psych.ox.ac.uk

Findings from family and twin studies mean that there is no doubt as to the fact that schizophrenia has a substantial genetic component. However, just about everything else about schizophrenia genes does remain controversial: their identity, number, interactions with each other and with the environment, and the molecular mechanisms of involvement. It is even unclear as to what will constitute sufficient evidence in each domain. The talk will introduce some of the core issues and summarise the key findings, before focusing on mechanism: how can we establish how and why a gene contributes to schizophrenia risk? To answer this question, it is necessary to know where and when the gene is expressed, what it does normally, and what is different in people who have schizophrenia or who carry risk alleles in the gene. A range of resources and techniques are being applied, including direct studies of tissue and cells from affected and unaffected individuals, as well as studies of the gene and the consequences of its manipulation, *in vitro* and *in vivo*. One complexity that is becoming apparent is that most of the schizophrenia-associated polymorphisms in most of the genes are non-coding (i.e. the amino-acid sequence of the encoded protein is unchanged). Thus, the mechanism of involvement in the disorder likely involves altered regulation of gene expression, and hence the approaches taken need to take this into account. As gene regulation can be temporally, spatially, molecularly, sexually, and species specific, this poses a substantial problem. Prefacing the more detailed presentations to follow, the talk will outline in general terms the multidisciplinary approach to the biology of schizophrenia risk genes, and how the difficulties are being addressed. Finally, the clinical implications of progress in the genetic understanding of schizophrenia will be briefly summarised.

S2

NRG1 SIGNALING BIOLOGY IN SCHIZOPHRENIA: FROM BRAIN TO BLOOD

Law AJ, Wang Y, Sei Y, Harrison PJ, Kleinman JE, Weinberger DR. Psychiatry, Univ of Oxford, Warneford Hosp, Headington, Oxford, OX3 7JX, amanda.law@psych.ox.ac.uk

Introduction: The NRG1/ErbB4 signaling pathway occupies a central role in neurodevelopment and adult brain function. These diverse events are mediated primarily via a central component of intracellular signaling, PI3-Kinase. Genetic association has identified NRG1 and ErbB4 as susceptibility genes for schizophrenia and we have previously shown that a molecular mechanism behind the association with schizophrenia involves altered transcriptional regulation and splicing of the genes (Law et al, 2006 ProcNatlAcadSciUSA. 2006 Apr25;103(17):6747-52; Law et al, 2007. HumMolGenet. 2007 Jan15 ;16(2):129-41). Here we provide a systems biology approach utilizing molecular genetic and cellular investigations to interrogate interacting biological pathways downstream of main effects of DNA variation in the ErbB4 gene. Using human brain and peripheral blood cells we have uncovered a specific downstream target of NRG1 signaling in relation to ErbB4 genetic risk for schizophrenia, the PI3-kinase gene-PI3KCD.
Methods: Expression of the six class 1A PI3-Kinase genes (p55γ,p85α,p85β and p110α,β,δ-aka. PI3KCA,B,D) were examined in the brain (DLPFC) of 84 controls and 48 patients with schizophrenia and in a separate collection of lymphoblastoid cell lines from 30 controls and 30 patients with schizophrenia. Human lymphoblastoid cell lines were subsequently used as a cell model system to study NRG1-ErbB4-PI3-Kinase signaling. NRG-induced PI3-Kinase intracellular signaling was examined using Fluorescence Activated cell Sorting (FACS) and cell migration assays. The effect of a 3 marker DNA haplotype in the ErbB4 gene (rs7598440, rs707284, rs839523), previously reported to constitute a schizophrenia-risk haplotype associated with expression of a PI3-Kinase linked CYT-1 ErbB4 isoform[2] was investigated in relation to PI3-Kinase and migration phenotypes. **Results:** Disease state and the ErbB4 risk haplotype were associated with increased expression of a PI3KCD/p55gamma complex in lymphoblasts, downstream of increases in ErbB4 splice gene expression (CYT-1) and upstream of altered NRG1-mediated intracellular PI3-Kinase signaling and NRG1-induced cell migration. Expression related changes in the PI3-Kinase complex were confirmed in the human brain in relation to ErbB4 genetic variation. **Discussion:** We have used a dual human tissue approach to demonstrate that dysregulation of the ErbB4 gene in relation to risk for schizophrenia has downstream functional consequences for the PI3-Kinase pathway at both the molecular and cellular phenotype level. Our results suggest that complex diseases such as schizophrenia are likely emergent phenomena of interacting molecular networks modified by genetic loci. We propose that a systems biology approach to elucidating the architecture of aberrant signaling networks in schizophrenia in relation to genetic risk has significant value for the identification of novel risk genes and for the development of new targeted therapeutics.

S3

THE CELL BIOLOGY OF DISC1

Millar JK. Centre for Molecular Medicine, University of Edinburgh, Crewe Road, Edinburgh EH4 2XU, Kirsty.Millar@ed.ac.uk

We first identified Disrupted In Schizophrenia 1 (DISC1) as a risk factor for schizophrenia, bipolar affective disorder and recurrent major depression because it is directly disrupted by a chromosomal t(1;11) translocation that co-segregates with these disorders in a large family. Its involvement in psychiatric illness has since been supported by multiple genetic studies from our laboratory and elsewhere. DISC1 function, and how this may cause psychiatric disorders when altered, is now the subject of intense investigation.
Within the brain, DISC1 expression is widespread and prominent in many regions implicated in psychiatric illness. In the hippocampus, expression is particularly strong throughout development and into adulthood. Within cells, DISC1 has been detected in multiple cellular locations including the post-synaptic density, which suggests a role in receptor signalling.
Much of the work aimed at understanding DISC1 function has focussed upon identification and study of its binding partners. A very large number of putative interactors have now been identified, although few have been studied in any detail. These binding partners highlight potential critical roles for DISC1 in the developing and adult brain. Confirmed interactors include PDE4B, a protein that modulates cAMP signalling by hydrolysing cAMP, and NDEL, a centrosomal protein essential for the migration of neurons into the developing cortex. Consistent with the NDEL interaction, in utero knockdown of mouse DISC1 inhibits neuronal migration. Intriguingly however, in adult mice DISC1 knockdown results in overextended migration of newborn neurons in the hippocampus and demonstrates a role for DISC1 in integration of these neurons into existing circuitry.
A number of DISC1-based mouse models of psychiatric illness have now been generated. These include two strains of mice carrying missense mutations that confer behavioural, anatomical and pharmacological phenotypes related to schizophrenia and depression. The mutations are both located in binding sites for PDE4B, suggesting that the phenotypes of these mice may be related to altered DISC1/PDE4B interaction. Other models have attempted to mimic the effects of the t(1;11) translocation by expressing truncated forms of DISC1. Again these mice exhibit phenotypes related to features of human psychiatric illness. Thus overall, the emerging biological function of DISC1 supports the genetic data that identify it as a risk factor for major mental illness.

S4

MUTATION FOR GENES ASSOCIATED WITH RISK FOR SCHIZOPHRENIA: PHENOTYPIC CHARACTERISATION

Waddington JL, O'Tuathaigh CM, Babovic D. Molecular & Cellular Therapeutics, Royal College of Surgeons in Ireland, St. Stephen's Green, Dublin 2, jwadding@rcsi.ie

Research seeking to implicate specific genetic loci in schizophrenia susceptibility has been long confounded by difficulties in replicating numerous findings. Over recent years several genes have been associated more consistently with risk for schizophrenia, such as neuregulin-1 (NRG1), disrupted-in-schizophrenia 1 (DISC1) and dysbindin (DTNBP1); however, how these genes might relate to individual psychopathological, cognitive or biological aspects [endophenotypes] of schizophrenia is poorly understood. For other genes, such as catechol-O-methyltransferase (COMT), evidence for association with risk for schizophrenia is inconsistent but COMT genotype may be associated with a cognitive endophenotype. Genetic animal models involving targeted mutation via gene knockout/knockin or transgenesis have the potential to inform on the impact of a specific susceptibility gene on the behaviour and development of the whole organism and whether disruption of gene function translates into schizophrenia-related structural and functional deficits; as a specific example, mice with targeted deletion [knockout] of NRG1 and COMT are not models of schizophrenia per se but, rather, constitute fundamental tools for clarifying the functional roles of these genes in the regulation of behaviours relevant to psychosis. Furthermore, it is unclear whether the several genes now associated with schizophrenia susceptibility and/or schizophrenia endophenotypes contribute additively to overall risk for schizophrenia, perhaps via expression in convergent pathways, or act independently to influence risk for distinct endophenotypes of the disorder. Molecular genetic tools are now available to examine how genes interact with each other and with environmental factors to disrupt normal brain development and behaviour; one goal is phenotypic resolution, using behavioural, imaging and cellular techniques, of gene × gene and gene × environment relationships in the context of putative schizophrenia endophenotypes. This review focuses on summarising data regarding the behavioural phenotype of mice mutant for schizophrenia susceptibility genes; as exemplar, we outline our recent findings on the extent to which the social and cognitive phenotype of NRG1 mutants is similar to or different from that of COMT mutants. We also consider methodological issues that are likely to influence phenotypic effects, as well as the limitations associated with existing molecular techniques. The authors' studies are supported by Science Foundation Ireland.

S5

THE METHODOLOGY OF PSYCHOMETRIC SCALES: NEW OPTIONS FOR ANALYSIS

Croudace TJ. Dept of Psychiatry, University of Cambridge, Box 189, Addenbrookes Hospital, Hills Road, CAMBRIDGE CB2 2QQ, tjc39@cam.ac.uk

Psychometrics is the science of psychological assessment. Psychological assessments of clinical and other phenomena are play an important role in psychopharmacological studies and other psychiatric research including epidemiology and intervention studies. Psychometric statistics has been boosted recently by more powerful and flexible statistical software, new analysis models and computational procedures. Clinical researchers and statisticians in the pharmaceutical industry now have a range of more powerful tools for understanding their psychometric data. Many of these developments are recent and not widely known. The author will introduce and illustrate recent developments using examples drawn from psychiatric, public health, clinical trial and quality of life studies. Particular attention will be given to procedures available by linking routines and models available in Stata and Mplus software, with some pointers also to methods available in R. Instruments under investigation will include Goldberg's General Health Questionnaire (screening applications), the Beck Depression Inventory (clinical outcome measurement), the Mood and Feelings Questionnaire (affective psychopathology in adolescents) and measures from clinical trials in adult schizophrenia and depression. Pointers will be given to UK training events in psychometric methods and approaches, and a web resource developed with support from a UK research council will be introduced.
The author is a Dept of Health Career Scientist award holder and has experience of psychiatric epidemiology cohort studies, clinical trials and psychometric development and evaluation work in all these areas. He is director of research at the Psychometrics Centre, University of Cambridge and a Senior Lecturer in Psychometric Epidemiology at the University of Cambridge, Department of Psychiatry. He collaborates with international birth cohort studies and is methodological adviser to psychiatric trials in the East Anglia Hub of the Mental Health Research Network. He has also collaborated with industry statisticians on patient reported outcome measurement (PROS) in psychiatry and other application areas. He is co-author of a book (in preparation) with Pickles and Dunn, on latent variable modelling, including psychometrics and clinical trial analyses, due in 2009.

S6

GENERALISED ANXIETY INVENTORY (GADI)

Argyropoulos SV, Ploubidis GB, Bailey JE, Palm ME, Anderson IM, Nutt DJ, Potokar JP. Section of Neurobiology of Psychosis, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, s.argyropoulos@iop.kcl.ac.uk

A few years ago, we observed that the psychometric tools used for the assessment of generalised anxiety disorder (GAD) either did not conform to the current concept of the condition nor had some important limitations. We sought to develop and validate a new questionnaire for the assessment of symptom profile and severity of GAD. We subjected an original pool of potential scale items (derived from the DSM and ICD classificatory systems) to a series of studies in non-clinical and clinical populations, in order to determine the final composition of the scale. We evaluated the psychometric properties of the new scale, the Generalised Anxiety Disorder Inventory (GADI), using a factor analytic model suitable for ordinal data and the Graded Response Model. We quantified the precision of measurement of the GADI through the item information functions. The final 18-item scale (Argyropoulos et al, 2007, J Psychopharmacology, 21: 145-152) showed good reliability, convergent and divergent validity. The scale comprises three factors, relating to cognitive, somatic and sleep symptoms. It distinguishes accurately GAD patients from non-patient controls. The cognitive factor also distinguishes GAD from other anxiety disorders and depression. We concluded that the GADI is a useful tool in the assessment of the breadth of symptoms and the severity of generalised anxiety disorder in clinical settings. The sensitivity of the GADI to detect changes in symptom levels was tested in two experimental models of anxiety induction; the inhalation of 7.5% CO2 over a period of 20 minutes, which models generalised anxiety, and a single vital capacity inhalation of 35% CO2, which models panic anxiety (Bailey et al, 2005, Depression & Anxiety, 21: 18-25; Bailey et al, 2007, J Psychopharmacology, 21: 42-49). We found that the GADI was able to detect the differential drug effect of a benzodiazepine (alprazolam) and placebo in the anxiety induced by these tests in healthy volunteers. Finally, we used the GADI to explore the question of whether generalised anxiety disorder (GAD) is mainly defined by individual personality characteristics or by contextual influences. The neuroticism trait was associated with all three factors of the GADI, anxiety & worry (r=0.59), sleep problems (r=0.29) as well as somatic symptoms (r= 0.33), and the total GADI total score (r=0.59). We concluded that GAD, as quantified by the GADI, is partly a stable trait, but there remains substantial variation that cannot be explained by personality alone.

S7

VISUAL ANALOGUE SCALES

Tiplady B. Anaestheics, University of Edinburgh, Edinburgh, EH16 4SA, brian@penscreen.com

Visual analogue scales (VAS) come in several varieties. The one most commonly used in psychopharmacology consists of a horizontal line 100 mm long, the ends marked with two opposite descriptive words such as "Alert -- Drowsy" or "Interested-- Bored". This is referred to as a bipolar scale. Unipolar scales have a single descriptor, such as "Anxious", with the ends of the lines marked with quantifiers, typically "Not at all" and "Extremely" or "Couldn't be worse". The respondent makes a mark on the line to indicate the feeling between the two extremes. The scale is scored by measuring the position of the mark in mm (i.e. % of scale length). A key feature of this type of scale is that the numerical score is not apparent to the respondent, who simply sees a mark on a line. Other variants of the VAS have the scale marked with numerical values from 0 - 100, so that the user can see the numerical value. An example is the VAS from the EQ-5D health status measure, which is a vertical scale, with 0 representing "Worst imaginable health state" and 100 representing "Best imaginable health state".

This presentation will review the evidence for different scale types from the perspectives of both clinical and experimental psychopharmacology. VAS will be compared to other formats such as verbal rating scales, where each option is given a description, such as “Mild”, “Moderate”, or “Severe”. The number of response options that can be given a distinct defined meaning is limited, usually to a maximum of about seven levels. This may lead to loss of sensitivity compared to a scale such as the VAS with 101 possible outcomes. A scale with no definitions other than at the extremes may also show better scaling properties than one with a few discrete defined levels. On the other hand, defined levels may be easier to interpret, a feature that may be important in clinical studies. The effect of type of scale and definition of response options on sensitivity to change will be considered.

There may also be difference between scale types in ease of use. It has been suggested that some older respondents may have difficulty with the basic concept of the analogue scale, and that defined response options are easier to understand. Different modes of presentation, for example comparisons between paper and various forms of electronic administration will also be considered.

S8

SUBJECTIVE WELL-BEING UNDER NEUROLEPTIC TREATMENT. RELATIONSHIPS TO PSYCHOPATHOLOGY, COMPLIANCE AND REMISSION

Naber DN Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, naber@uke.uni-hamburg.de

Only recently, and strongly related to the development of atypical antipsychotics, success criteria became more ambitious and include a more thorough consideration of negative symptoms and cognitive dysfunction, both of major importance for long-term prognosis. The most important change within the last decade is the long overdue consideration of the patient's perspective. His/her subjective well-being, often unchanged or even worsened by typical antipsychotics, was neglected for a long time. One reason was the prejudice that schizophrenic patients are not able to self-rate their mood, well-being or quality of life. Another reason was the belief that such data are not necessary because the psychiatrists’ perspective, “objective” psychopathology, includes these domains. Among other scales, a self-report instrument has been constructed to evaluate “subjective well-being under neuroleptics” (SWN). This scale was used in numerous open and controlled trials, indicating: a) schizophrenic patients, if no longer acutely psychotic or suffering from severe cognitive deficits, are able to reliably assess their subjective well-being, b) high SWN is correlated with high compliance, c) atypical antipsychotics increase SWN, d) individual improvements of SWN and of PANSS are not strongly related (r=-.30 - -.40), and e) dopamine D2 receptor blockade is highly correlated to reduced SWN (r = .66 - .76). Two recent open trials reveal the relevance of early improvement of subjective well-being: In a 12-week trial with 727 patients, 95% of those with early subjective response (within 4 weeks) showed later subjective and/or psychopathological improvement, but only 9% without early subjective response showed later improvement. In another 3-year trial of 2690 patients, again psychopathological response as well as symptomatic and functional remission were not only related to young age and treatment with atypical antipsychotics, but mostly to early (within the first 3 months) subjective improvement. Early improvement of subjective well-being is a major predictor for the chance of remission. Risk factors for insufficient subjective improvement need to be identified early with subsequent treatment adaptations.

S9

GLUTAMATE IN COCAINE AND HEROIN ADDICTION, FROM ANIMALS TO MAN

LaLumiere RT. Neurosciences, Medical University of South Carolina, 173 Ashley Avenue, Charleston, SC 29425 USA, lalumie@musc.edu

Accumulating evidence strongly implicates a critical role for glutamate in drug addiction, particularly in the risk of relapse. As relapse remains the most serious problem facing the treatment of addiction, understanding the neurobiology underlying relapse and identifying potential therapeutic targets remain significant goals in the study of drug addiction. Through the use of the drug self-administration and reinstatement models, we have found that glutamate in the nucleus accumbens (NA) core is essential for driving the reinstatement of drug seeking for both heroin and cocaine. It appears that drug and cue-prime reinstatement increase glutamate levels in the NA core. Inactivation of the prelimbic cortex prevents this increase, suggesting that the projection from the prelimbic cortex to the NA core is critically involved in driving drug seeking. Moreover, after cocaine self-administration, there is a decrease in basal glutamate levels in the NA core due to dysfunction in glutamate-cystine exchange activity in the glial cell regulation of extrasynaptic glutamate. The reduced glutamate levels provide less inhibitory tone on the presynaptic glutamate receptors, enabling a cocaine injection to produce an excess release of glutamate and drive the reinstatement behavior. In cocaine-withdrawn rats, N-acetylcysteine, a cysteine prodrug, increases glutamate-cystine exchange activity, restores glutamatergic tone, and reduces cocaine and heroin-seeking, suggesting that restoring glutamate levels is a potent therapeutic target. In addition, clinical studies suggest that N-acetylcysteine reduces craving in cocaine addicts. In the reinstatement model used in many studies, rats undergo extinction training prior to the reinstatement testing, indicating that neural circuitry responsible for suppressing drug seeking must exist. Recent findings from our laboratory have found that, akin to the prelimbic-NA core circuitry that drives drug-seeking, a more ventral circuitry including the infralimbic cortex and NA shell is responsible for suppressing drug-seeking behavior in rats having undergone extinction training. Inactivation of the infralimbic or NA shell following extinction produces reinstatement of drug-seeking behavior, whereas activation of AMPA glutamate receptors in the infralimbic cortex reduces cocaine-prime reinstatement. Moreover, inactivation of the infralimbic cortex after early extinction sessions impairs retention of the extinction on subsequent tests, suggesting that the infralimbic cortex is critically involved in learning to suppress drug-seeking behavior. These findings suggest that it is possible to enhance the rate of extinction of drug-seeking, thus providing another method by which drug-seeking behavior can be modified.

S10

EXPLORING GLUTAMATE FUNCTION IN SMOKERS

Jackson A. School of Pharmacy and Biomolecular Sciences, University of Brighton, Moulsecoomb, Brighton BN2 4GJ, aj4@bton.ac.uk

Preclinical studies indicate that nicotine, at concentrations achieved during smoking, can enhance the release and function of glutamate through an action at presynaptic acetylcholine receptors (eg McGehee et al, 1995. Science, 269, 1692). Such studies have determined that nicotine can alter glutamate release in several different areas of the brain, including the pre-frontal cortex, the hippocampus, the ventral tegmental area and the nucleus accumbens; these are areas associated with the cognitive and addictive effects of nicotine. Consistent with this, there is a growing body of evidence implicating a role for glutamate in the behavioural actions of nicotine in models of cognition and addiction (eg, Paterson et al, 2003. Psychopharmacology, 167, 257). In humans, smoking has a range of nicotine-mediated actions, including reinforcing, subjective and positive cognitive effects, but little is known about which of these might involve changes in glutamate function. Our studies have therefore been directed at exploring the involvement of glutamate in the effects of smoking and in particular, the putative role of the N-methyl-D-aspartate (NMDA) receptor. In experiments in moderate – heavy smokers, we investigated how the acute administration of memantine (an antagonist at NMDA-receptors) and d-cycloserine (a partial agonist at the glycine site of the NMDA-receptor) modulated smoking-induced changes in craving, subjective effects and performance on a task of sustained attention. As the pharmacological action of d-cycloserine may depend on endogenous levels of neurotransmitter, we also studied its effects on responses to different amounts of smoking. Both memantine (Jackson et al, 2008. Neuropsychopharmacology, in press) and d-cycloserine were found to alter the subjective effects of smoking although neither affected craving measures. In contrast, a different pattern of results emerged for the effects of the two drugs in the task of sustained attention, where d-cycloserine (but not memantine) interacted with smoking on a measure of inhibitory control. Overall, our studies are consistent with preclinical evidence in that they indicate that changes in glutamate release may underly some of the effects of smoking. Our studies also suggest however, that in terms of a role for the NMDA-receptor, there may be a dissociation between the mechanisms underlying the effects of smoking on dependence-related measures and its cognitive (attention-enhancing) benefits.

[Studies were funded by Wellcome Trust grant number 074354]

S11

ROLE OF NMDA AND AMPA RECEPTORS WITHIN THE DOPAMINERGIC SYSTEM ON COCAINE AND ALCOHOL REINFORCEMENT

Spanagel R. Department of Psychopharamcology, Central Institute of Mental Health, J5, 68159 Mannheim, Germany. rainer.spanagel@zi-mannheim.de

Synaptic plasticity within the mesolimbic dopamine system is considered as a neural substrate for core aspects of addiction. In particular, alterations in NMDA and AMPA receptor subunit composition in dopaminergic neurons as well as in dopaminoceptive neurons may underlie the addictive properties of drugs of abuse. To elucidate the functional role of these subunits in cocaine and alcohol reinforcement, sensitisation, extinction and reinstatement/ relapse behaviour we generated mice with NR1, GluR1, and GluR2 deletions specifically in dopaminergic and dopaminoceptive cells using the Cre-loxP system (using DAT-Cre and DAD1-Cre line). Measurements on AMPA receptor-mediated excitatory postsynaptic currents (AMAPR EPSCs) and the AMPAR:NMDAR ratio confirmed the specificity of the genetic deletions. On the behavioural level, we found to our surprise that NR1, GluR1 and GluR2 subunits expressed in dopaminergic neurons are not critical for cocaine sensitization and conditioned place preference. However, whereas wild type mice show extinction of conditioned place preference, GluR1 mutants show no extinction. Thus, our data show that GluR1 in dopaminergic cells is essential for extinction of conditioned cocaine reinforcement. In addition we found that the NR1 subunit is crucial for reinstatement behaviour.

S12

GLUTAMATE MECHANISMS IN APPETITIVE INCENTIVE LEARNING

Crombag HS. Psychology, University of Sussex, John Maynard Smith building, 5D9, Brighton, h.crombag@sussex.ac.uk

In Pavlovian conditioning, the establishment of a predictive relationship between a relatively neutral conditioned stimulus (CS) and a motivationally significant unconditioned stimulus (US or reward) can endow that CS with motivational or emotional powers. For example, the conditioning of incentive motivation to a CS paired with food delivery enables that CS to reinforce later Pavlovian or instrumental learning and to modulate the performance of other learned (e.g., lever-pressing for food, e.g. Holland and Gallagher 2003) or unlearned (e.g. feeding, Holland et al. 2002) responses. Many authors have described how such incentive learning can play important roles in the control of aspects of motivated behavior relevant to issues of public health, such as substance abuse and weight control. In particular, it has been widely noted that drug-related cues can both enhance craving and drug-seeking behavior and serve as potent conditioned reinforcers for those behaviors, especially in drug-deprived addicts (e.g., Everitt et al. 2000). Making use of a number of different transgenic mouse models, we have recently embarked on a series of studies exploring the role of glutamatergic mechanisms in various manifestation of Pavlovian incentive learning in drug and non-drug settings. More specifically, these studies have explored how factors that regulate AMPA receptor function, a critical mechanism in the establishment and expression of synaptic plasticity in the brain, may also be involved in the ability of cues to acquire and maintain motivational significant and impact behavior. For instance, we have found that a specific kinase pathway involved in AMPA phosphorylation (and presumably AMPA receptor trafficking) is critical in the effects of cues for natural reward to serve as reinforcers (a process thought critically involved in relapse induced by cues in addicts). Second, we have explored the role of Neuronal-Activity Regulated Pentraxin (NARP), an immediate early gene (IEG) product that is secreted into the extracellular space where it co-clusters with AMPA receptors, in drug and non-drug incentive learning. Although we found little direct influence on incentive learning, our findings reveal a potential role for NARP in the longer-term maintenance of acquired associations between cues and drug or non-drug rewards. While our studies are preliminary, and in need of future experimentation, they provide some intriguing new insights into role of glutamatergic mechanisms in complex psychological phenomena thought to be important for normal, adaptive motivated behavior, as well a maladaptive conditions such as drug-addiction.

S13

IDENTIFYING TREATMENTS FOR COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA: LESSONS FROM MATRICS, TURNS, AND CNTRICS
Gever MA. Psychiatry, University of California San Diego, 9500 Gilman Dr., La Jolla, USA 92093-0804, mgeyer@ucsd.edu

The NIMH-funded MATRICS Program (Measurement and Treatment Research to Improve Cognition in Schizophrenia) developed a broad consensus regarding the nature of the cognitive impairments in schizophrenia and how they might best be assessed and treated. The subsequent NIMH-funded TURNS Program (Treatment Units for Research on Neurocognition in Schizophrenia) is developing clinical trial approaches and biomarkers for use in assessing the efficacy of compounds intended to treat cognitive deficits in schizophrenia patients already maintained on stable antipsychotic medications. CNTRICS (Cognitive Neuroscience measures of Treatment Response of Impaired Cognition in Schizophrenia) was a subsequent series of workshops on how to better utilize neuroscience- and brain-based translational approaches to the understanding of cognition. The goal of these meetings was to further improve the clinical assessment of potential pro-cognitive agents in schizophrenia. The lessons learned from these consensus-building programs will be summarized. There is an urgent need for improved translational tools to facilitate preclinical drug discovery and associated clinical proof of concept studies relevant to developing new treatments for cognition in schizophrenia. Of paramount importance in this regard is the identification and validation of efficacious treatments that can serve as positive control compounds in the validation of new preclinical and clinical test paradigms. Hence, this presentation will focus on the status of ongoing discussions regarding how preclinical scientists can develop and refine animal test batteries to identify novel pro-cognitive agents having potential utility in the treatment of antipsychotic-treated schizophrenia patients. One major aspect of this effort is to foster the essential dialogue between the preclinical and clinical cognitive neuroscience communities in order to enhance novel and improved approaches to the treatment of cognitive deficits in schizophrenia.

S14

WOOLLEY-ROBERTS

NO ABSTRACT PROVIDED FOR THIS PRESENTATION

S15

COGNITIVE ENHANCEMENT IN SCHIZOPHRENIA
Spence SA Academic Clinical Psychiatry, University of Sheffield, Norwood Grange Drive, Sheffield S5 7JT, S.A.Spence@Sheffield.ac.uk

Schizophrenia is a heterogeneous disorder characterized by psychotic symptoms, disturbances of thought, speech, behaviour and affect. Deficits in cognitive function are generally of the order of 1 - 3 standard deviations below 'normal' function. Hence, the desirability for cognitive remediation may be great but the prospects for such improvement are generally modest. I shall review the cognitive deficits associated with schizophrenia, their biological substrates, where known, and the prospects for amelioration based upon peer-reviewed published data.

S16

TACKLING COGNITIVE DYSFUNCTION IN MOOD DISORDER: OUTCOME OF THE BAP SPONSORED WELLCOME MASTERCLASS

McAllister-Williams RH, and the CADENCE group Psychiatry, Institute of Neuroscience, Newcastel University, Leazes Wing, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, r.h.mcallister-williams@ncl.ac.uk

Although mood disorders are defined clinically by alterations in affect, they are also characterised by cognitive abnormalities including episodic and spatial memory, attention, executive function and emotional processing. These abnormalities can have a major impact on patients functioning and quality of life and their further study may provide fundamental information regarding underlying pathophysiological processes. Numerous lines of evidence support hypotheses for a role of monoamines both in the pathothology and treatment of mood disorders as well as the pathology of the associated cognitive abnormalities. Likewise, alterations in the hypothalamic-pituitary-adrenal axis are well characterised in mood disorders and adrenal steroids (e.g. cortisol) have marked effects on cognition. In 2007 the Wellcome Trust awarded a grant for a Masterclass in Clinical Neuroscience titled "Tackling cognitive dysfunction in affective disorders: focus on monoamines and corticosteroids". The Masterclass was sponsored by the BAP and the Institute of Neuroscience at Newcastle University. Following the creation of an interactive web forum used to identify topic areas and key questions a residential meeting was held in Northumberland in March 2008 with delegates from the UK, Europe, USA and Australia. The outcome was the creation of a special interest group titled "Cognition in Affective Disorders: Experimental Neurobiology and Clinical Evaluation (CADENCE: http://research.ncl.ac.uk/cadence/). In addition a publication in the Journal of Psychopharmacology is in preparation which highlights the key issues and potential avenues for research in the field. It is hoped that this initiative will increase the profile of cognitive abnormalities in mood disorders as a topic for research and potentially therapeutic targets in the management of these conditions.

S17

APPLICATIONS OF FMRI TO TRANSLATIONAL MEDICINE IN PSYCHIATRY

Matthews PM. Head, GSK Clinical Imaging Centre, Hammersmith Hospital, London, Professor of Clinical Neurosciences, Imperial College, London, Hon. Professor of University College London in the Institute of Neurology, paul.m.matthews@gsk.com

Functional magnetic resonance imaging (fMRI) already has had a major impact in cognitive neuroscience. There is a wider potential for clinical fMRI in applications to psychiatry ranging from presymptomatic diagnosis, through drug development and individualisation of therapies, to understanding functional brain disorders. Applications to the development and evaluation of new therapies can be powerfully exploited in the context of translational medicine: biology-led, integrated clinical and preclinical investigations. Because preclinical models allow invasive approaches to be coupled to imaging studies and because similar imaging measures can be used in both preclinical and clinical investigations, translational studies provide a particularly useful paradigm for validation of fMRI for experimental medicine studies. Examples will be presented of well-controlled preclinical systems that allow primary neuronal and vascular drug responses to a novel molecule to be distinguished (see, Magn Reson Med 49(5):838-847; Neuroimage 2007;34(4):1627-36). The functional neuroanatomy of brain system drug response can be characterised in pharmacodynamic studies (Neuropsychopharmacology. 29(9):1715-22) and potentially used to differentiate drug action. In some cases, information related to potential toxicity or adverse events can be defined. Benefits come from more indirect inferences in which characterisation of drug responses at a cellular or local circuit level inform the interpretation of human studies (Biol Psychiatry. 58(6):488-94). With the potential for in vivo characterisation of white matter connectivities (Biol Psych. 56(9):613-9), anatomical contrasts can be made across species, illuminating differences in behaviours (Cereb Cortex. 16(6):811-8). Imaging thus provides a potentially powerful tool for more efficiently translating pre-clinical and clinical studies and enhancing confidence in progression through early phase clinical development. There is a strong rational for investment in pHMRI for early phase clinical development, but that the short- to medium-term impact on late phase clinical development likely will be modest. However, the scientific community still faces challenges for implementation of this vision because of differences in skill sets needed for preclinical and clinical investigations. Realisation of the full promise of imaging for translational medicine will demand changes in the way clinical neuroimaging is planned and delivered in both academia and industry.

S18

GENETICS AND NEUROIMAGING IN PEOPLE AT RISK OF DEVELOPING PSYCHOSIS

Lawrie S. Division of Psychiatry, University of Edinburgh Royal Edinburgh Hospital, Edinburgh EH10 5HF Scotland, UK s.lawrie@ed.ac.uk

Introduction - We have recently completed a ten year longitudinal study of brain structure and function in a group of individuals at high risk of schizophrenia for familial reasons, and have taken blood for genetic analyses.
Methods - Initially healthy people aged 15-25 at high genetic risk of schizophrenia were examined with structural MRI and functional MRI.
The development of psychotic symptoms and/or schizophrenia itself was monitored at serial assessments, which most participants had at 18-24 month intervals over up to 10 years.
Results - 21 developed schizophrenia during the study and an additional 66 subjects had psychotic symptoms at one or more assessments. 78 of the subjects were genotyped. Single nucleotide polymorphisms in the Brain Derived Neurotrophic Factor (BNDF) and D-amino acid oxidase (DAO) genes were associated with abnormalities of frontal and temporal function in the high risk cohort as a whole. A risk allele in the Neuregulin 1 (NRG1) promoter region, on the other hand, was associated with the development of psychotic symptoms and decreased premorbid IQ, as well as decreased activation of pre-frontal and temporal lobe regions. The Val(158)Met polymorphism in the Catechol-O-MethylTransferase (COMT) gene predicted schizophrenia in this cohort in a dose-dependent manner and was also associated with reduced gray matter density and BOLD signal in anterior cingulate cortex.
Conclusions - These patterns of altered brain structure and function have previously been associated with schizophrenia in this and other samples. BDNF and DAO may have trait effects, while the NRG1 variant seems to be a risk factor for an extended or intermediate phenotype and the COMT Val allele appears to be associated with an increased risk of schizophrenia.

S19

BIOMARKERS IN PSYCHIATRIC DISEASE: PERSPECTIVE FROM THE PHARMACEUTICAL INDUSTRY

Hurko O Translational Medicine, Wyeth Research, Sir James Black Centre, Dow Street, Dundee DD1 5EH, HURKOO@wyeth.com

The last decade has seen an almost universal adoption of target-based drug discovery by the Western pharmaceutical industry. This new approach was inspired by confidence in current molecular theories of psychiatric disease. This novel approach has been facilitated by the nearly contemporaneous emergence of three key technologies: the sequencing of the human genome, combinatorial chemistry, and high-throughput screening. The target-based approach has increased the output of Discovery organizations dramatically. However, not only the proportion but also the absolute number of novel drugs approved for clinical use has continued an uninterrupted yearly decline since the introduction of this approach.

Among all therapeutic areas, neuropsychiatry holds pride of place in the discordance between preclinical productivity and clinical disappointment. In the last decade, less than 5% of compounds proven safe and effective in animal models of neuropsychiatric diseases have gained clinical approval. IIn the last decade, the peak of clinical failures have shifted from Phase I safety and tolerability studies to Phase 2 efficacy studies. For this reason, there is emerging interest in a requirement for success in biomarker studies before investment in more costly registration studies that use clinical endpoints.

As a first approximation, compounds can be considered to fail in Phase 2 studies for either of five major reasons: (1) the compound is given to the wrong patients, (2) the compound is given at the wrong dose, (3) the compound's efficacy is not detectable with clinical measures (4) the compound induces unacceptable side effects in some recipients, or (5) the drug target is important in animal models but not in the human disease selected for treatment. Ideally, specific biomarkers would be used to minimize each of these causes of failure. Experience from other therapeutic areas indicates that a given biomarker is usually suitable for only one of these five purposes.

The utility of a given biomarker as well as the degree of validation required, varies depending on its intended use, The highest degree of validation is required for surrogate measures of efficacy, i.e., those which regulatory agencies accept as primary endpoints in lieu of clinical measures. Only half a dozen efficacy biomarkers that are recognized as true surrogates. None of these are for neuropsychiatric disease. The ultimate utility of a biomarker for internal decision-making in translational studies depends on the expected frequency of false negatives and false positives resulting from its use, the relative costs of biomarker and clinical studies, and the historical rates of stage-specific failure for a given indication.

S20

THE PHENOTYPE IN MOLECULAR GENETIC STUDIES OF PSYCHIATRIC ILLNESS

Craddock N. Psychological Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN
craddockn@cardiff.ac.uk

Recent experience in many common non-psychiatric diseases provides grounds for optimism that increasingly large-scale molecular genetic studies have the power to identify common DNA variation that influences susceptibility to major psychiatric illness. By pinpointing the biological systems involved in disease pathogenesis this will provide opportunities for major advances in clinical psychiatry. Much of the promise of a revolution in psychiatric genetics stems from improvements in molecular genetic technology. However, realizing the potential of the technical breakthroughs in molecular genetics depends upon us finding ways to overcome the major limitations imposed by current diagnostic classifications; we must move understanding of clinical phenotype beyond the categories of, for example, schizophrenia and bipolar disorder and towards biologically valid entities. This presentation will consider approaches that may be helpful, and indeed necessary to realize the potential power of molecular genetics for psychiatric phenotypes. This will include more refined approaches to using clinical phenotypic variables as well as approaches that are predicated on using phenotypic measures that are believed to be "closer" to the underlying biology (so-called intermediate phenotypes or endophenotypes). The discussion will be illustrated by examples from the literature on non-psychiatric diseases and examples using the Wellcome Trust Case Control Consortium dataset for bipolar disorder (1868 bipolar cases, 2938 controls genotyped for 500,000 polymorphisms). The different approaches are complimentary. It is likely, on both theoretical and practical grounds, that a more sophisticated use of clinical phenotype data will usually be most helpful for initial identification and broad characterization of polymorphisms that influence susceptibility to, or modify the course of, illness. Use of intermediate phenotypes (endophenotypes) is likely to be most helpful for exploring the phenotypic spectrum and mode of action associated with such polymorphisms.

S21

NEUROSTEROIDS MEDIATE ALCOHOL SENSITIVITY: MECHANISMS AND THERAPEUTIC RELEVANCE

Morrow AL. Psychiatry and Pharmacology, UNC School of Medicine, Thurston-Bowles Building, Chapel Hill, morrow@med.unc.edu

The molecular basis of ethanol action involves the production of GABAergic neuroactive steroids, including 3α-hydroxy-5α-pregnan-20-one (3α,5α-THP) and 3α,21-dihydroxy-5α-pregnan-20-one (3α,5α-THDOC). Ethanol elevates brain levels of these steroids in rodents to enhance GABA-A receptor activity. Neuroactive steroids modulate anticonvulsant effects, sedation, impairment of spatial memory, anxiolytic-like, antidepressant-like and reinforcing properties of ethanol. Each of these responses is inhibited by pretreatment with the biosynthesis inhibitor finasteride and/or prior adrenalectomy. These studies suggest that neuroactive steroids are responsible for many of the GABAergic effects of ethanol in vivo and the elevation of neuroactive steroids may determine sensitivity to the behavioral effects of ethanol. We investigated whether the effects of ethanol on 3α,5α-THP levels are dependent upon ethanol induction of ACTH, adrenal steroids, de novo synthesis of steroidogenic acute regulatory protein (StAR) or the mitochondrial benzodiazepine receptor in the adrenals to produce the precursor pregnenolone and it's neuroactive metabolites. ACTH was inhibited by pretreatment with dexamethasone and the role of adrenal steroids was tested in adrenalectomized rats. The importance of de novo StAR synthesis was tested by inhibition with cyclohexamide following ethanol but prior to steroid determinations. ACTH induction, intact adrenals and de novo synthesis of adrenal StAR are required for ethanol-induced increases in both plasma and brain neuroactive steroids. These results emphasize that the systemic effects of ethanol are important contributors to ethanol effects on brain that mediate it's behavioral actions. Low sensitivity to the behavioral effects of ethanol is a risk factor for development of alcoholism. Moreover, individuals with the GABRA2 polymorphism linked to alcoholism exhibit blunted sensitivity to subjective effects of ethanol and insensitivity to finasteride. Alcoholic subjects show blunted activation of the HPA axis and this may lead to dysregulation of neurosteroid levels that would normally contribute to alcohol sensitivity. Hence, neurosteroid production in response to physiological challenge may be protective against the development of alcoholism. GABAergic neuroactive steroids may be therapeutic for alcoholism since they are known to substitute for ethanol in discrimination studies, increase alcohol sensitivity, reduce ethanol consumption using various drinking paradigms, reduce ethanol withdrawal anxiety and seizure susceptibility, restore physiological responses to stress challenges, prevent neurotoxicity and promote neurogenesis.

S22

THE NEUROTOXICITY OF ALCOHOL WITHDRAWAL

Little HJ. Biomedical Sciences and Mental Health, St George's, University of London, Cranmer Terrace, London SW17 0RE, hilary.little@sgul.ac.uk

Up to 80% of alcoholics exhibit cognitive deficits, that not only affect their quality of life but also ability to benefit from treatment programmes. The great majority of alcoholics relapse back to heavy drinking after periods of abstinence. Evidence suggests alterations in neuronal function during the acute phase of alcohol withdrawal may have prolonged consequences, including memory deficits. Studies examined neuronal changes during acute alcohol withdrawal and the neuronal and behavioural alterations that are seen during longer abstinence periods following cessation of long term alcohol consumption. Electrophysiological recordings from hippocampal and midbrain slices in vitro were made after withdrawal from chronic alcohol consumption in vivo. Measurements were also made on neurotoxicity in organotypic cultures of hippocampal slices following cessation of chronic alcohol treatment. Behavioural studies examined locomotor effects of cocaine, amphetamine and nicotine during the abstinence phase and the memory loss that follows chronic alcohol consumption and withdrawal. During the acute phase of alcohol withdrawal, excitatory amino acid transmission and calcium conductance were increased in hippocampal CA1 neurones but there was no evidence of reduced inhibitory transmission. In the organotypic cultures, corticosterone applied in vitro considerably increased both the neurotoxic effects and the increased calcium influx that followed alcohol withdrawal. The firing rates of dopaminergic neurones in the ventral tegmental area were decreased after withdrawal from chronic alcohol treatment in vivo, but this effect declined during the abstinence phase and was not apparent at 2 months abstinence. Enhancement of the locomotor effects of cocaine, amphetamine and nicotine was demonstrated during the abstinence phase. Glucocorticoid concentrations in specific brain areas were increased for up to two months after withdrawal from chronic alcohol consumption. The memory deficits seen later during the abstinence phase after withdrawal from chronic alcohol intake were prevented by administration of either a glucocorticoid Type II receptor antagonist or a dihydropyridine calcium channel antagonist. This was seen when these drugs were effective only during the acute alcohol withdrawal phase although the memory testing was carried out later during the abstinence phase when acute actions of these drugs would have ceased. The data shows that alterations in neuronal function during acute alcohol withdrawal have prolonged consequences, including memory deficits. The acute phase of alcohol withdrawal therefore offers a window of opportunity for pharmacological treatments that could prevent some of the important detrimental consequences of long term excess alcohol consumption.

S23

WHAT ARE THE ROLES OF GABAA RECEPTOR SUBTYPES IN ADDICTIONS?

Stephens DN, Dixon CI, King SL. Psychology, University of Sussex, Falmer, Brighton BN1 9QG, d.stephens@sussex.ac.uk

The mesolimbic dopamine pathway projecting from the ventral tegmental area (VTA) to nucleus accumbens is centrally implicated in the actions of drugs of abuse. Activity of dopamine neurones in VTA is strongly influenced by GABAergic inputs, while GABAergic medium spiny neurones are the major neuronal type within the accumbens, their activity being regulated by glutamatergic and dopaminergic inputs. The integrated output of the medium spiny neurones to the pallidum and ventral tegmental area is subject to inhibition by GABAergic collateral connections between individual spiny neurones. Thus, GABAA receptors are likely to play multiple roles in mediating, and modulating transmission within the "reward" circuitry. GABAA receptors are heterogeneous in their structure, synaptic function, distribution within the brain, and behavioural role. Structurally, the majority of these oligomeric protein complexes are made up of subunits from the alpha subunit family, in combination with beta and gamma or delta subunits. Within the rodent VTA, alpha1 and alpha3 subunits predominate, while alpha2 is rare or absent in adults. Pallidal GABAA receptors express predominantly alpha1 subunits. GABAA receptors utilising alpha2 subunits are heavily represented in accumbens, where they are likely targets of the collateral projections between spiny neurones. Correspondingly, deletion of the gene encoding the alpha2 subunit reduces synaptic GABAA receptor-mediated responses within medium spiny neurones. Behaviourally, the deletion abolishes the ability of cocaine both to potentiate behaviours conditioned to rewards, and to support behavioural sensitization. Conversely, activation of alpha2-containing receptors, even in the absence of cocaine, induces behavioural sensitization. Thus, activation of alpha2-containing GABAA receptors is both necessary to permit cocaine sensitization, and sufficient to support behavioural sensitization in its own right. Haplotypes of the GABRA2 gene encoding alpha2 subunits are associated in humans with both alcohol and cocaine abuse. Together, these data indicate a role for alpha2 subunit-containing GABAA receptors in addiction. However, their role is not simple, and deletion of alpha2 subunits gives rise to complex effects on measures of drug and alcohol reward that suggest that alpha2-containing GABAA receptors do not directly signal reward. We propose that they may, instead, play an important role in determining the relative weights of outputs to the pallidum and/or VTA, and thus play a role in selection of motivational outputs.

S24

NO ABSTRACT PROVIDED FOR THIS PRESENTATION

S25

POLYMORPHISMS OF 5-HT RECEPTORS AND THEIR ROLE IN CONSEQUENCES OF ANTIPSYCHOTIC TREATMENT

Reynolds GP. Division of Psychiatry and Neuroscience, Queen's University Belfast, Whitla Medical Building, 97 Lisburn Rd, Belfast BT9 7BL, g.reynolds@qub.ac.uk

There are substantial differences between individuals in the effects of antipsychotic drugs. This is apparent in two of the major limitations to the treatment of schizophrenia: the poor response of negative and cognitive symptoms, and the weight gain and metabolic pathology associated with use of some antipsychotics. Genetic variation is likely to contribute to these individual differences. While dopamine receptor antagonism is central to antipsychotic action, the newer drugs are all antagonists at the 5-HT2A receptor, several with effects at other 5-HT receptors. Thus these pharmacological effects, among others, provide valuable working hypotheses for the study of mechanisms of action, as well as indicating useful candidate genes, an approach which Rob Kerwin's group has been focused on for over 15 years. In particular, action at the 5-HT receptors has been suggested to be involved in the admittedly limited response to drugs of negative symptoms. However, receptor mechanisms, including effects at 5-HT receptors, also mediate the unwanted side effects of drug treatment, including the metabolic effects mentioned above. Our recent findings demonstrate the functional 5-HT1A receptor promoter polymorphism associates with negative and depressive symptom at baseline and in response to drug treatment in a drug-naive patient group (Reynolds et al, 2006 Am J Psychiat 163, 1826-1829), while a study in first-episode psychosis series shows a greater effect of a common 5-HT transporter polymorphism on negative symptom response. This and other studies support the growing evidence that, despite substantial inconsistencies between studies, polymorphisms in 5-HT-related genes, particularly those influencing synaptic 5-HT, associate with improvement in negative symptoms. 5-HT receptor polymorphisms also influence side effects including drug-induced weight gain and metabolic syndrome, weight gain in particular showing a strong pharmacogenetic association with promoter region polymorphisms in the 5-HT2C receptor and leptin genes, respectively being associated with shorter and longer-term consequences of treatment (Templeman et al, 2005 Pharmacogenetics 15, 195-200). Further study in chronically-treated patients with schizophrenia has revealed effects of the leptin gene polymorphism on the incidence of metabolic syndrome (Yevtushenko et al, 2008 Brit J Psychiat, in press). These findings point towards underlying mechanisms, as well as indicating the potential for genetic testing for these limiting side effects.

S26

HORMONAL AND IMMUNE SYSTEM GENES REGULATING OUTCOME TO TREATMENT IN MENTAL HEALTH

Pariante CM. Stress, Psychiatry and Immunology Section and Laboratory (SPI-Lab), Institute of Psychiatry, King's College London, 125 Coldharbour Lane, London SE5 9NU, c.pariante@iop.kcl.ac.uk

Clinical studies have demonstrated an impairment of glucocorticoid receptor (GR)-mediated negative feedback on the hypothalamic-pituitary-adrenal (HPA) axis in patients with major depression (GR resistance), and its resolution by antidepressant treatment. This GR impairment is driven by different pathophysiological mechanisms, including the effects of inflammatory mediators, changes in GR-associated proteins, reduction of intracellular access of glucocorticoid hormones, and GR gene variants. Our research, which started under the guidance of Professor Kerwin more than 10 years ago, has looked at the multitude of pathways affecting GR and MR function, using both clinical models and experimental systems, including most recently the use of prednisolone as a new neuroendocrine test, the in vitro evaluation of GR function in peripheral blood cells from depressed patients, the use of mice with knockout glucocorticoid transporter (p-glycoprotein) genes, and the examination of polymorphisms in inflammatory genes. This presentation will review our most important recent findings in this field, including: 1) that GR in peripheral blood mononuclear cells is resistant to the modulating effects of antidepressants in the context of increased activation and production of interleukin (IL)-6; 2) that p-glycoprotein knockout animals have normal entry of corticosterone into the brain but do not show the effects of antidepressants on the HPA axis; 3) that polymorphisms in the IL-6, IL-10, phospholipase A2 (PLA2) and cyclooxygenase-2 (COX-2) genes regulate the interaction between stress, inflammatory challenges and the development of mood and somatic symptoms; and 4) that, in contrast to the GR, the mineralocorticoid receptor (MR) function remains intact in depression, except in a subgroup of individuals who do not respond to treatment. The breadth and complexity of these research themes is an ongoing testimony of the scientific curiosity that Rob Kerwin inspired in our team.

S27

PHARMACOGENETICS OF ANTIPSYCHOTIC RESPONSE

Arranz MJ. Psychological Medicine, PO51, Institute of Psychiatry - King's College London, 1, Windsor Walk, London SE5 8AF, m.arranz@iop.kcl.ac.uk

It is well documented that environmental, clinical and demographic factors influence response to antipsychotic drugs. However, the magnitude of their contribution is difficult to determine, and may reflect dynamic interactions between the contributing factors. Several papers provide evidence of similarities between twins in their response to antipsychotic treatment, which confirms a genetic contribution. Nevertheless, family studies investigating concordance of treatment response in relatives and in adoptees are required to accurately assess the magnitude of environmental and genetic contributions. Pharmacogenetic research has succeeded in identifying several genetic factors that influence antipsychotic response. Polymorphisms in genes coding for CYP enzymes, dopamine and serotonin receptors have been repeatedly associated with response variation. In particular, CYP2D6 and CYP2C19 polymorphic variants have been associated with drug-induced adverse reactions and with drug metabolising rates. Functional polymorphisms in CYP1A2 and are also known to affect metabolising rates and contribute to treatment efficacy. Several tests are available to characterise these polymorphisms and determine the patients' metabolising status. Surprisingly, these tests are rarely used in clinical practice, in spite of the proven validity of this genetic information in the adjustment of therapeutic doses and reduction of toxic reactions. Polymorphisms in the genes coding for D2, D3, 5-HT2A and 5-HT2C receptors have been found to be associated with the level of response to antipsychotic treatment and with adverse reactions such as tardive dyskinesia and weight gain in independent studies. Additionally, genetic variants in glutamatergic and adrenergic receptors, and in genes involved in synaptic plasticity and regulation, have been associated with treatment response, although these findings require further confirmation. However, most of these findings have a moderate genetic effect, and have limited clinical value if considered individually. Nevertheless, tests combining information in several genes to give a prediction of response to clozapine, risk of agranulocytosis and hyperlipidemia have been developed, and tests for the prediction of response to a variety of antipsychotics, tardive dyskinesia and weight gain are under development. However, the implementation of genetic tests in clinical practice is very limited. Only some tests, determining patients' metabolising status, are routinely used in some laboratories and clinical institutions, whereas other tests for the prediction of response are still under trial. Improvement of prediction levels and better information on their utility will hopefully achieve an increase in use by clinicians.

S28

PHARMACOGENETIC AND PHARMACOGENOMIC STUDIES WITH ANTIDEPRESSANTS AND ANTIPSYCHOTICS

Aitchison KJ. MRC, Social Genetic and Developmental Psychiatry Centre, Institute of Psychiatry at King's College London, 16 De Crespigny Park, London, SE5 8AF, katherine.aitchison@iop.kcl.ac.uk

Introduction: The field of pharmacogenetics in psychiatry owes a lot to the late Professor RW Kerwin. This presentation will outline work conducted by myself and others working with him on the pharmacogenetics/genomics of antidepressant and antipsychotic response. This will include data on the pharmacogenetics of antidepressant and antipsychotic pharmacokinetics, candidate gene association studies of antidepressant and antipsychotic treatment response including adverse drug reactions (ADRs), and more recent pharmacogenomic analyses.
Methods: Samples were collected from individuals treated with antipsychotics and antidepressants from South London and Maudsley NHS Trust and collaborating centres. Subjects were genotyped for cytochrome P450 polymorphisms and other relevant candidate genes, and data analysed versus response to treatment and also ADRs. In addition, *in vitro* and *in vivo* work has been conducted, including treating cell lines with antidepressants and the use of informative rodent models.
Results: A significant association was found between CYP2C19 genotype and response to treatment with tricyclic antidepressants, and a significant association between CYP2C19 genotype and steady-state escitalopram level in a separate, larger collection (GENDEP). In the latter we also found an association between serotonin transporter promoter polymorphism (5-HTTLPR) genotype and response to escitalopram. *In vitro* and *in vivo* work in GENDEP has revealed loci that are invariant by treatment, and loci with differential gene expression by treatment condition. Prior work with a CYP1A2 knock-out mouse has shown an association between raised plasma clozapine levels and ADRs.
Conclusions: Our work points towards the clinical utility of genotyping CYP2C19. In addition, we have replicated the association between polymorphism in the 5-HTTLPR and response to antidepressants in a large European Caucasian sample. The CYP1A2 knock-out mouse is an informative model for individuals with low CYP1A2 enzyme activity. *In vitro* and *in vivo* work has revealed loci that are invariant by treatment, and loci with differential gene expression by treatment condition.
Acknowledgements: Work reported here was funded by a Wellcome Trust Mental Health Research Training Fellowship to Dr Aitchison, Lilly Travelling Fellowships to Drs Aitchison and Tsapakis, the European Commission (GENDEP, under Framework 6 Programme, contract number LSHB-CT-2003-503428), and Johnson and Johnson Pharmaceutical Research and Development.

S29

NEUROETHICAL ISSUES IN NEUROIMAGING

Farah MJ. Psychology, University of Pennsylvania, 3720 Walnut St., Philadelphia PA 19104, mfarah@psych.upenn.edu

In this presentation I will present an overview of the ethical, legal and social issues raised by advances in neuroimaging. I will argue that, on the one hand, the public and even clinicians and scientists often attribute more capability to neuroimaging than is warranted. I will also relate how, on the other hand, recent developments in neuroimaging portend spectacular new progress in the understanding of normal and abnormal brain function and in the measurement and prediction of traits and behaviors in clinical and other applied contexts. Brain images may be the scientific icon of our age, much as the Bohr atom was to the last century. I will review evidence concerning the powerful impact of brain images on people's thinking about psychology and the causes of behavior, and what we know about the public's understanding of mind-brain relations. I will also discuss some of the problems that can be caused by inflated assessments of the accuracy, objectivity and determinism of brain imaging. I will then focus on an issue of special relevance to psychiatry, namely the uses and abuses of neuroimaging in research on neuropsychiatric disease and treatment, in delineation of diagnostic categories, and in the process of diagnosis itself. I will argue that the first application is sound and indeed has been tremendously productive, the second is more controversial but potentially productive, and the third is premature and unfortunately becoming more prevalent. Finally, I will review recent progress in the development of brain imaging methods and applications. Most recent improvements have involved data analysis (signal processing and statistics) rather than data acquisition (the physics and chemistry of brain imaging), and I will highlight some of the recent advances in the former category, along with examples of psychologically relevant information that can now be extracted from brain images using these data analysis methods. Although inflated assessments of the capabilities of brain imaging remains an important ethical issue here, these examples also raise the additional ethical issues that ensue from successful reading of psychological information from brain imaging. Chief among these ethical issues is individuals' privacy.

S30

THE NEUROETHICS OF COGNITIVE ENHANCEMENT

Sahakian BJ, Dept of Psychiatry, Univ of Cambridge, Cambridge CB2 2QQ
Jenny.hall@cambsmh.nhs.uk

Neuroethics is the study of the ethical, legal and social questions that arise when scientific findings about the brain are carried into medical practice, legal interpretations and health and social policy (Marcus D, 2002. Neuroethics: Mapping the field conference proceedings. May 13-14, 2002, San Francisco, California. New York, The Dana Press). This talk will focus on some of these important questions as they relate to the use of cognitive enhancing drugs (Farah MJ et al 2004 Neurocognitive enhancement: what can we do and what should we do? *Nature Reviews Neuroscience* 5, 421-425; Turner DC and Sahakian BJ, 2006a. Neuroethics of cognitive enhancement. *BioSocieties* 1 113-123).
The prospect of being able to take safe and effective drugs to improve mental functioning is fast becoming a reality. Cognitive enhancement is of great interest to the general public and has implications for society, particularly in regard to the increasing use of cognitive enhancing drugs in school age children and university undergraduates and academics (Sahakian B and Morein-Zamir S, 2007; Professor's little helper. *Nature* 450. 1157-1159; Turner DC and Sahakian BJ, 2006b. The cognition-enhanced classroom. In *Better Humans* edited by Paul Miller and James Wilsdon. Published by DEMOS Collection 21: 79-85). The enormous and obvious potential benefits of 'smart drugs' need to be considered against the perhaps less obvious potential harms, for example unknown effects on the developing brain or coercion at school or work.
The talk concludes by urging neuroscientists to explore the implications of their work and engage in active debate with a wide range of interested stakeholders about the ethical and moral consequences of these new technologies to ensure maximal benefit to Society with minimal harm (see e.g. 'Neuroethics needed' www.nature.com/nature vol. 441, issue no. 7096, 22 June 2006, p907).

S31

PUBLIC ENGAGEMENT IN SCIENCE, INCLUDING NEUROETHICS

Campbell P Editor-in-Chief, Nature, 4 Crinan St, London N1 9XW, p.campbell@nature.com

The journal 'Nature' has long advocated public engagement in relation to science funding and policy development, and has also implemented it. I will describe past initiatives by others in several scientific and policy contexts, their achievements and limitations, and will also describe Nature's recent exploration of the use of cognitive enhancing drugs by healthy people.

S32

ETHICAL ISSUES IN CONSENTING ADULTS FOR NEUROSCIENCE RESEARCH

Pickard JD Clinical Neurosciences (Neurosurgery), University of Cambridge, Addenbrookes Hospital, Hills Road, Cambridge CB20QQ, prof.jdp@medschl.cam.ac.uk

'No individuals should be disqualified, by virtue of their group membership, from participating in research (as a result of incompetence to give consent or other reason) that could be of benefit in relation to the disease, disorder or disability from which they suffer' (Royal College of Psychiatrists 2000). The incorporation of the European Convention on Human rights within certain Acts and Regulations [Mental Capacity Act 2005; Adults with Incapacity (Scotland) Act 2000; Medicines for Human Use (Clinical Trials) Regulations 2004; Human Tissue Act 2004] has led to helpful support for research in incapacitated adults but also to some confusion surrounding implementation. A person is deemed unable to make a decision if he or she fails: • To understand relevant comprehensible information • To retain the information relevant to the decision • To use or weigh the information, or • To communicate the decision (by any means). There is debate over the use of the Mini Mental Score in defining capacity. Where an individual is found to be incapable, a close family member or partner should be identified who is willing to be consulted about the appropriateness of his or her involvement. Where such a person cannot be identified, a mechanism for nominating somebody independent of the research should be agreed with the Research Ethics Committee. Nature of research in incapacitated adults: • research involving incapacitated adults must be related to the condition that contributes to his/her impairment of the mind or brain • where the research is not expected to deliver direct benefit to the patient, the risk must be negligible • where the research might benefit the individual directly, the risks must not be excessive in relation to the anticipated benefits. The advent of functional brain imaging has greatly advanced our ability to safely study the vulnerable. In emergency situations, it is acceptable to proceed without the assent of a relative if that cannot be obtained in time subject to the Medicines for Human Use (Clinical Trials) Regulations 2004 where applicable. The risks and benefits should be judged in relation to those associated with existing treatments or outcomes (rather than minimal risks in an absolute sense). The application of these principles will be discussed in relation to patients in altered states of consciousness, dementia and explanatory and studies of conventional and novel therapy in acute brain injury where the therapeutic window of opportunity is very short.

S33

MOOD STABILISERS AND MONOAMINES

McQuade R. Institute of Neuroscience, Newcastle University, Newcastle upon tyne NE2 4HH, richard.mcquade@ncl.ac.uk

Mood stabilisers, including lithium, have been used for over 50 years in the maintenance treatment of bipolar disorder, yet the mechanism underlying their therapeutic effect is still poorly understood. The pathophysiology of bipolar disorders is similarly poorly understood, although monoamine dysregulation has been associated with the disease. Dopamine hyperfunction in particular is associated with manic symptoms. This presentation describes preclinical studies using a rodent model of long-term lithium administration to investigate how central dopamine function may be affected by chronic lithium treatment. Rats treated with lithium exhibit attenuated dopaminergic behaviours, in response to the dopamine releasing agent amphetamine, but normal dopaminergic behaviousr in response to the dopamine receptor agonist apomorphine. These data indicate that lithium induces a decrease in dopamine neurotransmission due to a decrease in presynaptic dopamine function. In support of this, dopamine release (as measured by microdialysis) in mesolimbic brain regions is attenuated after chronic lithium treatment. Further investigation to determine possible mechanisms underlying this decrease in dopamine release reveal that chronic lithium treatment does not affect dopamine uptake, autoreceptor (D2/3) sensitivity, or firing rate of dopaminergic neurones in the ventral tegmental area, the main body of dopaminergic neurones projecting to limbic areas. Finally, chronic lithium treatment does not affect the expression of dopamine synthetic (tyrosine hydroxylase), metabolic (monoamine oxidase) enzymes or vesicular proteins (VMAT2). These studies reveal an important neurobiological effect of lithium, attenuation of dopamine release, which leads to a decrease in dopamine neurotransmission. Given the association between dopamine hyperactivity and the manic state, the effect of lithium on dopamine function is a valid candidate for mediating the drugs therapeutic effect. Furthermore, the relevance of this is supported by finding of increased dopamine neurotransmission in a rats with elevated glucocorticoids (a model of the glucorticoid dysregulation common in bipolar disorder). However, further work is required, firstly to elucidate in more detail the mechanisms underlying lithium effect on dopamine function, and secondly to confirm whether these effects of lithium also occur in humans.

S34

ANTIPSYCHOTIC AUGMENTATION OF ANTIDEPRESSANTS IN MAJOR DEPRESSION

El Mansari M, Dremencov E, Blier P. Psychiatry, University of Ottawa Institute of Mental Health Research, 1145 Carling Avenue, Room 7407, Ottawa, Ontario, K1G4C7, Canada, mostafa.elmansari@rohcg.on.ca

There is now considerable evidence for the beneficial action of adding atypical antipsychotic drugs to selective serotonin (5-HT) reuptake inhibitors (SSRIs) in treatment-resistant depression. SSRIs are known to act by increasing 5-HT, but this effect results in dampening norepinephrine (NE) and dopamine (DA) transmission. Since monoaminergic neurons have physiologically important reciprocal interactions, preventing the effect of enhanced 5-HT levels using specific 5-HT antagonists restores catecholaminergic activity. To identify the receptors involved in the atypical antipsychotics risperidone or paliperidone-mediated alteration of locus coeruleus (LC) NE neuronal firing, the effects of alpha2-adrenergic (idazoxan), 5-HT2C- (SB 242084), 5-HT2A- (MDL 100907), or D2- (haloperidol) receptor antagonists were examined, alone and in their combination with the SSRI escitalopram. Escitalopram (10 mg/kg/day using osmotic minipumps implanted s.c.) and risperidone (1 mg/kg/day, s.c.) or paliperidone (1 mg/kg/day, s.c.) were administered alone and in combination for 2 and 14 days. Rats were anesthetized with chloral hydrate and glass electrodes were lowered into the LC. Sustained administration of escitalopram increased 5-HT transmission and consequently attenuated NE neuronal firing. MDL 100907 by itself was without effect in control animals, but reversed the escitalopram-induced inhibition of NE neuronal firing. Concomitant administration of risperidone prevents this suppression, apparently because of its 5-HT2A receptor antagonistic effect. However, haloperidol and SB 242084 did not affect NE neuronal activity alone or in combination with escitalopram. Idazoxan caused the same relative increase in the firing rate of NE neurons in control and escitalopram-treated animals. Furthermore, paliperidone, the 9-OH metabolite of risperidone, did not alter the firing rate of NE neurons by itself but reversed the escitalopram-induced suppression of NE neuronal firing after short- or long-term co-administration. In addition, paliperidone unlike risperidone did not alter the effect of sustained escitalopram administration on dorsal raphe 5-HT neuronal firing activity. Thus, the capacity of paliperidone to reverse the SSRI-induced inhibition of NE neuronal firing rate, without decreasing 5-HT neuronal activity, suggests that this compound may be beneficial in SSRI-resistant depression. Chronic and sub-acute escitalopram decreased NE neuronal firing, possibly via the elevation of the synaptic availability of 5-HT in the LC. Risperidone and paliperidone abolished this inhibition of NE neurons as was reported by another group for the combination of olanzapine and fluoxetine. Since this was obtained with a 5-HT2A receptor and an alpha2-adrenoceptor antagonist, and that olanzapine is devoid of alpha2-adrenergic activity, antipsychotic drugs may thus be effective in SSRI-resistant patients mainly because of their 5-HT2A receptor antagonism.

S35

BIPOLAR AND UNIPOLAR DEPRESSION: IDENTIFYINIG DIAGNOSTIC AND RISK MARKERS USING NEUROIMAGING IN DEPRESSED ADULTS AND ADOLESCENT OFFSPRING

Phillips ML, Almeida J, Versace A, Hassel S, Kupfer DJ Psychiatry, University of Pittsburgh, 121 Meyran Avenue, Pittsburgh 15213, phillipsml@upmc.edu

Background: Identifying neural markers that confer risk for bipolar disorder (BD) is key to: 1. improving diagnostic accuracy of BD in depressed adults, who are frequently misdiagnosed with unipolar depressive disorder (UPD); and 2. Identifying endophenotypic markers in BD offspring that may confer risk for future development of BD. We have aimed to use different neuroimaging techniques to identify structural and functional neural abnormalities in mood regulation neural circuitry that distinguish BD from UPD depression and that confer risk for BD in adolescent offspring of BD parents.
Methods: We have used fMRI and effective connectivity analyses to examine activity within, and connectivity between, prefrontal cortical and limbic/paralimbic neural regions implicated in mood regulation to different emotion facial expressions in BD and UPD depressed, versus healthy control (HC), adults, and in healthy at-risk adolescent offspring of BD parents (HRBD), healthy adolescent offspring of UPD parents (HRUPD), versus healthy, age-matched adolescent offspring of healthy adults (HA). Results: To date, our findings indicate that depressed and remitted BD – but not depressed UPD - adults show patterns of increased striatal activity to happy faces relative to HC. UPD depressed adults, however, are distinguished from HC by increased striatal and amygdala activity to sad faces. Emerging data from effective connectivity analyses also reveal that BD adults are distinguished from HC by increased paralimbic-ventromedial prefrontal cortical effective connectivity to happy and neutral faces. We also show that HRBD – but not HRUPD - are distinguished from HA by decreased dorsomedial prefrontal cortical activity to happy faces, and that HRUPD –but not HRBD – are distinguished from HA by decreased striatal activity to happy faces. We are examining further patterns of limbic/paralimbic-prefrontal cortical effective connectivity to different faces in all groups.
Discussion: Our findings to date indicate that remitted and depressed BD are distinguished from UPD adults by different patterns of abnormal striatal activity to emotional facial expressions. Furthermore, our emerging data indicate that abnormal prefrontal cortical and striatal activity also distinguish HRBD from HRUPD. Effective connectivity analyses will expand upon these findings. Our findings highlight the utility of neuroimaging in identification of potential risk markers for BD in adult and adolescent populations.

S36

MONOAMINES AND EMOTIONAL PROCESSING

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

There is growing interest in the effects of antidepressant drug treatment on measures of emotional processing. Such actions may help us understand the role of monoamines in emotional dysfunction in depression and how antidepressant drug treatments work. We have previously shown that antidepressant drugs increase the processing of positive vs negative emotional information across a variety of paradigms and in the absence of changes in subjective mood in healthy volunteers. Here I will be presenting some recent data examining the response of acutely depressed patients to single dose antidepressant drug treatment. These results suggest that the reduced positive vs negative processing seen in depression is remediated with acute antidepressant drug administration in the absence of changes in symptoms. However, early change in emotional bias significantly predicted clinical response with 6 weeks continued treatment, consistent with the hypothesis that these early effects are important for subsequent mood change. fMRI studies have further examined the neural basis of these changes in emotional bias in healthy volunteers and have identified a particular role for amygdala based circuitry. Such effects appear to operate at relatively early stages of processing and disappear when the task demands particular focus on the facial emotion. By contrast, acute and sub-chronic antidepressant drug administration appears to leave prefrontal cortex responses to emotional stimuli relatively unaffected. These neuroimaging findings are consistent with behavioural data which suggest modulation of early attentional processing of emotional stimuli following antidepressant drug administration in the absence of differences in tasks demanding more strategic processing. These antidepressant drug effects may also be relevant to screening novel candidate agents for depression and which may provide more information than yielded from animal models alone. For example, the NK1 antagonist aprepritant appeared successful in preclinical screens yet failed in the clinic. Consistent with this, aprepritant was found to produce only modest effects on emotional processing in healthy volunteers in the absence of change in amygdala responses. Together these results suggest that antidepressant drug effects on emotional processing may be important in the therapeutic actions of these treatments in depression and as such may be useful biomarker assessments in drug development programs.

MA01

ATTENTIONAL BIAS TOWARDS HEALTH-THREAT INFORMATION IN CHRONIC FATIGUE SYNDROME

Hou R, Moss-Morris R, Bradley B, Peveler R, Mogg K School of Medicine, University of Southampton, Royal South Hants Hospital, Southampton SO14 0YG, r.hou@soton.ac.uk

Introduction: Chronic fatigue syndrome (CFS) is characterised by debilitating and unexplained fatigue lasting at least six months, associated with profound impairment in daily functioning. Recent cognitive-behavioral models of CFS suggest that CFS patients have specific underlying cognitions which are important in both the onset and perpetuation of CFS. The aim of this preliminary study was to investigate whether individuals with CFS show an attentional bias (AB) for health-threat information. We hypothesised that individuals with CFS would show an enhanced AB for health-threat information, relative to controls, and that this bias would be found across different stimulus types (words and pictures).
Methods: 11 participants with CFS (3 male, 8 female; mean age 42 years, SD =17) and 17 healthy controls (6 male, 11 female; mean age 35 years, SD =15) gave their informed written consent and completed all the tests. AB was assessed using a visual probe task which presented health-threat and neutral words and pictures for 500 ms. Reaction times to probes provide a measure of AB. Self-report questionnaires which include the Profile of Fatigue-Related Symptoms (PFRS) and the Hospital Anxiety and Depression Scale (HADS), were used to assess CFS symptoms, depression, anxiety and social desirability. Bias scores were entered into an analysis of variance with group (CFS, control) and stimulus type (picture, word) as independent variables, and analyses of covariance which included RT on neutral baseline trials and mood scores as covariates.
Results: The groups did not differ significantly in age, gender, education status, or employment status. The CFS group had significantly higher PFRS and HADS-depression scores than controls [$p<0.01$]. Compared to a healthy control group, the CFS group showed an enhanced AB towards heath-threat stimuli relative to neutral stimuli [$F(1,26)=8.36$, $p=.01$]. The AB was not influenced by the type of stimulus (pictures vs. words) [$F<1$].
Conclusions: In support of our hypothesis, this is the first study that found an AB towards both pictorial and linguistic health-threat stimuli in individuals with CFS. A bias in selective attention to health-threat information may lead to greater preoccupation with illness and thus perpetuate feelings of ill-health. AB to health-threat information may be an important maintaining factor and thus a target for cognitive-behavioural therapy.

MA02

EFFECTS OF THE CB1 ANTAGONIST, RIMONABANT, UPON EMOTIONAL PROCESSING IN HEALTHY VOLUNTEERS

Horder J, Cowen PJ, Harmer CJ Psychiatry, University of Oxford, Warneford Lane, Oxford OX3 7JX, jamie.horder@googlemail.com

Introduction: Rimonabant (SR141716) is a cannabinoid CB1 receptor antagonist effective in the treatment of obesity but has been associated with psychiatric side-effects including depression, anxiety and suicidal ideation. We wished to test the hypothesis that some of these side effects are attributable to the induction of negative biases in the processing of emotional information, by measuring the effects of an oral dose of rimonabant (20mg) upon performance in psychological tasks which have previously been shown to be sensitive to single and subacute doses of antidepressant drugs. We were also interested in measuring the effects of rimonabant upon verbal memory, as rimonabant has been shown to enhance memory encoding in several animal models. Finally, we measured the effects of rimonabant upon salivary cortisol levels, since in rodents, rimonabant acutely raises corticosterone levels. Methods: 30 healthy adult volunteers, free of current or past psychopathology (on SCID-IV), were randomly assigned to receive a single dose of rimonabant (20mg) or lactose placebo in a double-blind, between-groups, experiment. Approximately 180 minutes after administration, subjects began a battery of psychological tasks including facial emotion recognition, emotional word attentional dot probe, self-relevant word classification and memory, and the Rey Adult Verbal Learning Task (AVLT). Emotion-potentiated acoustic startle response was assessed using ocular EMG. Subjective state was assessed via self-report. Salivary cortisol levels were measured at ten time-points following administration (30 to 330 minutes).
Results: Rimonabant selectively reduced incidental recall of positive self-relevant adjectives, an effect contrary to that seen following the administration of antidepressants (t-test $p=0.024$). In the acoustic startle paradigm, rimonabant had no clear effects, but possibly affected habituation (split plot anova: (group x block interaction $p<0.05$). However, rimonabant had no significant effects on facial emotion recognition, attentional processes as measured in the dot probe task, or on latency to classify self-relevant words. Rimonabant had no effect upon general verbal memory. Finally, rimonabant did not affect salivary cortisol.
Conclusions: A single oral dose of the CB1 antagonist rimonabant affects memory for self-relevant words but has no clear effects upon other measures of emotional processing in healthy adults. Further studies, perhaps using repeated doses of rimonabant, and / or vulnerable subject populations (e.g. patients recovered from depression), are needed to understand the mechanisms by which rimonabant increases the risk of anxiety and depression during clinical use.
This study was supported by the Medical Research Council.

MA03

IMPROVEMENT OF PREPULSE INHIBITION AND EXECUTIVE FUNCTION BY THE COMT INHIBITOR TOLCAPONE IN COMT RS4818 G/G HOMOZYGOTES

Giakoumaki SG, Roussos P, Bitsios P Department of Psychiatry & Behavioural Sciences, University of Crete, Greece, Heraklion 71003, sgiakoum@med.uoc.gr

Introduction: There is evidence that executive function depends on prefrontal cortex (PFC) dopamine (DA) signaling and recent studies show that Prepulse Inhibition (PPI) levels relate to executive function [Giakoumaki et al (2006) *Brain Research* 1078:168-170; Bitsios et al (2006) *Neuropsychologia* 44:2494-2499] possibly via a PFC DA link. The catechol-O-methyltransferase (COMT) enzyme is the main mechanism for degradation of released DA in the PFC. We have recently shown that Val/Val individuals have the lowest PPI, Met/Met the highest and Val/Met intermediate [Roussos et al (2008) *Psychological Medicine*, in press]. We have also shown that COMT inhibition by tolcapone, improves PPI and working memory in Val158 homozygotes only [Giakoumaki et al (2008) *Neuropsychopharmacology*, submitted]. The aim of the present study was to explore the effects of enhanced PFC DA signaling by tolcapone on PPI and PFC-dependent tasks in subjects with low and high PFC DA levels as determined by the rs4818 C/G polymorphism, which seems to account for a greater variation of the COMT activity compared to the Val158Met polymorphism.
Methods: Thirteen G/G (low PFC DA) and twelve C/C (high PFC DA) healthy male subjects, matched for age, education and smoking habit, were selected from a previously genotyped cohort. A single dose of tolcapone 200 mg was administered according to a double blind, placebo controlled, crossover design in two weekly sessions. PPI was assessed with 75-dB and 85-dB prepulses at 30-, 60-, and 120-ms prepulse-pulse intervals. Subjects also underwent the N-back and the letter-number sequencing (LNS) tasks and the POMS questionnaire to test for tolcapone effects on mood and activation. Statistical analyses were conducted with repeated measures ANOVAs.
Results: Tolcapone did not affect baseline startle amplitude, startle habituation, startle onset and peak latencies, or any of the POMS subscales. PPI levels of the GG group were lower than PPI levels of the CC group in the placebo condition ($p=0.049$). Tolcapone increased PPI ($p=0.038$) and improved performance in the LNS task ($p=0.024$) in the G/G group only. In the C/C group there were no significant effects although PPI reductions were observed.
Conclusions: We demonstrated parallel improvement of working memory and PPI in normal COMT rs4818 G/G homozygote subjects, after PFC DA increases by the COMT inhibitor tolcapone. These results confirm previous findings and suggest that early information processing and executive function are both dependent on PFC DA signaling and that they both relate to PFC DA levels according to an inverted U-shaped curve function.
This project was supported by the University of Crete Research Funds Account (ELKE 1348).

MA04

DO 5-HT6 RECEPTOR ANTAGONISTS ALTER EMOTIONAL LEARNING IN A CONTEXTUAL FEAR CONDITIONING PARADIGM?

Woods S, Clarke NN, Topham IA, Layfield R, & Fone KCF. Institute of Neuroscience, University of Nottingham Medical School, Queen's Medical Centre, Derby Road, Nottingham. NG7 2UH, mbxsw@nottingham.ac.uk

Serotonin6 (5-HT6) receptors are located almost exclusively in the central nervous system where they are thought to be involved in psychosis, cognition and nociception. The high abundance of 5-HT6 receptors in brain areas such as the hippocampus, nucleus accumbens and striatum support their role in learning and memory. Furthermore, selective, potent 5-HT6 receptor antagonists, such as 5-chloro-N-(4-methoxy-3-piperazin-1-yl-phenyl)-3-methyl-2-benzothiophenesulfonamide (SB-271046) enhance cognition in several different behavioural paradigms, such as novel object discrimination and Morris water maze (Woolley et al (2004) CNS and Neurological Disorders 3: 59-79), although some groups have failed to replicate this (Russell and Dias (2002) Current Topics in Medicinal Chemistry 2: 643-654). The current study determined the role of 5-HT6 receptors in a hippocampal-dependent learning and memory task by testing the effects of SB-271046 on acquisition and consolidation in contextual fear conditioning (CFC).

Adult male Lister Hooded rats (n=8-10/group) were placed in the light side of a two chamber CFC apparatus (30s) prior to opening an intra-chamber door. On entry into the dark chamber the door closed and rats received either 0 or 3 mild footshocks (0.4mA, 1s, US) immediately after a 5s light and tone (89dB) cue (CS). SB-271046 (10 mg/kg, i.p.) or vehicle (3 ml/kg, i.p.) was administered either 30 min prior to or immediately after CFC training. Rats were placed directly in the dark chamber (5min) daily 24-96 h post-conditioning and the time spent freezing was recorded. To determine the main effect of treatment and shock on freezing behaviour a 2-way ANOVA with repeated measures was performed followed by Tukey's post-hoc.

Pre-training administration of SB-271046 attenuated the CFC-induced freezing ($p<0.05$) 24h after the US-CS trial by 53% from that in vehicle controls. In contrast, the 24% reduction in CFC-induced freezing 24h after the US-CS trial was not significantly different from the vehicle controls when SB-271046 was administered post-training. The data suggests that pre-administration of SB-271046 caused a dissociation between the context and the aversive stimuli in CFC, as the reduced freezing behaviour was not observed with post-training administration. This reduced freezing behaviour could result from an anti-nociceptive or anxiolytic effect of 5-HT6 receptor blockade (Finn et al (2007) European Journal of Pharmacology 569: 59-63) during CFC training rather than an impairment of memory in this paradigm. Further studies are required to determine if the attenuation of CFC-induced freezing behaviour is replicated by other 5-HT6 receptor agonists and antagonists.

Supported by the MRC.

MA05

DONEPEZIL REVERSES A SCOPOLAMINE-INDUCED LEARNING DEFICIT IN CONTEXTUAL FEAR CONDITIONING

Clarke NN, Woods S, Layfield R, Fone KCF Institute of Neuroscience, School of Biomedical Sciences, University of Nottingham, Queen's Medical Centre, Nottingham, NG7 2UH, mbxnc1@nottingham.ac.uk

Cognitive impairment in Alzheimer's disease and schizophrenia has been linked to a reduction in central cholinergic function. The acetylcholinesterase inhibitors, donepezil and galantamine, are the major drug therapy for cognitive impairment in Alzheimer's disease. However, the effects of these drugs on specific learning and memory processes have not been fully evaluated. The present studies assessed the effects of donepezil and galantamine on fear-motivated long-term memory following cholinergic disruption by the muscarinic receptor antagonist, scopolamine.

Three separate experiments were performed using adult male Lister hooded rats (200-350g). In all studies, scopolamine hydrobromide (0.3mg/kg, i.p., N=8-9) was administered 20 min prior to fear conditioning. In the first study, scopolamine hydrobromide was compared to an equivalent dose of scopolamine methylbromide or saline. In subsequent experiments, donepezil (1 or 2mg/kg, i.p., N=9), galantamine (3 or 4.5mg/kg, i.p., N=9) or saline, was administered 10 or 20 min before scopolamine hydrobromide or saline, respectively. For fear conditioning, rats were placed in the light side of a two-compartment shuttle box for 30 sec before entering the dark compartment for another 30 sec exploration which was followed by three presentations, at 1min intervals, of a light and tone (3kHz, 89dB, 5 sec) with or without an inescapable footshock (0.4mA, 1 sec). At 24 h after fear conditioning, each rat was placed directly into the dark compartment for 5 min and freezing behaviour was timed.

Statistically significant differences between treatment groups were determined by a 2-way and 1-way ANOVA followed by Tukey's post hoc test. In all experiments, saline treated shocked rats froze significantly more than saline treated non-shocked rats ($p<0.001$) and scopolamine hydrobromide significantly reduced this response ($p<0.01$). In contrast, scopolamine methylbromide, which poorly penetrates the blood brain barrier, did not alter freezing time compared to the saline shocked group. Donepezil (2mg/kg) reversed the scopolamine-induced impairment ($p<0.05$), while neither 3 nor 4.5mg/kg galantamine altered the reduction in freezing behaviour at 24 h after fear conditioning.

These data suggest that the cholinergic system plays an important role in fear-motivated learning. In agreement with previous studies, acute administration of scopolamine hydrobromide alters learning and memory by disrupting central cholinergic function which was reversed by donepezil in this model. Current studies are utilising proteomic techniques to determine if donepezil and galantamine produce similar changes in hippocampal protein expression.

This work was funded by the University of Nottingham.

MA06

THE EFFECT OF CYCLOPHOSPHAMIDE ON MEMORY AND NEUROGENESIS IN RATS

Lyons LJ, Wigmore P, Bennett GW School of Biomedical Sciences, University of Nottingham, Queens Medical Centre, Nottingham, mbxll@nottingham.ac.uk

Chemotherapeutic drugs are used in many different combinations and doses as an adjuvant treatment for cancer. However, they are infamous for their unpleasant side effects, one of which, reported by patients, is deterioration in memory and confusion, referred to as "chemobrain". Our hypothesis is that this cognitive defect could be due to the drugs' cytotoxic effect on the proliferation of new neurons in the hippocampus, a process known as adult neurogenesis. We also aim to identify which specific drugs within combinations may have an effect. Although there have been previous patient based studies investigating this deficit, these have been limited by confounding factors. This study looks at a widely used chemotherapeutic drug, cyclophosphamide (CP), which is used to treat a range of cancers including ovarian, breast and leukaemia and it is able to cross the blood brain barrier and have a direct effect on the brain. We wish to investigate the effect of CP on both cognitive performance and cellular changes in the hippocampus.

Lister Hooded rats were administered (IV) a 30mg/kg dose of CP (n=12) or equivalent volume of saline (n=12), with a total of eight injections over three weeks. Memory was tested six days after the final injection using the novel object location test. A western blotting assay was used to quantify double cortin (a protein expressed in immature neurones) in the hippocampi and frontal cortices (a positive control) of the animals after death.

Paired Student's t-tests were used, revealing both the drug treated and control group to retain the ability to distinguish an object in a novel location from that in a familiar one ($p<0.05$). No significant difference ($p<0.05$) was found between the quantities of double cortin in each group.

The results indicate that CP has no short term effect on hippocampal dependant memory formation or hippocampal neurogenesis. The longer term effects of CP need to be investigated along with more in-depth cellular analysis.

This is a project from the University of Nottingham and is funded by Cancer Research UK.

MA07

EVALUATION OF THE PRO-COGNITIVE EFFECTS OF THE AMPA RECEPTOR POSITIVE MODULATOR, CX691, IN THE RAT

Lacroix LP, Waters K, Jennings CA, Southam E, Woolley ML, Dawson LA GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, CM19 5AW, laurent.p.lacroix@gsk.com

Glutamatergic hypofunction in the central nervous system has been suggested to play a role in cognitive deficits associated with psychiatric disorders. The α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor has been shown to mediate rapid excitatory neurotransmission and is implicated in synaptic plasticity thought to underlie mnemonic processing. Allosteric modulation of AMPA receptors by compounds such as CX691 enhances ion flux through the ion channel pore when the receptor is activated and has been shown to improve performance in animal models of cognition and memory, possibly through an enhancement of synaptic plasticity.

In separate groups of male Lister hooded rats we assessed: 1) the effects of acute (0.03, 0.1, 0.3, 1.0 mg/kg p.o., n=11-12) and sub-chronic (0.01, 0.03, 0.1, 0.3 mg/kg p.o., n=11-12) administration of CX691 on a temporally (24 h)-induced deficit in the rat novel object recognition (NOR) task; 2) the effects of acute administration of CX691 (0.1, 0.3, 1.0 mg/kg p.o., n=6-9) on dopamine (DA), noradrenaline (NA) and acetylcholine (ACh) in the dorsal hippocampus (dHipp) and anterior cingulate cortex (aCC) using in vivo microdialysis; 3) the hippocampal expression of brain derived neurotrophic factor (BDNF) mRNA by in situ hybridisation following acute and sub-chronic (7 days) administration of CX691 (0.1 mg/kg p.o., n=6). All data were analysed using analysis of variance (ANOVA) followed by planned comparison or post-hoc tests where appropriate (Statistica 6.0, StatSoft Inc., Tulsa, OK, USA). Statistical significance was set at $P < 0.05$ against vehicle control groups.

CX691 attenuated the temporal deficit in NOR when administered both acutely ($P < 0.05$ for 0.1 and 1.0 mg/kg) and sub-chronically ($P < 0.05$ for 0.01 mg/kg and $P < 0.01$ for 0.03 and 0.1 mg/kg). These pro-cognitive effects were complemented by increased extracellular levels of ACh in the dHipp ($P < 0.05$ for 1.0 mg/kg) and aCC ($P < 0.05$ for 0.1 mg/kg and $P < 0.01$ for 0.3 and 1.0 mg/kg) and DA in the aCC ($P < 0.01$ for 1 mg/kg) following acute administration of CX691. Finally, hippocampal expression of BDNF, a putative molecular marker of synaptic plasticity, was significantly elevated in both the whole ($P < 0.05$) and CA1 region ($P < 0.05$) following sub-chronic but not acute administration of CX691.

In summary, these data provide behavioural, neurochemical, and molecular support for the pro-cognitive activity of CX691 in rats which suggests that AMPA receptor positive modulators may be of benefit in treating disorders characterised by mnemonic deficits such as schizophrenia and Alzheimer's disease.

MA08

THE NR2B SUBUNIT SELECTIVE NMDA ANTAGONIST, RO25-6981 HAS SELECTIVE EFFECTS ON THE ACQUISITION OF A SIMPLE VISUO-AUDITORY DISCRIMINATION BUT DOES NOT IMPAIR RECOGNITION MEMORY.

Potts S, Potts S, Thomas Y, Cross L, Dix S Eli Lilly, Erl Wood Manor, Sunninghill Road, Windlesham, Surrey, GU20 6PH, slavinka@lilly.com

N-methyl-d-aspartate receptor (NMDAR) antagonists have been shown to produce cognitive and sensorimotor deficits in rodents and humans, which can mimic symptoms observed in schizophrenia and Alzheimer's disease (AD). In this study, the NR2B antagonist, RO25-6981 was profiled in male Lister Hooded rats in a battery of operant cognitive tests and the spontaneous object preference test of recognition memory. This operant battery taps in to reference memory, working memory and higher order cognitive function. These processes may potentially be impaired in AD and schizophrenia.

Five cohorts of animals were used in this study. In Experiment 1, RO25-6981 (0, 1, 3 10 mg/kg; sc; -30 min, n = 12 per group) was profiled through a within-subject operant cognitive test battery. The battery comprised four stages: (1) discrimination acquisition (reference memory) where naïve animals learned a simple visuo-auditory discrimination in a discrete-trial procedure; (2) delayed discrimination (working memory) where delays were imposed between presentation of the stimulus and the levers; (3) extinction where only one lever was rewarded and (4) extinction consolidation (drug-free) in which the extinction test was repeated. In Experiments 2-5, RO25-6981 was profiled in the object preference task with delay periods of 2 (Expts 2 and 4) or 24 (Expts 1 and 3) hours. Following two habituation sessions, the animals had a sample phase of 5 min during which the animals were allowed to explore freely two identical objects. After the delay period, the animals were reintroduced to the arena for the test phase in which a duplicate of the sample phase objects (*familiar*) and a previously unseen, *novel* object were presented. RO25-6981 (0, 1, 2.5 and 5 mg/kg; sc; -30 min, n = 10 per group) was administered either pre-sample (Expts 1 and 2) or pre-test (Expts 3 and 4). Behaviour in the arena was recorded and analysed using an automated image analysis system (Topscan, CleverSys inc.). The data were analysed using ANOVAs and appropriate post-hoc tests.

RO25-6981 blocked the acquisition of the discrimination in a dose-dependent manner ($p < 0.001$). There was a dose-dependent increase in the head entry rate ($p < 0.001$). The results of the object preference task showed that RO25-6981 increased exploration of the objects ($p < 0.05$) but did not affect novel object discrimination.

RO25-6981 was found to have selective dose-dependent effects on the acquisition of the simple discrimination, exhibiting a similar profile to other NMDAR antagonists in the operant test battery. In contrast, RO25-6981 (0, 1, 2.5 and 5 mg/kg) did not impair recognition memory.

Funded by Eli Lilly & Co.

MA09

SIGNIFICANT PREFERENCE FOR A NOVEL OBJECT AT LONG DELAYS IS DISRUPTED BY THE ADDITION OF A 'DISTRACTER' PHASE BETWEEN SAMPLE AND TEST IN THE RAT

Thomas Y, Dix S Neurodegeneration, Eli Lilly Erl Wood Manor, Sunninghill Road, Windlesham Surrey GU20 6PH, thomasy@lilly.com

Introduction. The spontaneous preference test is a widely used assay of recognition memory. It relies on an animals' innate preference for a novel object compared to a familiar one. Deficits in performance are commonly produced by imposing a delay between the sample phase (i.e. initial exposure to the familiar objects, A1/A2) and the test phase in which the animals are exposed to a familiar (A3) and novel object (D1). In experiment 1 we attempted to demonstrate delay-dependent forgetting with delays imposed of up to 72 hours. In experiment 2, we investigated the effect of adding a 'distracter' phase between sample and test. The aim of these experiments was to further investigate behavioural manipulations that would produce a recognition memory deficit.

Methods. Naïve male Lister Hooded rats (n=10 per group)were used as subjects in each experiment. Animals first received two handling sessions. The following week, they were habituated in a rectangular arena for two (Exp 2) or three (Exp. 1) daily ten minute sessions. Both the sample and test phases each lasted 5 min. In experiment 1, a delay of either 2, 24, 48 or 72 hours was imposed between the sample and test sessions. In experiment 2, animals received a distracter phase 24 hours after the sample phase. In this 5-min session, half of the animals were exposed to two completely new objects (B1/C1) and half were exposed to an empty arena. Animals were then tested using objects (A3/D1) with a delay of either two or eight days between sample and test. Behaviour in the arena was recorded and assessed using an automated video analysis system (Topscan; CleverSys, Inc.).The data were analysed using ANOVAs and appropriate post-hoc tests.

Results. In experiment 1, we were unable to demonstrate delay-dependent forgetting. Discrimination levels did not decrease between the 2hr and 72hr delays. In experiment 2 we found that rats which received no distracter phase showed significant preference for the novel object at both delays. However the inclusion of a distracter phase clearly disrupted performance.($p=0.026$)

Conclusions. In this study we were unable to demonstrate significant forgetting. It was shown that rats can demonstrate significant preference for a novel object even at the long delay of 8 days. However, adding interference with the inclusion of a 'distracter' phase clearly disrupted the rats' ability to discriminate between the objects. This version of the task may provide a useful assay for profiling potential nootropic compounds.

MA10

PCP IMPAIRS RECALL IN AN EPISODIC MEMORY TASK: INFLUENCE OF DISTRACTION

Grayson B, Kirun A Neill JC Pharmacy, University of Bradford, Richmond Road, Bradford, b.grayson@bradford.ac.uk

Introduction: Memory impairment is a core feature in schizophrenia and short-term memory has been shown to be more susceptible to distraction in schizophrenic patients (Cellard C, et al. 2007, Brain & Cognition, 64; 201-207). We have consistently shown that sub-chronic phencyclidine (PCP) treatment in female hooded-Lister rats produces robust cognitive disruption in the object recognition test which can be successfully reversed by atypical, but not classical antipsychotic agents and novel targets (Grayson B, et al. 2007 Behav B Res, 184; 31-38). In the novel object recognition (NOR) procedure, we use a relatively short inter-trial interval of 1min, whereby the rats treated with sub-chronic PCP fail to differentiate between the novel and familiar objects in retention. The aim of this study was to explore the influence of distraction and context on the effects of PCP in the NOR task. Our overall aim is to enhance understanding of the mechanism(s) by which PCP impairs episodic memory in this task.
Methods: 40 Adult female hooded-Lister rats received either PCP-20 (2mg/kg) or saline-20 (0.9% NaCl) i.p. twice per day for 7-days, followed by 7-days washout. Testing consisted of a 3min acquisition phase whereby rats explored two novel objects followed by a differential ITI and location (NOR box or home cage). In the retention trial, rats explore a familiar and a novel object for 3min. The ITI conditions were: 1min in the home cage, our standard conditions; 10s in the home cage; 1min in the NOR box; 1min in the NOR box with a distracter, an unfamiliar object; 0min in the NOR box.
Results: There was no difference in exploration time (s) of the two familiar objects in the acquisition trial in any group. With a 0min ITI and 1min ITI in the NOR box, both vehicle and PCP treated rats significantly ($p<0.05$) differentiated between novel and familiar objects in retention. However in PCP treated rats with ITI conditions of 10s (home cage), 1min (home cage), 1min (NOR box with distracter) failed to differentiate between the novel and familiar object.
Conclusion**:** Sub-chronic PCP induces a disruption in recognition memory when animals are removed from the NOR box to their home cage or given a distracter within the box. This suggests that it is not the 1min ITI that triggers recall failure of the familiar object but the influence of distraction. The PCP deficit in NOR may therefore have particular relevance for the psychopathology of schizophrenia.

MA11

OBJECT RECOGNITION DEFICITS INDUCED BY CHRONIC TRYPTOPHAN DEPLETION IN THE RAT ARE ATTENUATED BY ATYPICAL BUT NOT TYPICAL ANTIPSYCHOTIC DRUGS

Jenkins TA, Ardis TC, Elliott JJ, Cahir M, Reynolds GP, Cooper SJ and Bell R School of Psychology, and Division of Psychiatry and Neuroscience, Queens University Belfast, University Road, BT7 1NN, j_elliott79@hotmail.co.uk

Introduction: Serotonin (5-HT) is known to regulate many physiological and behavioural functions including mood, anxiety and cognition and is synthesized from its amino acid precursor tryptophan (TRP). Dietary TRP depletion is a non-pharmacological method to reduce central 5-HT and has been frequently used as a tool to assess the role of 5-HT in cognitive functioning in both humans and animals. TRP depletion has been shown to impair object recognition memory in humans. The Object Recognition Task (ORT) is used to evaluate object recognition memory in rodents. Deficits in object recognition memory in the rat have been reported following acute (ATD) and chronic tryptophan depletion (CTD). The aim of this study was to investigate the affects of antipsychotic drug treatment on CTD-induced object recognition memory deficits in the rat.
Methods: Fifty group-housed male hooded-Lister rats were used in this study. Rats were divided into five weight-matched groups (n=10/group). The control group had free access to control diet (0.7% TRP), while the four TRP-free groups had free access to a TRP-free diet for three weeks. On the experimental day groups received vehicle (0.9% saline, i.p.), risperidone (0.2 mg/kg, i.p.), haloperidol (0.1 mg/kg, i.p.) or clozapine (5 mg/kg, i.p.) 30 min prior to the retention trial of the ORT. The ORT consisted of a 3min acquisition trial, in which animals explored two identical objects, a 1 hr inter-trial interval and finally a 3min retention trial that incorporated a familiar object and a novel object. Exploration time (sec) of each object during both trials was recorded. The discrimination index (DI) was calculated for the retention trial. Following completion of the ORT animals were sacrificed, blood samples were taken for measurement of free plasma TRP and, brains were removed for analysis of central neurotransmitters by HPLC. Data was analysed using ANOVA.
Results: Three week CTD significantly ($p<0.001$) reduced free plasma TRP in rats fed the TRP-free diet as compared to controls. DI values reveal a significant difference between the groups ($p<0.001$). Control fed rats spent more time exploring the novel compared to the familiar object, an effect not observed in TRP-free vehicle rats. Risperidone and clozapine but not haloperidol significantly attenuated the CTD-induced impairment.
Conclusion: Antipsychotic drug administration but not haloperidol attenuates CTD-induced object recognition deficits in the rat, demonstrating the importance of 5-HT function in working memory in this paradigm.

MA12

EFFECTS OF SEASONAL ALLERGIC RHINITIS ON DRIVING ABILITY, COGNITIVE FUNCTIONING AND QUALITY OF LIFE

Verster JC, Mets MAJ, Dunnebier EA, de Senerpont Domis LM, Olivier B, Volkerts ER Psychopharmacology, Utrecht University, PoBox 80082, 3508TB Utrecht, The Netherlands, j.c.verster@uu.nl

The use of antihistamines may affect cognitive functioning and daily activities such as driving a car. Generally, the adverse effects of treatment are tested in healthy volunteers who do not suffer from seasonal allergic rhinitis (SAR) symptoms. However, in patients antihistamines may improve SAR symptoms and thus improve driving ability. It is unknown whether the effects measured in patients are caused by antihistamines or SAR symptoms itself. Therefore, the objective of this study was to compare driving ability, memory, and psychomotor performance during grass pollen season with winter in untreated patients with SAR. Patients with SAR were trained and tested during the grass pollen season (summer) and winter. An on-the-road driving test during normal traffic was performed. Primary parameter is the Standard Deviation of Lateral Position (SDLP), i.e. the weaving of the car. In addition, a word learning test and continuous performance test were performed and quality of life was assessed. Patients were included if in winter the T5SS score was < 3 and in summer the T5SS score was > 3. 70 patients were recruited of which 22 started the study. Fifteen patients completed the study of which 11 met the inclusion criteria. These 11 patients had a mean T5SS score of 6.8 in summer and 0.6 in winter. Patient reported a significantly reduced overall quality of life during grass pollen season ($p<0.0001$). No significant effects were found on the driving test, except a significant (but not relevant) decrease in mean speed during the grass pollen season ($p<0.035$). No significant effects were found on the word learning test and continuous performance test. Moderate SAR symptoms do not impair driving ability, memory functioning and cognitive. These findings suggest that psychopharmacological research on the effects of antihistamines performed in healthy volunteers gives an adequate view of the effects in patients. However, future studies with a larger sample size should confirm our findings.
This study was supported by UCB Pharma.

MB01

THE EFFECTS OF ARIPIPRAZOLE IN COMBINATION WITH CLOZAPINE: PATIENT FUNCTIONING RESULTS FROM A DOUBLE-BLIND, 16-WEEK STUDY IN PATIENTS WITH SCHIZOPHRENIA (CN138-170)

Millar H, Felter C, Landsberg W. The Carseview Centre, 4 Tom McDonald Avenue, Dundee DD2 1NH, h.millar@nhs.net

Introduction: This 16-week, double-blind study investigated the effects of aripiprazole in combination with clozapine on metabolic (primary endpoint=mean change in weight) and efficacy parameters in patients with schizophrenia. We describe the results of patient-related secondary endpoints from this study to provide an overview of the effects of aspects relevant to the patient's well-being. Methods: Suboptimally controlled outpatients with schizophrenia on a stable dose of clozapine (≥3 months) and who gained ≥2.5 kg of weight since starting clozapine were randomized to adjunctive aripiprazole (5–15 mg/day, n=108) or placebo (n=99). Secondary endpoints included the Investigator Assessment Questionnaire (IAQ, ANCOVA model with treatment and country as main effects and baseline CGI-S as covariate), Global Assessment of Functioning (GAF ANCOVA model with treatment and country as main effects and baseline score as covariate), social cognition in schizophrenia scale (GEOPTE, ANCOVA with treatment as main effect and baseline as covariate), Epworth Sleepiness Scale (ESS, ANCOVA with treatment as main effect and baseline as covariate) for Alertness, and Fatigue Syndrome Inventory (FSI, ANCOVA with treatment as main effect and baseline as covariate). Results: At the end of 16 weeks, aripiprazole was associated with a significant decrease in mean weight (aripiprazole –2.53 kg, placebo –0.18 kg; $p<0.001$), and waist circumference (aripiprazole –2.00 cm vs. placebo 0 cm; $p<0.001$) compared with clozapine alone. The adjusted mean IAQ Total Scores at Week 16 (LOCF) were 28.1 for placebo and 26.8 for aripiprazole group at Week 16 ($p=0.006$). The adjusted mean change from baseline in the GAF (LOCF) showed improvement in both treatment groups at Week 16 (placebo 5.5, aripiprazole 6.0; $p=0.651$). Improvements in GEOPTE score were also similar between groups (placebo –1.7, aripiprazole –3.1; $p=0.348$). Improvement from baseline to all timepoints was reported in the ESS for alertness for both treatment groups up to Week 16 (placebo –0.6, aripiprazole –1.4); a statistically significant difference in favour of aripiprazole was seen at Week 1 only (placebo –0.1, aripiprazole –0.8; $p=0.049$). Similarly, improvements from baseline to all timepoints were reported in the FSI Disruption Index for both treatments, with a statistically significant difference in favour of aripiprazole at Week 1 only.
Conclusion: The addition of aripiprazole to clozapine may provide benefits to patients with schizophrenia by reducing metabolic risk factors associated with clozapine treatment without deterioration in patient-related outcomes. Consideration of patient perspectives will help us to optimize care of patients with schizophrenia.
Study funded by Bristol-Myers Squibb and Otsuka.

MB02

WEIGHT OUTCOMES IN AN OPEN-LABEL COMPARISION OF SWITCHING STRATEGIES FROM RISPERIDONE TO ARIPIPRAZOLE IN PATIENTS WITH SCHIZOPHRENIA (CN138-169)

Millar H, Felter C, Dudley E, Sullivan G. The Carseview Centre, 4 Tom McDonald Avenue, Dundee DD2 1NH, h.millar@nhs.net

Introduction: This 12-week, multicentre, open-label study evaluated safety, tolerability and effectiveness of titrated- versus fixed-dose switching from risperidone to aripiprazole. Secondary endpoints included mean changes in weight and weight-related quality of life. Weight gain is a distressing side effect of antipsychotics, and guidelines recommend monitoring and managing it. Methods: Patients with schizophrenia experiencing insufficient efficacy and/or safety/tolerability issues with risperidone for ≥6 weeks were randomized to titrated-dose (n=200) or fixed-dose (n=200) switching. Primary endpoint was proportion discontinuing due to AEs at Week 12 (Cochran–Mantel–Haenszel test stratified by reason for switch in medication). Secondary endpoints included Positive and Negative Syndrome Scale (PANSS), Impact of Weight on Quality of Life (IWQoL-Lite), Investigator Assessment Questionnaire (IAQ), Subjective Well-being under Neuroleptics (SWN) and Preference of Medication (POM) scales. Results: Discontinuations due to AEs were similar between titrated- and fixed-dose groups (3.5% and 5.0%; $p=0.448$). Patients switching medication due to insufficient efficacy alone (29.0%) cited negative symptoms as the main reason (69.0%); those switching due to safety/tolerability issues (14%) cited weight gain as primary reason (33.0%). Titrated- and fixed-dose groups showed statistically significant improvements (Week 12) in mean PANSS Total (–14.8 vs. –17.2; $p<0.001$; post-hoc analysis, paired t-test; LOCF). There was a mean weight loss in both groups (titrated-dose –1.37 kg and fixed-dose –1.27 kg, descriptive statistics: 95% CI –1.11; +0.90). Comparing titrated- and fixed-dose strategies, similar proportions had ≥7% weight loss (11.0 vs. 10.0%) or gain (94.0 vs. 3.0%). At Week 12, there were similar improvements from baseline between the titrated- and fixed-dose strategies in the IWQoL-Lite Total (+6.22 vs. +5.45 [observed case (OC)]; +6.22 vs. +5.68 [LOCF, descriptive statistics: diff +0.54, 95% CI –2.52; +3.60]), in mean IAQ Total (24.6 vs. 24.5; LOCF, ANCOVA model, controlling for switching strategy, reason, country and baseline CGI-S score: $p=0.876$) and in SWN scores (+8.6 vs. +10.3; $p=0.223$ by ANCOVA model using baseline as covariate; switching strategy and reason as main effect; OC). Preference for aripiprazole compared to risperidone using either titrated- or fixed-dose (LOCF, Cochran-Mantel-Haenszel test controlling for switch reason) was reported by patients (47% vs. 55%, $p=0.097$) and caregivers (40 vs. 41%, $p=0.858$).
Conclusion: Switching to aripiprazole from risperidone can be effectively and safely achieved in general practice, with an improved weight-related QoL and positive effect on patients' well-being, using a slow, down-titration of risperidone and either a titrated- or fixed-dose switch to aripiprazole.
Study funded by Bristol-Myers Squibb and Otsuka.

MB03

EFFICACY AND SEXUAL FUNCTIONING DURING ARIPIPRAZOLE TREATMENT: A PROSPECTIVE NATURALISTIC STUDY IN INDIA

Singh AN, Behere P. Dept Psychiatry, Pilgrim Hospital, Sibsey Rd, Boston PE21 9QU, Ashok.Singh@LPT.nhs.uk

Aripiprazole has proved effective in the treatment of stable schizophrenia, but its effectiveness in the treatment of severely psychotic patient is unclear. We describe the findings of a small prospective naturalistic study of the use of Aripiprazole to treat acutely psychotic patients with schizophrenia and other psychoses and its effect on sexual experience, a problem that has received little research interest. Acutely psychotic patients with schizophrenia (N14) psychotic depression (N2) schizoaffective schizophrenia (N1) total (17) consecutively admitted to acute psychiatric unit, must have scored more than 40 on the Brief psychiatric rating scale. Clinical Global Impression more than moderately ill and for extra pyramidal side effects Simpson and Angus Scale, and patient subjective experience about Aripiprazole treatment were also asked. Their sexual experience was assessed on Arizona Sexual Experience Scale. Patients were assessed at the time of inclusion in the study and again following Aripiprazole 15 to 30 mg daily orally for at least six weeks. Aripiprazole could be discontinued if there was an adverse reaction or poor response and if necessary there was concomitant prescription of Benzodiazepines or antidepressants. BPRS, EPS effects and sexual experience were assessed by an independent psychiatrist after six weeks. 12 patients were exposed to other antipsychotics prior to commencement on Aripiprazole and the primary reason of switch was adverse drug reaction, none or poor compliance and side effects. 3 patients gained 2 kg of weight and 2 patients gained 1 kg of weight in six weeks period and no increase was found in 12 patients. The BPRS at the time of inclusion was (mean 63) and six weeks later (mean 19). This showed an average improvement of 69%. The Clinical Global Impression improved significantly in most patients. 5 male and 10 female patients experience significant improvement on all 5 items of Arizona Sexual Experience Scale. Aripiprazole can be safely and effectively used in the acute hospital setting to treat acutely psychotic patient with schizophrenia and other psychoses. Therapeutic doses 15 to 30 mg daily significantly reduce psychotic symptoms in six weeks. Additionally, Aripiprazole treatment was well tolerated and majority of patient's subjective experience was either satisfied or very satisfied with Aripiprazole treatment (up to 94%). This study also suggests that Aripiprazole improves sexual experience in both males and females.
No Conflict of Interest. No funding.

MB04

HORMONAL SIDE-EFFECTS IN PREMENOPAUSAL WOMEN TREATED WITH PROLACTIN-SPARING AND PROLACTIN-RAISING ANTIPSYCHOTIC MEDICATION

Bhairavi Sapre BS, Haddad PM, Wieck A. Psychiatry, Wythenshawe Hospital, Southmoor Rd, Manchester M23 9LT, bsapre@doctors.org.uk

Background: In women with hypothalamo-pituitary disorders it has been reported that hyperprolactinaemia is associated with an increased rate of sexual dysfunction (Lundberg et al 1991. Exp Clin Endocrinol:98; 81-88). The aim of this study was to test the hypothesis that the prevalence of sexual dysfunction is greater in premenopausal women with antipsychotic-induced hyperprolactinaemia than in women who did not develop hyperprolactinaemia during antipsychotic treatment.
Methods: Included were women of premenopausal age (18-45 years) who had a DSMIV diagnosis of schizophrenia or schizoaffective disorder, and had been treated with antipsychotic medication for >/= six months. Exclusion criteria were major physical problems, pregnancy, use of hormonal contraceptives, treatment with antidepressants and current substance abuse. For the assessments of mental state and sexual function the Positive and Negative Symptoms Scale (PANSS), the Beck Depression Scale (BDI) and the self rated Arizona Sexual Dysfunction Scale (ASEX) were used. Hormone measurements included prolactin, FSH, LH, oestradiol, progesterone, total and free testosterone, and sex hormone binding globulin. A clinically relevant elevation of prolactin was defined as a level of >/= 1000 mU/l.
Results: Twenty-three women were included. Nine had clinically relevant hyperprolactinaemia (PRL+ group, mean prolactin level 2879 mU/L, SD 754) and 14 had normal or minimally elevated prolactin levels (PRL- group, mean 357mU/L, SD 248). The mean age of the subjects was 38 (SD 6.30) and the median number of previous admissions two (range 0-20). Fifteen (65%) women had a diagnosis of schizophrenia and 8 (34.8%) had schizo-affective disorder. The PANSS and BDI scores did not differ between the groups (PANSS PRL+ : 48.2, SD15.1/ PRL- :46.7, SD8.5). As expected oestradiol levels were significantly lower in the PRL+ group ($p<0.04$) and there were no other endocrine differences. Scores of the individual items of the ASEX or its total score did not differ between groups (total mean scores in PRL+ and PRL- groups were 22.3, CI: 17-27 and 22.0, CI: 18-26).
Conclusion: The prevalence of sexual dysfunction and its severity were very high in this sample of psychotic women treated with antipsychotic medication. In contrast to patients with hyperprolactinaemia unrelated to drug treatment there was no evidence that prolactin contributed to sexual dysfunction. There are many other causes for sexual dysfunction in this patient group including illness related factors and other pharmacological actions of antipsychotics. It is possible that these mechanisms are more important in psychotic patients.
Funding: Wythenshawe Hospital Departmental Research Fund.

MB05

DOES MORNING CORTISOL INFLUENCE COGNITIVE FUNCTION IN FIRST EPISODE PSYCHOSIS?

Aas MA, Mondelli, V, Toulopoulou T, Reichenberg A, Handley, R, Taylor H, Hepgul N, David A, Murray R, Dazzan P, Pariante CM. Psychological Medicine, Institute of Psychiatry, 125 Coldharbour Lane, London SE5 9NU, monica.aas@iop.kcl.ac.uk

Background: High level of morning cortisol and hyperactivity of the Hypothalamic-Pituitary-Adrenal (HPA) Axis has been observed in first episode psychosis. Furthermore, cognitive abnormalities have been linked to HPA axis hyperactivity. Method: We recruited 15 patients with first episode psychosis and 21 controls as part of the Genetic and Psychosis (GAP) study carried out in South London. Patients and controls underwent neuropsychological assessment to measure general cognitive performance from WAIS-III (Information, Block Design, Digit Symbol Coding and Matrix Reasoning) executive function from the Trails (Trail A and Trail B) and immediate and delayed memory from WMS-III (Logical Memory and Visual Reproduction). Salivary cortisol was collected on two consecutive days, just after awakening. The saliva was centrifuged at 3000 rev/min for 5 minutes and frozen at -20°C. The patients and controls were divided in two groups based on the cortisol median of the controls (9.40 nmol/l).8 patients and 10 controls were in low range cortisol group and 7 patients and 11 controls were in the high range cortisol group. Two-way ANCOVAs, covariating for age, were used to test the effect of cortisol levels on cognition in patients and controls. Results: The mean age of the patient group was 28±8 yrs, and 35% of these subjects were females. The mean age of the controls was of 27±5 yrs, and 28% of these subjects were females. For all tests presented the patients scored significantly worse than the controls ($P<0.05$ for all tests). For executive and memory tasks patients with high cortisol did worse than the patients with low cortisol, while the opposite or no effect was found in the controls. Specifically, the P values for the statistical interaction, covariate for age, were: Trail A, P=0.005; Trail B, P=0.014; Logical Memory Delayed Recall, P=0.020; Logical Memory Immediate Thematic Score, P=0.020; Logical Memory Delayed Thematic Score, P=0.031; Visual Reproduction Percentage Retention, P=0.005; Visual Reproduction Immediate Recall, P=0.046; and Visual Reproduction Delayed Recall, P= 0.010. No effect of stress was found for general cognitive performance or verbal cognition from the WAIS-III. Conclusions: The present data show that patients with first episode psychosis may be particular vulnerable to an increased HPA axis, shown by significant stress effect on performance on executive tasks, such as Trail A and Trail B and immediate and delayed memory from WMS-III Logical Memory and Visual Reproduction. Acknowledgement: This study is funded by the British Academy and the NARSAD.

MB06

STRESS AND HYPOTHALAMIC-PITUITARY-ADRENAL AXIS ACTIVITY IN FIRST EPISODE PSYCHOSIS

Mondelli V, Hepgul N, Mushtaq F, Aas M, Taylor H, Di Forti M, David AS, Dazzan P, Murray RM, Pariante CM. Departement of Psychological Medicine, Institute of Psychiatry, King's College London, 125 Coldharbour Lane, London, SE5 9NU, valeria.mondelli@iop.kcl.ac.uk

Background: Hypothalamic-pituitary-adrenal (HPA) axis is the main biological system involved in the stress response. The aim of our study was to evaluate objective and subjective stress together with HPA axis activity in first-episode psychosis patients and healthy controls. Methods: We recruited 41 first-episode psychosis patients (mean±SEM age: 29.4±1.2 yrs; gender: 34.1% females) and 30 controls (mean age: 27.4±1.0 yrs; gender: 23.3% females) as part of the large Genetic And Psychosis (GAP) study, carried out in South London. We collected information about childhood trauma, recent stressful events and perceived stress, using validated schedules. Salivary cortisol was obtained at awakening, at 15, 30, and 60 minutes after awakening, and at 12 pm, and 8 pm. To investigate the effect of antipsychotic treatment on cortisol levels, we divided the patients in two groups: one group with less than 2 weeks of treatment (n=14) and one group with more than 2 weeks of treatment (n=27). An independent t-test and a chi square test were used to analyze differences in the stress variables. An ANOVA for repeated measure was conducted to analyze differences in cortisol levels during the day (0 minutes after awakening, 12 pm and 8 pm) and delta cortisol levels after awakening (0, 15, 30, 60 minutes). Results: First-episode psychosis patients reported more childhood trauma, recent stressful events, and higher perceived stress compared with controls ($p<0.001$). Patients showed no significant difference in cortisol levels during the day compared with controls ($F=1.9$; $p=0.2$). However, patients with less than two weeks of treatment had higher cortisol levels during the day than both patients with more than two weeks of treatment ($F=8.0$, $p=0.007$) and controls ($F=8.1$, $p=0.007$). In contrast, patients with more than two weeks of treatment did not differ from controls in cortisol levels during the day ($F=0.1$, $p=0.8$). Patients showed a significantly lower cortisol awakening response than controls ($F=4.68$, $p=0.034$). No difference in the cortisol awakening response was found between the two groups of patients ($F=1.3$, $p=0.3$). Conclusions: Our data suggest that stressful events are more frequent in first-episode psychosis patients than in controls, and that these patients present an HPA axis hyperactivity that seems to be normalized by the antipsychotic treatment. Moreover, first-episode psychosis patients showed a blunted cortisol awakening response that is not restored with the antipsychotic treatment. Acknowledgement:
This research is funded by NARSAD Mental Health Research Association, British Academy, and NIHR Biomedical Research Centre Institute of Psychiatry (Kings' College London).

MB07

GENETIC VARIATION OF THE 5-HT TRANSPORTER IS ASSOCIATED WITH IMPROVEMENTS IN NEGATIVE SYMPTOMS FOLLOWING TREATMENT FOR A FIRST EPISODE OF PSYCHOSIS

Barrett SL, Armstrong RDJ, Anderson R, McCaul R, Rushe TM, Turkington A, Mulholland C, Cooper SJ, Reynolds GP. Psychiatry & Neuroscience, Queens University Belfast, 97 Lisburn Road, Belfast BT9 7BL, s.l.barrett@qub.ac.uk

Introduction: Polymorphisms in the 5-HT1A receptor may account for a portion of the inter-individual variability in symptom response to antipsychotic treatment. For example, the -1019C/G polymorphism is associated with changes in both negative and depressive symptoms, but not positive symptoms after three months treatment following a first episode of psychosis (Reynolds et al., Am J Psychiatry, 2006 Oct;163(10):1826-9). The 5-HT transporter presents itself as another candidate gene that may influence treatment efficacy: the 5-HTT short/long (S/L) represents a common polymorphism which has a profound influence on 5-HTT mRNA transcription.
Aim: to examine the effects of variation of the 5-HT1A receptor gene and the 5-HT transporter on long-term clinical outcome in a first episode psychosis sample.
Method: Ninety-five subjects from the Northern Ireland First Episode Psychosis Study were genotyped for -1019C/G and 5-HTT S/L polymorphisms. Patients' symptoms were assessed at baseline and after 12 months of standard clinical treatment using the Positive and Negative Syndrome Scale (PANSS).
Results: Polymorphisms in the -1019C/G gene were not associated with differences in symptom severity at baseline or with change in symptoms over time. The 5-HTT S/L genotype was associated with both baseline variation in PANNS negative symptoms ($p<0.05$) and changes in negative symptoms following treatment ($p<0.001$). Post-hoc tests indicated that LL individuals showed improvements in negative symptoms after 12 months treatment when negative symptoms at baseline were controlled for ($p = 0.01$).
Conclusions: The 5-HTT S/L genotype may contribute to negative symptom response to antipsychotic treatment. It is conceivable that the different alleles have different effects on synaptic 5-HT, influencing the effectiveness of antipsychotic drugs. Failure to replicate the association between the -1019C/G polymorphism and changes in negative symptoms after long-term antipsychotic treatment may relate to differences in sample characteristics and/or the timing of clinical assessment across studies.

MB08

THE NEUREGULIN1 RISK POLYMORPHISM ASSOCIATES WITH GREY MATTER VOLUME IN FIRST EPISODE PSYCHOSIS – A PRELIMINARY INVESTIGATION

Harte MK, Watson DR, Barrett SL, McCaul R, Anderson R, Turkington A, Bridcutt R, Mulholland CC, Cooper SJ, Reynolds GP. Division of Psychiatry & Neuroscience, Queens University Belfast, 97 Lisburn Road, Belfast, BT9 7BL, M.K.Harte@qub.ac.uk

Introduction: The neuregulin1 (NRG1) gene encodes multiple protein isoforms that play an important role in the development of many organs. In the brain it plays a crucial role in neuronal development, migration and plasticity. To date numerous genetic studies have reported association of the NRG1 gene with schizophrenia, despite inconsistencies between studies in the identified at risk haplotype (Harrison and Law, 2006 Biol. Psych.60: 132-140). Recently post-mortem transcript analysis has shown that several at-risk single nucleotide polymorphisms are associated with altered ratios of NRG1 mRNA isoforms in human brain. Furthermore the apparently functional SNP8NRG243177 risk allele has been shown to be associated with the emergence of psychotic symptoms in a genetic high risk sample, as well as with premorbid IQ and fMRI activation by cognitive tasks (Hall et al., 2006 Nature Neuroscience 9 (12): 1477-1478).
Methods: In the present study, 171 first episode psychotic patients were genotyped for the single nucleotide polymorphism SNP8NRG243177. We investigated the association of genotype with symptoms assessed by PANSS, including the positive and negative subscales. In a subset of these patients (N=35) we also investigated if this risk variant was associated with grey matter volume in a number of brain regions, based on structural MRI images normalised to MNI space and segmented using SPM5.
Results: We found no relationship between SNP8NRG243177 genotype and symptom severity at baseline, or at the twelve month follow up; no significant association with change in negative or positive symptoms was observed. However, the SNP8NRG243177 T/T genotype (risk variant) was associated with reduced grey matter volume in both the left frontal ($Z=-2.268, p<0.05$) and parietal ($Z=-2.404, p=0.01$) cortices compared to C/C or C/T with no effect in the temporal, occipital or limbic regions.
Conclusion: Our findings indicate that variation in the NRG1 gene is associated with abnormalities in grey matter volume in both left frontal and parietal regions in psychotic patients. This may relate to our previous findings of an association of this polymorphism with a glutamatergic marker in the striatum, innervated from the frontal cortex (Piyabhan and Reynolds, unpublished findings). We found no evidence for an effect on symptom severity or response to treatment in these patients. These preliminary data provide further evidence for a relationship between genetic variation in the NRG1 gene and neuronal pathology in psychotic subjects.

MB09

GENE EXPRESSION PROFILING OF THE HIPPOCAMPUS IN NEUREGULIN 1 (NRG1) TYPE I OVER-EXPRESSING MICE

Deakin IH, Law AJ, Huang GJ, Nave KA, Bannerman DM, Harrison PJ. Psychiatry, Oxford University, Warneford Hospital, Oxford, OX3 7JX, inga.deakin@keble.ox.ac.uk

Background. NRG1 is a leading schizophrenia susceptibility gene, and the NRG1 type I isoform is over-expressed in the prefrontal cortex and hippocampus in the disorder. We are investigating a transgenic mouse that over-expresses type I NRG1 under a Thy1-promoter (Michailov et al 2004 Science 304: 700) with increased expression in many brain regions including the hippocampus.
Methods. Hippocampal RNA was extracted from 24 adult mice: 6 wild-type (wt) females, 6 trangenic (tg) females, 6 wt males and 6 tg males. Extracted and amplified cRNA from each mouse was hybridised to Illumina Mouse v1.1 chips. Each chip has 30 copies of ~46,000 oligonucleotide probes specific to ~29,000 genes. After quality control and normalisation procedures, the expression data were investigated with the Limma program, which generated lists of differentially-expressed probes in wild-type (wt) vs. transgenic mice (tg), male mice vs. female mice, and any probes that had a genotype*sex interaction. Criteria for altered expression were an absolute fold-change in expression (FC) >1.5, and an adjusted p-value < 0.05 (Benjamini-Hochberg false discovery rate [FDR] method). Results. In the wt vs tg list, there were 182 probes (corresponding to 141 genes) that were differentially expressed in the transgenic mice, of which 29 were expressed at a lower level in the transgenic mice and 153 were expressed at a higher level. Transcripts up-regulated in NRG1 type I over-expressing mice include BDNF (FC = 2.76; p = 8.0 x 10-7), dopamine D1 (FC = 2.72; p = 8.0 x 10-7) and D4 (FC = 2.90; p = 3.0 x 10-5) receptors, neuropeptide-Y (NPY, FC = 2.46; p = 9.9 x 10-6) and glial fibrillary acid protein (GFAP, FC =1.62, p = 0.014¬). Increased NPY and GFAP expression has been confirmed with quantitative real-time PCR ($p < 0.02$) and further confirmations are underway. The DAVID online gene ontology database was used to investigate common functions and locations of gene products from the differentially expressed genes. In the transgenic mice there was significant over-representation of extracellular region proteins in the group of differentially-expressed genes (Benjamini-Hochberg adjusted p = 6.5 x 10-5), consistent with the location and major functions of NRG1.
Conclusions. These findings demonstrate that over-expression of one isoform of one gene (NRG1 type I) influences the expression of many other genes, including some known to be functionally related to NRG1 and others that may provide novel insights into its biology and into the convergence of proposed schizophrenia susceptibility genes and disease processes.
IHD is a student on the Wellcome Trust Oxford Neuroscience MSc/DPhil program.

MB10

IDENTIFICATION OF FUNCTIONAL VARIATION WITHIN THE SCHIZOPHRENIA SUSCEPTIBILITY GENE CHI3L1.

Hill MJ, Hawi Z, Anney RJ, Gill M. Neuropsychiatric Genetics Research Group, Trinity College Dublin, St James, Dublin, D8, hillma@tcd.ie

Introduction: Chitinase-3 like gene (CHI3L1) encodes for a cell survival factor, expressed in multiple tissue types, mediating cellular response to physiological insults. The expression of chi3l1 has previously been reported to be altered in the post-mortem schizophrenic brain. Recently two studies have shown that promoter polymorphisms, rs4950928 and rs10399805, in CHI3L1 are associated with schizophrenia; the first in a Chinese population (Zhao X et al., 2007) and the second an Irish population (Yang MS et al., 2008). Furthermore, rs4950928 was shown to be functional using a multiple techniques. This studied sought to replicate some of the functional findings and screen for additional cis acting variation on a Caucasian haplotype background using allelic expression imbalance (AEI). AEI is a powerful quantitative technique for investigating cis-acting variation while minimizing confounding trans-acting factors. The functional elucidation of the association will further our understanding of disease aeitology and perhaps provide novel mechanisms for pharmacotherapy.
Methods: 38 CEU HapMap lymphoblast cell lines heterozygous for the transcribed marker SNP rs880633 were used as the source material for allelic quantification. Allelic ratios were quantified, using a TaqMan SNP genotyping assay, for genomic DNA and cDNA. All CHI3L1 HapMap SNPs were phased relative to the marker SNP. Individuals were grouped according to risk, neutral and protective haplotypes, as designated by Zhao X et al., 2007. Differences in AEI between each diplotype group were assessed using ANOVA.
Results: Substantial allelic imbalance was observed for ~50% of the samples. In the extreme 95% of the expression was from a single allele. 10/10 heterozygotes for rs4590928 (neutral:risk diplotype) showed pronounced and statistically significant AEI ($P<0.001$, ANOVA) with the disease susceptibility allele showing decreased relative expression.
Conclusion: Potent cis-acting variation exists within CHI3L1, as measured by allelic expression imbalance. We have replicated the finding that heterozygosity at rs4590928 is associated with substantial AEI. rs4590928 appears to be the major cis-acting SNP in the Caucasian population as it is in the Chinese. Several individuals in the homozygote group(neutral:neutral and protective:neutral diplotypes) showed substantial AEI not explained by variation in the current HapMap SNP database indicating that additional uncharacterised functional variation exists within CHI3L1. A schizophrenia suspetability allele showed decreased relative expression indicating that susceptibility to schizophrenia may, in part, be mediated by the consequences of decreased CHI3L1 expression. This work was funded by the Health Research Board Ireland (HRB)

MB11

DETECTION OF SPLICE VARIANTS OF GRM3 (METABOTROPIC GLUTAMATE RECEPTOR 3) MRNA IN MOUSE BRAIN

Lane TA, Tunbridge EA, Harrison PJ. Psychiatry, Oxford University, Warneford Lane, Oxfordshire, OX3 7JX, tracy.lane@psych.ox.ac.uk

Introduction. Group II metabotropic glutamate receptors (mgluR2/3, GRM2/3) are presynaptic inhibitory autoreceptors that modulate glutamate release and are implicated in psychiatric disorders such as schizophrenia, anxiety and addiction. The recent publication of a clinical trial demonstrating the effective antipsychotic action of an mGluR2/3-selective agonist has raised the profile of these receptors in schizophrenia. One potential complexity is that these genes, like several other mGluRs, might exist as more than one isoform that differ either in their involvement in the disease process or in their pharmacological properties. No GRM2 variants have been identified, but a recent study reported the first evidence of splice variants of human GRM3 (Sartorius et al, J. Neurochem 2006), As part of the further characterization of GRM3, the present study aimed to determine if GRM3 splice variants are also present in the mouse brain.
Methods. Total RNA from mouse whole brain and frontal brain regions was reverse transcribed. We performed PCR using (a) intron-spanning primers, (b) primers targeted to hypothesized splice variants based on the human data, as well as (c) long range PCR to detect splice variants. For verification, PCR products were ligated into PGEM-T vector and subcloned in JM-109 E.Coli cells, following which plasmid DNA was extracted and purified using the phenol-chloroform technique, and sequenced.
Results. A number of variants were discovered including the exon 4 deletion (GRM3Δ4) that was observed in humans. However, murine GRM3Δ4 results in a frame shift that would result in a truncated protein with only 10 amino acids following the splice site, and so would likely undergo nonsense-mediated decay. A second variant, with exons 4 and 5 deleted (GRM3Δ4Δ5) was also detected and more robustly amplified than GRM3Δ4. GRM3Δ4Δ5 is an in-frame variant that is predicted to encode a protein retaining the ligand binding domain and the usual C-terminal domain, but missing the transmembrane domain. Other putative variants have been identified and are being verified.
Conclusions. Two GRM3 splice variants have been found in murine brain RNA, one of which has a potentially functional ligand binding domain and G-protein binding domain, and might encode a soluble form of mGluR3. Further characterization of these and other GRM3 variants in mouse brain is underway.
Funding provided by the Stanley Medical Research Institute.

MB12

VESICULAR GLUTAMATE TRANSPORTER-1 CHANGES IN THE RAT HIPPOCAMPUS FOLLOWING SUB-CHRONIC PHENCYCLIDINE

Piyabhan P, McKibben CE, Harte MK, Jenkins TA, Reynolds GP. Psychiatry & Neuroscience, Queen's University Belfast, Lisburn Road, Belfast BT9 7BL, cmckibben02@qub.ac.uk

Introduction: Glutamatergic hypofunction has been implicated in the pathophysiology of schizophrenia. The NMDA receptor antagonist, phencyclidine, produces a behavioural symptomatology in rodents that replicates many aspects of schizophrenia. Concurrent pathophysiological changes are observed with a reduction in expression of parvalbumin immunoreactivity in the hippocampus. The aim of this study was to determine effects of sub-chronic phencyclidine on glutamatergic systems in the rat brain using the presynaptic marker, the vesicular glutamate transporter-1 (VGluT1).
Methods: Male Lister-hooded rats (n=18) were administrered phencyclidine at a dose of 2mg/kg bi-daily for one week, controls receiving an identical vehicle regime. Six weeks post-drug administration rats were killed and their brains removed, formalin fixed, and wax embedded. 10µm sections of prefrontal cortex, temporal cortex, striatum and hippocampus were processed for VGluT1-like immunoreactivity (VGluT1-LI), determined as optical density. Results: Results showed a significant increase in hippocampus VGluT1-LI overall ($p=0.007$); ANOVA with an increase observed in subfield CA2/3 ($p<0.001$), but not CA1 ($p=0.09$) or dentate gyrus ($p=0.42$) after sub-chronic phencyclidine treatment. No significant changes were observed in prefrontal cortex, temporal cortex or striatum. Previous studies using these animals found a deficit of the parvalbumin-containing subgroup of GABAergic neurons in the dentate gyrus. This deficit was found to demonstrate a significant negative correlation with the increase in VGluT1-LI in CA2/3 observed in the present study.
Conclusions: Sub-chronic phencyclidine administration resulted in an increase in a marker of glutamatergic innervation, VGluT1, in the hippocampus, primarily in the CA2/3 subfield. This is likely to reflect an enhancement of glutamatergic innervation in this region, perhaps a response to the deficit in inhibitory GABAergic effects, demonstrated by parvalbumin deficits, on the glutamate-containing neurons of the hippocampus. These findings contrast with the deficit in VGluT1-LI observed in the hippocampus in schizophrenia (Piyabhan and Reynolds, BAP abstract MB6, 2006).

MB13

SUB-CHRONIC ADMINISTRATION OF PHENCYCLIDINE MODULATES ARC MRNA INDUCTION BY MDMA IN RAT BRAIN IN A REGIONALLY SPECIFIC MANNER

Collins CM, Elliott JM. Leicester School of Pharmacy, De Montfort University, The Gateway, Leicester, LE1 9BH, jme@dmu.ac.uk

Repeated intermittent administration of the NMDA receptor antagonist phencyclidine (PCP) to rats induces behavioural changes which have formed the basis of an animal model of schizophrenia. Such treatment has also been reported to alter sensitivity to the dopamine releasing drug amphetamine, although our previous study found no changes in either the locomotor response or the degree of neuronal excitation indicated by the reporter gene Arc (Collins et al, BAP July 2006). MDMA (3,4-methylenedioxymethamphetamine) is an amphetamine analogue which induces release of both dopamine and serotonin and in a previous study we have shown that Arc induction by MDMA is regionally modulated by co-administration of the NMDA receptor facilitator D-serine (Haggren et al BPS, Dec 2005). In this study we have investigated the effect of sub-chronic administration of PCP on locomotor activity and neuronal activation (as reported by the effector immediate-early gene Arc) induced by acute challenge with MDMA. Adult male Lister-hooded rats (n=8 per group) were pretreated with either saline or PCP (5 mg/kg i.p.) twice daily for 7 days then left undisturbed for 7 days. On day 15 a challenge dose (s.c.) of either saline or MDMA (7.5 mg/kg) was administered, rats were tested for locomotor activity for 1 hour, killed and the brains removed. Arc mRNA expression was analysed by in situ hybridisation histochemistry using [35S]-dATP labelled oligonucleotide probe. Statistical comparisons were made by two-way ANOVA followed by Bonferroni t-test. MDMA caused a significant ($p<0.001$) increase in locomotor activity in the rats. However, the history of sub-chronic PCP administration had no effect on the magnitude of the locomotor response to MDMA. In the medial prefrontal cortex MDMA substantially increased Arc expression ($p<0.001$) and this response was significantly attenuated ($p<0.05$) following sub-chronic administration of PCP. In the parietal cortex and dorsomedial caudate MDMA similarly increased Arc expression ($p<0.001$) but this response was not significantly altered following PCP pretreatment. In the hippocampal CA1 region no changes in Arc expression were observed following either MDMA challenge or PCP pretreatment. This study demonstrates that sub-chronic administration of PCP modifies neuronal activation induced by MDMA in the medial prefrontal but not parietal cortex although the effect of MDMA is mediated predominantly by serotonin in both regions. Within dorsomedial caudate the effect of MDMA is predominantly mediated by dopamine and is not altered by PCP pretreatment, similar to the previous finding with amphetamine. We conclude that sub-chronic PCP administration may alter serotonergic but not dopaminergic sensitivity in rat brain in a regionally specific manner.

We acknowledge support from BBSRC and GSK.

MB14

RISPERIDONE INDUCED POTENTIATION OF TAURINE IS DIRECTLY MEDIATED VIA THE NMDA RECEPTORS

Ge J, Andrews N, Marston HM. Pharmacology, Organon Laboratories Ltd, Newhouse ML1 5SH, j.ge@organon.co.uk

Previously we have demonstrated that intracerebral administration of NMDA enhanced taurine levels in the rat brain (Ge et al., E-Journal of the British Pharmacological Society 092P, 2004). Co-administration of atypical, typical or putative antipsychotics with NMDA significantly potentiated taurine levels (Ge et al., E-Journal of the British Pharmacological Society 148P, 2005). Such findings implicate that antipsychotics may directly or indirectly interact with NMDA receptors to potentiate NMDA receptor function. To further explore the nature of the interaction of an atypical antipsychotic with the NMDA receptor complex, the present study investigated the effect of the non-competitive NMDA receptor antagonist MK801 and the strychnine insensitive glycine site NMDA receptor antagonist L-701,324 on taurine levels induced by co-administration of risperidone with NMDA. Male rats (Wistar, 250 - 300 g, Harlan) were anaesthetised using 3% isoflurane/95% oxygen. Guide cannulae were stereotaxically inserted, and the rats allowed at least a week for recovery during which time post-operative analgesia was administered once per day for up to 3 days. A microdialysis probe (4 mm membrane) was inserted into the striatum (mm, A -0.8, L -3.0, V -4.5), and perfused with artificial cerebrospinal fluid (aCSF) at 2 ml/min 18 hr before the experiments commenced. Dialysate samples were collected every 20 min, and dialysate taurine was analysed by HPLC coupled with fluorescence detection. Intra-striatal administration of a sub-effective concentration of NMDA (50 mM) confirmed no significant effect on taurine levels. Risperidone (0.3 and 1.0 mg/kg, i.p.) also showed no effect on taurine levels. However, co-administration of risperidone (0.3 and 1.0 mg/kg, i.p.) with NMDA (50 mM) significantly increased taurine levels to 187 ± 13 and 313 ± 60 % ($n=4$-6, $P<0.05$, one way ANOVA followed by Dunnett's t test) respectively, of the basal. Pre-treatment with either MK801 (0.15 mg/kg, i.p.) or L-701,324 (5 mg/kg, i.p.) completely prevented the increase in taurine seen following co-administration of risperidone (1.0 mg/kg, i.p.) with NMDA (50 mM)($n=4$-6, $P>0.05$, one way ANOVA followed by Dunnett's t test). Both MK801 and L-701,324 had no effect on taurine levels when administered alone. The data demonstrate that risperidone has the ability to evoke taurine levels when in combination with a sub-effective concentration of NMDA. Such an effect is most likely to be mediated via the NMDA receptors, however the exact site of action is not clear, since the response was completely prevented by both MK801, a potent, selective and non-competitive NMDA receptor antagonist and L-701,324, a highly selective strychnine insensitive glycine site NMDA receptor antagonist. Over all, the present study provides direct neurochemical evidence to indicate that risperidone directly or indirectly interact with NMDA receptors to potentiate NMDA receptor function, and taurine may be an important biomarker of such an interaction.

MB15

REVERSAL OF COGNITIVE DEFICITS BY AMPAKINE (CX-516) AND SERTINDOLE IN A NEURODEVELOPMENTAL MODEL OF SCHIZOPHRENIA – EARLY POSTNATAL PCP TREATMENT IN ATTENTIONAL SET-SHIFTING

Broberg BV, Glenthøj BY, Olsen CK. Psychopharmacology, H-Lundbeck A/S, Ottiliavej 9, Dk-2500 Valby, bbs@lundbeck.com

In schizophrenia, cognitive impairment is believed to be one of the overall decisive factors for a patients' community functioning. Healthy subjects receiving the NMDA antagonist phencyclidine (PCP) have been reported to experience a schizophrenia-like psychotic state. Concordantly, injection of PCP in laboratory animals has been shown to induce abnormalities similar to those observed in patients with schizophrenia. The purpose of this study was to evaluate early postnatal treatment of PCP in rats as a preclinical model of schizophrenia. In brief, 50 male Lister Hooded rats were treated with PCP (20 mg base/kg) on postnatal days (PNDs) 7, 9, and 11 and tested in adulthood (i.e. after PND 56). Rats were tested in an attentional set-shifting task addressing cognitive deficits, specifically deficits in executive functioning (Birrell and Brown, 2000, J.Neurosci, 20, 4320-4324). The test requires subjects to respond to various extra dimensional-intra dimensional (EDID) shifts in accordance with changing rules. Data analyses were performed using a general linear model followed by Bonferroni post-hoc analyses. The data showed that rats treated with PCP at the early postnatal state were selectively impaired in performing the extra dimensional shift compared to a control group ($p<0.05$). Moreover, the performance of PCP treated animals was not different from their control counterparts at any other step of the performed test ($p>0.05$). In order to further validate the preclinical model, we tried to reverse the PCP induced deficit with two drugs, which were chosen due to their potential as clinically relevant drugs in the treatment of cognitive deficits associated with schizophrenia. Sertindole, a 2nd generation antipsychotic, which has shown to reverse cognitive deficits significantly more than haloperidol (Gallhofer et al. 2007, Pharmacopsychiatry, 40, 275-286; Rodefer et al. 2007, Neuropsychopharmacology, doi: 10.1038/sj.npp.1301654) and the AMPAkine (i.e. potentiator of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor function) CX516 (Black 2005, Psychopharmacology (Berl),179,154-163). Both sertindole (1.25 mg/kg) and CX516 (10 and 20 mg/kg) showed significant ($p<0.05$) effects in their ability to reverse the PCP induced deficits to the levels of the control group. Taken together, these data suggest that the early postnatal PCP treatment as a neurodevelopmental model of schizophrenia, demonstrates a phenotype, which in some aspects resembles the symptoms observed in patients with schizophrenia. The model also seems to have some predictive value. However, this cannot be fully concluded until the effect of the tested drugs on the cognitive domain has been firmly established in clinical trials.

Funding from H. Lundbeck A/S, the Faculty of Health Sciences, University of Copenhagen, and the Graduate School of In Vivo Pharmacology, University of Copenhagen, supported this research.

MB16

REVERSAL OF A SUBCHRONIC PCP INDUCED DEFICIT IN ATTENTIONAL SET SHIFTING PERFORMANCE IN RATS BY THE MGLUR5 POSITIVE MODULATOR CDPPB

Goetghebeur PJD, Bundgaard C, Bruun T, Spang Pedersen C, and Dias R. Psychopharmacology, H. Lundbeck A/S, Ottiliavej, 2500 Valby - Copenhagen, pgo@lundbeck.com

Subchronic PCP treatment has been shown to impair executive function, characterised by an inability to shift attentional set between perceptual dimensions in a rodent ID/ED task, a deficit reminiscent of that observed in schizophrenia patients. Here, the effect of the mGluR5 positive modulator CDPPB given alone or in combination with the antipsychotic haloperidol against the subchronic PCP induced ID/ED performance impairment was examined.
Rats were dosed with saline or PCP for 7d followed by 7d washout, after which they were habituated and trained to dig for a food reward in one of two pots using either digging medium or pot odour as the relevant cue dimension. On the test day, rats were pre-treated with vehicle or CDPPB (80 mg/kg, p.o.) alone or with haloperidol (0.1 mg/kg s.c.) or with the positive control modafinil (64mg/kg p.o.), and presented with a series of discriminations (n=10 for all groups). After completion of the test, brain and plasma exposures of CDPPB were determined and extrapolated to 5 hours post drug administration and correlated to the ID/ED score.
Subchronic PCP treated rats were selectively impaired in their ability to shift attentional set, in comparison to vehicle treated controls ($p< 0.05$). Like modafinil, acute administration of CDPPB was able to reverse the selective ED shift performance deficit ($p<0.01$), with CDPPB brain concentrations correlating positively to the individual ED score ($r = 0.6$). However, the positive effect of CDPPB was not apparent when combined with haloperidol. Overall, the present findings provide preliminary evidence to support the potential use of mGluR5 modulators in the treatment of cognitive symptoms of schizophrenia.

MB17

EVALUATION OF ATTENTIONAL SET-SHIFTING (ID/ED) PERFORMANCE IN RATS FOLLOWING SUB-CHRONIC INFUSION OF PCP VIA OSMOTIC MINI PUMPS

Spang Pedersen C, Bruun T, Lund Petersen T, Nørgaard Johansson C, Goetghebeur P, Dias R. Psychopharmacology, H. Lundbeck A/S, Ottiliavej 9, 2500 Valby Copenhagen, chsp@lundbeck.com

We have shown previously that sub-chronic phencyclidine (PCP) treatment induces a deficit in executive function in adult LH rats reminiscent of that observed in schizophrenia patients, characterised by an impaired ability to shift responding from one rule to another in a test of attentional set-shifting (ID/ED). The aim of the present study was to determine 1) if a similar deficit could be obtained by PCP delivery via osmotic mini-pump, 2) if the deficit could be reversed using modafinil as observed in the clinic.
All rats were implanted with an osmotic mini pump (model 2ml2, 14days Alzet®) s.c. parallel to the spine via an incision across the lower part of the shoulder blades. The mini pumps were filled with either saline or PCP (15mg/kg/day). After 14 days, the mini pumps were removed surgically and rats were given a 7 day washout period. Subsequently, rats were habituated and trained to dig for a food reward in one of two pots using either digging medium or pot odour as the relevant cue dimension. On the test day, both the saline- and PCP- infused rats were pre-treated with vehicle or for the latter group only, modafinil (64mg/kg p.o.), and presented with a series of discriminations (all groups n=10): a simple discrimination (SD), a compound discrimination (CD), two intra-dimensional shifts (ID1, ID2), an intra-dimensional shift reversal (ID2R), an extra-dimensional shift (ED), and an extra-dimensional shift reversal (EDR) within a single session.
The data show that the saline infused/vehicle treated animals are able to form, maintain and shift an attentional set. In contrast, those rats that had undergone the PCP delivery via osmotic mini pump were selectively impaired in their ability to shift an attentional set ($p<0.05$), resulting in a specific deficit in performance at the ED shift. Importantly, this deficit is similar to that obtained previously in our laboratory with sub-chronic systemic administration of PCP. Furthermore, acute administration of modafinil reversed the ED shift performance deficit in the PCP mini-pump group compared to the PCP infused/vehicle-treated group($p<0.05$), , again reminiscent of the improvement observed in the clinic and our previous study.
Overall, the present findings confirm the use of mini pumps to deliver PCP sub-chronically to induce a deficit in executive function as measured using the ID/ED task, and demonstrate this as an alternative method for use in rodents when wishing to assess cognition related to schizophrenia.

MB18

PCP-INDUCED PERFORMANCE DEFICITS IN THE 5-CHOICE SERIAL REACTION TIME TASK ARE MINIMALLY RESPONSIVE TO CLOZAPINE TREATMENT

Thomson DM, McVie A, Morris BJ, Pratt JA. PsyRING, SIPBS,, University of Strathclyde, Taylor St, Glasgow G40NR, dt49x@udcf.gla.ac.uk

Cognitive deficits are a core feature of schizophrenia that are inadequately treated by current antipsychotic drugs. We have demonstrated that repeated PCP treatment reproduces neuropathological and cognitive aspects of the disease including hypofrontality and attentional set-shifting deficits. In line with clinical studies, clozapine was unable to restore hypofrontality, yet could restore GABAergic interneurone deficits. (Cochran et al (2003) Neuropsychopharmacology 28: 265-75; Egerton et al (2005) Psychopharmacology 179: 77-84; Pratt et al (2008) Brit. J. Pharmacol, in press;). Since hypofrontality correlates with cognitive performance in schizophrenia, the aim of the present study was to determine if clozapine was able to restore cognitive deficits in a task that recruits the prefrontal cortex.
Male hooded Long Evans rats were trained to criteria in the 5-choice serial reaction time task (5-CSRTT). Rats were then administered PCP (2.6 mg/kg i.p.) repeatedly according to our previous treatment regime in the presence or absence of clozapine (20mg/kg/day; delivered via subcutaneous osmotic mini-pump). A range of attentional performance and inhibitory control measures were recorded.
There was a marked increase in anticipatory responding 30min following PCP injections that was maintained throughout the four-week treatment protocol. Clozapine did not reduce the PCP-induced increases in anticipatory responding although there was a modest ability to partially restore sustained PCP-induced deficits in perceptual sensitivity. Clozapine did not alter attentional measures. These results suggest that PCP-induced deficits in the 5-CSRTT may mirror inhibitory control deficits observed in schizophrenia and other psychiatric disorders. The lack of ability of clozapine to restore these deficits is in line with the minimal effects of the drug in restoring cognitive processes in the clinic and its inability to restore hypfrontality. The minimal effects of clozapine in the 5-CSRTT compared to its ability to restore deficits in other tasks of cognition such as the novel object recognition test raises an important question about the measurement of cognitive domains in preclinical models and their relevance to those employed in the clinic.
In conclusion, determination of cognitive enhancing agents of drugs for schizophrenia and psychiatric disorders requires careful evaluation of drugs in several cognitive domains; PCP-induced deficits in the 5-CSRTT may be a useful model for identifying such agents.
This work was supported by Mitsubishi Pharma Co.

MB19

LATENT INHIBITION IN DOPAMINE D2 AND D1 RECEPTOR KNOCKOUT MICE

Bay-Richter C, O'Tuathaigh CM, O'Sullivan G, Heery DM, Waddington JL, Moran PM. Psychology, University of Nottingham, University Park, Nottingham NG7 2RD, lpxcb2@nottingham.ac.uk

Latent inhibition (LI) is a model of information filtering abnormalities in schizophrenia. LI is disrupted by psychotomimetics while antipsychotics enhance experimentally induced low-LI. Based on pharmacological evidence using ligands that are not specific for D1 or D2 dopamine receptor subtypes, it is assumed that enhancement of low-LI is mediated through the dopamine D2 receptor. We investigated the role of dopamine receptor subtypes in LI using congenic dopamine D2 knockout (D2-KO) and D1 knockout (D1-KO) mice, compared to wild-type (WT) littermates.

For consistency with studies showing locomotor activity (LMA) and motor-coordination changes in dopamine-KO mice, mice were tested in open-field and rotarod. The conditioned emotional response where thirsty mice stop drinking upon presentation of a tone (85dB) previously paired with foot-shock (0.38mA) was used. LI consisted of pre-exposure (PE), conditioning and test phases. During PE mice received either 40 (low-LI) or 60 (high-LI) unreinforced pre-exposures (PE) of the tone while controls were not pre-exposed (NPE). During conditioning, two tone-shock pairings were presented. During test, time to complete 10 licks prior to (T1) and during presentation of the tone (T2) was measured. Suppression ratio (SR) was calculated as T2/[T1+T2]. LI is demonstrated as higher SR in PE compared to NPE. Analysis of variance (ANOVA) with genotype (WT/KO), exposure (NPE/PE) and sex as factors was used. There were 7-15 mice per group.

In high-LI no genotype effect was found in D2-KO mice ($F(1,46)=0.948$, NS). D2-KO mice showed clear enhancement of low-LI (genotype: $F(1,34)=6.812$, $p=0.01$; exposure X genotype interaction: $F(1,34)=5.667$, $p<0.05$) and no sex effect ($F(1,34)=0.001$, NS). This enhancement reproduces antipsychotic drug effects in LI. Enhancement was not seen in male D1-KO mice (genotype $F(1,34)=0.034$, NS). However, a significant effect of genotype ($F(1,29)=15.649$, $p<0.001$) and an exposure x genotype interaction ($F(1,29)=5.754$, $p<0.05$) was found in female D1-KO mice. D2-KO showed impaired motor-coordination (genotype: $F(1,42)=12.328$, $p<0.001$) and decreased LMA (genotype: $F(1,40)=90.840$, $p<0.001$). In contrast, D1-KO showed normal motor-coordination (genotype: $F(1,41)=0.097$, NS) and increased LMA (genotype: $F(1,41)=40.596$, $p<0.001$). No sex differences in locomotor or motor-coordination tasks were found.

These data demonstrate that the dopaminergic mechanism underlying the antipsychotic profile in LI differs between the sexes and is mediated by D2 receptors in males but by both D1 and D2 receptors in females. This suggests that the D1 receptor may be important for understanding sex-differences in mechanisms of action of antipsychotic drugs and the aetiology of aberrant salience allocation in schizophrenia.

Funding source: University of Nottingham.

MB20

CB1 RECEPTOR MEDIATED DISRUPTION OF SENSORY GATING IN THE RAT HIPPOCAMPUS AND MEDIAL PREFRONTAL CORTEX

Dissanayake WDN, Zachariou M, Marsden CA & Mason R. School of Biomedical Sciences, University of Nottingham, Derby Road, Nottingham NG7 2UH, dilshani2003@yahoo.co.uk

Sensory gating, assessed using an auditory conditioning-test paradigm which measures the reduction in the auditory evoked response (AER) produced by a test stimulus following an initial conditioning stimulus (Bickford et al., 1990, Biol. Psychiatry 27:183-192), is found to be disrupted in schizophrenic patients (Cadenhead et al., 2000, Am. J. Psychiatry 157:55-59). Dysregulation of the endocannabinoid system has been suggested to be involved in the pathogenesis of schizophrenia (Emrich et al., 1997, Pharmco. Biochem & Behav. 56:803-807). This study examined the effects of the non-selective cannabinoid agonist, WIN55,212-2, on auditory gating in CA3 region of the rat hippocampus and medial prefrontal cortex (mPFC). Local field potential (LFP) activity was recorded using multielectrode arrays in the CA3 and mPFC in isoflurane-N_2O:O_2 anaesthetised adult male Lister hooded rats (n=12). Paired auditory stimuli (3 kHz tones, 10ms duration, 90dB intensity, 0.5s inter-stimuli interval, 10s inter-trial interval) were presented binaurally over 128 trials. The effect of a single dose of WIN55,212-2 (1.2mg/kg, i.p; n=6) on the Test/Condition-evoked (T/C) N2 LFP wave amplitude ratio was assessed, 15 and 45min after drug administration. T/C values <50% were indicative of gating. One way analysis of variance (ANOVA) for repeated measures with post hoc Tukey t test was used to compare the basal and the drug induced changes and $P<0.05$ was considered statistically significant. Sensory gating of the N2 wave was observed in both CA3 (T/C=28±5%; mean±s.e.m) and mPFC (T/C=43±5%) prior to drug administration. WIN55,212-2 disrupted auditory gating in CA3, both 15 min (T/C=94±6%; $P<0.01$) and 45 min (T/C=92±5%; $P<0.001$) after drug administration. Disruption of auditory gating was also observed in mPFC, 15 min (T/C=93±22%; $P>0.05$) and 45 min (T/C=177±42%; $P<0.01$) after WIN55,212-2 administration. In rats pre-treated with the CB1 receptor antagonist SR141716A (1mg/kg, i.p; n=6), there were no significant changes in T/C% ($P>0.05$) in CA3 or mPFC at 15 min or 45 min after WIN55,212-2 administration. This study demonstrates that cannabinoid receptor activation disrupts auditory gating in both CA3 region of the hippocampus and mPFC, with deficits similar to those seen following phencyclidine administration (Adler et al., 1986, Biol. Psychiatry 21: 787-98). Prevention of WIN55,212-2 induced disruption of gating by CB1 antagonism suggests that the effects of WIN55,212-2 on gating in both CA3 and mPFC were mediated via CB1 receptors.

Acknowledgments: Government of Sri Lanka and the International Office of the University of Nottingham for funding.

MC01

A NATURALISTIC STUDY ON PHARMACOLOGICAL TREATMENT OF AGITATION IN NON-CONSENTING PATIENTS ADMITTED TO A UK PSYCHIATRIC INTENSIVE CARE UNIT (PICU)

Mantua V, Travis MJ, Atakan Z, Isaac MB, Isaac MT, Smith S, Sweeney C, Komeh J, Rucci P, Kerwin RW. Psychiatry, Institute of Psychiatry, De Crespigny Park, London, v.mantua@iop.kcl.ac.uk

The SLAMICUTE (South London and Maudsley Intensive Care Unit Trial Evaluation) is a naturalistic, observational study aiming to inform best clinical practice in the treatment of behavioural disturbances in non-consenting acutely ill psychiatric patients in an intensive care setting. Management of acute agitation involves the use of PRN ("as required") medications and behavioural nursing interventions. Here we describe current clinical practice in UK PICUs.

Over 12 months data were collected on every violent/aggressive incident requiring an intervention that occurred on each of the four PICUs based within the SLaM NHS Trust. Information on type of incident and subsequent intervention was collected including a 72hrs period of observation of outcome. Interventions were carried out as per Trust procedures and clinical need. The study was approved by the local research ethics committee.

309 patients (246 males, 63 females, mean age 33.2±10) were admitted consecutively. 638 incidents were recorded. Incidents definition is broad and includes: "Increased agitation" (n=119 18.7%), "Threat of violence" (n=239 37.5%), "Act of violence" (n=239 37.5%), "Absconding behaviour" (n=13 2.0%) and "Refusal to take medications" (n=28 4.4%). 4.1% of patients presenting with "Threat of violence" and 5.5% presenting with "Acts of violence" were put in supervised confinement.123/638 incidents received only behavioural interventions: 52/123 "de-escalation", 94/123 "time out" and 4/123 "special observation" ("de-escalation" and "time out" were carried out together in 31.5% of the cases). 30.9% of pharmacological interventions were administered intramuscularly (IM). Benzodiazepines were prescribed in 300 cases, mostly in combination with antipsychotics (193/300). Acuphase was given in 7 cases (6/7 associated with lorazepam). Haloperidol is the most prescribed antipsychotic. Total 117 cases; IM in 44 cases (40/44 in combination with lorazepam) and orally in 67 cases (58/67 cases in combination with benzodiazepines, mainly lorazepam). Olanzapine is the second most prescribed antipsychotic. Total 110 cases, IM in 32 cases (25/32 in combination with lorazepam). The velotab was prescribed in 51 cases (38/51 in combination with lorazepam) and the tablet formulation in 27 cases (20/27 associated with lorazepam). The Haloperidol IM and the Olanzapine IM groups (both in combination with lorazepam) did not differ significantly in the type of incident.

Common current practice has little support from randomised trials in this population and is based on clinical experience. The further analysis of this dataset for the outcome of intervention will help to guide future studies in this patients' group.

MC02

CYPROTERONE ACETATE IN AGGRESSIVITY ASSOCIATED WITH DEMENTIA – CASE REPORT AND SYSTEMATIC LITERATURE REVIEW

Bolea-Alamanac BM, Christmas D, Baxter H, Cullum S, Davies SJC. Psychopharmacology Unit, University of Bristol, Dorothy Hodgkin Building, Whitson Street, BRISTOL BS1 3NY, blanca.bolea@bristol.ac.uk

Aggressivity is a common problem in the management of elderly patients with Alzheimer's disease. Most drug classes currently used to diminish aggressive behaviour in elderly people with dementia have problematic side effects limiting their utility. We present a case and a review of the current knowledge about the use of the anti-androgen drug cyproterone acetate to treat aggressivity (excluding hypersexuality related behaviours) in the context of dementia.

An 82 year old man under outpatient assessment for memory loss required psychiatric inpatient admission due to agitation and aggressivity and was diagnosed with Alzheimer's disease. Small quantities of lorazepam (up to 1mg prn) taken at home were ineffective. After admission he took increasing doses of rivastigmine and later memantine, each with no improvement. Two failed trials of atypical antipsychotics (quetiapine and risperidone) meant that all standard drug classes had been introduced without success. He was started on cyproterone acetate titrated up to 50 mg twice daily, with liver function tests checked regularly. After 2 weeks he was calmer and did not express aggresivity, his behaviour improving to a point 2 months later where he could be discharged to a community placement where he has remained settled on cyproterone.

We reviewed literature on the use of cyproterone in aggressivity associated with dementia. We searched the main medical databases (Medline, Embase, Psychinfo, Web of Science, Institute of Health and Science, Cochrane, Clinical Effectiveness and Evaluation Guidelines, Duets, Biosis) since 1978 including articles in English, Spanish, French or Italian using appropriate search terms.

Three papers providing clinical evidence for this use of cyproterone were identified, all involving small numbers. Only one randomized double blind trial was found, which compared cyproterone with haloperidol (n= 27). Cyproterone was more effective controlling aggressivity measured by the Staff Observation Aggression Scale and had lower incidence of side effects. In the one uncontrolled naturalistic observational study identified (n=19), cyproterone was associated with significant reductions in aggressivity rated with the Cohen-Mansfield Agitation Inventory without causing major side effects. One paper provided a small case series (n=3) where cyproterone had ameliorated aggresivity in dementia. Further literature was limited to theoretical discussions without incorporating any clinical evidence.

Despite there being literature to support our own observations of a role for cyproterone in aggressivity in dementia, high quality evidence underpinning this intervention is very limited. Further studies are needed to establish the efficacy and safety of cyproterone for aggressivity in people with dementia.

[No external funding]

MC03

CURRENT EVIDENCE FOR THE USE OF CLOZAPINE IN BORDERLINE PERSONALITY DISORDER: SYSTEMATIC REVIEW

Chikodzore MLD, NAbdelmawla N, Mitchell AJ. Psychiatry, Northamptonshire Healthcare NHS Trust, London Road, Kettering NN15 7PW, nasser.abdelmawla@nht.northants.nhs.uk

In schizophrenia and schizoaffective disorders, clozapine has been shown to control psychotic symptoms, to reduce suicidal behaviour, to have a mood stabilizing and anti-impulsivity effects (Spivat et al., Clin Neuropharmacol., 1997, 20: 442-446; McElory et al., J Clin Psychiatry, 1991, 52: 411-414). These behavioural features are present in borderline personality disorder (BLPD). Earlier case reports have shown some usefulness of clozapine in treating BLPD.

Aiming at evaluating the current evidence for the use of clozapine in patients with BLPD, we conducted a systematic search of the literature using the following data bases midline, PsychInfo & Embase, and the combination of the following keywords: Clozapine, borderline personality, emotionally unstable and personality disorder. We found 13 case reports, case series, surveys and preliminary studies. No randomised control studies found.

Overall, these studies showed positive response of different symptoms (including psychotic symptoms, self-mutilation and mood instability) to clozapine in BLPD. The responses were usually occurring with the use of low doses of clozapine, typically about 100 mg/day. The studies, however, were lacking in the use of objective outcome measures specific for borderline symptom cluster and have other methodological limitations.

There is limited evidence for the usefulness of low doses of clozapine in patients with BLPD. Randomised controlled trials are needed for more conclusive evidence for the use of clozapine in this patient population.

MC04

CHARACTERISATION OF DRUG-DRUG INTERACTIONS IN PSYCHIATRIC AND GENERAL HOSPITAL IN-PATIENTS PRESCRIBED PSYCHOTROPIC MEDICATIONS

Sinclair LI, Davies SJ, Parton G, Potokar JP. Montpellier Unit, 2gether Foundation Trust, Wotton Lawn Hospital, Horton Road, Gloucester GL1 3WL, lindseysinclair@doctors.org.uk

Adverse drug reactions (ADRs) are common, increasing both morbidity and mortality. A US study estimated 100 000 annual deaths due to ADRs, making them the fourth to sixth leading cause of death (Lazarou et al, 1998). Both pharmacokinetic and pharmacodynamic effects may contribute to ADRs. Psychotropic prescribing has increased and many psychotropic medications are substrates for and affect the CYP450 enzyme system. The potential for interactions leading to ADRs has thus increased. We have previously studied ADRs in psychiatric hospital settings using an experts' panel to assess potential CYP2D6/3A4 mediated pharmacokinetic drug interactions (Davies et al, 2004 & 2007). In this study we aimed to identify putative drug-drug interactions, their mechanisms and potential seriousness using the online interaction prediction tool genemedrx.com among patients prescribed psychotropic agents in both psychiatric and general hospital inpatients settings.

This was a survey of psychotropic prescribing within a large mental health trust's in-patient sites and the Bristol Royal Infirmary, a 500 bed general hospital. Ward based pharmacists identified all inpatients prescribed one or more psychotropic drugs. Data collected included dose and regimen of all prescribed medications. Data was collected on a standardised form over a period of 3 months (Dec'06 to Feb'07) with 16 representative psychiatric wards and all wards within the general hospital being visited once in this period. For each patient a full list of prescribed medications was entered into www.genemedrx.com.

Thirty seven General Hospital patients and 221 Psychiatric Hospital patients were prescribed >40 different psychotropic agents. Of these, the General Hospital inpatients had 3.3 potential interactions per person and inpatients on psychiatric units 1.6 per person. Significantly fewer of the interactions identified at the General Hospital (53.7%) involved a psychotropic than in the Psychiatry wards (90.1%) (X^2 statistic 75.1, $p < 0.001$). Ten different CYP enzymes were predicted to be involved in the potential interactions , the most frequent being 2D6 (24%), 3A4 (40%) and 2C19 (13%). Some potential interactions mediated through phase II conjugation pathways e.g. glucuronidation (28 instances) were identified. In both groups potentially serious interactions were identified e.g. >150% increase in [drug] in 8 instances (5 General Hospital, 3 Psych units). There were also 44 instances where agents prolonging QTc were co-administered (88.6% of psychiatric units).

Drug interactions involving psychotropic medications are relatively common among patients prescribed psychotropic drugs, in both psychiatric and general hospital settings, are potentially harmful and are mediated through a range of different mechanisms.

No external funding was received.

MC05

MONOAMINERGIC INTERACTIONS OF DUAL AND TRIPLE UPTAKE INHIBITORS

Scheel-Krüger J, Weikop P. Microdialysis, NeuroSearch A/S, Pederstrupvej 93, DK2750 Ballerup, jsk@neurosearch.dk

Preclinical studies strongly suggest that triple-acting reuptake inhibitors, which increase extracellular levels of all three monoamines may represent a promising strategy in the development of novel antidepressant drugs, since all 3 monoamines show mutual interactions (Weikop et al., 2007, J. Psychopharmacol, 21, 795-801;Weikop et al., 2007,Eur. Neuropsychopharmacol, 17, 658-71). In our laboratory we have found the interaction of constructed monoamine reuptake inhibitors was dependent on the schedule of pre-treatments of the respective reuptake inhibitors. The brain levels of the monoamines were measured in vivo by microdialysis in the rat prefrontal cortex (PFC) and hippocampus (Hipp). One schedule included: (1) pretreatment of desipramine with citalopram (1, 2.5 and 5mg/kg), (2) pre-treatment of methylphenidate with citalopram and (3) pretreatment of GBR 12909 with venlafaxine.
Desipramine and methylphenidate or GBR12909 did not per se influence the levels of 5-HT in the Hipp or the PFC. The citalopram (5mg/kg) induced increase in 5-HT levels in the PFC was markedly decreased by co-administration of desipramine, methylphenidate or GBR12909. However, desipramine did not significantly modulate either the low or medium 1 and 2.5mg/kg doses of citalopram, a finding suggesting a state dependency of the endogenous tonus of 5-HT. In contrast, the citalopram enhancement of 5-HT levels in the Hipp were not significantly influenced by desipramine and only moderately enhanced by adjunctive methylphenidate treatment. Similarly, the combination of GBR12909 and venlafaxine caused also a marked reduction of PFC 5-HT levels compared to the effects induced by venlafaxine (10 mg/kg) alone. The extracellular levels of PFC DA levels were enhanced and NA levels were only marginally affected by treatments with combined reuptake inhibitors compared to the effects induced by methylphenidate or venlafaxine alone. The α_2 antagonist idaxozan produced a minor reduction of the desipramine suppression on 5-HT levels indicating that α_2 adrenoceptors are probably less important for mediating the desipramine effect. However, the modulatory effects of combined pre-administration of the DA/NA reuptake inhibitors with the 5-HT reuptake inhibitors (citalopram and venlafaxine) on attenuation of 5-HT efflux and enhancement of DA were completely reversed by a pre-treatment with the 5-HT_{1A} receptor antagonist WAY100635 (0.1mg/kg).
A role of NA/ DA re-uptake inhibition in dual and triple antidepressant drugs may be to restrict an abnormal high 5-HT tonus in the PFC.Our findings suggest a distinctive control of Hipp 5-HT levels by the NA/DA systems.

MC06

POTENT, DOSE-DEPENDENT AND BEHAVIOURALLY-SELECTIVE ANORECTIC EFFECTS OF SIBUTRAMINE IN MALE RATS

Rodgers RJ, Tallett AJ, Blundell JE. Institute of Psychological Sciences, University of Leeds, Woodhouse Lane, Leeds LS2 9JT, r.j.rodgers@leeds.ac.uk

Sibutramine (Meridia®; Reductil®), a dual noradrenaline (NA) and serotonin (5-HT) reuptake inhibitor, has been licensed as an anti-obesity treatment for over a decade (Luque & Rey, 2002, *Eur J Pharmacol*, 440: 119-128). Sibutramine weight loss involves both NA and 5-HT mechanisms (Jackson et al., 1997, *Br J Pharmacol* 121: 1613-1618) and is thought to occur as the combined result of reduced intake (Stricker-Krongrad et al., 1995, *Int J Obes*, 19: 145) and increased thermogenesis (Connoley et al., 1999, *Br J Pharmacol* 126: 1487-1495). Although comparatively little in-depth behavioural profiling has been done, the results of an early study on rats were consistent with satiety enhancement (Halford et al., 1995, *Br J Pharmacol*, 114: 387) while recent findings in baboons are indicative of a selective suppression of consummatory behaviour (Woltin, 2006, *PHB*, 87: 280-286). The present study was designed to assess the acute effects of sibutramine on food intake, the behavioural satiety sequence (BSS) and post-treatment weight gain in male rats.
Subjects were 10 non-deprived adult male Lister hooded rats (Charles River UK) housed individually under a 12h reversed LD cycle. All procedures were performed under dim red light during the dark phase. Following thorough habituation, each subject was assigned to receive (IP, 1 ml/kg) four treatments (saline, 0.5, 1.5 & 3.0 mg/kg sibutramine HCl; Tocris UK) spaced 1-week apart and in an order predetermined by Latin Square. 30 min following each treatment, animals were placed individually in a large arena with water and preweighed mash. Food intake was measured at the end of the 1h videorecorded test sessions. DVDs were scored blind, and data analysed by parametric or non-parametric procedures.
Sibutramine dose-dependently reduced food intake ($F3,27 = 11.08$, $p < 0.001$), with significant suppression evident at even the lowest dose tested ($p < 0.05$). DVD analysis revealed few behavioural effects, except for a dose-dependent reduction in feeding duration and an increase in rest frequency ($F3,27 \geq 7.66$, $p \leq 0.001$). Behavioural specificity was supported by timebin analysis which revealed normal behavioural structure but a dose-dependent acceleration in the BSS. Single dosing with sibutramine (particularly at 3 mg/kg) also suppressed daily weight gain over the 24-72h period post-dosing ($p \leq 0.02$).
Present data show that the acute anorectic and weight loss efficacy of sibutramine (0.5-3.0 mg/kg) in adult male rats is not secondary to changes in non-ingestive behaviours or behavioural disruption but, instead, seems largely due to an acceleration in behavioural satiety. [AJT is supported by an MRC Doctoral Training Award]

MC07

DISRUPTION OF PREPULSE INHIBITION BY LISURIDE: INVOLVEMENT OF DOPAMINE D2/3 AND SEROTONIN 5HT1A RECEPTORS

Halberstadt AL, Geyer MA. Psychiatry, Univ. California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0804, ahalbers@ucsd.edu

Introduction: Lisuride is an ergot derivative that is used as a treatment for Parkinson's disease. Lisuride is structurally similar to the hallucinogen lysergic acid diethylamide (LSD); like LSD, lisuride acts as an agonist at a variety of monoamine receptors including serotonergic 5-HT1A and 5-HT2A and dopaminergic D2 receptors. Classical hallucinogens such as LSD are believed to exert their behavioral effects via activation of the 5-HT2A receptor. Nonetheless, lisuride does not produce hallucinogenic effects in man, a finding that is paradoxical given its activity at 5-HT2A receptors.
Methods: LSD and other hallucinogens have been shown to disrupt prepulse inhibition (PPI), an operational measure of sensorimotor gating, by activating 5-HT2A receptors (Ouagazzal et al. (2001) Neuropsychopharmacology 25:565; Vanover et al. (2006) J Pharmacol Exp Ther 317:910). The objective of the present investigation was to examine whether lisuride disrupts PPI in male Sprague-Dawley rats. Experiments were also conducted to identify the mechanism(s) responsible for the effect of lisuride on PPI.
Results: Administration of lisuride (0.035, 0.07, and 0.14 mg/kg, s.c.) reduced PPI [n=9-10/group; $F(3,34)=12.74$, $p<0.0001$]. The PPI disruption induced by lisuride (0.07 mg/kg) was prevented by pretreatment with the D2/D3 antagonist raclopride (0.1 mg/kg, s.c) [n=11-12/group; $F(1,42)=6.18$, $p<0.02$] and partially attenuated by pretreatment with the selective 5-HT1A antagonist WAY-100635 (1.0 mg/kg, s.c.) [n=8-10/group; $F(2,64)=3.62$, $p<0.04$]. By contrast, pretreatment with the selective 5-HT2A agonist MDL 11,939 (0.3 mg/kg, s.c.) failed to alter the disruption of PPI induced by lisuride [n=10-12/group; $F(1,41)=0.38$, n.s.].
Conclusions: It is concluded that D2/D3 receptors, and to a lesser extent 5-HT1A receptors, are responsible for lisuride-induced disruption of PPI in rats. Conversely, activation of 5-HT2A receptors does not appear to contribute to the behavioral effects of lisuride. In combination with previous results, these experiments demonstrate that lisuride and LSD disrupt PPI via distinct receptor mechanisms. These findings provide additional support for the classification of lisuride as a non-hallucinogenic 5-HT2A agonist.
Acknowledgements: This project was supported by the National Institute on Drug Abuse (DA02925).

MC08

INHIBITION OF PRANDIAL AND WATER SPRAY-INDUCED RAT GROOMING BY 8-OH-DPAT

Montgomery AMJ, Hartley JE. Department of Psychology, University of Greenwich, Avery Hill Road, London SE9 2UG, A.M.J.Montgomery@gre.ac.uk

In addition to its hyperphagic effect in rats, 8-OH-DPAT also reduces grooming, but it is uncertain whether the inhibition of grooming is a specific effect or a consequence of response competition from eating. The present experiments explored the effects of 8-OH-DPAT on periprandial grooming and grooming elicited by spraying rats with water.

Momentary time sampling over 30 or 60 min, with behaviour scored in one of 6 or 7 (depending on food availability) mutually exclusive categories (feeding, active, scratching, face grooming, body grooming, genital grooming and resting) at 15s intervals, was used for data collection. Non-deprived rats were tested in the presence and absence of food and baseline grooming levels were manipulated by spraying the dorsal surface of the back with water. Data were submitted to ANOVA.

The first experiment confirmed that 8-OH-DPAT increased food intake and that this was associated with a parallel increase in feeding observations; active observations were also increased, but resting and total grooming observations were reduced: scratching was reduced even at 0.003mg/kg, face- and body-grooming were reduced at doses $\geq$ 0.03mg/kg and genital-grooming was least sensitive, only being reduced at 0.1mg/kg. The second experiment revealed that spraying with water had no effect on food intake, feeding or resting observations, but increased total grooming (largely due to increased body-grooming) and reduced activity observations. In rats sprayed with water, 8-OH-DPAT increased food intake (0.1mg/kg) and observations of feeding (0.003 & 0.1mg/kg), but total grooming was dose-dependently inhibited, with genital-grooming most sensitive($\geq$ 0.003mg/kg), followed by face-grooming ($\geq$ 0.01mg/kg) and body-grooming ($\geq$0.03mg/kg), whilst low levels of scratching were unaffected. The final experiment tested water-sprayed rats in the absence of food: 8-OH-DPAT increased resting and reduced total grooming, mostly as a consequence of reductions in face- and body-grooming, but there were also modest reductions in scratching.

These results confirm that 8-OH-DPAT has a suppressant effect on all aspects of grooming, except where there are probable floor effects, and that this is independent of response competition from increased eating.

MC09

EFFECTS OF THE D2-RECEPTOR ANTAGONIST METOCLOPRAMIDE ON 5-HYDROXYTRYPTOPHAN (5HTP) INDUCED ACTIVATION OF THE HYPOTHALAMUS-PITUITARY-ADRENAL (HPA) AXIS

Jacobs GE, Hulskotte EGJ, de Kam M, Zitman FG, van Gerven JMA. Centre for Human Drug Research, Zernikedreef 10, 2333 CL Leiden, gjacobs@chdr.nl

Introduction: A biomarker test investigating vasopressinergic drive of the HPA axis may be helpful in examining this system in depression and in innovative antidepressant drug development. The vasopressin (AVP) analogue desmopressin (dDAVP) causes small increases of ACTH and cortisol. Systemic dDAVP-administration however may have indirect (systemic) effects on ACTH-release, which is less physiological than stimulation of endogenous AVP release. This may not be the case with the dopamine-2 (D2)-receptor antagonist metoclopramide (MCP), which is believed to stimulate AVP release from the hypothalamus and/or the pituitary. CRH release can be evoked via central serotonergic projections, using a challenge test with the serotonin precursor 5-HTP. Since AVP and CRH are co-activators of the HPA axis, stimulation of AVP release would be expected to potentiate CRH-effects induced by 5-HTP. This hypothesis was tested in healthy male volunteers.

Methods: A randomized, double blind, placebo-controlled, four-way crossover study was performed in 12 healthy volunteers. An oral 5-HTP challenge test was administered and followed 60 minutes later by a one minute bolus infusion of metoclopramide 10 mg. The neuroendocrine effects (ACTH, cortisol and prolactin) were investigated. Safety was assessed by adverse events (AE) reporting. Pharmacodynamic endpoints were analyzed by mixed model analyses of variance. The effects of of MCP and MCP combined with 5-HTP were assessed over a period of 70 minutes and that of 5-HTP over a period of 130 minutes. Potential MCP/5-HTP synergism was investigated by contrasting MCP combined with 5-HTP minus 5-HTP alone, to MCP minus placebo.

Results: Neuroendocrine results are presented as estimates of percentual difference from placebo, with 95% confidence intervals. Plasma ACTH increased by 43.9 (23.4, 67.8) % during MCP alone; by 55.3 (32.6, 81.9) % during 5HTP alone; and by 166.8 (126.5, 214.2) % with the combination. Similar effects were seen for cortisol. The differences between the responses with the combination minus those of 5-HTP alone, compared to the effects of MCP alone minus placebo, were statistically non-significant for both ACTH and cortisol. Prolactin was not influenced by dDAVP. All adverse events were compatible with the side-effect profile of MCP (drowsiness) and 5-HTP (nausea, abdominal discomfort, headache and vomiting) and no SAE's occurred.

Conclusions: Metoclopramide causes a limited release of ACTH and cortisol. Endogenously MCP-induced HPA axis activation is somewhat larger and better tolerated than previously reported exogenously dDAVP-induced activation. MCP-induced HPA axis activation (via AVP) seems to be additive to 5-HTP induced (serotonergic) HPA axis activation (via CRH), but there was no proof for synergism in these healthy subjects.

This study was in part sponsored by NV Organon part of Schering-Plough Corporation.

MC10

SPECIFICITY OF THE ACUTE TRYPTOPHAN DEPLETION AND LOADING TESTS: NORMALISATION OF THE TRYPTOPHAN AND TYROSINE RATIOS IN THE CONTROL FORMULATION BY DECREASING THE CONTENT OF BRANCHED-CHAIN AMINO ACIDS

Badawy AA-B[1], Dougherty DM, Marsh-Richard DM. [1]University of Wales Institute Cardiff, Wales, UK and University of Texas Health Science Center at San Antonio, TX, USA (ABadawy@uwic.ac.uk)

We have previously shown that the tyrosine plus phenylalanine ([Tyr + Phe]) to large neutral amino acid (Val, Leu and Ile) plus tryptophan ([LNAA + Trp]) ratio is decreased during acute Trp depletion and loading and suggested that the likely inhibition of catecholamine synthesis may confound interpretation of behavioural data. We also found that the above ratio and that of Trp to the sum of its 5 competitors (Val, Leu, Ile, Phe and Tyr) ([Trp]/[CAA]) are decreased in the control formulation. We suggested that, because of the larger contents of Leu, Val and Ile, relative to Tyr, Phe and/or Trp, decreasing the first 3 should normalise these ratios. In the present work with the control formulation, we demonstrate normalisation of these ratios by this strategy.

Four groups of healthy US subjects (12 each) received a 50g dose of a balanced control drink containing 16 amino acids. The contents of Trp (1.15g), Phe (2.85g) and Tyr (3.45g) were fixed, whereas those of Leu, Val and Ile were decreased from those in the traditional formulation (F0) (6.75g, 4.55g and 4.00g respectively) by 20% (F1), 30% (F2) and 40% (F3). The differences were made up by increasing the contents of non-competitors in the formulation. Fasting plasma was analysed for amino acids before (zero h) and at hourly intervals for 7h after the 4 different drinks.

As expected, dose-dependent decreases over the entire 7h time course were observed in plasma levels of the 3 branched-chain amino acids, but not in those of Trp, Phe or Tyr. Compared to baseline, the traditional formulation (F0), showed significant decreases in the [Total Trp]/[CAA] (31-45%; P=0.03-0.0002) and [Tyr + Phe]/[LNAA + Trp] (29-46%; P=0.01-0.0005) ratios during the first 5h (1-way ANOVA with replicated measures). Partial reversal of these decreases was observed in F1 and F2 subjects, whereas full reversal was achieved in the F3 group receiving 40% less branched-chain amino acids.

We propose that: (1) because a control formulation must be associated with normal Trp and Tyr ratios, its composition should be altered to include 40% less of the 3 branched-chain amino acids Val, Leu and Ile; (2) applying this modification to the depletion and loading formulations will enhance the specificity of these Trp manipulation tests; (3) the same principles should apply to tyrosine depletion and loading formulations regarding the Trp ratio.

DMD and AA-BB thank respectively the NIH for funding and the Wellcome Trust for equipment used in this study.

MC11

DIFFERENTIAL PRE- AND POST-SYNAPTIC EFFECTS OF 5-HT1A RECEPTOR AGONISTS: INFLUENCE ON 5-HT LEVELS IN HIPPOCAMPUS AND ON DOPAMINE LEVELS IN FRONTAL CORTEX OF FREELY MOVING RATS

Assié MB, Ravailhe V, Benas C, Newman-Tancredi A. Neurobiology II, Centre de Recherche Pierre Fabre, 17 avenue Jean Moulin, 81106 CASTRES, marie.bernadette.assie@pierre-fabre.com

5-HT_{1A} receptor agonists decrease 5-HT release in terminal regions by activating somatodendritic inhibitory receptors (e.g., Assié and Koek, 2000. Eur.J.Pharmacol. 409, 173-177). In addition, 5-HT_{1A} agonists preferentially increase dopamine levels in the medial prefrontal cortex (mPFC) by activating postsynaptic receptors (Arborelius et al., 1993. Acta Physiol.Scand. 148, 465-466; Tanda et al., 1994. Psychopharmacology 115, 285-288). *In vivo* microdialysis was used to measure the effects of a series 5-HT_{1A} agonists (F15599, repinotan, xaliproden, S15535, piclozotan, flibanserin and F13714) on extracellular 5-HT levels in the ventral hippocampus and on extracellular dopamine levels in the mPFC of freely moving rats.

Male Sprague Dawley rats (3-5 per dose) were used in the experiments. 5-HT or dopamine levels were determined by in vivo microdialysis coupled to HPLC-EC. 24h after implantation of a guide cannula in the brain area of interest, a probe was inserted and 20 min samples were collected and analysed for 5-HT or dopamine content. After four stable baseline samples, saline or WAY100635 (0.16 mg/kg s.c.) were injected followed, 40 min later, by i.p. administration of a 5-HT_{1A} agonist. Samples were collected for an additional 140 min period. Data were analysed by one-way ANOVA followed by Dunnett's test, $p<0.05$ was considered significant.

All the compounds dose-dependently decreased 5-HT levels in hippocampus, an effect inhibited by the selective 5-HT_{1A} antagonist, WAY100635. In contrast, the compounds did not produce similar effects on dopamine levels in the mPFC. While F15599 and repinotan increased dopamine to approximately 200% of basal levels at doses lower than those necessary to decrease 5-HT levels, other compounds produced a lower increase and flibanserin was inactive. WAY100635 prevented the increase in dopamine induced by F15599, repinotan, F13714, piclozotan, xaliproden and S15535 indicating that their effects are mediated by 5-HT_{1A} receptor activation.

In summary, the agonists exhibited different profiles of pre- or post-synaptic 5-HT_{1A} receptor activity. F15599 and repinotan potently increased mPFC dopamine levels, suggesting marked activation of post-synaptic 5-HT_{1A} receptors. In contrast, piclozotan and flibanserin had little or no influence on dopamine levels but decreased 5-HT release, consistent with preferential activation of pre-synaptic 5-HT_{1A} receptors. These data demonstrate that 5-HT_{1A} receptor agonists can differentially act at sub-populations of 5-HT_{1A} receptors. Further, these data suggest that by increasing dopaminergic activity in the mPFC cortex at low doses, compounds such as F15599 may have potential for the amelioration of cognitive impairments in schizophrenia and/or depression.

Supported by Pierre Fabre Médicament.

MC12

THE EFFECTS OF 5-HT1A RECEPTOR AND 5-HT TRANSPORTER POLYMORPHISMS ON 5-HT TURNOVER IN HUMAN POST-MORTEM BRAIN TISSUE

Armstrong RDJ, Jenkins TA, Reynolds GP. Psychiatry & Neuroscience, Queen's University Belfast, 97 Lisburn Rd, Belfast BT9 7BL, a1692601@qub.ac.uk

INTRODUCTION There is substantial inter-individual variability in the response to psychotropic drug treatment. This is likely to have a genetic component; we have, for example, demonstrated associations of both the 5-HT1A receptor C-1019G polymorphism and the serotonin (5-HT) transporter (5-HTT) short/long (S/L) polymorphism on negative symptom response to antipsychotic treatment of first-episode patients. Therefore these polymorphisms are functional in clinical response as well as in the activity of their respective gene products, which is already well established. As both the 5-HT1A receptor and 5-HTT can influence 5-HT neuronal activity, we have investigated the effects of genotype on brain neurotransmitter availability and turnover.

METHOD We have determined neurotransmitter and metabolites by HPLC from two cohorts of human post-mortem brain tissue: samples of striatal tissues from 26 previously healthy control subjects and cortical tissues from 60 subjects including controls and subjects with major psychiatric disorders. Each subject was genotyped for both the 5-HT1A and the 5-HTT polymorphisms and the association between genotype and 5-HT turnover expressed as the ratio of the concentrations of 5-HIAA to 5-HT.

RESULTS A significant association of the 5-HTT S/L promoter polymorphism on 5-HT turnover was found in both the striatal and the cortical samples. SS individuals showed the highest turnover in the striatal cohort, while conversely SS individuals from the cortical cohort showed the lowest turnover. Cofactor analyses and stepwise linear regressions showed no significant effects of sex, age, post-mortem delay, disease status or treatment status in either cohort. We found no significant effect of the 5-HT1A polymorphism on changes in 5-HT turnover for either cohort.

CONCLUSIONS These results demonstrate a significant effect of the 5-HTT S/L promoter polymorphism in influencing 5-HT turnover in both human striatum and cortex. However, the direction of the effect differs between the regions. The striatal effect can be interpreted as greater turnover of transmitter being a consequence of lower activity of 5-HT uptake known to be associated with the S allele in the synapse. The cortical result may be a consequence of the lower density of transporter in the cortex, resulting in turnover reflecting neuronal activity under the control of somatodendritic transporter in the raphe nucleus.

MD01

PATIENT OPINION OF A NEW METHADONE MAINTENANCE PROGRAM AND NOVEL DISPENSING SYSTEM

Deslandes PN, Xiao X, Thomas A, Jones N, Sewell RDE. Pharmacy Department, Whitchurch Hospital, Park Road, Cardiff, CF14 7XB, paul.deslandes@cardiffandvale.wales.nhs.uk

Introduction: The most effective setting and mode of delivery for providing methadone maintenance treatment to opiate addicts have yet to be determined (BAP 2004 J. Psychopharmacol. 18(3): 293-335). The recently established Cardiff Drug Intervention Program (DIP) is part of government strategy to help opiate users into appropriate treatment, and uses a novel, automated methadone dispensing system -Methadose. The aim of this study was to evaluate clients' views of the new Cardiff DIP service compared to their previous experiences of receiving methadone. Of particular interest were opinions of overall satisfaction, privacy, waiting times, and the novel Methadose dispensing system.

Method: The study employed a self-administered questionnaire which surveyed client opinion using a five point Likert scale ranging from "very happy" (VH) to "very unhappy" (VU). The questionnaire was administered to consenting clients attending Cardiff DIP between March and April 2007.

Results: 31 clients completed the questionnaire, a response rate of 70%. 96% were either "VH" or "happy" (H) with the overall service, and 90% were "VH" or "H" with the novel Methadose system. Of the 31 respondents, 14 had previous experience of receiving methadone maintenance treatment from another service. Overall, 93% of these clients were either "VH" or "H" with DIP, compared to 50% with their previous experience. The mean score of overall satisfaction was significantly greater for DIP compared to the previous service ($p< 0.01$, Wilcoxon matched pairs test). 85% were either "VH" or "H" with privacy at DIP, compared to 46% with the previous service; the mean score for privacy was significantly greater for DIP ($p< 0.05$, Wilcoxon matched pairs test). There was no significant difference between opinions of waiting time at each service.

Conclusions: Overall opinion of Cardiff DIP and the Methadose system was positive. The 96% response of "VH" or "H" is comparable to data from the National Treatment Agency for Substance Misuse (NTA) 2005 survey of user satisfaction, where 91% of respondents "strongly agreed" or "agreed" that they were satisfied with the program. Overall opinion of Cardiff DIP appeared to be more favourable than clients' experience of previous services. However, it must be noted that numbers in this study were limited, and rating of previous service required a retrospective view which may be subject to a degree of bias. The extension of this study to include a greater sample number is the subject of further work.

Acknowledgement: No external funding was received for this study. The authors thank Mrs W. Davies for the opportunity to conduct this work.

MD02

ACUTE TASTE CHANGES FOLLOWING OPIATE AGONISTS (BUPRENORPHINE & METHADONE) AND ANTAGONISTS (NALTREXONE) IN HUMAN ADDICTS: A NOVEL BIOMARKER OF TOLERANCE?

Kaul A, O'Shea J, Green A, Sharma E, Nutt DJ, Donaldson LF, Melichar JK. Psychopharmacology Unit, University of Bristol, Whitson Street, Bristol BS1 3NY, jan.melichar@bris.ac.uk

Mu-opioid receptors are present in both taste buds and areas of the brain involved in taste processing. Increased refined sugar consumption is noted in human heroin addicts as well as animal experimental models of opiate dependence. This behaviour in humans chronically using opiates could represent either a change in a cognitive (taste perception) or physiological (taste detection) process. Looking at possible biomarkers, our group has previously shown significant acute changes in taste after manipulation of serotonin levels in humans. To therefore investigate whether there is a link between opiates and taste changes, we assessed taste changes in opiate addicts following administration of the full agonist methadone or the partial agonist buprenorphine and in detoxified addicts after oral naltrexone.

Specifically, we aimed to test the hypotheses that taste changes in addicts are enhanced by methadone / buprenorphine and reversed by naltrexone. We determined sweet taste thresholds of subjects by presenting a series of sucrose solutions to the tip of the tongue. Subjects indicated whether they could recognise the taste stimuli at each concentration and recognition thresholds were calculated from psychophysical taste function curves. Taste perception was examined using labelled magnitude scales that measured intensity and pleasantness to a suprathreshold sucrose (1M) and salt (1M) solutions. Taste parameters were determined before and 2-4 hours after: 1) Methadone (n=7 opiate users) 2) Buprenorphine (n=7) 3) Oral naltrexone (n=6 recently detoxified addicts) This was compared to a cohort of healthy control volunteers (n=48). Opiate users on either methadone or buprenorphine have significantly blunted sweet taste at baseline compared to controls. This was also seen in the recently detoxified users. The blunting of taste was not significantly changed after having maintenance methadone or buprenorphine. Most interestingly, a test dose of naltrexone rapidly returned sweet taste in recently detoxified opiate users to control levels. Controls: 30±4mM; All p values are vs non-opiate using controls. Methadone Before: 130±30 ($p<0.05$) After: 220±80($p<0.001$); Buprenorphine Before: 220±90($p<0.001$) After: 140±50($p<0.05$); Naltrexone: Before: 170±40($p<0.001$) After: 60±9 (NS). These results suggest that opiate use does alter sweet perception. This altered sweet perception does not immediately reverse on detoxification, but unexpectedly seems to be acutely reversed by opioid antagonism using naltrexone. Changes in sweet taste perception may underlie altered consumption of refined sugars in opiate users. As current and recent opiate users have significantly blunted sweet taste responses, taste tests could have a role as objective markers of opiate dependency.

MD03

IMPULSIVITY, COMPULSIVITY, DECISION-MAKING AND RECENT LIFE STRESS ARE INDEPENDENT PREDICTORS OF RECREATIONAL DRUG AND ALCOHOL USE

Ward ER, Powell J. Psychology, Goldsmiths, University of London, New Cross, London SE14 6NW, e.ward@gold.ac.uk

This cross-sectional study aimed to investigate the contributions of impulsivity, compulsivity, risky decision-making and recent life stress to recreational substance use in a non-addicted population, given previous research implicating dysfunction of mesocorticolimbic pathways and in particular orbitofrontal cortex in both substance dependence and obsessive compulsive disorder. The sample consisted of 213 undergraduate students (24% male), aged between 18 and 21.

Substance use was assessed using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST; World Health Organisation, 2002); trait impulsivity via the IVE (IVE-Imp; Eysenck & Eysenck, 1991) and the Novelty-Seeking subscale of the Tri-dimensional Personality Questionnaire (TPQ-NS; Cloninger, 1987); decision-making by the number of advantageous decisions on the Iowa Gambling Task (IGT; Bechara et al, 2004); and Life Stress over the preceding 12 months by the Revised Life Changes Questionnaire (Miller & Rahe, 1997). Compulsive tendencies were measured in a subset of 100 participants using the Padua Inventory (Sanavio, 1988) which comprises four subscales: Impaired control over mental activities (Pad-MentCont); Fear of contamination (Pad-Contam); Checking behaviours (Pad-Check); and Impaired control over motor behaviours (Pad-MotorCont). Multivariate relationships were evaluated by multiple linear regressions using SPSS version 14.0 for windows. In the full sample, 32.2% of the variance in ASSIST scores was predicted by the combination of TPQ-NS, IVE-Imp, Life Stress, and IGT scores ($F=94.7$, $p < 0.001$), with each making independent contributions ($p < 0.02$ in each case). In the 100 participants for whom Padua scores were additionally available, the MotCont subscale was a significant predictor ($r = 0.26$, $p < 0.01$). When included alongside the other four variables, it emerged along with EPQ-Imp and Life Stress as an independently significant predictor of substance use; jointly, they accounted for 26% of the variance ($F = 7.2$, $p < 0.001$).

The study confirms a significant association between trait impulsivity and recreational substance use, and additionally demonstrates that recent life stress, a behavioural index of decision-making ability, and compulsive tendencies account for further variance in substance use. All of these variables have been associated with alterations in the functioning of dopaminergic mesocorticolimbic circuitry, and these data suggest that their effects may be additive. The independent contributions of impulsivity and compulsivity, which were not significantly correlated with each other, are of particular interest.

This research was supported by a studentship from the Economic and Social Research Council (ESRC).

MD04

ACTIVATION OF LIVER TRYPTOPHAN PYRROLASE MEDIATES THE ETHANOL-INDUCED DEPLETION OF BRAIN SEROTONIN IN NORMAL SUBJECTS

Badawy AA-B[1], Dougherty DM, Marsh-Richard DM, Steptoe A[1] [1]University of Wales Institute Cardiff, Wales, UK and University of Texas Health Science Center at San Antonio, TX, USA (ABadawy@uwic.ac.uk)

We have previously shown that acute ethanol consumption by normal volunteers decreases circulating tryptophan (Trp) concentration and availability to the brain, expressed as the ratio of [Trp] to the sum of its 5 competing amino acids [CAA], namely Val, Leu, Ile, Phe and Tyr, and suggested that this may explain alcohol-induced depression, and aggressive behaviour in susceptible individuals. These changes were suggested to involve activation of Trp pyrrolase (Trp dioxygenase), the first and rate-limiting enzyme of the hepatic kynurenine pathway, because the decreases in both free (ultrafiltrable) and total (free + albumin-bound) Trp were relatively similar and therefore not associated with altered albumin binding, which is typical of Trp pyrrolase activation. In the present work, we provide evidence supporting this hypothesis by demonstrating the elevation of plasma kynurenine concentration in association with the decrease in [Trp].

Ten healthy US subjects received a placebo drink or various doses of ethanol (0.2-0.8g/kg body wt) between 09.00 and 09.15. Two hours later, blood samples were withdrawn. Plasma was analysed for various parameters of Trp metabolism and disposition using newly developed GC and HPLC methodologies. Ultrafiltrates were not prepared in this study. Because the subjects consumed a light breakfast before placebo or ethanol, a fasting control group closely matched for age, ethnicity and gender was included for comparison with the placebo (zero-ethanol) group. Control and test group data were compared statistically using one-way ANOVA with replicated measures. Compared with placebo, doses of ethanol of 0.2, 0.4, 0.6 and 0.8g/kg significantly ($P= 0.0264$-0.0000) decreased plasma total [Trp] by 26, 42, 47 and 53% respectively, but exerted no significant effect on [CAA]. As a result, the [Trp]/[CAA] ratio was decreased by the above ethanol doses by 27, 35, 38 and 39% respectively. Compared to placebo, ethanol significantly ($P= 0.0034$-0.0003) decreased this ratio following all doses except the 0.2g/kg dose. Under these conditions, plasma kynurenine concentration was significantly ($P= 0.0000$) elevated by 78, 67, 72 and 77% respectively. The kynurenine/Trp ratio percentage was consequently increased by a staggering 142, 188, 228 and 274% respectively, suggesting activation of liver Trp pyrrolase by ethanol.

We conclude that alcohol decreases Trp availability to the brain and thus inhibits central serotonin synthesis by activating liver Trp pyrrolase and suggest that the extent of this activation will determine the level of serotonin depletion after alcohol consumption. We also propose that liver Trp pyrrolase may be a major determinant of alcohol-induced aggressive behaviour in susceptible individuals.

DMD and AA-BB thank respectively the NIH for funding and the Wellcome Trust for equipment used in this study.

MD05

RECLASSIFYING PSYCHOACTIVE SUBSTANCES ON THE BASIS OF THEIR ACTUAL HARMS: AN INTERNET SURVEY OF DRUG USERS

Morgan CJA, Muetzelfeldt L, Curran HV. Clinical Psychopharmacology Unit, University College London, Gower St, LONDON WC1E 6BT, c.morgan@ucl.ac.uk

Introduction: The extent of worldwide psychoactive substance use is estimated at 2 billion alcohol users, 1.3 billion smokers and 185 million drug users. However much controversy and confusion exists concerning the actual harms associated with the use of these substances. Nutt et al (2007) published a 'rational' scale used by two groups of experts to assess these harms. Drug users were not included in these expert panels despite their unique perspective on the harms of psychoactive substances. This survey aimed to assess drug users' views on the harms of drugs using the rational scale developed by Nutt et al. As users' choice of which drug to take is likely to be based on a risk/benefit analysis, we additionally assessed the perceived benefits of taking psychoactive substances.
Method: The survey was hosted on www.nationaldrugsurvey.org. All participants were required to be over 18 years old and residents of the U.K. The respondents completed a section detailing their experience of the 20 substances included in the original survey with the addition of crack cocaine. Only respondents with direct experience of the drugs rated their perceived harms. There were nine scales of harm under three sub-headings: physical harms, dependence-related harms and social harms. Each drug was rated on a four point scale, from no risk to extreme risk. The acute and chronic benefits of each drug were also rated on a similar four point scale.
Results: 1501 users completed the survey. Users rated heroin as the most harmful drug, followed by crack cocaine, cocaine, street methadone and alcohol. There was no correlation between classification under the Misuse of Drugs Act and ranking of harms by users (Kendall's rank correlation 0.234; $p=0.18$). Despite being unclassified drugs; alcohol, solvents and tobacco were all rated within the top ten most harmful drugs. There was a high correlation overall between users rankings and the experts rankings from Nutt et al.'s study ($r = 0.896$, $p<0.001$). Ecstasy, cannabis and LSD were rated consistently highly on both acute and chronic benefits.
Conclusions: The results of this study suggest that users are relatively well informed about the harms associated with the drugs they are using. They also imply that the current legal classification system of psychoactive substances may be in need of an overhaul as Class A substances such as Ecstasy and LSD are both rated as relatively low on harms by experts and users and high on benefits.
This project was funded internally.

MD06

EXPOSURE TO RECREATIONAL DRUGS IN UTERO: REVISED NEUROBEHAVIORAL OUTCOMES FROM THE DAISY PROJECT

Ribeiro H, Goodwin J, Turner JJD, Lynch S, Moore DG, Parrott AC, Axelson E, Fulton S, Frostick C, O Min M, Singer LT. School of Psychology, University of East London, Romford Road, London, h.s.p.ribeiro@uel.ac.uk

Introduction: The Development and Infancy (DAISY) project is an ongoing prospective longitudinal study exploring maternal drug use and developmental outcomes to age 24 months in infants exposed to various recreational substances during pregnancy. A preliminary presentation of data (BAP, 2007) indicated some negative effects of MDMA and alcohol on motor quality in exposed infants. Revised findings of maternal MDMA and other drug use and its relationship to child outcomes on the NICU Network Neurobehavioral Scale (NNNS), from a larger cohort, are reported.
Methods: 78 participants (22 MDMA-users, 56 non-users) were interviewed and systematically assessed on measures of drug use, medical, psychological, and intellectual characteristics. The NNNS is a set of standardised measures designed to comprehensively assess neurobehavioral functioning in infants, and was administered to participants' babies at 4 weeks postpartum.
Results: MDMA-users were more likely to have a male child; had fewer previous births/pregnancies; were younger; reported heavier tobacco, marijuana, and cocaine use during pregnancy and heavier lifetime use of marijuana, tranquilizers, amphetamines (all $p<0.03$), cocaine and ketamine (both $p<0.001$). The MDMA-users did also show higher DAST (Drug Abuse Screening Test) scores ($p=0.04$), but did not reach the threshold for dependency. Regression analyses on the NNNS, controlling for other drug use, revealed a negative relationship of lifetime MDMA use to Quality of movement ($p<0.01$); negative relationships of marijuana use during pregnancy on Orientation and Regulation (all $p<0.05$); and a positive relationship of tobacco use during pregnancy to Orientation ($p<0.01$).
Conclusions: MDMA use during pregnancy was associated with heavier lifetime drug use and polydrug use during pregnancy. Marijuana and tobacco use during pregnancy was related to infant outcomes, as was lifetime MDMA use.
Supported by NIDA grant DA-14910

MD07

PREVALENCE OF SUBSTANCE ABUSE COMORBIDITY IN PSYCHIATRIC INPATIENTS AND ITS IMPACT ON LENGTH OF HOSPITAL ADMISSION

Bekoe OO, Walters P, Baldwin DS, Sinclair JMA. Department of Psychiatry, Royal South Hants Hospital, Brintons Terrace, Southampton, SO14 0YG, obed.bekoe@hantspt-sw.nhs.uk

Introduction: Alcohol or drug misuse or dependence syndromes are common in the general population, but substantially more common in patients with severe and enduring psychiatric illness. This pattern of comorbidity ('dual diagnosis') is associated with higher rates of attempted suicide and violence, and greater use of health service resources. It is uncertain whether it is associated with longer duration of inpatient care following admission to hospital, and we therefore sought to establish whether length of stay differed significantly in psychiatric inpatients with or without comorbid substance misuse.
Methods: All patients admitted to two general psychiatry wards over 12 months were considered for study participation, exclusion criteria being limited to mental disorders that were secondary to physical ill-health or the direct consequences of substance misuse, or when admission was solely for alcohol or drug detoxification. Assessments included demographic and clinical characteristics, use of ICD-10 criteria for psychiatric diagnosis, completion of the Brief Psychiatric Rating Scale (BPRS) at admission, and urine drug analysis. Length of stay was calculated from hospital discharge summaries.
Results: 218 patients (135 men, 83 women: mean age 38.6 years) consented to participate in the study. 96 patients (44%) fulfilled ICD-10 criteria for harmful use or dependence on alcohol (30, 13.8%) or drugs (53, 24.3%) or both (13, 6.0%). Substance misuse comorbidity was more frequent among men than women (51.1% vs 32.5%: $\chi 2 = 7.2$, d.f.=1, $p<0.01$). The proportion of patients with comorbid substance misuse did not differ significantly, across three broad diagnostic groups: schizophrenia/schizoaffective disorder (39/76, 51.3%), bipolar disorder (14/38, 36.8%), unipolar depression (28/72, 38.9%). Mean length of hospital stay was shorter in dually diagnosed patients than in patients without comorbid drug/alcohol misuse (37 days vs 45 days, respectively: Mann-Whitney, $Z=-1.96$, $p<0.05$). Patients with comorbid alcohol misuse had the shortest mean duration of admission (24 days). Conclusions: Alcohol and drug misuse or dependence syndromes are frequently comorbid with severe and enduring mental illness in psychiatric inpatients, but are not associated with an increased duration of hospital admission. Conversely, comorbid substance misuse (particularly alcohol misuse) is associated with shorter length of hospital stay, reducing the opportunity to optimise clinical outcomes.
Source of funding: No external funding was sought for this study.

MD08

REPORTED ALCOHOL CONSUMPTION, DEPRESSIVE AND ANXIETY SYMPTOMS, AND MENTAL WELL-BEING AMONG UK VETERINARY SURGEONS: CROSS-SECTIONAL QUESTIONNAIRE SURVEY

Bartram DJ, Yadegarfar G, Baldwin DS. Clinical Neuroscience Division, School of Medicine, University of Southampton, RSH Hospital, Southampton, SO14 0YG, djbartram@hotmail.com

Veterinary surgeons are at high risk of suicide, with a proportional mortality ratio around four times that of the general population and approximately twice that of other healthcare professions. Although there has been much speculation regarding mechanisms of increased suicide risk in the profession, there is scant empirical research, and the contribution of alcohol misuse, anxiety and depression is uncertain. We wished to examine relationships between alcohol consumption, depressive and anxiety symptoms, and overall mental well-being through a questionnaire survey of a large stratified sample of veterinary surgeons practising within the UK. The questionnaire was mailed to 3,200 veterinary surgeons (approximately 20% of the membership of the Royal College of Veterinary Surgeons). Reported alcohol consumption was graded through completion of the Alcohol Use Disorders Identification Test alcohol consumption Questions (AUDIT-C), individuals being classified into non-drinkers, low-risk drinkers (score 1-3 for women and 1-4 for men) and at-risk drinkers (score ≥4 for women and ≥5 for men). Depressive and anxiety symptoms were assessed through completion of the Hospital Anxiety and Depression Scale (HADS) and mental well-being through the Warwick Edinburgh Mental Well-being Scale (WEMWBS). 1796 participants returned the completed questionnaire, a response rate of 56.1%: after imputation of minor omissions, valid data was available for 1757 individuals (881 men, 876 women). There were 95 non-drinkers (5.4%), 563 low-risk (32.0%) and 1099 (62.5%) at-risk drinkers. Mean scores on the HADS anxiety (HADS-A) and depression (HADS-D) sub-scales in the overall sample were 7.92 and 4.65, respectively. Mean HADS sub-scale scores and WEMWBS did not differ significantly (One-way ANOVA and Kruskal-Wallis tests) between non-drinkers, low-risk and at-risk drinkers: HADS-A, 7.96 vs 7.69 vs 8.04; HADS-D, 5.02 vs 4.67 vs 4.61; WEMWBS, 47.27 vs 49.42 vs 48.79. In this population, self-reported depressive and anxiety symptom severity did not differ significantly across three levels of reported alcohol consumption. The high prevalence of at-risk alcohol consumption and the HADS-A score indicating anxiety symptoms of possible clinical significance require further exploration and, if substantiated, would cause some concern if this sample is representative of the UK veterinary profession. Sources of funding: Veterinary Business Development printed and mailed the questionnaires; BUPA Giving provided financial support for the project.

MD09

ETHANOL AND PERFORMANCE IN THE LABORATORY AND EVERYDAY LIFE

Tiplady B, Oshinowo B, Thomson J, Drummond G. Anaesthetics, University of Edinburgh, Edinburgh, EH16 4SA, u8901@penscreen.com

Most research on the effects of ethanol on performance is carried out in the laboratory, with epidemiological studies confirming the significance of performance impairment in domains such as driving. There is increasing interest in assessment in an everyday life setting, using methods such as the internet, handheld PCs and mobile phones. Using the same volunteers, we compared assessments of the effects of ethanol on performance, in a controlled laboratory study and in normal life using mobile phones. 38 healthy volunteers (20 male) aged 18-54 years (mean 22.8) took part. They were asked not to alter their drinking habits. Text (SMS) messages were sent twice a day to the mobile phones at different times over 14 days. The application collected information on ethanol consumed, visual analogue ratings, and administered tests of memory, attention, and reaction time. 26 of the volunteers took part in the lab study. They received ethanol and placebo on separate days in random order and completed the same assessments at intervals up to 2h after the drink. Thirty volunteers reported consuming at least five units of ethanol in the previous 6h at least once during the two week period. Performance was compared to similar times with no ethanol in the past 24h in the same volunteers. Mean blood alcohol concentrations in the lab study were 124 mg/100 ml. The expected drunkenness and impairments to speed and accuracy of performance were seen in both settings. Performance was slower in the everyday setting, and the ethanol impairment greater, particularly for errors, although the inferred ethanol levels in the everyday setting were somewhat lower. The mean number of incorrect responses for number pairs (attention) was 6.52 for placebo, 9.28 for ethanol in the lab ($p<0.01$, ANOVA); and 6.45 (no ethanol), 12.2 (ethanol) in the everyday setting ($p<0.05$ Paired t-test). Laboratory and everyday assessments differ in many ways, including: the rate of drinking, distraction, time of day, and social context. It is therefore not surprising that results are not identical. The poorer performance in the everyday setting could be due to greater distraction, which should be further investigated. Two overall conclusions may be drawn (1) Performance impairments are found in both settings, and are at least as great in real life as in the lab, and (2) Lab results suggesting that errors are an important aspect of alcohol impairment are supported by this study of volunteers in their everyday circumstances. No external funding.

MD10

EFFECTS OF ACUTE ALCOHOL CONSUMPTION ON THE PROCESSING OF PERCEPTUAL CUES OF EMOTIONAL EXPRESSION

Ataya AA, Attwood. A, Benton C, Penton-Voak I, Munafò M. Department of Experimental Psychology, University of Bristol, 12a Priory Road, Bristol, BS8 ITU, aa6613@bris.ac.uk

Introduction: The mechanisms underlying the relationship between alcohol and aggression are not particularly well understood. Alcohol may facilitate aggression via alterations in the processing of the emotional content of facial cues. Studies have reported impairments in the processing of emotional facial cues in alcohol dependent participants (Townshend & Duka 2003). Recently, studies have shown modified processing of emotional facial cues after acute doses of alcohol in non-dependent social drinkers (Kano et al. 2003). The studies reported here further explore these effects using adapted psychophysical tasks in order to measure threshold sensitivity and categorization of emotional expressions, and examining the effects of alcohol dose and expectancy. The effect of alcohol dose on the processing of facial cues in male and female social drinkers was also examined. Both studies were funded by the Alcohol Education and Research Council (AERC)

Method: Study 1 (n = 100) was a between-subjects balanced placebo design, in which participants attended one session (0.0 or 0.4 g/kg alcohol) and were randomly allocated to one of four groups; received alcohol/told alcohol, received alcohol/told placebo, received placebo/told alcohol, received placebo/told placebo. A psychophysical task in which two faces were presented for each trial (neutral vs emotional) was employed, and participants were required to identify the emotional face. This task enables identification of perceptual sensitivity to small changes in facial emotional expressions. Sad, happy and angry emotional expressions were tested in male and female target faces. Study 2 (n = 96) employed a similar design to Study 1 however a miscategorisation task was used. A target face was presented consisting of a morph between two emotional exemplars (e.g., happy and angry face) and participants were asked to identify the emotion of the face (i.e., happy or angry). This task was run separately for angry-happy and angry-disgusted facial morphs. Results: : Data were analyzed within 2x2x2x2 mixed model ANOVAs with drink (alcohol, placebo), expectancy (told alcohol, told placebo) and participant sex (male, female) as between subject factors and target sex (male, female) as a within-subjects factor. Emotion was also included as a within-subjects factor compromising there levels for Study 1 (happy, angry, sad) and two levels for Study 2 (angry-happy, angry-disgusted).Study one revealed a near significant emotion by drink interaction ($F [2, 178] = 2.94$, $p = 0.055$), with higher thresholds after alcohol for sad, but not happy or angry, emotional expressions .Study two indicated a significant emotion x target sex x alcohol interaction ($F [1, 72] = 5.52$, $p = 0.02$), with participants showing a bias towards categorisation of disgusted faces as angry after alcohol but not after placebo consumption. There were no effects of alcohol on the angry-happy categorisation condition ($ps > 0.05$)

Conclusions: These data suggest that alcohol may differentially affect processing of different emotional expressions. In study one, after alcohol consumption, participants showed reduced sensitivity to recognising sad emotion in faces compared to placebo, but no effects were found for angry or happy emotions. Study two showed that alcohol may lead to individuals miscategorising negative (disgusted), but not positive (happy), faces as angry, which has implications for real world situations in which a negative facial expression may be erroneously perceived as provocative. However these miscategorisation effects were obtained in male, but not female, targets, possibly due to greater expectancy of alcohol-related aggression in men.

MD11

EFFECTS OF ALCOHOL ON FACIAL CUES OF ATTRACTIVENESS

Adams S, Parker L, Attwood AS, Penton-Voak IS, Munafò MR. Experimental Psychology, University of Bristol, 12a Priory Road, Bristol, BS8 1TU, sally.adams@bristol.ac.uk

A strongly held popular belief is that alcohol consumption increases the perceived attractiveness of members of the opposite sex. Despite this, there is remarkably little experimental data that investigate this possibility. We therefore explored the relationship between acute alcohol consumption and ratings of attractiveness of facial stimuli.

We included male and female participants (n = 84; 50% male), and male and female facial stimuli, in order to investigate possible sex differences, and in particular whether any effects of alcohol are selective to opposite-sex facial stimuli. Finally, we tested participants immediately following alcohol consumption and approximately one day later, in order to investigate whether any effects of alcohol consumption on ratings of facial attractiveness result in differences in the encoding of these stimuli beyond the acute effects of alcohol. In order to examine the effects of acute alcohol consumption on ratings of facial attractiveness and subjective mood, data were analyzed within a 2 × 2 × 2 mixed model repeated measures ANOVA framework, with drink (alcohol, placebo) and participant sex (male, female) as between-subjects factors. In order to test the effects of prior alcohol consumption on later ratings of facial attractiveness in the second test day, data were analyzed separately for ratings of male and female faces within a linear regression framework.

Our results indicate that alcohol consumption increases ratings of attractiveness of facial stimuli (F [1, 80] = 4.35, p = 0.040), and that this effect is not selective towards opposite-sex faces. We did not observe marked effects of alcohol consumption on other self-report measures of mood, suggesting that the effects on ratings of attractiveness were not due simply to global hedonic effects or reporting biases. In addition, our results also suggest that the effects of alcohol consumption on ratings of attractiveness persists for up to 24 hours after consumption, but only in male participants when rating female (i.e., opposite-sex) faces (B = +0.22, t = 2.02, p = 0.047). This effect appears to be due to the effects on ratings during the period of acute intoxication, suggesting an encoding effect on facial stimuli at the time of first rating, and was not observed among females. Research funded by the Alcohol Education and Research Council (AERC)

MD12

ACUTE EFFECTS OF ALCOHOL ON SPONTANEOUS MEMORIES

Bisby JA, Brewin CR, Curran HV. Sub-Department of Clinical Health Psychology, University College London, Gower Street, London, WC1E 6BT, j.bisby@ucl.ac.uk

Alcohol is frequently involved in real-life traumas such as violent crime and road traffic accidents. Despite this, virtually nothing is known of the interaction between alcohol, traumatic processing and trauma memory. A hallmark symptom of posttraumatic stress disorder is the repeated intrusive imagery of the traumatic event that is both vivid and rich in sensory detail. Dual representation theory (Brewin, 2001, Behaviour Research and Therapy, 39, 373–393) proposes that a trauma is processed in two distinct memory systems: verbally accessible memories forming an individual's verbal reports of the event and situationally accessible memories primarily consisting of visuo-spatial information in the form of images, which may be re-experienced spontaneously in the form of emotion-laden flashbacks. Based upon robust evidence that alcohol impairs episodic memory (e.g., Curran & Hildebrandt, 1999, Consciousness and Cognition, 8, 497-509), we hypothesised that alcohol would reduce conscious encoding of a traumatic event and thus lead to decreased encoding in the verbal accessible memory system and a subsequent overrepresentation in the situation accessible memory system, seen in increased flashbacks or memory intrusions.

Utilising an independent group, double-blind design, 48 healthy volunteers were randomly allocated to receive alcohol 0.4 g/kg or 0.8 g/kg or a matched placebo drink. A stressful film paradigm (Holmes et al., 2004, Journal of Experimental Psychology: General, 133, 3-22) was studied 40 minutes post-drink with heart rate and skin conductance being monitored throughout. Mood and dissociative symptoms were also indexed. Volunteers recorded their spontaneous intrusive memories of the film daily over the following week and their explicit memory for both gist and details of the film clips was tested on day 7.

Preliminary analyses showed the expected dose-related impairments of episodic memory for details and suggest differential effects of alcohol on memory for items encoded under differing levels of physiological arousal. Our findings will be discussed in relation to alcohol's effect on both memory intrusions and explicit trauma memory as well as in terms of dual representation theory. This study was carried out as part of a PhD funded by the ESRC.

MD13

STUDENT'S ALCOHOL CONSUMPTION AND STUDY PERFORMANCE

Verster JC, van Herwijnen J, Wiers RW. Psychopharmacology, Utrecht University, PoBox 80082, 3508TB Utrecht, The Netherlands, j.c.verster@uu.nl

A negative relationship between alcohol consumption and study performance has been shown in several American studies. Increased alcohol consumption showed to be related to poor study outcomes among US students. European data on this relationship is scarce. This study examined the influence of alcohol use and misuse on two Dutch student samples.

Two surveys were conducted among Dutch university students in the cities Nijmegen and Utrecht (N=1356). Weekly alcoholic consumptions were recorded and the number of study credit points they earned over the past year. Students were divided into different drinking groups (0, 0-20, 21-40 and over 40 weekly alcoholic drinks) and number of study credit points were compared using ANOVA. In addition, the correlation between weekly drinks and number of study credit points was computed. 1135 surveys were eligible for statistical analysis.

The drinking groups differed significantly on number of credit points ($p<0.0001$). Paired comparisons showed no significant difference between non-drinkers and those who consumed less than 21 alcoholic drinks a week. The other groups differed significantly from the non-drinkers ($p<0.01$). The differences between the heavy drinking groups were also significant, with the heaviest drinking group showing the poorest study outcomes ($p<0.01$). A significant negative correlation was found between the number of weekly alcoholic drinks and the earned study credit points ($r = - 0.243$, $p< 0.0001$).

Alcohol consumption is negatively associated with study performance. Future studies should examine possible moderating factors and prevention should inform students about the negative relationship between drinking and study results.

This study was supported by internal funding.

MD14

EFFECTS OF ALCOHOL AND DUAL TASK INTERFERENCE ON PERFORMANCE IN THE DASS DRIVING SIMULATOR

Verster JC, Goorden M, Van Wieringen J-P, Wester AE, Olivier B, Volkerts ER. Psychopharmacology, Utrecht University, PoBox 80082, 3508TB Utrecht, The Netherlands, j.c.verster@uu.nl

Alcohol use negatively impacts driving ability and increases the risk for traffic accidents. Driver distraction is one of the most common reasons for accidents on the road. In this study we examined the effects of 4 different dosages of alcohol and placebo on driving performance, with and with performance of a secondary peripheral search task. Sixteen men and sixteen women participated in this randomised, single-blind crossover trial.

All subjects received alcohol to reach a BAC of 0.02%, 0.05%, 0.08%, and 0.10%, or alcohol-placebo. Then a 30 minutes drive in the Divided Attention Steering Simulator (DASS) was performed. Primary outcome measure is the standard deviation of the car from the centre of the road (steering error, SDLP). Sixteen of the subjects also performed the test while conducting a secondary visual search task. Subjects had to respond by button press if to digits appearing in the corners of the computer screen. Data were analyzed using GLM for repeated measures with the factor BAC (5 levels) as within-subjects variable and the factor TASK (2 levels) as between-subjects variable. Dose-dependent SDLP increments were found on the driving task ($p<0.0001$). Performance at all BAC levels differed significantly ($p<0.05$) from alcohol-placebo, except 0.02% BAC. Driving performance was significantly worse when subjects performed the secondary task ($p<0.05$). With increasing BAC levels, subjects made significantly more errors on the peripheral visual search task ($p<0.05$).

These findings confirm that with increasing blood alcohol concentration driving performance becomes worse. Also, when performing a secondary task, attention is divided between the driving task and secondary task, resulting in poorer driving performance.

This study was supported by internal funding.

MD15

ALCOHOL INCREASES RISK TAKING BEHAVIOUR AND IMPAIRS COGNITIVE PERFORMANCE IN YOUNG SOCIAL DRINKERS

Scaife JC, Duka T. Psychology, Univ of Sussex, Pevensey 1, Falmer, j.scaife@sussex.ac.uk

Alcohol given acutely is known to impair planning and decision making (Weissenborn & Duka, 2003). The present study aimed at examining further the acute effects of alcohol in two tasks from the CANTAB battery: The Cambridge Gambling Task (CGT), a task assessing risk-taking behaviour and the Intra-Extra Dimensional Set Shift (IED Shift), a task that challenges shift of attention and discrimination ability of subjects.

64 (32 males) young social drinkers [average age 22 (stdev 3.84)], participated in the study and were randomly allocated to receive alcohol (0.8 g/kg) or placebo. The two groups were matched for gender, age & IQ as measured by the National Adult Reading Test (NART). Alcohol increased risk taking behaviour in the gambling task with participants betting more under alcohol in situations when the size of bet offered to them was increasing ($p<0.05$) or decreasing ($p=0.005$) with time. When the odds of winning were even, subjects under alcohol also made larger bets compared to placebo treated subjects ($p<0.01$).

In the IED shift subjects under alcohol were impaired in discrimination performance when reward contingencies were reversed [(i.e. reversal following intradimensional and extradimensional shift performance ($p<0.05$)]. When binge pattern of drinking was taken into account, an interaction was found between binge group and beverage (alcohol versus placebo), in the reversal phase of IED task; bingers were impaired more in the presence of alcohol than non-bingers ($p<0.05$).

These results demonstrate that alcohol increases risk taking and impairs performance in a reversal task. Furthermore these data show that pattern of drinking interacts with the effects of alcohol on cognitive flexibility, with binge drinkers being more impaired by alcohol.

This study was supported by Medical Research Council Grant; MRC G0400568

MD16

THE EFFECT OF 'BINGE DRINKING' ON HUMAN PAVLOVIAN TO INSTRUMENTAL TRANSFER

Trick LV, Duka T. Department of Psychology, University of Sussex, Pevensey Building, Falmer, Brighton BN1 9QH, l.trick@sussex.ac.uk

A human Pavlovian to instrumental transfer (PIT) task has been developed (Trick et al., 2007. *Journal of Psychopharmacology*, **21**(7): A50) which demonstrates that conditioned stimuli augment the rate of an avoidance response to the extent that they predict an aversive outcome during Pavlovian training. The current study sought to investigate whether binge drinking is related to impairments in PIT.

Thirty-eight male and female participants (mean age 20 years) were selected on the basis of 'binge drinking' scores. Twenty-one were classified as 'binge drinkers' and 17 were 'non-binge drinkers'. All participants underwent Pavlovian training in which three visual stimuli predicted the occurrence of an aversive noise with a 90%, 50% or 10% probability, respectively. Then, in separate instrumental training participants acquired an instrumental avoidance response that functioned to cancel the aversive noise. Finally, in the transfer phase the Pavlovian stimuli were presented in the instrumental context to determine if they would transfer control over the rate of the instrumental avoidance response. Expectancy ratings of the aversive noise following the stimuli and rates of avoidance response were the main variables.

A mixed ANOVA with stimulus as within and binge group as between factors showed that while expectancy ratings (of the aversive noise) were significantly different ($F(2, 72)=83.248$, $p<0.001$) for each of the three visual stimuli in the expected direction (90%>50%>10%; $p<0.001$ in each case) there was no difference in ratings made by binge drinkers compared to non-binge drinkers ($F(1, 36)=1.071$, $p>0.05$). In terms of the magnitude of avoidance response, a significant stimulus effect ($F(2, 72)=4.327$, $p<0.05$) was found with the instrumental avoidance response being significantly greater in the presence of the 90% contingent ($p<0.05$) and 50% contingent ($p<0.05$) stimuli compared with the 10% contingent stimuli. In addition, there was a significant stimulus by binge group interaction ($F(1, 72)=3.382$, $p<0.05$). When the binge and the non-binge groups were separately analysed a stimulus effect was found only for the binge group ($F(2, 40)=5.017$, $p<0.05$).

These results suggest that conditioned stimuli which differentially predict an outcome control the rate of an avoidance response more in binge drinkers compared to non-binge drinkers, although binge drinkers do not differ from non-binge drinkers in their expectancy of the aversive event.

Acknowledgements: This work was supported by MRC Grant G0400568.

ME01

EFFECTS OF MODAFINIL ON MEASURES OF ALERTNESS AND PSYCHOMOTOR FUNCTIONS IN MULTIPLE SCLEROSIS

Szabadi E, Niepel G, Vilisaar J, Langley RW, Constantinescu C, Bradshaw CM. Psychiatry, University of Nottingham, Queen's Medical Centre, Nottingham, NG7 2UH, elemer.szabadi@nottingham.ac.uk

One of the most troublesome symptoms of multiple sclerosis (MS) is fatigue (Racke et. al., 2004, Arch Neurol, 61: 176-177). The wakefulness-promoting drug modafinil has been reported to alleviate MS fatigue (Rammohan et. al., 2002, J Neurol Neurosurg Psychiatry, 72:179-183). However, fatigue in MS patients may be contaminated with excessive daytime sleepiness (EDS) (Attarian et. al., 2004, Arch Neurol, 61: 525-528), and modafinil's action may be selective for EDS. We examined the effects of a single dose of modafinil on measures of alertness and psychomotor functions in MS patients.

Three groups of subjects (age [mean ± SD]: 43.7 ± 10.8 years) matched for age, were recruited: 1. MS patients with prominent complaints of fatigue (identified by the Fatigue Assessment Instrument and the Fatigue Severity Score) (17: 12 female, 5 male); 2. MS patients with no fatigue (9: 5 female and 4 male); 3. healthy control subjects (9: 5 female, 4 male). After an initial induction session, the subjects received, double-blind, a single dose (200 mg) of modafinil in one session and placebo in another session; the order of sessions was randomized. Tests included: subjective rating of alertness (Epworth Sleepiness Scale, Stanford Sleepiness Scale, battery of Visual Analogue Scales [VAS]), instrumental measurement of alertness (Critical Flicker Fusion Frequency [CFFF], Pupillographic Sleepiness Test [PST]), psychomotor tests (choice reaction time [CRT], digit cancellation time, speech pause time). Measurements were taken before and two hours after treatment. Data were analysed with ANOVA with multiple comparisons (least significant difference test); criterion $p<0.05$.

Comparison of the three groups prior to treatment revealed that Group 1 was less alert than Group 3 on the Epworth and Stanford scales, on VAS and CFFF, and displayed elongated motor response times on the CRT. There was no difference between the three groups on the amount of pupillary fatigue waves recorded by the PST; these waves were reduced by modafinil. Modafinil also increased CFFF and reduced motor response time in the CRT; these effects were present in all three groups.

These results show that MS patients with fatigue, selected upon the basis of clinical interviews and established fatigue assessment scales, show evidence of reduced alertness and impaired psychomotor functions. These impairments were not present in MS patients who did not complain of fatigue. The single dose of modafinil showed some alerting effects and improved psychomotor performance; however, this effect was not restricted to the MS fatigue group.

Supported by Cephalon.

ME02

PERCEPTION OF DRUG TREATMENT IN PATIENTS WITH CHRONIC INSOMNIA

Wilson SJ, Green A, Hicks J, Nutt DJ. Psychopharmacology, University of Bristol, Whitson St, Bristol BS1 3NY, sue.wilson@bris.ac.uk

NICE guidance on the treatment of insomnia (NICE 2004) called for research on the best ways to provide information to sufferers. The main aim of this study was to evaluate patients' perceptions of the information they had received about insomnia and about the treatment they had been given, using a questionnaire.

We sent the questionnaire to 157 patients with chronic insomnia who had been referred to a specialist sleep clinic (a psychiatric clinic specialising in anxiety, mood disorders and sleep problems such as insomnia and parasomnias). Group T comprised 91 patients who had completed an insomnia group treatment programme, which included education about sleep science and medication, sleep hygiene and strategies to improve sleep, and cognitive-behavioural treatment (CBT). Group C was 66 patients who had attended the sleep clinic in a similar period and were eligible for the psychological treatment but had been unable to attend. We report here only answers to questions about medications and attitudes toward treatment.

Fifty-one completed questionnaires were returned by course participants (T) (56%) and 17 by attenders at clinic (C) (26%), an overall response rate of 43%. 88% of patients were currently taking regular sleep medication or had tried it in the past. Of these 87% (T 90%, C 80%) said their medication helped them sleep, 80% (T 86%, C 63%) said it helped them feel better in the daytime and 73% (T 79%, C 53%) said it helped them to do more in the day. When asked if they were nervous about taking medication for a long time, 30% said they were, with a lower incidence of nervousness in the group who had received psychological treatment (T 22%, C 53%). Overall, 41% said they were satisfied with treatment, 31% neither satisfied nor dissatisfied and 27% dissatisfied. Free text (qualitative) data will also be presented. When asked about alternative and complementary therapies, 88% said they had tried them and of these 8% reported that they helped a great deal, 39% said they helped a little or for a short time and 52% said they did not help at all.

This small study provides data about the perceptions of patients with chronic insomnia in the UK. Patients reported marked beneficial effects of medication on daytime function, although there may be a responder bias.

ME03

COMPARISON OF BETAHISTINE AND DIPHENYDRAMINE ON ALERTNESS AND AUTONOMIC FUNCTIONS IN HEALTHY VOLUNTEERS

Baqui Q, Banjar WMA, Gazzaz J, Hou RH, Langley RW, Szabadi E, Bradshaw CM. Psychiatry, University of Nottingham, Queen's Medical Centre, Nottingham NG7 2UH, mcxqb@nottingham.ac.uk

The central histaminergic neurones located in the tuberomamillary nucleus of the hypothalamus play an important role in the regulation of arousal (Szabadi 2006, Br J Clin Pharmacol, 61, 761-766) and autonomic functions (Brown et al. 2001, Prog Neurobiol 63, 637-672), the activation of excitatory H1 histamine receptors leading to both alerting and sympathomimetic effects. Central histaminergic effects can be enhanced by H3 histamine receptor antagonists blocking release-inhibiting receptors on histaminergic nerve terminals (Passani et al. 2004, TIPS, 25, 618-625). Betahistine, an H1 receptor agonist with H3 receptor antagonistic property (Fossati et al. 2001, Pharmacol Res, 43, 389-392), has been shown recently to exert weak alerting effects in healthy volunteers (Vermeeren et al. 2006, J Psychopharmacol 20, A31). We compared the effects of betahistine with those of diphenhydramine, an H1 receptor antagonist with documented sedative and sympatholytic effects (Hou et al. 2007, J Psychopharmacol 21, 567-578) on alertness and autonomic functions.

16 healthy male volunteers participated in four experimental sessions at weekly intervals according to a double-blind, balanced design. Each session included the oral administration of one of four treatments: betahistine 64 mg, diphenhydramine 75 mg, betahistine 64 mg + diphenhydramine 75 mg, placebo. Betahistine was administered 1 hour and diphenhydramine 2 hours prior to testing. Alertness was measured using critical flicker fusion frequency (CFFF), visual analogue scales (VAS), and the Pupillographic Sleepiness Test (PST), a measure of pupil fluctuations in darkness. Resting pupil diameter at different luminance levels was recorded using binocular infrared television pupillometry. Non-pupillary autonomic functions (blood pressure, heart rate, core temperature, and salivation) were recorded conventionally. Repeated-measures ANOVA with multiple comparisons (criterion $p<0.05$) were used to analyse the data.

Diphenhydramine, and the combination of diphenhydramine and betahistine, showed sedative effects, as indicated by the subjective ratings of alertness and lowering of CFFF. Diphenhydramine also reduced resting pupil diameter in darkness and at the three increasing luminance levels tested, and salivation. Betahistine did not have any effects on alertness and autonomic functions.The present results confirm previous reports of the sedative and autonomic effects of diphenhydramine. The reduction in pupil diameter indicates a sympatholytic effect and the reduction in salivation the additional anticholinergic property of the drug. We did not detect any effect of betahistine tested at the expected peak plasma level of the drug.

Funded internally (Psychopharmacology Laboratory, University of Nottingham).

ME04

PRELIMINARY INVESTIGATIONS OF THE USE OF AROMATHERAPY FOR TREATING MILD TO MODERATE INSOMNIA

Alford C, Austin L, Bachel T, Bulbrooke E, Taylor E, Lewith G. Psychology, University of the West of England (UWE Bristol), Coldharbour Lane, Bristol BS16 1QY, Chris.Alford@uwe.ac.uk

Introduction: A local survey indicated CAM treatments for insomnia were more popular than prescription hypnotics, leading to a series of preliminary studies investigating aromatherapy essential oils.
Methods: Studies employed single-blind crossover designs, re-analysed blind, with balanced treatment order and washout periods (up to 1 week), with self-declared insomniacs (estimated sleep latency of more than 30mins. or less than 6.5 hours sleep with Pittsburgh Sleep Quality index: PSQI or similar). Treatments were 3 drops (0.15ml) of essential oil self-administered to bedclothes at home for 2 nights, with actigraphy (CNT) and subjective scales assessing mood and sleep (e.g. Leeds Sleep Evaluation Questionnaire: LSEQ, PSQI, VAS). Almond oil is believed to lack treatment effects and was used as placebo. The first study compared lavender to jasmine (stimulant) and almond oil in 12 females, 50-59 years, the others employed mixed sex groups of 10 or 12 participants, 19-53 years, comparing geranium and bergamot respectively to almond oil together with a no treatment control to investigate possible placebo effects, including extended treatment of 2 weeks geranium or almond in a fourth study. A recent study investigated the use of lemon balm (1 drop) in a mixed sex group of 12 older insomniacs 50-73 years.
Results: Anova determined overall significant effects ($P<0.05$ or better) followed by 2-tailed paired comparisons for data re-analysed blind. Significant findings included some placebo effects (almond oil) contrasting with the no treatment control, generally reflecting trends for longer sleep, less waking and reduced fragmentation with actigraphy and improved subjective sleep. Some further improvements (% difference) were seen with active treatments producing significant placebo contrasts including greater actigraphy sleep time (8.4 %) with lavender, improved perceived sleep onset (25%) and quality (32%). Improved, but marginal for geranium, sleep onset (geranium 45%), actual sleep time (bergamot 8% and geranium 14%) and reduced fragmentation (bergamot 38%, extended geranium 43%) recorded with actigraphy, supported by improved perceived sleep onset (bergamot 18% and geranium 9%) though no morning hangover and improved mood reflecting better alertness/arousal after bergamot 33% and geranium 13%.
Conclusions: Placebo effects were seen with both subjective and objective measures reflecting expectancy, and only limited further improvements were seen for lemon balm with older participants. However, increased sleep time seen with acute administration for the other 3 essential oils against placebo and supported by subjective measures, suggests aromatherapy may be a useful treatment in mild to moderate insomnia and provide an alternative to prescription hypnotics.

ME05

CLOMIPRAMINE ENHANCES MOOD AND MELATONIN LEVELS IN NORMAL SUBJECTS

Carvalho LA, Franco DG, Gentil V, Gorenstein C, Markus RP. Pharmacology, Universidade de Sao Paulo, Rua do Matão, travessa 14 sala 323, CEP 05508-900, São Paulo - SP Brazil, l.carvalho@iop.kcl.ac.uk

Previous work from our group has shown that antidepressants increase the pineal hormone, melatonin, in depressed patients. Moreover, the effect of antidepressants on melatonin does not occur after placebo, despite similar clinical improvement. To further understand the effect of antidepressants on melatonin, we have evaluated the major melatonin urinary metabolite, 6-sulphatoxymelatonin (aMT6s) and mood in healthy subjects before, one day and 21 days after administration of clomipramine (10-40 mg/day).
Thirty four healthy subjects were selected and mood evaluated by two independent psychiatrists blind to the treatment. A qualitative approach using semi-structured interview was used to evaluate mood, and response categorized as sustained changes in 3 out of 4 subjective domains: 1) interpersonal tolerance, 2) efficiency (improved decision making, ability to prioritize demands, and self-confidence), 3) wellbeing, and 4) feeling substantially changed from usual self. aMT6s was measured by Bulhmann ELISA kit in total 24h urine and in four 6h samples (06–12, 12–18, 18–24, 24–06 h). The data was expressed in ng/mg creatinine. Mean age was 33.0 ± 6.3 years, and weight 63.5 ± 8.3 Kg. First, we used the mixed models analysis to test whether there an influence of treatment day (day 0, day 1 and day 21) and time (6h intervals) on aMT6s. We found a significant overall effect ($F(1,411) = 243.2$, $P \leq 0.0005$) and a significant effect of time ($F(3,411) = 47.7$, $P \leq 0.005$). To further analyse the data, we compared 24h aMT6s before and after 1 and 21 days of clomipramine. Compared to the baseline (day 0), clomipramine increased 24h aMT6s since the first day of treatment; however, the increase only reached significance on day 21 (day 0 51.0±6.7, day 1 66.0±11.0, day 21 70.0±12.0, paired t-test, $p\leq0.05$). Finally, clomipramine improved the mood of 13 out of 34 subjects. Baseline 24h aMT6s did not differ between responders and non responders (responders 12.0±3.3, non responders 13.0±1.9, $p>0.05$). Only in responders, however, clomipramine increased peak (24-06h) aMT6s after 1 day of treatment (day 0 2.1 ±0.2, day 1 2.5± 0.1, paired t test, one tail); an effect that returned to baseline on day 21 (day 21 2.1±0.2, $p>0.05$).
In conclusion, melatonin predicts mood improvement after 1 day of clomipramine. This data might be relevant for the mechanism of action of antidepressants. Financial Support: FAPESP/CNPq/CAPES.

ME06

MORNING CORTISOL RESPONSE IN PATIENTS WITH PARASOMNIAS AND INSOMNIA

Wilson SJ, Dickens R, Jessop D, Lightman S, Nutt D. Psychopharmacology, University of Bristol, Whitson St, Bristol BS1 3NY, sue.wilson@bris.ac.uk

Primary insomnia is associated with a disturbance of the HPA axis as demonstrated by the awakening salivary cortisol response (ACR). Cortisol levels are low during the night in normal subjects and rise when the subject gets up. Cortisol immediately after awakening has been reported to be significantly decreased in primary insomnia and correlated negatively with the subjective estimation of sleep quality. Patients with parasomnias experience a high level of distress from their sleep disturbance; however cortisol regulation has never been studied in these patients. The purpose of this study was to compare awakening cortisol responses in patients with parasomnias with those in insomnia and normal controls and relate this to sleep disturbance that night.
Methods: 7 patients with primary insomnia, 9 patients with parasomnias (2 sleepwalkers, 6 night terrors, 1 REM sleep behaviour disorder), and 15 age and sex matched controls took part. Subjects completed baseline questionnaires concerning sleep disturbance, anxiety, depression and general health and gave 2 saliva samples, the first immediately on waking and the second 30 minutes later, together with subjective ratings of the night's sleep including description of dreams. Parasomnia patients followed this procedure on 2 mornings, one after a 'bad' night with an episode of parasomnia, the other on a relatively good night. Salivary cortisol was measured by radioimmunoassay.
Results: Baseline questionnaire measures showed significantly higher ratings of anxiety and sleep disturbance (in both sleep disorder groups compared with controls, and the insomnia group had significantly higher depression ratings. Absolute levels of cortisol were higher in both sleep disordered groups than in controls but there was no significant difference. Insomnia patients and parasomnia patients on 'good' nights had similar ACR slopes to controls, but there was a variable response on parasomnia 'bad' nights with some patients having a fall rather than a rise after waking. Initial cortisol levels were significantly positively correlated with decreased subjective measures of sleep quality ($p=0.02$). Reported early waking was significantly correlated with a decreased ACR ($p=0.011$). Cortisol levels on awakening showed higher variability in those subjects reporting anxiety dreams or episodes of night terrors during the night.
Conclusions: We demonstrated a significant relationship between cortisol levels and subjective measures of poor sleep quality and early awakening. Occurrence of episodes of parasomnia was associated with cortisol response unlike that of controls.

ME07

SLEEP STAGES AND AUTOMATIC OVERNIGHT CORTISOL SAMPLING

Wilson SJ, Phillips S, Lightman S, Nutt DJ. Psychopharmacology, University of Bristol, Whitson St, Bristol BS1 3NY, sue.wilson@bris.ac.uk

Sleep and the hypothalamic-pituitary-adrenal (HPA) axis have a complicated relationship that is the subject of much research. Plasma cortisol is the end point which is often used to investigate the HPA axis response to stressful stimuli. An automated blood sampling machine has been used at Bristol University in the investigation of the rat HPA axis for a number of years (Windle et al 1997) and the technology is now developed so that automated sampling can be carried out in humans. A peristaltic pump is linked to a computer and fraction collector designed to enable the collection of multiple small samples of blood at specified time points over a long period of time i.e. 24 hours. The objective of this study was to pilot the use of automatic blood sampling overnight synchronized with polysomnography in 6 normal subjects, to assess the minute by minute effect of sleep stage on cortisol measures, and to compare plasma cortisol and salivary cortisol on awakening

Methods: Six healthy volunteers slept in the sleep laboratory, five overnight and one during the afternoon after partial sleep deprivation the previous night. They were prepared for polysomnography (PSG) and had an indwelling cannula connected 'through the wall' to the sampling machine. Blood samples (1ml) were taken every 10 minutes, synchronised with the PSG recording. On waking, a saliva sample was taken and another 30 minutes later with the subject still in bed. Blood and saliva samples were later assayed for cortisol concentration using radioimmunoassay. Sleep was scored using R&K criteria and the cortisol levels were related to different sleep stages.

Results: Cortisol levels fell during the first few hours of sleep and then showed a rise independent of sleep stage about halfway through the night, consistent with the literature. In addition, both awakenings and REM sleep tended to increase cortisol level. An increase in cortisol similar to but smaller than that seen in the normal wakening response could be found after waking periods during sleep or periods of REM sleep, particularly towards the end of the night. Rise in cortisol after waking was similar in magnitude to previously reported values in spite of the subjects remaining in bed.

Conclusions: The automatic sampling method was reliable and effective in obtaining frequent cortisol samples without interfering with sleep. There was evidence of both circadian and sleep-stage-dependent regulation of night-time cortisol level.

ME08

ACTIGRAPHIC ASSESSMENT OF CIRCADIAN RHYTHMS IN ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Coogan AN, Baird AL, Forbes-Robertson S, Siddiqui A, Thome J. Neuroscience and Molecular Psychiatry,
Institute of Life Science, Swansea University, Singleton Park, Swansea SA2 8PP, asiddiqui@hotmail.com

Introduction: ADHD is one of the most frequent disorders in child and adolescent psychiatry, with a prevalence estimated at about 3.5%. Symptoms associated with ADHD in adults include attentional difficulties, motor hyperactivity, impulsivity and sleep disturbance. Recent genetic evidence has indicated a putative role for the circadian clock in adult ADHD. In this study we have used actigraphy to assess measures of circadian rhythmicity in adult ADHD.

Methods: Patients (n=9) attending an adult ADHD outpatient clinic were recruited for this study, as were age-matched controls (n=17) who also underwent screening for ADHD. Informed consent was received from all participants. Subjects were asked to wear an ActiWatch (Cambridge Neurotechnology, UK) on the non-dominant wrist for a period of between 7 and 14 days. Data was collected in 30 second bins, and analysed off-line. Data on light-exposure was also captured on the ActiWatch, as light is the dominant Zeitgeber for the mammalian circadian system. Statistical significance was assessed by the Mann-Whitney U test, with $p<0.05$ considered significant.

Results: Adult ADHD subjects exhibited significant changes in a number of circadian parameters. The peak correlation on the chi-squared periodogram was significantly shorter (23.6 ± 0.14h ADHD vs. 23.97 ± 0.05h control, $p<0.05$). The relative amplitude of the rhythm, that is the activity during the least active 5 hours (L5) and the most-active 10 hours (M10), was also significantly weakened (0.85 ± 0.02 for ADHD vs. 0.9 ± 0.01 control, $p<0.05$), and L5 was higher in ADHD (1995 ± 557 ADHD vs. 1185 ± 184 control, $p<0.05$). There were no statistically significant changes in other circadian parameters (intradaily variability, interdaily stability, M10, onset of M10, onset of L5, amplitude, acrophase), nor in the average or maximum light exposure between ADHD and control groups.

Conclusion: These data support the contention that ADHD in adults is associated with significant pertubations of the circadian timekeeping system.

We acknowledge financial support from the Welsh Office for Research and Development (WORD) and Swansea NHS trust.

ME09

INFECTION WITH TOXOPLASMA GONDII ALTERS CIRCADIAN CLOCK GENE EXPRESSION IN CORTICAL AND SUB-CORTICAL STRUCTURES OF THE MOUSE BRAIN

Coogan AN, Wyse C, Guy E, Mack D, Thome J. Neuroscience and Molecular Psychiatry, Institute of Life Science, Swansea University, Singleton Park, Swansea SA2 8PP, a.coogan@swan.ac.uk

Introduction: Disturbances to circadian rhythms such as the sleep-wake cycle and body temperature rhythm are common to a number of infective and inflammatory diseases, and these changes may be mediated by alterations in clock gene expression in the brain. Alterations in circadian timekeeping processes may contribute to the syndrome of sickness behaviour and other behavioural alterations induced during infections. The aim of this study was to investigate the effect of *Toxoplasma gondii* infection on the expression of the core clock gene proteins, Per1, Per2, and Clock in the cortical and subcortical structures of the mouse brain that have been implicated in circadian timekeeping. *T. gondii* infection has been linked with increased incidence of schizophrenia as well as behavioural changes in humans and animal models. It is possible that some of these behavioural effects are due to perturbations of the circadian timing system.

Methods: Male MF-1 mice were infected with *T. gondii* (RH strain) via intraperitoneal injection. On the morning of the third day post-infection animals were sampled one hour after lights on and the brains removed and fixed in paraformaldehyde. Immunohistochemistry was used to quantify the expression of Per1, Per2 and Clock in brain sections from mice infected with *T. gondii* ($n = 13$) and control mice ($n = 11$). Statistical significance was assessed with one-way ANOVA, with $p<0.05$ considered significant.

Results: The expression of Per1 protein, as measured by densitometry of immunostaining, was increased in the piriform cortex, cingulate cortex and medial habenula of infected mice compared with control animals sampled at the same time (piriform cortex 25 ± 0.81 vs. 38 ± 1.07, $p <0.05$; cingulate cortex 22 ± 0.63 and 32 ± 0.76, $p<0.05$; medial habenula 22 ± 0.54 versus 49 ± 1.46, $p<0.05$; all control vs. *T.gondii*). While expression of Per1 tended to be higher in infected animals than in control animals in the baslolateral amgydala, dentate gyrus and CA1 region of the hippocampus, this was not statistically significant. In contrast, there was no effect of infection on the expression of Per2 in any region of the brain. Clock protein showed significantly lower expression in *T.gondii* infected animals in the cingulate cortex (33 ± 0.27 control vs.26 ± 0.46 *T.gondii*, $p < 0.01$) and in the piriform cortex (41 ± 0.63 control vs. 32 ± 0.23 *T.gondii* , $p<0.05$).

Conclusion: Alterations of circadian timekeeping in these cortical and sub-cortical areas may represent a novel mechanism by which *T.gondii* infection may influence behaviour. Disruption of circadian timekeeping has been implicated in a number of psychiatric conditions, including bipolar disorder and schizophrenia, as well as having strong implications for sleep. Thus, these data indicate a putative link between *T.gondii* infection and behavioural changes/psychiatric illness via the circadian timekeeping system. We acknowledge financial support from Research into Ageing.

ME10

CHRONIC HALOPERIDOL TREATMENT ALTERS THE EXPRESSION OF CLOCK GENES IN THE HIPPOCAMPUS AND CEREBRAL CORTEX OF MICE

Coogan AN, Clemens CI, Zacchariou V, Thome J. Neuroscience and Molecular Psychiatry, Institute of Life Science, Swansea University, Singleton Park, Swansea SA2 8PP, a.coogan@swan.ac.uk

Introduction: Circadian clocks underlie a host of physiological oscillations that occur with periods of approximately twenty four hours. The molecular mechanisms that underpin these rhythms are known to consist of a number of clock genes and their protein products. Recently, genetic and animal studies have implicated the circadian clock in regulation of the dopaminergic system and implicated circadian dysfunction in a number of psychiatric conditions. To further examine this, we examined the effects of the typical antipsychotic haloperidol on clock gene expression in the mouse brain.
Methods: Male C57 Bl/6 mice were dosed with intraperitoeneal injections of haloperidol (1mg/kg), or saline (n=6), either acutely for 1 day (n=6), or chronically for 14 days (n=5). Animals were then sampled and the brains removed and fixed for immunohistochemistry. Primary antisera raised against the clock gene products Per1, Per2 and Bmal1 were used to probe expression, which was quantitated using densitometric analysis.
Results: One-way ANOVA revealed a main effect of drug treatment on Per1, but not Per2 and Bmal1 expression, in the CA1 ($p< 0.02$) and CA3 ($p<0.01$) of the hippocampus, and the cingulate cortex ($p<0.05$), but not in the striatum or the dentate gyrus. Post-hoc analysis by Tukey HSD test reveals a significant effect of chronic, but not acute, haloperidol treatment on Per1 expression in the cingulate, CA1 and CA3. Chronic haloperidol downregulated Per1-immunoreactivity in these regions (30.5 ± 1.5 vs. 18.9 ± 2.7 for CA1, 22.1 ± 1.4 vs. 12.9 ± 1.9 for CA3 and 13.7 ± 2.01 vs. 7.9 ± 0.5 for cingulate; saline vs. chronic haloperidol).
Conclusions: These results provide further evidence that modulation of circadian timekeeping processes may be involved in antipsychotic action, either in terms of their therapeutic mechanism or in terms of their side-effects such as insomnia.

MF01

SUPRA-FORMULARY DOSED SSRI IN A UK OCD CLINIC: A SYSTEMATIC CASE-NOTES STUDY

Pampaloni I, Sivakumaran T, Al Allaq A, Farrow J, Nelson S, Fineberg NA. National OCD Specialist Service (England and Wales), Queen Elizabeth II Hospital, Howlands, Welwyn Garden City (AL7 4HQ), ilepampa@libero.it

Introduction: Selective serotonin re-uptake inhibitors (SSRIs) are the main pharmacological treatments for OCD, however the treatment-response is characteristically partial. Increasing their dose above that recommended in the Summary of Product Characteristics (SPC) is a promising treatment-strategy. Positive results from two small double-blind trials of high-dose escitalopram (Rabinowitz et al 2008. Int. Clin.Psychopharmacol.2008 Jan;23(1):49-53) and sertraline (Ninan et al 2006. J. Clin. Psychiatry.Jan;67(1):15-22) hint at short-term efficacy in resistant OCD. Longer term clinical data is lacking. We report a systematic, retrospective case-note survey of a specialist OCD outpatient service including a high proportion of treatment-resistant cases to explore the frequency of 'high-dose' SSRI-prescribing and evaluate clinical outcomes over a sustained period in a naturalistic clinical setting.
Method: Case-notes of all clinic-attenders in September 2007 were reviewed. 'High-dose' was defined as SSRI monotherapy above UK SPC limits or maximum doses of one SSRI plus another SSRI or clomipramine.Patients receiving high-doses were compared on clinical ratings with a matched group of non high-dose 'control' cases at referral, initiation of high-dose (or matched equivalent time-period) and last assessment.
Results: Of 192 cases, 26(13.54%) were receiving high-doses. The duration ranged from 3-364 weeks (mean 77.4; SD±94.7).At referral, there were no statistically significant differences between the two groups in illness-duration, age of onset, presence of tics, depression or Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores. In contrast, high-dose patients were significantly more likely to be male [$X2(1,N=52)=3.91,p=.048$] and to have received CBT [$X2(1,N=48)=4.83,p=.028$]. All high-dose patients failed to respond to twelve weeks SSRI prior to dose escalation. Y-BOCS scores were significantly higher in the high-dose group than controls both at dose escalation (median 25 vs. 19.5; Mann-Whitney U=134, p=0.0009) and endpoint (median 20 vs. 16; Mann-Whitney U=168, p=0.025), indicating enduring treatment-resistance.Y-BOCS scores significantly improved following high-dose treatment (Wilcoxon Z = -2.199, p = 0.028). Frequency of adverse effects (reported in15 high-dose cases) did not significantly differ between the two groups and were not considered serious apart from one individual briefly admitted to hospital with an unexplained, self-limited illness.
Conclusion: 26 patients received sustained treatment with supra-formulary dosed SSRI. Patients receiving high doses were more likely to be male and showed greater enduring illness severity. High-dose SSRI was well-tolerated and associated with symptomatic improvement, though other factors may have contributed. Clinical response was poor compared to non high-dose treated counterparts. Further controlled studies are indicated to evaluate the role of high-dose SSRI in OCD.
No financial sponsorship was provided

MF02

FUNCTIONAL IMPAIRMENT ASSESSMENT SCALE, COMPULSIONS AND OBSESSIONS (FIASCO-13) - A 13 ITEM SCALE FOR EVALUATING FUNCTIONAL IMPAIRMENT ASSOCIATED WITH OCD: PRELIMINARY EVALUATION OF VALIDITY, RELIABILITY AND CLINICAL UTILITY

Johansen T, Dittrich WH, Fineberg NA. Psychology, University of Hertfordshire, College Lane, Hatfield, AL10 9AB, t.johansen@herts.ac.uk

Obsessive-compulsive disorder (OCD) is a disabling neuro-psychiatric disorder. Translational research has identified specific areas of neurocognitive impairment in the laboratory setting, though it remains unclear how far these impairments contribute to the clinical manifestation of the disorder. The Functional Impairment Assessment Scale, Obsessions and Compulsions (FIASCO) was designed as a novel instrument to comprehensively assess the clinical impact of symptoms, as an extension to the neurocognitive impairment found in the laboratory setting, on patients with OCD.
Initially 18 items (each scoring 0-6) were selected based upon observation in the neurocognitive and clinical research setting. The prototype was refined to a definitive 13-item scale after excluding 5 items that did not meet satisfactory statistical criteria. In a study involving two raters, 50 patients diagnosed with OCD at various levels of severity were assessed using both the self-rated and observer-rated versions of the new scale, as well as a battery of standard OCD and depression rating instruments for comparison.
OCD patients' scores fell in the region of moderate severity on both observer and self-rated versions of the refined FIASCO-13. Inter-rater reliability scores between observers ($r=.99$) and between each observer and the self-rated scales ($r= .91, .92$) and Cronbach's alpha (observer-rated=.92, self-rated = .93), indicated satisfactory reliability and internal consistency. Pearson correlation coefficients between individual items of FIASCO-13 with its total were satisfactory. Results also showed satisfactory correlations with standard comparator instruments including the Clinical Global Impression (severity) ($p<.001$) and the Yale-Brown Obsessive Compulsive Scale ($p<.001$). Discriminant analysis using a one-way ANOVA revealed significantly higher scores in the OCD group compared to a depression group matched at a similar level of syndrome intensity (n=31) and a healthy control group (n=55) ($p<.001$). The observer and self-rated versions of the 13-item FIASCO scale appear valid and reliable instruments for measuring the severity of clinical impairment associated with OCD including neurocognitive components of the disorder.
Further validation, including research into the relationship of the FIASCO-13 with laboratory measures of cognitive impairment and evaluation of its sensitivity to change with treatment, is indicated.
No external funding was sought for this study.

MF03

SELECTIVE SEROTONIN REUPTAKE INHIBITOR-REMITTED PATIENTS WITH GENERALISED ANXIETY DISORDER DO NOT SHOW AN INCREASE IN SYMPTOMS FOLLOWING ACUTE TRYPTOPHAN DEPLETION

Hince DA, Hood SD, Robinson H, Rich A, Potokar J, Davies SJC, Argyropoulos S, Nash J, Morris K, Potter J, Forward S, Morris L, Nutt DJ. Psychiatry and Clinical Neuroscience, University of Western Australia, 35 Stirling Hwy, Nedlands, Perth, 6009, dana.hince@uwa.edu.au

Selective serotonin reuptake inhibitors (SSRIs) are effective treatments for all DSM-IV defined anxiety disorders. Acute tryptophan depletion (ATD) is a dietary technique that transiently reduces plasma tryptophan levels, and brain serotonin synthesis. ATD increases the likelihood of a recurrence of anxiety-related symptoms in SSRI-remitted individuals with Panic Disorder (Bell et al., J Psychopharmacol. 2002;16(1):5-14) and Social Anxiety Disorder (Argyropoulos et al., Biol Psychiatry. 2004;1;56(7):503-9), following a disorder-specific provocation. This is consistent with the hypothesis that synaptic serotonin availability is important for SSRI efficacy. It is not known whether this is also the case for Generalised Anxiety Disorder (GAD). The effect of ATD on anxiety symptoms is most robustly shown when paired with a disorder-specific provocation. Inhalation of 7.5% CO2 induces symptoms in volunteers that are similar to that seen in generalised anxiety (Bailey et al., Depress Anxiety. 2005;21(1):18-25), and these responses are attenuated following 21 day treatment with paroxetine (Bailey et al., J Psychopharmacol. 2007;21(1):42-9).
We combined 7.5% CO2 inhalation and ATD to assess the effect of reduced serotonin availability in SSRI-remitted GAD SSRI–remitted patients with DSM-IV diagnosed GAD (n = 13; 6 males) were included in the study. Participants were tested twice separated by at least one week. On one occasion, an amino acid drink not containing tryptophan was consumed (depletion day). A similar drink, additionally containing tryptophan was taken on the alternate (control) day. The order of depletion was randomised and double-blind. Five hours post-drink, participants inhaled either 7.5% CO2 or air for 12-20 min, followed by the other gas. Gas order was only known to the researcher. Psychological responses were measured using the Spielberger State Anxiety Inventory (SSAI) and GAD-symptom Visual Analogue Scales (VASs) (worry, tension). Difference score data (baseline - CO2 or air scores) were analysed using repeated measures ANOVA.
Inhalation of 7.5% CO2 significantly increased SSAI ($p<0.01$), VAS-worry ($p<0.01$), and VAS-tense ($p<0.001$) compared with air, irrespective of depletion condition. ATD did not alter the response to challenge on these measures (depletion x challenge interaction, all $F<1$) despite the substantial reduction in free tryptophan: large neutral amino acid ratio (depletion day: - 94% v control day: + 6%).
Although SSRIs effectively treat GAD, these results suggest the mechanism of action is different to that in Panic and Social Anxiety Disorders. Successful SSRI treatment of GAD may involve long term receptor changes or alterations in other neurotransmitter systems downstream of serotonin.
Funding: Raine Medical Research Foundation Priming Grant, Perth and Wellcome Trust Project Grant, Bristol.

MF04

PRELIMINARY EVIDENCE OF EFFICACY OF A CRF1 RECEPTOR ANTAGONIST IN THE 7.5% CO2 MODEL OF ANXIETY

Bailey JE, Papadopoulos A, Diaper A, Phillips S, Schmidt M, van der Ark P, Nutt DJ. Psychopharmacology Unit, University of Bristol, Whitson Street, Bristol BS1 3NY, jayne.bailey@bristol.ac.uk

Introduction: We have validated the use of inhalation of 7.5% carbon dioxide (CO2) as a human model of anxiety and have shown that benzodiazepines and a serotonin reuptake inhibitor attenuate CO2-induced symptoms (Bailey et al 2007, Journal of Psychopharmacology21(1): 42-49). Preclinical evidence suggests that drugs acting at the corticotropin releasing factor (CRF) system may be useful for the treatment of depression, anxiety, and other stress related disorders (Valdez 2006, CNS Drugs 20(11): 887-896.), hence we have now examined the effects of a CRF1 receptor antagonist in the 7.5% CO2 model.
Methods: In a double-blind, placebo-controlled, randomised study in 32 healthy participants we examined the effects of 7 days treatment with a CRF1 receptor antagonist at a dose that shows a favourable safety profile and is comparable to those effective in preclinical models. On Day 8, eight of the placebo-treated group received lorazepam 2mg as a positive control. All volunteers underwent a 20 minute inhalation of 7.5% CO2. Subjective reports of peak gas effects were assessed using visual analogue scales and questionnaires.
Results: Mean age of subjects was 26 years, 13 were male. The peak effects of CO2 were expressed as a difference from baseline. Both drug groups when compared with placebo showed a decrease in all subjective symptoms, total score on the Panic Symptom Inventory (CRF 11 [2.6], PLAC 16.4 [3.1], LZP 2.9 [3.0]) and a GAD symptom scale (CRF 2.2 [1.5], PLAC 8.2 [2.2], LZP 1.1 [1.5]).
Conclusion: We have shown that a drug that acts to inhibit the CRF1 receptor shows efficacy in the 7.5% model of anxiety in healthy participants.
This study was sponsored by Johnson and Johnson.

MF05

A SINGLE DOSE OF MIRTAZAPINE DECREASES FEAR RECOGNITION IN HEALTHY SUBJECTS

Arnone D[1,3] Horder J[1], Cowen PJ[1], Harmer CJ[1,2] [1]Dept of Psychiatry, Oxford Univ, Warneford Hospital, Oxford, UK [2]Dept of Experimental Psychology, Oxford Univ, Oxford, UK [3]Current Address: Neuroscience and Psychiatry Unit, University of Manchester, Manchester. danilo.arnone@manchester.ac.uk

Introduction Acute administration of selective serotonin and noradrenalin re-uptake blockers to healthy volunteers produces positive biases in the processing of emotional information. Mirtazapine is a clinically established antidepressant with complex pharmacological actions involving blockade of a variety of monoamine receptors. The aim of the present study was to test the effect of acute mirtazapine administration on a number of models of emotional processing.
Methods Thirty healthy volunteers were recruited in the study. Thirty subjects received either a single dose of mirtazapine (15mg) or placebo in a parallel group, double-blind experiment. Subjective mood and experience was assessed throughout the test day and performance on a battery of emotional processing tasks (facial expression recognition, emotional categorisation and memory and emotion potentiated startle responses) was assessed 2 hours after drug administration. Statistical analysis was performed using analysis of variance with group and emotion as factors.
Results Volunteers receiving mirtazapine were significantly worse at recognizing fearful facial expressions compared to the placebo group ($p<.05$) and showed reduced startle responses in the emotion potentiated startle task ($p <.05$). Volunteers receiving mirtazapine were also quicker to respond to emotional self-relevant information in a categorisation task ($p<.05$) and showed a positive bias in memory recall compared to those receiving placebo ($p<0.05$).
Conclusion The findings from this report suggest that mirtazapine reduces fear processing in healthy volunteers, similar to effects seen with repeated SSRI administration. Consistent with this, mirtzapine also increased memory for positive self-relevant information. Such effects may be important for our understanding of how antidepressants work in both anxiety disorders and depression.
Source of funding: This study was supported by the MRC.

MF06

POTENTIATED STARTLE RESPONSE TO EMOTIONAL EXPRESSIONS IN SOCIAL ANXIETY

Baldwin DS, Garner M, Clarke G, Graystone HJ. University Department of Mental Health, RSH Hospital, University of Southampton, Brintons Terrace, Southampton, SO14 0YG, D.S.Baldwin@soton.ac.uk

Fear-potentiated startle refers to the augmentation of eye-blink startle responses under fearful and anxiety provoking conditions, such as fear conditioning, threatening contexts, and emotional stimulus processing. Neurocognitive models of social phobia suggest that dysfunction of the brain's primary fear network promotes the perceptions of threat and the social-evaluative concerns reported by socially anxious individuals. Previous studies have demonstrated elevated eye-blink startle in social anxiety in response to social threat words, imagined social scenarios, and anticipation of giving a speech. However, it is unknown whether the social cues typically encountered in feared social situations (e.g. emotional facial expressions) potentiate fear responses in socially anxious individuals.

Participants were selected according to scores on established self-report measures of social anxiety. 18 high socially anxious individuals (HSA; 14 females, 4 males; mean age = 24.39 yrs) and 19 low socially anxious individuals (LSA; 13 females, 6 males; mean age = 22.47 yrs) viewed a variety of static and dynamic 4 second clips depicting negative, positive and neutral social cues within a head-mounted visual display unit. Eye blink responses to auditory startle probes presented 3 seconds after picture onset were measured, along with skin conductance responses and explicit ratings. Startle response amplitude was defined as the difference in amplitude between the mean EMG in the 50 ms prior to the startle response, and the maximum EMG response between 20 ms and 250 ms after startle probe presentation. Skin conductance responses were defined as the maximum response occurring between 1 and 4 s after picture onset minus the mean baseline response during the 1 s prior to picture onset. Data were analyzed using mixed design analysis of variance.

HSA individuals had larger startle response magnitudes for emotional (positive and negative) social cues relative to neutral social cues, compared to LSA individuals, $p < .05$. Analysis of skin conductance measures showed that HSA individuals experienced greater arousal when viewing social cues, compared to LSA individuals, $p < .05$. The groups did not differ on baseline measures of startle reactivity or skin conductance. In addition HSA individuals explicitly rated all social cues less positively than LSA individuals, $p < .05$.

Results are discussed with reference to neurocognitive models that emphasize the role of sub-cortical stimulus appraisal mechanisms in fear and anxiety, and convergent evidence from neuroimaging. Implications for research into the neural and cognitive bases of emotion processing in anxiety are considered.

Funding: none to declare.

MF07

FACIAL EXPRESSION RECOGNITION IN SOCIAL PHOBIA

Bell C, Bourke C, Colhoun H, Carter F, Porter R. Psychological Medicine, Christchurch School of Medicine and Health Sciences, University of Otago, 4, Oxford Terrace, Christchurch, New Zealand, caroline.bell@otago.ac.nz

Introduction: Most cognitive models of social phobia suggest that people with social phobia are more likely to interpret social signals as threatening. Findings from studies investigating Facial expression Recognition (FER) in social phobia have not been consistent but have tended to suggest a negative interpretation bias towards threat related emotional stimuli. The aim of the present study was to investigate whether people with social phobia showed differences in accuracy and the speed of processing facial expressions, or biases in judgement of facial expressions compared with healthy controls. We hypothesised that the social phobia group would show an attentional bias towards threat relevant stimuli, specifically expressions of anger, disgust or fear. This would result in an increased speed in response and increased accuracy in recognition of these expressions. We also hypothesised that patients with social phobia would show a bias towards identifying more ambiguous expressions as being threatening rather than neutral.

Method: The study included 30 patients with social phobia (20 medication free) recruited through an article in the newspaper and 27 matched healthy controls. The FER task featured six basic emotions – happiness, sadness, surprise, fear, anger and disgust morphed between each prototype and neutral. Subjects made their responses by pressing a labeled key on a response box and were asked to respond as quickly and accurately as possible. Outcome measures included general accuracy, emotion specific accuracy, error bias, and response latency. Ratings of anxiety and mood were completed.

Statistics: Neuropsychological data were analysed using ANOVA with social phobia as a fixed factor. Main effects and the interaction between them were examined.

Results: No significant differences were found between the social phobia group and healthy controls on measures of accuracy of identifying specific emotions or reaction times.

Analysis of the error bias on the neutral facial expressions showed the social phobia group were significantly more likely to interpret neutral expressions as anger ($p=0.003$).

Conclusion: This study suggests that people with social phobia people are able to correctly identify facial expressions in others, but when the facial expression is ambiguous they are more likely to judge this as threatening (anger).

Funding for this study was a project grant from the Canterbury Medical Research Foundation, Christchurch, New Zealand.

MF08

EEG PREDICTORS OF RESPONSE TO SSRI TREATMENT OF PANIC DISORDER

Oros MM, Yevtushenko OO. Clinic "Vodolij", Pachovs'kogo str., 14, Khust, 90400 Ukraine, mihoros@meta.ua

Introduction Panic disorder is serious debilitating condition with a lifetime prevalence up to 5% (Roy-Byrne et al. Lancet 2006; 368:1023-1032). SSRIs demonstrate effectiveness in treating this disorder, although not all patients show benefit; some do not respond adequately, while others may develop adverse reactions. Some studies suggest quantitative EEG (qEEG) as an aid to clinical diagnosis and prediction of medication response (Knott et al. Psychiatry Res. 1996;68:31-39; Coburn et al. J Neuropsychiatry Clin Neurosci 2006;18:460-500) in patients with neuropsychiatric pathologies. We investigated association of qEEG with symptom response to SSRI treatment in patients with panic disorder.

Methods 108 patients, age 36.5±11.2 years, with a diagnosis of panic disorder took part in study. Clinical investigation which included general neurological investigation, qEEG, assessment according to the Hospital Anxiety and Depression Scale (HADS; Russian translation), CGI and panic attack frequency (per month) were assessed before and after SSRI treatment. Patients received sertraline (n=79) or paroxetine (n=29) 25mg/day for 6 days, followed by 50mg/day for 1 month. In every qEEG the predominating rhythm was identified. Normal qEEG was described as organized in time and zones, with domination of zonal differentiated alpha-rhythm with occipito-frontal gradient of EEG parameters and average amplitude 25-55 microV.

Results Before treatment 57% patients exhibited qEEG characterized by high amplitude 50-100 microV synchronized, monorhythmic, asymmetric alpha rhythm predominantly in right hemisphere with activation of right reticular-thalamic and septo-hippocampal zones. These patients showed the greatest improvement in HADS compared to those exhibiting other qEEG dominant rhythms before treatment (13.55±7.90 vs.9.16±7.86 for those with domination of desynchronized beta rhythm, slow disorganized theta or delta rhythms, or low amplitude beta rhythm with pathological epileptic patterns, $p=0.006$) This remained true for anxiety (8.02±5.38 vs. 5.36±4.93, $p=0.011$) and depression (5.56±3.45 vs. 4.02±4.01, $p=0.037$) subscale scores. Patients who showed improvement in qEEG to normal rhythm after treatment exhibited significant clinical improvement – decrease in frequency of panic attacks (6.83±5.90 vs. 2.25±5.58, $p=0.000$) and HADS change (17.00±6.40 vs. 6.45±6.02, $p=0.000$) as well as CGI scale change (1.55±1.15 vs. 0.65±1.57, $p=0.001$). Patients who had dominant theta and delta rhythms or low amplitude beta rhythm with pathological epileptic patterns of qEEG before treatment did not show significant improvement in changes in clinical symptoms or qEEG subtypes.

Conclusions These results indicate that qEEG subgrouping is associated with symptom severity in SSRI-treated patients with panic disorder and may also have predictive value in determining response to treatment with SSRIs in these patients.

MF09

GENETIC PREDICTORS OF RESPONSE TO SSRI IN TREATMENT OF PANIC DISORDER

Yevtushenko OO, Oros MM, Reynolds GP. Department of Neuropharmacology, Institute of Pharmacology and Toxicology AMS Ukraine, Eugene Potie str., 14, Kyiv 03057 Ukraine, o.yevtushenko@qub.ac.uk

Introduction Panic disorder is a chronic and disabling condition with a lifetime prevalence up to 5% (Roy-Byrne et al. Lancet 2006; 368:1023-1032). SSRIs demonstrate effectiveness in treating this disorder, although not all patients show benefit; some do not respond adequately, while others may develop adverse reactions. Pharmacogenetic studies have shown genotyping to have substantial potential in predicting efficacy of clinically prescribed drugs. We investigated the association of polymorphisms in two candidate genes (-1019 C/G 5-HT1A receptor and 44bp ins/del 5-HT transporter) with symptom response to SSRI treatment in patients with panic disorder.

Methods 108 patients, average age 36.5±11.2 years, with a diagnosis of panic disorder took part in study. Hospital Anxiety and Depression Scale (HADS; Russian translation) score, CGI and panic attack frequency (per month) were assessed before and after on month of SSRI treatment. Patients received sertraline (n=79) or paroxetine (n=29) 25mg/day for 6 days, followed by 50mg/day. All patients were genotyped for the two polymorphisms.

Results Following treatment panic attack frequency decreased significantly (9.38±6.81 before treatment, 4.79±6.25 after treatment, p=0.000, n=107). There was no association of the -1019C/G 5-HT1A polymorphism with frequency of panic attacks before treatment, but a significant effect on frequency after treatment (GG: 7.70 ±6.28 vs. CC: 3.29± 5.61 vs. CG: 4.66 ±6.38, p=0.04), in which GG subjects showed no improvement in attack frequency (change in attack frequency: GG: 0.25 ±2.83 vs. CC: 6.35± 6.75 vs. CG: 5.09 ±6.75, p=0.001). There was no significant association of 5-HT1A genotype with the total HADS score before treatment (p=0.98), but after treatment GG carriers exhibited significantly higher HADS score (GG: 20.40 ±6.52 vs. CC: 13.62± 7.91 vs. CG: 13.17 ±7.52, p=0.001). The change in HADS score with treatment showed highly significant association, in which patients with the GG genotype had substantially smaller changes (GG: 6.30 ±6.85 vs. CC: 12.18± 8.15 vs. CG: 13.30 ±7.76, p=0.003). The pharmacogenetic effect was apparent in both the anxiety and depression subscales. There was no association with CGI score before treatment, but the effect on CGI score change with treatment was significant; GG carriers again exhibited the smallest change (GG: 0.35±0.99 vs. CG: 1.11±1.45 vs. CC: 1.59±1.48; p=0.008). There was no significant association of the ins/del 5HT transporter polymorphism with any of the studied criteria.

Conclusion These results indicate that the 5-HT1A receptor gene -1019 C/G promoter region polymorphism could have predictive value in response to SSRIs in patients with panic disorder.

MF10

THE ANTI-OBESITY AGENT, SIBUTRAMINE, IS DEVOID OF ANXIOLYTIC-LIKE ACTIVITY IN THE MOUSE ELEVATED PLUS-MAZE

Rodgers RJ, Mumford RA, Storer NK. Institute of Psychological Sciences, University of Leeds, Woodhouse Lane, Leeds LS2 9JT, r.j.rodgers@leeds.ac.uk

The anti-obesity agent, sibutramine, is a dual noradrenaline (NA) and serotonin (5-HT) reuptake inhibitor (Luque & Rey, 2002, *Eur J Pharmacol*, 440: 119-128). Its ability to induce weight loss appears to depend upon indirect agonism of a1-, b1-, and 5-HT2A/2C receptors (e.g. Jackson et al., 1997, *Br J Pharmacol* 121: 1613-1618). Although acute treatment with other monoamine reuptake inhibitors (& direct 5-HT2C receptor agonists) generally increases anxiety-like behaviour in rodents (Millan, 2003, *Prog Neurobiol*, 70: 83-244), acute sibutramine (5-20 mg/kg) has recently been found to reduce measures of anxiety in the rat elevated T-maze and light/dark transition tests but not in the rat elevated plus-maze (Jorge et al., 2004, *Pharmacol Res*, 50, 517-522). In view of this unusual profile, we have examined the acute behavioural effects of sibutramine in the mouse elevated plus-maze test. Subjects were adult male BKW albino mice (Bantin & Kingman, Hull, UK) housed 10/cage under a 12h reversed LD cycle. All testing was performed under dim red illumination during the dark phase. Mice were randomly assigned to 5 conditions (n=8): vehicle, positive control (chlordiazepoxide HCl, 15 mg/kg; Sigma-Aldrich UK), 1.25, 2.5 or 5.0 mg/kg sibutramine HCl (Tocris UK). Drugs were dissolved in physiological saline and administered IP (10 ml/kg) 30 min prior to testing. Using well-established methods (e.g. Rodgers et al., 2006, *Psychopharmacology*, 187: 345-355), mice were tested (5 min) in an order counterbalanced for treatment condition. Videotaped tests were scored blind to drug condition and data analysed by parametric or non-parametric one-way analyses of variance. Post-hoc analyses revealed that the significant treatment effects on most recorded behaviours ($F4,35 \geq 2,71$, $p \leq 0.05$; $H\ (4, N=40) \geq 15.05$, $p \leq 0.005$) were due largely to CDP, which reduced ($p \leq 0.05$) all conventional measures of anxiety-related behaviour, as well as % mid time and % protected head-dipping. Although CDP concurrently increased total and closed arm entries (i.e. locomotor activity), analyses of covariance confirmed that effects on anxiety-related parameters remained statistically significant when closed arm entry data were used as covariate. The singular significant effect of sibutramine comprised an increase in closed arm entries at 2.5 mg/kg ($p < 0.05$).

Consistent with the findings of Jorge et al (2004) in rats, sibutramine was largely devoid of behavioural activity in the mouse elevated plus-maze test; if anything, higher doses produced trends towards anxiogenesis. The apparent test-specificity of acute sibutramine anxiolysis is clearly worthy of further investigation.

MF11

PHARMACOLOGICAL CHARACTERISATION OF GR73632 (NK1 RECEPTOR AGONIST) MEDIATED BEHAVIOURS IN THE MONGOLIAN GERBIL

Hill MDW, Woolley M, Murkitt G, Keerie A, Lucas A, Anderson GW, Gunthorpe J, dela Flor R, Bull S, Carter H, Bradford A, Jones DNC, Dawson LA in vivo biology, Glaxosmithkline, Third Ave, Harlow; CM19 5AW, mark.d.hill@gsk.com

Introduction: Central tachykinin receptors have been implicated as targets for potential therapeutics for a number of psychiatric disorders. The aim of these studies were to determine the effect of selective neurokinin antagonists NK_1, NK_2, & NK_3 on NK_1 receptor agonist driven gerbil behaviours in an attempt to increase understanding of central NK_1 receptor pharmacology. We investigated the effects of the selective NK_1 receptor antagonists GR205171A & MK869, upon GR73632 (NK_1 receptor agonist) induced hind limb foot tapping (FT) behaviour in gerbils. Furthermore, in the case of GR205171, we attempted to correlate the temporal profile of efficacy with receptor occupancy (RO) and compound exposure. Finally using selective NK_2 (GR159897A) and NK_3 (GSK172981A) receptor antagonists we assessed the selectivity of this reputed NK_1 receptor agonists driven behaviour.

Methods: Male mongolian gerbils (n=8-10 per dose group) were pre-treated with compound of interest or vehicle. Following a suitable pre-treatment time (ptt) animals were anaesthetised and 5µl of 3pmol concentration (0.46 µg/ml) GR73632 was injected directly into the lateral ventricle (ICV dosing). Upon recovery they were placed individually into clear observation boxes and the duration of repetitive hind foot tapping was recorded for 5 min. Terminal blood and brain samples were obtained from all experiments for drug measurements. For evaluation of the temporal efficacy of GR205171 ptt of 1, 24, 48 & 72 hours were used and parallel RO evaluations were performed (n=4 per group). FT data were analysed by Kruskal-Wallis followed by Dunns planned comparisons using Statistica V6.

Results: GR205171A (0.1-1mg/kg; po; 60min ptt) significantly inhibited GR73632 induced FT in a dose dependant manner reaching significance at 1mg/kg ($P<0.01$; RO>85%), however this dose failed to inhibit FT at any other ptt tested. MK869 (0.3-3mg/kg; po; ptt 1 h) also significantly inhibited FT in a dose dependant manner being significant at all doses tested 0.3mg/kg ($P<0.05$) 1 & 3mg/kg ($P<0.01$). Neither GR159897A nor GSK172981A (3, 10 & 30 mg/kg ip; ptt 1 h) had any effect on FT. Despite this, terminal blood and brain samples indicated that all compounds achieved the expected efficacious exposure levels.

Conclusion: Gerbil foot tapping behaviour, following central administration of the NK_1 receptor agonist GR73632, proved to be a robust behavioural readout. These data indicate good RO and FT correlation with a lack of prolonged activity for GR205171A, and confirm that GR73632-induced gerbil foot tapping behaviour is likely to be mediated solely by NK_1 receptors.

MG01

COMPARISON OF FLUOXETINE AND VENLAFAXINE CONFIRMS PREDICTIVE VALIDITY OF ANIMALS MODELS OF ANXIETY AND DEPRESSION

Royo NC, Castagné V, Porsolt RD, Moser P CNS Pharmacology, Porsolt & Partners, Paris, France, nroyo@porsolt.com

Selective serotonin reuptake inhibitors (SSRI) and mixed serotonin norepinephrine inhibitors (SNRI) have become part of the first-line treatment for depression and anxiety disorders. Their arrival therefore allows us to re-evaluate animal models that were initially identified and validated using older less selective agents. Using the modified version of the rat behavioural despair test, it has been shown that SSRI and SNRI have different profiles of activity (Cryan et al 2005). Here we investigated this further by comparing fluoxetine (SSRI) and venlafaxine (SNRI) in a battery of simple tests for anxiety and depression. For all tests, comparisons were considered significant for $p<0.05$ (Student's t-test). In the behavioural despair test, venlafaxine showed slightly greater efficacy than fluoxetine in both rats (n=6) and mice (n=10) over the dose range 16-64 mg/kg i.p. The test appeared more sensitive in the mouse than the rat. At 64 mg/kg, immobility was significantly reduced by both substances in both species (49 to 100% inhibition), although motor signs, excitation and aggressive behaviour were also observed. Similarly, venlafaxine (8-64 mg/kg i.p.) displayed greater efficacy than fluoxetine at reducing immobility in the tail suspension test in mice (95% and 46% inhibition at 64 mg/kg respectively; both effects $p<0.001$). In the elevated plus-maze test (n=10), venlafaxine (8-64 mg/kg i.p.) had no activity in the rat whereas it increased the time spent on the open arms in mice (+653% at 64 mg/kg, $p<0.01$). Fluoxetine (8-32 mg/kg i.p.) had no clear anxiolytic activity in either species. In the gerbil, however, fluoxetine (8-64 mg/kg i.p.) increased open arm exploration (+34% at 16 mg/kg, $p<0.01$, n=12) whereas venlafaxine (8-64 mg/kg i.p.) decreased exploration of the open arms (-26% at 64 mg/kg, $p<0.05$). In the marble burying test (n=12), both venlafaxine (1-32 mg/kg i.p.) and fluoxetine (1-32 mg/kg i.p.) completely abolished marble burying, although the result with fluoxetine was confounded by sedation at doses above 2 mg/kg. Finally, in the Vogel conflict test (n=10), venlafaxine and fluoxetine (8-32 mg/kg i.p.) both weakly but significantly increased punished drinking (maximum effects: 92% at 16 mg/kg and 69% increase at 8 mg/kg respectively). Altogether, these data confirm the antidepressant properties of venlafaxine and fluoxetine, and suggest signs of anxiolytic-like activity for both compounds. They also show that compared to venlafaxine, the preclinical efficacy profile of fluoxetine is less consistent. This corroborates clinical findings with SNRI and SSRI and suggests good predictive validity of animal models for anxiety and depression.

MG02

CHRONIC ROACCUTANE TREATMENT ALTERS SEROTONERGIC GENE EXPRESSION IN RAT RAPHE NUCLEI IN VIVO

Trent S, Bailey, SJ. Pharmacy & Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, s.trent@bath.ac.uk

Vitamin A and its derivatives (retinoids) play a host of roles in adult brain function (Lane & Bailey, 2005 Prog Neurobiol 75: 275). Roaccutane (13-*cis* retinoic acid, 13-*cis* RA) is a synthetic retinoid widely used for the treatment of severe cystic acne. However, its use is associated with adverse psychiatric events including depression, suicidal ideation and completed suicide (Hull & D'Arcy, 2003 , Am J Clin Dermatol 4:493). Previous work has shown that 13-*cis* RA induces depression-related behaviour in mice (O'Reilly et al, 2006, Neuropsychopharmacol 31: 1919) and increases the expression of the serotonin transporter (SERT) and the serotonin 1A receptor (5-HT1AR) protein *in vitro* (O'Reilly et al, 2007 Exp Biol Med 232: 1195). Retinoids mediate their effects by binding to nuclear retinoic acid receptors (RARs), which in turn regulate gene expression. The objective of this study was to determine whether chronic treatment with 13-*cis* RA *in vivo* alters the expression of the serotonergic genes tryptophan hydroxylase (TPH2), SERT and 5-HT1AR

Adult male Wistar rats were treated with either 1mg/kg 13-*cis* RA or 1ml/kg of vehicle (0.9% w/v saline:DMSO, 1:1 v/v) daily (ip) for 6 weeks (n=3 per group). At the end of treatment, brains were removed; the raphe nuclei dissected and total RNA extracted using Trizol. Expression of the genes of interest in rat raphe tissue and amplicon specificity were confirmed using one-step RT-PCR. Quantitative real-time RT-PCR with the threshold cycle method ($2^{-\Delta\Delta Ct}$) was used to determine the expression of the target gene mRNAs in treated raphe tissue relative to vehicle treated controls. In each case, gene expression was normalized to that of a housekeeping gene (rRNA).

RARα and the dopamine D2 receptor were used as positive controls and expression in treated animals increased by 7.8 fold (± 4.5) and 27.1 fold (± 22.5) respectively. Although the expression of the 5-HT1AR was not changed (1.5 ± 0.6 fold) , the expression of SERT and TPH2 was significantly increased following 13-*cis* RA administration (6.4 ± 2.9 and 43.4 ± 24.3 fold respectively).

Here we report for the first time a marked increase in the expression of TPH2 and SERT in rat raphe tissue following chronic 13-*cis* RA administration. Altered expression of TPH2 and SERT has been reported in depressed patients. The changes we see with 13-*cis* RA treatment may reflect pro-depressive changes in serotonergic neurotransmission.

ST is funded by a BBSRC studentship.

MG03

TRYPTOPHAN AND KYNURENINE METABOLISM IN YOUNG ADULTS WITH A POSITIVE FAMILY HISTORY OF DEPRESSION

Badawy AA-B[1], Alhaj HA[2], Jervis V[3], Selman M[3] and McAllister-Williams RH[2]. [1]The Cardiff School of Health Sci, Univ of Wales Inst Cardiff, Western Avenue, Cardiff, [2]Psychobiology and [3]Clinical Psychology, Inst of Neuroscience, Newcastle Univ, UK abadawy@uwic.ac.uk

In our pilot study on tryptophan depletion in healthy young adults with a positive family history (FH+ve) of depression, we found baseline free tryptophan (Trp) levels higher than literature values for healthy adults with no family history of psychiatric illness. To explore this further, we compared plasma Trp and kynurenine levels before and after a Trp load in this FH+ve group and a separately recruited cohort with a negative family history (FH-ve) of depression. Sixteen healthy young adults with at least one first degree relative with a history of major depression (assessed using an adaptation of the Family History Research Diagnostic Criteria) were recruited (age - 21.4 ± 2.0 years; 1 male). A second cohort of healthy FH-ve individuals was separately recruited in the United States [age: 27.3 ± 5.4 years (n=12), 5 males]. In both cohorts, fasting blood samples were taken before and 5h after a 1.15g Trp load given in the balanced control formulation for the acute Trp depletion test. Ultrafiltrates were analysed for free Trp fluorimetrically and whole plasma for total Trp, kynurenine and other metabolites of the kynurenine pathway by HPLC. Control and test data (means ± SD) were compared by one-way ANOVA with replicated measures and covaried for effects of age and gender. At baseline, free Trp was significantly ($P= 0.0001$) higher in the FH+ve cohort (7.5 ± 1.4 vs 4.7 ± 0.7 μM) but there was no significant difference in plasma total Trp (38.0 ± 8.8 vs 43.5 ± 9.2 μM), kynurenine, total kynurenines, or the kynurenine(s)/total Trp ratios. Kynurenine(s), as a ratio of free Trp, were 44-48% lower in the FH+ve group ($P= 0.0046$-0.0001), consistent with a lower level of Trp oxidation. After Trp loading, the FH+ve group accumulated less kynurenine(s) than the FH-ve subjects, also consistent with a lower rate of Trp oxidation. Although these findings are tentative, given that the cohorts were not matched, they suggest a lower rate of Trp oxidation in FH+ve subjects. Possible explanations include this being a defensive mechanism aimed at conserving Trp availability to the brain to maintain higher levels of serotonin, or a reactivity response to the experimental procedure in FH+ve subjects. We thank Prof D M Dougherty (University of Texas Health Science Center at San Antonio, TX, USA) for permission to use data from his control subjects. AA-BB thanks the Wellcome Trust for equipment.

Study supported by NTW NHS Trust and Newcastle University.

MG04

LOW DOSE ACUTE TRYTOPHAN DEPLETION TO EXPLORE COGNITIVE VULNERABILITY IN HEALTHY ADULTS WITH A FAMILY HISTORY OF DEPRESSION

Selman M, Jervis V, Alhaj HA, Rodgers J, Barton S and McAllister-Williams RH Clinical Psychology, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne NE1 4LP, matthew_selman@yahoo.com

Acute tryptophan depletion (ATD) has been used to examine the role of the 5-HT system in depression by examining effects on mood and cognition in healthy subjects, recovered depressives and groups at risk of depression, such as those with a positive family history. Many ATD studies have used a 100g amino acid drink which brings about temporary depressive symptoms in recovered depressives and at risk subjects. However changes in mood may potentially confound changes in cognition. We have employed a 50g ATD drink with the intention of avoiding changes in mood to explore the interaction between biological and cognitive vulnerability in at risk individuals. In particular we explored the role of 5-HT in two memory processes possibly associated with vulnerability or maintenance of depression, autobiographical memory and affective working memory. It was hypothesised that ATD would impair working memory and reduce the specificity of autobiographical memory. Nineteen healthy young adults with at least one first degree relative with a history of a major depression (assessed using the Family History Research Diagnostic Criteria) were recruited (age - 21.4 ± 2.0 years; 1 male). ATD drinks containing 1.15g of tryptophan (T+) or not (T-) were administered on two separate occasions, in a double blind crossover design. The Autobiographical Memory Test (AMT) was administered together with a variant of the n-back task testing interpersonal–affective working memory 5 hours after drink administration. ANOVA revealed a significant difference in the effects of ATD drinks on plasma free tryptophan (T- 72% decrease from baseline; T+ 10%; $p < 0.001$). There was no mood change with either drink (assessed with HDRS and POMS). Contrary to the hypotheses there was no within subject main effect of ATD on either memory task. However, there was a main effect of order of T+/T- drink administration. Exploratory analysis of visit 1 data indicated a large between subject effect ($d = 1.36$) of ATD on AMT with T- associated with less specificity in response to negative cue words ($F(1, 17) = 8.71$, $p = 0.009$). Overgeneralisation of AMT is viewed as a potential cognitive vulnerability to depression.

The current findings suggest that this may be 5-HT dependent and may illustrate a mechanism through which a biological vulnerability (altered 5-HT function) can result in a cognitive vulnerability. However this conclusion awaits replication of the study including subjects not at risk of depression.

Study supported by NTW NHS Trust and Newcastle University.

MG05

THE EFFECT OF ACUTE TRYPTOPHAN DEPLETION ON THE NEURAL CORRELATES OF EMOTIONAL PROCESSING IN UNMEDICATED PATIENTS RECOVERED FROM DEPRESSION

Roiser JP, Levy J, Fromm S, Nugent AC, Talagala T, Hasler SL, Henn FA, Sahakian BJ, Drevets WC. Institute of Cognitive Neuroscience, University College London, 17 Queen Square, London, j.roiser@ucl.ac.uk

Major depressive disorder (MDD) is associated with both serotonin dysfunction and abnormal responses to emotional stimuli. However, no study to date has compared the effects of temporarily reducing brain serotonin synthesis on neural and behavioural responses to emotional stimuli in patients recovered from depression and healthy volunteers.

Seventeen remitted MDD patients (rMDD) and 17 controls underwent acute tryptophan depletion in a within-subjects double-blind placebo-controlled design. The rMDD patients were medication-free and the healthy controls had no personal history of psychiatric illness and no first-degree relatives with mood or anxiety disorders. Following tryptophan or sham depletion, participants performed the Affective Go/No-go task (AGNG) during functional magnetic resonance imaging. Resting-state regional perfusion was measured using arterial spin labelling with whole-brain coverage in half the participants. Tryptophan depletion differentially affected the groups in terms of neural responses to emotional words in a number of structures implicated in the pathophysiology of MDD, including medial thalamus, caudate and putamen ($Z>3.09$, $p<0.001$). In general, BOLD responses to emotional stimuli were increased in these regions in the control group following tryptophan depletion, with either no effect or effects in the opposite direction in the rMDD group. Following tryptophan depletion, resting-state blood flow in the habenula increased in the rMDD patients specifically (treatment x group interaction: $F(1,19)=8.3$, $p=0.010$). Increasing amygdala blood flow was strongly associated with more negative emotional bias scores across both groups following tryptophan depletion ($r=0.75$, $p<0.0005$). However, there were no effects of tryptophan depletion on behaviour on the AGNG or subjective mood state in either group.

These data support the hypothesis that serotonergically-mediated dysfunction in limbic-cortical-striatal-thalamic circuits controlling responses to emotional stimuli is causally related to vulnerability to MDD. Additionally, we demonstrate for the first time a strong relationship between resting-state blood flow in the amygdala and emotional bias following tryptophan depletion, suggesting that the amygdala plays a causal role in mediating attentional biases towards negative material.

Funding: National Institute of Mental Health

MG06

ACUTE TRYPTOPHAN DEPLETION DISRUPTS POSITIVE COGNITIVE BIASES UNDER NEUTRAL MOOD BUT INDUCES THEM UNDER NEGATIVE MOOD

Robinson OJ, Crockett MJ, Sahakian BJ. Department of Psychiatry, Behavioural and Clinical Neuroscience Institute, University of Cambridge, Addenbrooke's Hospital, Cambridge, CB2 2QQ, ojr23@cam.ac.uk

Reduction of the monoamine serotonin (5-HT) via the dietary manipulation of tryptophan (acute tryptophan depletion; ATD) has long been shown to induce negative cognitive biases, similar to those found in depression, in healthy individuals. However it is emerging that under certain conditions 5-HT can also induce positive cognitive biases. Recent findings have demonstrated that ATD can induce positive biases in subjects with the 'l' allele of the 5-HT transporter gene (Roiser et al. 2006) and in a subjects in induced negative mood (Robinson and Sahakian 2008a). ATD has also been shown to provoke positive mood in currently depressed patients (Delgado et al. 1994). Here we test the hypothesis that mood state can mediate the effect of ATD using an established paradigm measuring affective cognitive biases. Neuropsychological testing (self-referent encoding/retrieval task; SRET) was preceded by the dietary serotonin manipulation, tryptophan depletion, and established mood manipulation in a double-blind, placebo-controlled crossover design (N=18). Statistical significance was determined using analysis of variance. There was a significant interaction between mood state, tryptophan-depletion, and word valence on the recall of self-referent words on the SRET ($F2,14=3.31$, $p=0.05$). Under neutral MIP (N=9) a bias was seen at baseline (BAL) ($F2,14=11.37$, $p=0.001$) towards increased recall of positive self-referent words relative to negative ($p=0.001$) and neutral words ($p=0.001$) (i.e. a positive cognitive bias). This bias was also present under ATD ($F2,14=6.64$, $p=0.009$; positive vs negative $p=0.015$, positive vs neutral $p=0.006$) but was significantly reduced ($F1,15=7.03$, $p=0.018$; positive recall at baseline vs positive recall following ATD, SED=-0.12 $p=0.018$). In female subjects the bias was completely abolished ($F2,8=1.23$, $p=0.34$; positive vs negative $p=0.41$, positive vs neutral $p=0.47$). In contrast, under negative MIP (N=9), a positive bias was absent at baseline ($F2,14=3.05$, $p= 0.08$; positive vs negative $p=0.074$, positive vs neutral $p=0.066$) but was subsequently induced by ATD ($F2,14=8.41$ $p=0.004$; positive vs negative $p=0.005$, positive vs neutral $p=0.002$) These data demonstrate dissociable effects of ATD on cognitive biases depending on mood state. Whilst ATD disrupted positive cognitive biases in subjects in a neutral mood, it induced positive cognitive biases in subjects in a negative mood. This implicates serotonin in both appetitive and aversive processes and suggests that mood may mediate this effect.

Our results are consistent with findings of reduced 5-HT in both mania and depression, and may explain some of the apparent contradictory effects of ATD. These findings have implications for our understanding of 5-HT and its involvement in psychiatric disorders.

Funded by the Cambridge BCNI, supported by a joint award from the Medical Research Council and the Wellcome Trust.

MG07

TRIPLE DISSOCIATION OF SEROTONERGIC INFLUENCE ON MOTIVATIONAL BEHAVIOUR UNDER POSITIVE, NEGATIVE AND NEUTRAL MOOD

Robinson OJ, Cools R, Sahakian BJ. Department of Psychiatry, Behavioural and Clinical Neuroscience Institute, University of Cambridge, Addenbrooke's Hospital, Cambridge, ojr23@cam.ac.uk

Reduction of brain serotonin (5-HT) via acute tryptophan depletion (ATD) has been shown to induce negative biases and to disrupt motivated behaviour. These ATD-induced depression-like effects are particularly pronounced in certain vulnerable individuals. However, the mechanism underlying individual vulnerability is unknown. Here we examine the role of mood state as a risk factor for vulnerability to the affective biasing effects of ATD, as determined via an established paradigm measuring reward-induced speeding of responding. Neuropsychological testing was preceded by the dietary serotonin manipulation, tryptophan depletion, and established mood manipulation in a double-blind, placebo-controlled crossover design. Statistical significance was determined using analysis of variance. A significant interaction between mood state, treatment and motivational behaviour was observed in female subjects ($F(2,13)=7.2$, $p=0.008$) but not in male subjects ($F(2,10)=0.88$ $p=0.44$). After positive mood induction (N=9; 5 female), female subjects speeded their responding in anticipation of probable reward under baseline ($p=0.029$), but not after tryptophan-depletion ($p=0.084$). In contrast, female subjects experiencing negative mood induction (N=13; 5 female) demonstrated no reward-related speeding under baseline ($p=0.44$) but showed significant reward-related speeding following tryptophan depletion ($p=0.026$). No effects of tryptophan depletion were found after neutral mood induction (9; 6 female).

These findings demonstrate that mood state is a risk factor for vulnerability to the negative biasing effects of ATD, at least in females, and may have important implications for the understanding of vulnerability to affective psychiatric disorders such as major depressive disorder.

Funded by the Cambridge BCNI, supported by a joint award from the Medical Research Council and the Wellcome Trust.

MG08

DECREASES IN PERFUSION IN BOTH CG25 AND NUCLEUS ACCUMBENS ARE ASSOCIATED WITH GOOD OUTCOME IN ABLATIVE NEUROSURGERY FOR TREATMENT RESISTANT DEPRESSION

Malizia AL, Holmes R, Patel NK. Psychopharmacology, University of Bristol, DHB, Whitson Street, Bristol BS1 3NY, Andrea.L.Malizia@bristol.ac.uk

Deep brain stimulation (DBS) is emerging as a possible treatment for severe treatment resistant depression (TRD). However, unlike motor disorders, the chemical anatomy of affective disorders is poorly understood and evolution from previous ablative neurosurgical procedures is also limited by the fact that lesions used in the past to treat TRD such as stereotactic subcaudate tractotomy (SST) cannot be replicated by using DBS because of their position and extent. Currently two targets are being evaluated for DBS. The first, evolved from Dr Mayberg's studies of neuroimaging changes with successful antidepressant treatments, consists of stimulating the subgenual cingulate (Brodmann's area 25; Cg25). The second derived by extension of anterior capsulotomy (used mainly for treatment resistant obsessive compulsive disorder) and by theories of the anatomical and pharmacological substrate of anhedonia, aims to stimulate the ventral anterior capsule and nucleus accumbens (VACNAc). These areas have different connections and form part of distinct neurochemical systems. In order to investigate whether either of these targets were affected by SST and had an influence on outcome we examined HMPAO SPECT scans collected pre-surgery and six months after surgery on 10 patients undergoing SST. The data was analysed using SPM5 and MARSBAR to test differences at specific locations. Six patients had good outcome (GO) as measured at one year after surgery. Comparison of HMPAO SPECT scans at six months with preoperative scans showed that patients with GO had a larger volume of significantly decreased perfusion (11832 v 6753 voxels) and larger peak decreases (t 6.91 v 5.2) in the white matter of the orbitofrontal cortex. Comparison of 5 mm x 5mm x 5mm boxes centred around left and right Cg25 and VACNAc showed that both these areas had decreased perfusion in patients with GO but not in patients with poor outcome. (Left Cg25 t=4.77; Right Cg25 t=4.85; Left VACNAc t=4.4; Right VACNAc t=4.1). Conclusions: We have demonstrated that in patients who underwent SST, statistically significant decreased perfusion in Cg25 and VACNAc was present only in those who had a good outcome. While these results do not differentiate between the two targets currently explored for DBS in TRD, they contribute to underpinning the validity of using either of these targets and thus of modulating distinct monoaminergic projections.

No external funding for this project.

MG09

ACUTE DEEP BRAIN STIMULATION IN CG25 BUT NOT IN NUCLEUS ACCUMBENS IS ASSOCIATED WITH REM SLEEP RESTORATION DESPITE MAOI TREATMENT

Durant CF, Wilson, SJ, Paterson LM, Nutt DJ, Gill SS, Patel, NK, Malizia AL. Psychopharmacology, University of Bristol, Whitson Street, Bristol BS1 3NY, claire.durant@bristol.ac.uk

The use of deep brain stimulation (DBS) for the treatment of intractable psychiatric conditions, such as treatment resistant depression (TRD), is in the early stages of investigation. DBS for TRD has been carried out in approximately 50 patients, with reports of changes in Hamilton Depression Rating Scale (HAM-D) and subjective sleep measures, but with no objective assessment of sleep. Evidence suggests that DBS may normalise disturbed sleep in responders. We report changes in objective sleep during DBS of 2 different sites in a patient receiving chronic treatment with isocarboxazid (irreversible monoamine oxidase inhibitor- MAOI). Objective sleep was measured before and during DBS for TRD in a 60 year old female patient. Electrodes were implanted bilaterally in the subgenual cingulate (Cg25) and ventral anterior capsule/ nucleus accumbens (VACNAC). After a period of recovery, the patient was readmitted for stimulator parameter adjustment. Measures of depression included 17 item HAMD and the Montgomery-Asberg Depression Rating Scale (MADRS). Sleep recordings were performed at intervals throughout the treatment periods, and analysed according to R&K criteria. Reflecting a 5 year history of sleep disturbance related to TRD, patient baseline measures indicated poor sleep (sleep onset latency; (SOL) 53mins, total sleep time (TST); 227mins) and high depression ratings (HAMD; 34, MADRS; 51). In addition there was a complete suppression of REM sleep probably attributable to isocarboxazid. During acute stimulation of Cg25, remarkable REM restoration was observed (REM amount 105min) despite continued isocarboxazid administration, and this was accompanied by improvements in sleep initiation and continuity (SOL; 12mins, TST; 439mins) and depression scores (HAMD; 17, MADRS; 28). However, with chronic stimulation sleep deteriorated (SOL; 14, TST 131min) with recurrence of complete REM suppression and depressive symptoms (HAMD; 33, MADRS; 43). Acute stimulation of VACNAC was associated a lowering depression scores, (HAMD; 22, MADRS; 35) and although sleep improved (SOL; 5, TST 359 min) a smaller increase in REM of only 10mins was observed. These improvements were not sustained and we are currently stimulating both sites. These preliminary results suggest acute DBS may be associated with both sleep and depression score improvement. DBS appears to exhibit powerful effects on sleep, with REM restoration despite continuing MAOI administration. Specific effects on REM appear to differ based on stimulation target, and may be related to differing effects on ascending monoaminergic inputs, which will be discussed in this poster.

We thank; GSS; PNK, Department of Neurosurgery, Frenchay Hospital, Bristol, UK. The DBS equipment was provided with charitable donation from friends of Frenchay Hospital.

MG10

NAPSAQ II. NATIONAL PATIENT SLEEP ASSESSMENT QUESTIONNAIRE IN DEPRESSION; A SURVEY FOR GENERAL PRACTITIONERS

Paterson LM, Nutt DJ and Wilson SJ. Psychopharmacology Unit, University of Bristol, Dorothy Hodgkin Building, Whitson Street, Bristol, BS6 6PX, louise.paterson@bristol.ac.uk

Sleep disturbance is a common and distressing feature of depression. In a recent survey of a UK-based patient group we found that the vast majority of patients experienced sleep disturbance during depression. This often remained unresolved despite antidepressant treatment, and patients sought extra treatment in order to manage the problem. We have now asked GPs about their opinions of sleep disturbance in depression, and their strategies for treating them. 40794 GPs throughout the UK received a postal questionnaire: we received 5046 completed responses (12.4%). GPs were asked which symptoms patients complain about, prior to receiving a diagnosis of depression: sleep disturbance was the most often cited presenting complaint (63%), followed by low mood (58%) and fatigue (47%). GPs estimated that 70% of the patients they diagnose with depression include sleep disturbance among their symptoms, with insomnia being more common than hypersomnia. 10% were thought to suffer from insomnia as a side effect of their antidepressant medication and 10% to suffer insomnia as a residual symptom after depression has resolved. When asked about treating symptoms of insomnia associated with depression, GPs reported that they 'frequently' or 'almost always' rely on watchful waiting or promotion of good sleep hygiene (72 and 87% respectively) and rely on switches in antidepressant medication or treatment of symptoms with medication less often (21 and 15% respectively): it was estimated that 20% of depressed patients had their prescriptions altered as a direct result of insomnia. GPs were asked to what extent they agreed with statements about sleep problems in depression. Over 90% agreed that they are common, distressing, and should be managed in primary care. 67% agreed that they cause patients to visit more frequently. A significant proportion (42%) agreed that they were difficult to treat; many believed that they could be resolved by effective antidepressant medication (69%), or respond to add-on hypnotic medication (41%). 77% agreed that sleep problems can be reduced by good sleep hygiene, and 70% agreed that if left untreated they can lead to depressive relapse. Interestingly, GPs estimated that 50% of patients who present with sleep problems in primary care turn out to have depression. Our data suggest that sleep disturbance in depression is a well recognised problem in primary care. However, the best strategies for its successful treatment were less clear. Better management is required in order to minimise distress, improve long term outcome and reduce a factor in depressive relapse.

Funding provided by Servier Laboratories Ltd.

MG11

SLEEP AND DAYTIME PSYCHOMOTOR PERFORMANCE DURING ACUTE AND CONTINUATION TREATMENT OF MAJOR DEPRESSIVE DISORDER: DOUBLE-BLIND RANDOMISED CONTROLLED TRIAL OF ESCITALOPRAM VS PAROXETINE

Baldwin DS, Hou R, Dolberg OT, Schellberg S, Hindmarch I. Division of Clinical Neurosciences, School of Medicine, University of Southampton, Royal South Hants Hospital, Brintons Terrace, Southampton SO14 0YG, d.s.baldwin@soton.ac.uk

Introduction. Disturbed sleep is a common depressive symptom which often persists despite otherwise successful pharmacological or psychological treatment, and is associated with increased risks of recurrence. As both worsened insomnia and daytime drowsiness are reported as treatment-emergent adverse effects with antidepressants, we wished to evaluate the effects of acute and continuation treatment on sleep and daytime psychomotor performance.

Method. International, randomized, flexible-dose, parallel-group, comparator-controlled study involving 36 centres in 6 countries. Patients met DSM-IV criteria for current major depressive episode, with a baseline score of 22-40 on the Montgomery-Åsberg Depression Rating Scale (MADRS). After a single-blind one-week placebo run-in, patients were randomized to escitalopram (ESC) (10-20 mg/day) or paroxetine (PAR) (20-40 mg/day) for 8 weeks of acute treatment: those who were significantly improved could continue fixed-dose double-blind treatment for a further 19 weeks. Sleep and early morning behaviour were assessed by the Leeds Sleep Evaluation Questionnaire (LSEQ), psychomotor performance by Critical FIicker Fusion (CFF) and Choice Reaction Time, and cognitive function by the Cognitive Failures Questionnaire (CFQ). Assessments were undertaken at baseline and weeks 4, 8, 16 and 27.

Results. 323 patients (ESC, 165; PAR, 158) started acute treatment and received at least one dose of study medication. There were no significant differences between treatment groups in reduction of depressive symptoms from baseline to week 8, but in severely depressed patients (baseline MADRS >30) escitalopram was superior ($p<0.05$; ANCOVA) to paroxetine at week 27. Sleep and daytime performance improved as depressive symptoms reduced. Two patients withdrew from the study due to the adverse effect of insomnia, and 1 due to somnolence. There were no significant differences between treatment groups in change from baseline on the LSEQ sub-scales for 'getting to sleep', 'awakening from sleep', or 'behaviour following sleep' although at week 4 ESC was superior ($p<0.01$; ANCOVA) to PAR on 'quality of sleep'. There were no significant differences between treatment groups in the change from baseline in CFF, recognition or motor reaction times, or CFQ total score, at any of the scheduled assessments.

Conclusion. In this study, only a small number of patients withdrew from antidepressant treatment due to adverse effects on sleep or daytime alertness. Repeated assessments of sleep and daytime performance indicated a steady improvement during acute and continuation treatment of major depressive disorder with both escitalopram and paroxetine. Source of funding. The overall randomised controlled trial was sponsored by Lundbeck Ltd.

MG12

COST-EFFECTIVENESS OF SSRI ANTIDEPRESSANTS FOR MILD TO MODERATE DEPRESSION IN PRIMARY CARE: THE THREAD STUDY

Peveler RC, Thread study group. Clinical Neurosciences Division, University of Southampton, Southampton, rcp@soton.ac.uk

Introduction Guidelines recommend that antidepressants should not be used as first-line treatment for mild depression, yet GPs often prescribe for such patients. Placebo-controlled trials suggest that SSRI antidepressants may be efficacious in mild depression, but we do not know if prescribing them is cost-effective in primary care: this study was designed to address this question. Setting General Practices around three MHRN hubs: South-West, North-West, and London.

Methods Patients with a new episode of depression of moderate (Hamilton Depression Rating Scale (HDRS) score of 16-19) or mild (HDRS score 12-15) severity were randomised to supportive care plus SSRI (n = 112) or supportive care alone (n = 108). The primary outcome was 12 week HDRS score. Secondary outcomes included 26 week HDRS, amount and type of care received, and patient satisfaction. Cost data were gathered through modified Client Service Receipt Inventory plus examination of GP records. Quality adjusted life-years (QALYs) were derived from SF36 data.

Results Intervention and control arms were comparable on baseline measures. Follow-up rates were 85% at 12 weeks and 79% at 26 weeks. There were significant differences in HDRS scores at 12 weeks ($p = 0.003$) and at 26 weeks ($p = 0.03$) favouring the SSRI arm for both moderate and mild sub-groups, controlling for initial severity, centre and GP. Mean differences in HDRS scores at 12 weeks were 3.1 (for moderate) and 2.1 (for mild). The NNT was 6 (at 12 weeks). Costs were equivalent in the two arms. Incremental cost-effectiveness ratios and cost-effectiveness acceptability curves will be presented.

Conclusions SSRIs are effective in mild to moderate depression in primary care, even at initial severity as low as 12 on HDRS. To reflect this, guidelines should be changed to include antidepressants as first-line treatments for mild as well as moderately severe depression.

Source of funding: NIHR HTA programme.

MG13

PATIENT VIEWS OF ANTI-DEPRESSANTS AND FACTORS THAT INFLUENCE THEIR DECISIONS ABOUT TAKING THEIR MEDICATION

Wallace A, Schofield P, Crosland A, Dickens A, Gask L, Aseem S, Waquas A, Waheed W, Tylee A. Centre for Primary & Community Care, University of Sunderland, Green Terrace, Sunderland SR1 3PZ, annie.wallace@sunderland.ac.uk

Background Whilst anti-depressants are recommended as a first line treatment for people with moderate or severe depression who express a preference for medication, previous research indicates that patterns of usage vary (Hunot et al 2006) and many patients remain ambivalent about the drugs they are prescribed (Gask et al 2003). The factors behind this variation and the influences on patients' choices about whether to take their medication or not remain poorly understood.
Aim To explore patients' views about antidepressants and factors that influenced their choices in relation to taking anti-depressant medication
Methods Semi-structured interviews were conducted with a purposive sample of 65 primary care patients recently prescribed (in the past year) anti-depressants for depression or mixed anxiety / depression. These were conducted across three sites: London, Manchester and Sunderland, providing a range of study contexts and a sample of patients from different socio-economic and cultural backgrounds.
Findings The study found that the factors influencing patient's decisions about anti-depressant use are a complex mix of demographic and cultural variables, beliefs about depression, relationships with practitioners, perceived impact of taking medication on other aspects of their life and beliefs about treatment efficacy. When patients first sought help from a practitioner they describe themselves as being at "rock bottom" and anti-depressants were seen as offering immediate relief. Once this immediate relief had been achieved patients report a variety of ways of taking their medication which range from taking it prescribed, through to varying doses and frequency, or stopping medication altogether. Bound up in this decision making are beliefs about the nature of depression typically whether it is viewed as a one off illness, a recurring illness or a life long condition. This is further influenced by cultural beliefs about medication taking and a distrust of medication that are considered to impact upon emotions and thought processes

MG14

CLINICAL AND TREATMENT CHARACTERISTICS OF PATIENTS WITH SEVERE TREATMENT RESISTANT DEPRESSION

Srivastava S, Kaul A, Wood B, Nutt DJ, Patel NK, Malizia AL. Psychopharmacology Unit, University of Bristol, North Bristol and Avon Wiltshire Partnership NHS Trusts., Whitson Street, Bristol BS16 1WF, shrikant@doctors.org.uk

INTRODUCTION: The definition of treatment-resistant depression (TRD) is variable. There is a dearth of reports focusing on describing the characteristics of patients with severe TRD, warranting referral to tertiary services in the UK, Here we report on referrals to a tertiary service in Bristol that provides pharmacotherapy advice and assesses patients for deep brain stimulation (DBS) in TRD, The clinic accepts referrals from primary, secondary and tertiary care.
METHOD: For all patients on first consultation, detailed history of the current and past episodes, and prescribed treatments was recorded. Diagnosis was recorded according to MINI v6, and severity of depression measured with HAM-D and MADRS rating scales. All patients referred to the clinic from July 2006 till December 2007 comprised the sample. We discuss in detail patients with primary major depressive disorder (MDD).
RESULTS: A total of 83 patients (males=37, females=46) were referred to the clinic from primary (n=22), secondary (n=59) and tertiary (n=2) care. 57 patients were referred for advice on pharmacotherapy and 24 for suitability for DBS. The mean age of the sample was 52.2±13.1 years, with females (mean 55.6) being older than males (mean 48.1) and taking longer to receive first treatment (37 v 8 months), There was significant amount of comorbidity, with 53% of all patients having more than one diagnosis, and 20% having as many as 3 diagnoses. 58 had primary MDD (single episode = 9, recurrent disorder = 49). In those with primary diagnosis of major depressive disorder, the highest comorbidity were Panic Disorder (n=11) and Social Phobia (n=5); average MADRS and HAM-D scores were 34.5±11.4 and 21.6±6.4 respectively. The mean age at first episode of depression was 32±15.8 years, although patients in their first episode had developed MDD later in life.. For recurrent MDD average number of episodes was 4.4±6.6, and the duration of the longest episode was 46.4±42.9 months. The number of suicide attempts was higher in females 1.3±3.2 vs 0.3±0.7. Patients from primary care had fewer treatments although the use of some categories of antidepressant or augmenter was not different from secondary care. Patients referred for DBS became ill younger, had more suicide attempts, were more depressed, had longer episodes and had more treatments.
CONCLUSIONS This is a very disabled, treatment resistant and chronic group of patients whether referred by primary or secondary care. Only about a third of patients referred for DBS had however reached the level of resistance that would warrant such intervention without trying alternative pharmacological strategies first.

TA01

PREVALENCE OF, AND RATIONALE FOR, THE PRESCRIPTION OF HIGH DOSE AND COMBINED ANTIPSYCHOTICS IN FORENSIC SETTINGS IN THE UK

Paton C, Barnes TRE, Brooke D, Petch E, Shingleton-Smith A. Oxleas NHS Foundation Trust, Pinewood House, Pinewood Place, Dartford DA2 7WG, Carol.Paton@oxleas.nhs.uk

Patients in forensic settings are characterised by psychotic illness with high levels of comorbidity, such as personality pathology and substance misuse. The majority present to services with violence originating in complex and enduring psychiatric and social problems. For many, all evidence-based pharmacological approaches have been exhausted. Thus, it might be expected that medication strategies for treatment-resistant psychosis, such as high-dose and combined antipsychotic prescriptions, would be more commonly used in forensic than acute adult inpatient settings. In March 2007, forensic services in 21 NHS Trusts participated in a quality improvement programme. A baseline audit was conducted to allow benchmarking of prescribing practice against 3 standards derived from evidence-based guidelines: 1. A standard dose of a single antipsychotic should be used; 2. Combinations of antipsychotics should only be used when switching from one drug to another, or for the augmentation of clozapine; and 3. First-generation and second-generation antipsychotics (FGAs and SGAs) should not be co-prescribed. Data were submitted for 1848 patients from 155 forensic wards. In the total sample, 34% of patients were prescribed a high dose of antipsychotic medication, 46% combined antipsychotics, and 31% a combination of FGA(s) and SGA(s). These figures are similar to those found in a 2006 POMH baseline audit of prescribing practice for 3492 acute adult patients; 26%, 43% and 31% respectively. In both clinical settings, the major cause of high-dose was combined antipsychotics and the major clinical reason for combining antipsychotics was PRN prescription for acute behavioural disturbance. In forensic settings, 15% of combinations (6% of all patients) were for the augmentation of clozapine, where the most commonly used second antipsychotic was amisulpride, haloperidol or sulpiride. In acute settings, the proportion of combinations due to clozapine augmentation was only 4%. There is little difference in the prevalence of high dose and combined antipsychotic prescribing between forensic and acute adult inpatient settings. A major barrier to implementing standards regarding the routine use of antipsychotic monotherapy in standard doses in both clinical settings is the established practice of prescribing PRN antipsychotics. In forensic settings, the use of clozapine augmentation as a strategy to manage treatment-resistant psychosis is more common than in non-forensic settings. The antipsychotics most often chosen by clinicians to augment clozapine are potent D_2 antagonists with a relatively low propensity to cause metabolic side effects, suggesting that attempts to maximize response and minimize side-effects with such a strategy are based on a common pharmacological rationale. This work was funded partly by a grant from the Health Foundation and partly by subscriptions from member Trusts.

TA02

THE USE OF HIGH-DOSE ANTIPSYCHOTICS IN AN ADOLESCENT PICU

Zaw KM, Osunsanmi, S. Division of Neurosciences - Department of Psychiatry, University of Birmingham, 5 , Avenbury Drive, Solihull, West Midlands B91 2QZ, zawfw@aol.com

Introduction Despite several reports on the use of High-dose antipsychotics in adults, there is a dearth of literature in the adolescents. To our knowledge, our study on an adolescent PICU over a 5 year period is the first.
Method Our 72 patients included 29 females and 43 males, aged between 13 and 18. We excluded 9 for either not being on antipsychotics or because of their short medication free assessment The diagnoses using ICD-10 and DSM IV included: Schizophrenia ,Psychotic Depression, Bipolar Affective Disorder , Complex PTSD, and Others The nature and degree of their mental illnesses necessitated detention under the Mental Health Act (1983) on admission. We defined the use of High-Dose in accordance with the Royal College of Psychiatrists Council Report 1993 (CR26) and the updated review of 2006 (CR136) We studied the clinical records, drug used and the side effects, weekly multidisciplinary care plans and discharge summaries.
Results 16 different antipsychotic preparations were used. Amongst them were 7 second generation including Clozapine and 4 IM depots including Rispidal consta. The majority of our patients, 52 (82.6%) received dosages within the BNF limits. 11 (17.4%) of our patients received High-dose antipsychotics. 7 were males. The main diagnosis was Schizophrenia. In 3, more than one antipsychotic were used as regular medication ,in 4 ,apart from one regular medication, Haloperidol and Olanzapine were used as prn. The other 4 were on monotherapy and received above BNF limits. In only 2, the duration was for over 6 months. The side effects in our sample included EPSE in 6 (1 on High-Dose), raised Prolactin Levels with clinical galactorrhoea in 5(2 on High-Dose) and prolonged QTc interval in 3(2 on High-Dose).
Conclusion Our 17.4%. prevalence for use of High-dose antipsychotics compared very favourably with studies in the adults which indicated 25% amongst in-patient units and polypharmacy at 90%. Polypharmacy did happen in 3 amongst our sample. This is less than 5% of our entire sample and about a quarter amongst our high-dose group. The prevalence of raised prolactin with clinical galactorrhoea and prolonged QTc were higher in the high-dose group. The good control of psychotic symptoms and successful discharge of our patients to less restricted environments, the majority to their own homes and non secure environments is a good indicator that antipsychotics are effective in the adolescent population and the BNF limits are appropriate for the majority.
Source of Funding: Huntercombe Hospital-Stafford.

TA03

STUDY ON THE USE OF HIGH DOSE ANTIPSYCHOTICS IN HOSPITAL

Almoshmosh N, Benaris M, Rafiq A. Adult Psychiatry, Princess Marina Hospital, Kent Rd, Northampton NN5 6UH, nadim.almoshmosh@nht.northants.nhs.uk

The Royal College of psychiatrists published a report (1997) which highlighted the use of high dose antipsychotics and the association between antipsychotic drugs and sudden death. The aim is to audit the use of high dose antipsychotic (above BNF limits) medication for inpatients, and assess the level of concordance with current guidelines in Northampton. The high dose antipsychotic monitoring sheets were collected from pharmacy from 1st January 2005 to 1st October 2007. These were used to identify case notes and data was collated on to the data sheet. Information was used from the monitoring sheet, the case notes and drug charts.
A total of 18 patients were audited aged between 26 years and 77 years, 56% of who were male and 94% were white. 11 patients (61%) were detained under sections of MHA 1983, and seven (39%) patients were informal. The majority of the patients had a diagnosis of paranoid schizophrenia (67%); the other diagnoses being bipolar affective disorder, schizoaffective disorder and depression (2% each). The medications used included combinations of both typical and atypical antipsychotics and depot injections. The doses ranged from 108% of BNF maximum to 373%. Only three (16%) patients were informed of the decision to start high dose antipsychotics, no carers were consulted and the multidisciplinary team was involved in the decision 28% of the time (5 patients). 50% of the notes had clearly stated that the patient was on high dose antipsychotics and 28% of the drug charts had this documented inside or on the front, although four drugs charts were missing from the notes.
In 9 (50%) cases there was no documented consideration for any risk factors and in 2 (11%) cases all the risk factors were considered. 11 (61%) had an initial ECG of which only 3 were repeated and 5 (28%) had baseline observations and bloods. 17 patients were reviewed after 3 months and 12 of these had their medication decreased or changed. The 5 patients who were reviewed but continued on high dose antipsychotics had documented reasons for continuing, and only one of these did not have a second opinion. This study identified: 1-Lack of documentation of the commencement and the reasons for commencement of high dose antipsychotics above BNF limits. 2-Lack of discussion with patients, carers and MDT. 3-Consideration of risk factors not been documented. 4-Investigations prior to initiation and continuous monitoring were not undertaken. This audit was limited by the fact that the data was collected by requesting monitoring sheets from pharmacy. The patients' files reviewed showed a general lack of documentations in patients receiving above BNF dosages of antipsychotics and reasons for its use. Damage caused to patients in relation to this unlicensed use can be indefensible. Documentation needs to be clear in what issues have been discussed and with whom. Reasons for limited communications should also be documented. Risk factors and results of investigations need to be clearly identified and both positive and negative findings must be documented. The responsible clinician to ensure that the relevant forms are filled appropriately.

TA04

THIS ABSTRACT HAS BEEN WITHDRAWN

TA05

ZUCLOPENTHIXOL INTERACTIONS WITH PAROXETINE, FLUOXETINE, CARBAMAZEPINE AND LEVOMEPROMAZINE: DATA FROM A ROUTINE THERAPEUTIC DRUG MONITORING SERVICE

Davies SJC, Westin AA, Castberg I, Lewis G, Lennard MS, Spigset O. Psychopharmacology Unit (Dorothy Hodgkin Building), University of Bristol, Whitson Street, BRISTOL BS1 3NY, simon.davies@bristol.ac.uk

Zuclopenthixol, a conventional antipsychotic administered orally or intramuscularly (as a long acting depot or as "Acuphase" for emergency settings) is widely prescribed in many countries. The use of the Acuphase preparation has declined following concerns about QTc prolongation and sudden death, although it is still used in 5% of emergency tranquillisations (Nnaji 2007). Data on the pharmacokinetics of zuclopenthixol are limited. The absence of such data is surprising, since patients in psychiatric emergencies are particularly vulnerable to side effects, toxicity or decreased effect through pharmacokinetic interactions with co-prescribed medication mediated through cytochrome P-450 (CYP) enzymes. Here we aimed to determine whether the zuclopenthixol concentration/dose ratio (ZUCDR) was affected by the concurrent prescription of CYP inhibitors/inducers.

The influence of co-prescribed drugs on the ZUCDR was examined by linear regression analyses on data from a routine therapeutic drug monitoring service. All samples from patients prescribed zuclopenthixol with one of four potentially interacting drugs were examined. These drugs were paroxetine (a CYP2D6 inhibitor), fluoxetine (a CYP2D6/CYP3A4 inhibitor), carbamazepine (an inducer of CYP3A4 and other CYPs) and levomepromazine (a CYP2D6 inhibitor). Samples from a random selection of patients prescribed zuclopenthixol without potentially interacting drugs were used as controls. Oral and depot zuclopenthixol data were analysed separately. Independent variables included age, gender, interval after dose, a clustering variable, and a) binary or b) continuous variables for prescription and daily dose (or concentration), respectively, of co-prescribed drugs.

For oral zuclopenthixol we included 490 serum samples, 274 from individuals co-prescribed one potentially interacting drug. Prescription of each interacting drug was associated with a highly significant change in ZUCDR ($p \leq 0.001$). As hypothesised, carbamazepine caused dose dependent reduction in the ZUCDR ($p<0.001$), and fluoxetine ($p<0.001$) and paroxetine ($p=0.011$) caused dose dependent increases. The ZUCDR was not related to levomepromazine dose, but there was a significant relation between ZUCDR and the serum concentration of levomepromazine ($p<0.001$). For depot zuclopenthixol, 433 serum samples (206 from individuals co-prescribed interacting drugs) were included. All changes in the ZUCDR were in the same directions as for oral zuclopenthixol, but not all reached statistical significance.

Our hypothesis was that the ZUCDR would be higher in patients co-prescribed CYP2D6 and CYP3A4 inhibitors and lower in patients co-prescribed carbamazepine, and that these changes would be related to dose or concentration of the interacting drug. Our results support this hypothesis. Consideration should be given to amending prescribing guidelines to incorporate these interactions. Their role in toxicity associated with Acuphase requires further exploration. [No external funding]

TA06

DELTA-9-TETRAHYDROCANNIBINOL INDUCED PSYCHOSIS AS RATED BY SELF AND OTHER

Morrison PD, Murray RM, Kapur S. Psychological Medicine, Institute of Psychiatry, De Crespigny Park, London, paul.morrison@iop.kcl.ac.uk

The use of high potency THC amongst young people in the West has become a public health concern. Sinsemilla, characterised by high Δ9-tetrahdrocannibinol (THC) but negligible cannabidiol (CBD) concentration, is now the most prevalent form of cannabis in England. Cannabis is one of the first consistently identified risk factors for schizophrenia (Arseneault L. et al. (2004) Br J Psychiatry 184: 110-117). Here we report the acute psychotogenic effects of pure-synthetic THC in a sample of 22 healthy male volunteers. Previous work utilised The Positive & Negative Syndrome Scale (PANSS), an investigator-rated scale, to measure THC-psychosis (D'Souza CD. et al (2004) Neuropsychopharmacology 29: 1558-72). To control for possible observer bias, we have incorporated a participant-rated scale: The Community Assessment of Psychic Experiences (CAPE), (Stefanis NC. et al (2002) Psychological Medicine 32: 347-58). We hypothesized that investigator-rated THC-psychosis and participant-rated THC psychosis would show agreement. The local ethics committee approved all protocols. Participants were recruited from King's College London by email advertisement. Exclusion criteria included personal or family history of major mental illness and personal drug/alcohol dependence. Participants were required to be over 21 and be willing to give fully informed consent. Synthetic THC (2.5mg) was administered intravenously (IV) over 5 minutes, in a double-blind, placebo controlled manner. Psychotic responses were assessed using The PANSS and CAPE at 30, 80 and 120 minutes post injection. Within group differences in psychopathology were investigated using Friedman's test. Scores on the PANSS positive subscale increased from baseline following THC but not placebo administration ($\chi 2=62$, $p<0.001$). At 30 minutes post THC, PANSS-positive scores had increased by a mean of 3.7 points (range 0-17), returning to baseline levels by 120 minutes. Similarly, participant-rated positive psychotic symptoms as measured by The CAPE-state increased from baseline following THC but not placebo administration ($\chi 2=20$, $p=0.005$). Investigator-rated (PANSS) and participant-rated (CAPE-state) positive psychotic scores post-THC administration were correlated (Kendall's tau=0.50, $p<0.001$). Synthetic intravenous Δ9-tetrahdrocannibinol was shown to elicit positive psychotic symptoms in a proportion of healthy individuals. This held whether subjects rated themselves or were rated by a blinded psychiatrist. These findings add to a growing body of evidence that THC confers risk for acute and chronic psychoses. This study was funded by The Psychiatric Research Trust.

TA07

HIPPOCAMPAL EXPRESSION OF CATECHOL-O-METHYLTRANSFERASE (COMT) MESSENGER RNA IN SCHIZOPHRENIA AND BIPOLAR DISORDER

Laatikainen LM, Godlewska BR, Harrison PJ, Tunbridge EM. Psychiatry, Oxford University, Warneford Hospital, OXFORD OX3 7JX, linda.laatikainen@psych.ox.ac.uk

Catechol-o-methyltransferase (COMT) metabolises catechol-containing compounds, including the neurotransmitter dopamine. Given its role in regulating dopamine levels in the cortex, COMT is of interest as a risk gene for psychiatric disorders and several positive associations have been reported, notably with schizophrenia and obsessive compulsive disorder. Studies of COMT to date have typically focussed on its role in the prefrontal cortex. However, emerging data also suggest that COMT may be of importance for regulating hippocampal function. Therefore, we examined the expression of COMT mRNA in the human hippocampus in healthy controls and individuals with psychiatric disorders, and in relation to COMT genotype.

RNA from 35 control subjects, 35 patients with schizophrenia and 34 with bipolar disorder was extracted from postmortem hippocampal tissue obtained from the Stanley Medical Research Institute and was quantified using quantitative real-time polymerase chain reaction (qRT-PCR). We also genotyped individuals for five single nucleotide polymorphisms (SNPs) in the COMT gene (rs4680 [Val158Met], rs4633, rs4818, rs6269, rs2075507 [A-287G]). The effects of diagnosis and genotype were investigated using ANOVA with LSD post-hoc tests.

There were no significant differences in COMT mRNA level between diagnostic groups. Neither did COMT mRNA relate to any of the SNPs, or to homozygosity for a haplotype shown to affect COMT protein abundance (all $p>0.1$). Within the schizophrenia group, COMT mRNA did not correlate with clinical or therapeutic variables such as antipsychotic exposure or duration of illness. These data show that expression of hippocampal COMT mRNA is not altered in schizophrenia or bipolar disorder, nor affected by COMT genotype.

These findings are consistent with studies in prefrontal cortex. Furthermore, they support data suggesting that functional SNPs within the gene do not operate via modulation of COMT mRNA expression. Further studies are required to investigate whether there are diagnostic or genotype-related differences in COMT expression within specific hippocampal subfields, or selective effects on any of the recently-reported COMT splice variants.

This research is funded by the Medical Research Council.

TA08

VALIDATION OF LENTIVIRAL TECHNOLOGY TO MANIPULATE GENE EXPRESSION IN THE PREFRONTAL CORTEX

Pratt JA, Thomson DM, Cochran S, Kennedy M, Paterson C, de Groote C, Morris BJ, Winchester CL. PsyRING, University of Strathclyde, Taylor Street, Glasgow, c.winchester@bio.gla.ac.uk

Schizophrenia is a polygenic disorder and numerous genes and convergent dysfunctional pathways have been identified. However, the role and interaction of these genes in relation to disease pathology, symptoms and treatment response are not understood. Over-expression or knockdown of specific genes in the prefrontal cortex would enable the dissection of the function of specific gene products in relation to the cognitive deficits of schizophrenia. Viral mediated gene transfer into specific sites within the brain allows precise manipulation of transgene expression in both time and space (Davidson and Breakefield 2003, Nature Reviews Neuroscience 4: 353-364). Lentivirus transduction of differentiated non-dividing cells, such as neurones, and the resultant stable integration of its genome can be exploited to enable long-term modifications for *in vivo* applications. Thus the aim of these studies was to develop this approach to manipulate gene expression in the prefrontal cortex, a brain region of considerable importance in the cognitive deficits of the disease (Morris *et al.,* 2005, Current Opinions in Pharmacology 5: 101-106).
Rat cDNAs for schizophrenia-associated genes, including *GABRA2*, and a GFP cDNA were cloned into the ViraPowerä Promoterless Lentiviral Gatewayâ system (Invitrogen). Gene expression was driven by the *aCamk2* promoter to drive expression in neurones of the forebrain. The expression constructs were tested *in vitro* for functionality before being used to generate VSV-G pseudotyped lentiviral particles. These viral vectors were also tested *in vitro* prior to their stereotaxic injection in the prelimbic region of the rat prefrontal cortex. Immunofluorescence was used to assess over-expression of GFP and schizophrenia associated genes.
The genomes of the modified lentiviruses were tested *in vitro* by transfection of NG108-15 cells with lentiviral expression constructs. Western blotting confirmed the over-expression of GFP and GABRA2 proteins in the transfected cells. VSV-G pseudotyped lentiviral particles were generated from these validated expression constructs and immunofluorescence was used to demonstrate GFP over-expression in transduced NG108-15 cells, organotypic cortical cultures and rat prelimbic cortex after stereotaxic injection of the pseudotyped lentiviral particles. Specific subsets of GABAergic interneurones were also visualised in the prefrontal cortex by parvalbumin and GAD67 immunofluorescence for confirming cell specific expression of lentiviral transgenes. These experiments highlight the potential for lentiviral-mediated gene manipulation in the rodent brain as a valuable tool for dissecting the role of schizophrenia-associated genes in the prefrontal cortex and cognitive deficits of the disease.
This work was funded by Mitusbishi Pharma Corporation and Clare Paterson has a BBSRC GlaxoSmithKline case award PhD studentship.

TA09

NMDA ANTAGONISTS AND PALATABILITY IN RATS

Lydall ES, Dwyer DM, Gilmour G. School of Psychology, Cardiff University, Tower Building, Park Place, Cardiff, CF10 3AT, LydallES@cardiff.ac.uk

Introduction: The psychotomimetic drugs phencyclidine (PCP) and MK-801 can induce symptoms of schizophrenia. Thus the acute effects of these compounds might include the production of anhedonia. The value of a reward can be measured in rats by examining its palatability via the microstructural analysis of licking (e.g. Davis & Smith (1992) Behavioral Neuroscience, 106, 217-228.) Rats rarely show continuous consumption of a liquid. Instead, they perform repeated bouts of licking, separated by pauses. An analysis of the microstructure of licking shows that the number of licks in each bout is related directly to the palatability of the solution.
Methods: 28 food-restricted rats received 10 min daily access to 10% sucrose in lickometer cages. 14 rats received PCP (vehicle, 0.25mg/kg, 0.5mg/kg, 1mg/kg and 2.5mg/kg), and 14 received MK-801 (vehicle, 0.0125mg/kg, 0.025mg/kg, 0.05mg/kg and 0.1mg/kg). Drug tests were separated by two weeks to minimise tolerance effects. The data was analysed using repeated-measures ANOVA (with dose as the single factor) and planned contrasts compared each individual dose to vehicle.
Results: PCP produced overall effects on consumption ($p < .001$), bout size ($p < .001$) and average inter-lick interval (ILI) ($p < .001$). With respect to consumption the 0.25mg/kg dose was above vehicle ($p = .009$) and the 2.5mg/kg dose below ($p < .001$). Bout size was numerically, but not significantly, higher than vehicle after 0.25mg/kg ($p = .123$). The 2.5mg/kg dose significantly reduced bout size ($p = .022$). ILI was significantly increased by 0.5mg/kg, 1mg/kg, and 2.5mg/kg (ps $< .042$). MK-801 produced overall effects on consumption ($p < .001$), bout size ($p < .001$) and ILI ($p = .001$). In the case of consumption the 0.025mg/kg and 0.05mg/kg doses were above vehicle (ps $< .015$). Consumption for the 0.1mg/kg dose was below vehicle ($p = .003$). Bout size was numerically, but not significantly, higher than vehicle after 0.0125mg/kg ($p = .205$). Bout size was significantly reduced after 0.1mg/kg ($p < .001$). ILI was significantly increased by the 0.1mg/kg dose ($p = .005$).
Conclusions: We found no evidence of a reduction in reward value in terms of either amount consumed or palatability that was independent of the motor effects indicated by raised ILIs. Indeed, low to moderate doses of both PCP and MK-801 actually increased consumption and produced a trend to an increase in palatability. Thus the acute effects of these compounds do not seem to include the production of anhedonia.

TA10

NICOTINE ANTAGONISES PCP-INDUCED REVERSAL LEARNING AND EPISODIC MEMORY DEFICITS INVOLVEMENT OF DOPAMINERGIC NEUROTRANSMISSION AT D1 RECEPTORS

Idris NF, Grayson B, Neill, JC. Pharmacy, University of Bradford, BD7 1DP, nfidris@bradford.ac.uk

Introduction: Nicotinic cholinergic systems are important for cognitive functioning, in particular, alterations in strategy and capacity for accurate performance (Levin and Rezvani, 2007, Biochem Pharmacol; 74:1182-91). Dopaminergic and glutamatergic systems are also known to be involved (Buchanan et al., 2007 Schizophr Bull; 33:1120-30). However, there is only a limited amount of information concerning the interaction(s) between these systems and cognition. Nicotine has been found in a variety of species and behavioural paradigms to improve cognitive performance.
Objectives: We investigated the interaction between cholinergic and dopaminergic systems in the impairment of performance in reversal learning and novel object recognition (NOR) paradigms induced by the N-methyl-D-aspartate (NMDA) receptor antagonist, phencyclidine (PCP).
Methods: 50 adult female hooded-Lister rats were trained to perform an operant reversal learning task to 90% criterion. After training, rats were treated with PCP at 2 mg/kg (i.p.) or vehicle twice daily for 7 days, followed by 7 days washout. For NOR, 50 separate rats were tested up to 10 weeks following the same sub-chronic PCP dosing regime. Rats were then treated with vehicle or the D1 receptor antagonist, SCH-23390 (0.05mg/kg, i.p) 15 min prior to acute doses of nicotine (0.2mg, s.c.) d-cycloserine (45mg/kg, i.p.) a direct co-agonist at the NMDA receptor, or vehicle. 30 Min following acute drug treatment, animals were tested for performance in the reversal learning task or the NOR task by methods previously described in detail (Idris et al., 2005; Psychopharmacology, 179: 336-348; Grayson et al., 2007 Behav Brain Res. 184: 31-8). Data are expressed as mean ± SEM and analysed by ANOVA followed by post-hoc Dunnett's t-test.
Results: Sub-chronic PCP induced a significant impairment in performance of the reversal learning ($P<0.001$) and NOR tasks ($P<0.01$). Nicotine and d-cycloserine significantly attenuated the cognitive impairment induced by PCP in the both tasks ($P<0.05$-$P<0.01$). SCH23390 significantly reversed the effect of nicotine ($P<0.05$-$P<0.001$) but not d-cycloserine in both paradigms.
Conclusions: These new data demonstrate the importance of the dopamine system, acting through D1 receptors in mediating the effect of nicotine to reverse a PCP-induced deficit in cognitive function in two paradigms assessing different aspects of cognitive function. These findings improve our understanding of the mechanism underlying PCP-induced cognitive deficits and have important implications for development of novel treatment strategies for cognitive deficit symptoms of schizophrenia.

TA11

AMPAKINES CX-516 AND CX-546 REVERSE A PCP INDUCED DEFICIT IN THE NOVEL OBJECT RECOGNITION TASK

Damgaard T, Plath N, Hansen SL, Neill JC. Faculty of Pharmacy, University of Copenhagen, Denmark (and H. Lundbeck A/S, Valby, Denmark), Universitetsparken 2, DK-2100 Copenhagen, trined@gmail.com

Animal models involving treatment with the NMDA receptor antagonist phencyclidine (PCP) have proven to be useful tools in mimicking several pathological aspects of schizophrenia, including positive, negative, and cognitive symptoms. Previous work in Bradford has shown that sub-chronic PCP induces an enduring episodic memory deficit in female Lister Hooded rats in the novel object recognition (NOR) task PCP treatment has been suggested to affect expression of NMDA receptor subunits and is likely to involve changes in downstream glutamatergic signalling pathways. The AMPA receptor provides the initial depolarisation necessary for activation of the NMDA receptor. Positive modulators of the AMPA receptor (AMPAkines) may alleviate the PCP induced change in glutamatergic signalling. AMPAkines have previously been shown to attenuate memory deficits in preclinical studies in this and other models. The aim of this study was to examine the potential of the AMPAkines CX-516 and CX-546 in reversing a PCP induced episodic memory deficit.

To this end adult female Lister Hooded rats were dosed IP with vehicle (n=20) or PCP 2 mg/kg (n=80) twice daily for 7 days followed by at least 7 days washout. Animals were then tested in the NOR task which consisted of a 3minute acquisition trial in which rats explored two identical objects, followed by a 1minute intertrial interval, during which animals were returned to their home cage. Rats were re-introduced into the arena, and allowed to explore a triplicate of the familiar object and a novel object for a 3 minute retention trial. Animals were dosed with CX-516, CX-546 (10, 40, or 80mg/kg) or vehicle (SC) 30 minutes prior to testing. Object exploration was scored manually from videotape and the discrimination index (DI) calculated as [(time spent on novel – time spent on familiar)/total exploration time]. These data were analysed using a one way ANOVA followed by a post hoc Dunnett's t-test.

In both experiments the DI was significantly lower for animals subchronically treated with PCP compared to animals treated with vehicle ($p<0.05$), indicating a deficit in recognition memory. This effect of PCP was fully reversed at all doses tested of CX-516 ($p<0.05$) whereas only the highest dose (80 mg/kg) of CX-546 was effective to reverse the PCP-induced deficit in DI ($p<0.05$). In conclusion, both AMPAkines, CX-516 and CX-546, were effective in attenuating a PCP induced deficit in episodic memory in the NOR paradigm.

This suggests that positive AMPA receptor modulation may represent a mechanism for treatment of cognitive deficit symptoms in schizophrenia.

Acknowledgement: T Damgaard is funded by a Lundbeck-Drug Research Academy, Faculty of Pharmacy, University of Copenhagen PhD Studentship.

TA12

EFFECT OF PRETREATMENT WITH RISPERIDONE ON DISRUPTIONS IN OBJECT RECOGNITION IN THE PHENCYCLIDINE-TREATED RAT

Jenkins TA, Adams HN, Harte MK and Reynolds GP. Division of Psychiatry and Neuroscience, Queen's University, Whitla Medical Building, 97 Lisburn Road, Belfast, BT9 7BL, t.jenkins@qub.ac.uk

Introduction: The NMDA receptor antagonist, phencyclidine, produces behavioural disturbances in rodents that replicate certain features of schizophrenia. We have previously demonstrated that repeated exposure to phencyclidine results in long-lasting changes in working memory, as measured by the novel object recognition task, which may parallel the cognitive deficits seen in schizophrenia. Such deficits may reflect a progressive pathology of the disease which may be attenuated by some antipsychotic treatments (Lieberman, Perkins and Jarskog, (2006), CNS Spectr. 12:3(Suppl 4):1-16). The aim of this study was to investigate whether concurrent treatment with the atypical antipsychotic, risperidone, reversed the deficits in working memory observed after sub-chronic phencyclidine treatment.

Methods: Male Lister-hooded rats were administered phencyclidine at a dose of 2mg/kg bi-daily for one week (n=20), or vehicle (n=10). Ten of the phencyclidine group were concurrently treated with risperidone (0.5mg/kg i.p) twice daily for ten days, beginning three days before the start of phencyclidine administration. Following a 7-day drug wash-out period, novel object recognition testing took place. Rats were allowed to explore two identical objects during a 3 minute training phase. Following a 1 hour inter-trial interval during which the animals were returned to their homecage, a retention trial was carried out in which animals were exposed to a familiar object and a novel object for 3 minutes. Exploration time (s) of each object during the acquisition and retention trials was recorded. The discrimination index (novel-familiar/total exploration) was calculated for the retention trial. Rats were tested again at 6 weeks post-phencyclidine treatment.

Results: Bi-daily phencyclidine treatment produced a significant reduction in the discrimination ratio. This was not reversed by pre-treatment with the atypical antipsychotic, risperidone. (week1: PCP 0.17+0.04, PCP&risperidone 0.20+0.04, control 0.27+0.06; week6: PCP 0.16+0.07, PCP&risperidone 0.17+0.03, control 0.44+0.05; ($F(2, 26)=8.8$, $p=0.01$; RMANOVA).

Conclusions: Sub-chronic phencyclidine treatment resulted in a robust and enduring deficit in memory. This was not affected by co-administration of the antipsychotic, risperidone. These results suggest that the antipsychotic, risperidone, is not neuroprotective against the pathophysiological effects of phencyclidine, despite its neuroprotective influence in some neurodegenerative processes (Yulug et al., (2006), Brain Res Bull. 69(6):656-9).

TA13

TEMPORAL ANALYSIS OF PSYCHOTOMIMETIC-INDUCED DEFICITS IN REVERSAL LEARNING IN FEMALE RATS: EFFECT OF ANTIPSYCHOTICS

McLean SL[1], Woolley ML[2], Neill JC[1]. [1]School of Pharmacy, University of Bradford, Richmond Road, Bradford BD7 1DP, [2]Psychiatry CEDD, GSK, Third Avenue, Harlow CM19 5AW s.l.mclean@bradford.ac.uk

Introduction: The psycho-stimulant drugs, d-amphetamine and phencyclidine (PCP), can induce symptoms similar to those observed in schizophrenia. Previous results from our laboratory have shown that both produce significant impairments in a reversal learning task when given acutely (Abdul-Monim *et al.,* 2003, J. of Psychopharmacology 17: 57-66; Idris *et al.,* 2005, Psychopharmacology 179: 336-348). The aim of this study was to explore the temporal profile of d-amphetamine and PCP-induced deficits in this model, and temporal effects of risperidone and haloperidol to antagonise these deficits.

Methods: Adult female hooded-Lister rats were trained to perform the reversal learning task to 90% criterion as previously described (Abdul-Monim *et al.,* 2003, J. of Psychopharmacology 17: 57-66). Rats then received an acute dose of risperidone (0.2 mg/kg), haloperidol (0.05 mg/kg) or vehicle (1 ml/kg) 30 minutes prior to administration of PCP (1.5 mg/kg), d-amphetamine (0.075 mg/kg) or vehicle, all i.p, and then tested 30 min later. Testing consisted of a 5-min initial phase, followed by a 2-min time-out period and a 15-min reversal phase. Recordings of active and inactive lever pressing were made in the initial phase after 5 minutes and in the reversal phase every minute. Data were analysed by a one-way ANOVA followed by post-hoc Dunnett's t-test.

Results: Area under the curve was calculated for the extended reversal phase. Post-hoc comparisons showed a significant reduction in percent correct responding in PCP-treated rats compared to vehicle ($p<0.01$), an effect significantly improved by risperidone ($p<0.05$). D-amphetamine induced a marked and significant reduction in performance compared to vehicle ($p<0.001$); this effect was ameliorated by haloperidol, an effect that closely approached statistical significance ($p=0.059$). Close inspection of the temporal data show that, after a period of 5-min, PCP-treated rats begin to make more correct choices than incorrect; however, in d-amphetamine-treated rats this cross-over point is not reached until 13 minutes.

Conclusions: These data confirm that both PCP and d-amphetamine impair reversal learning, and offer insight into the temporal nature of their cognitive deficit. Risperidone fully reversed the deficit induced by PCP, whereas haloperidol, although improving the amphetamine-induced deficit, was unable to fully ameliorate its effects. These data demonstrate the action of antipsychotics over time, which may be used as a potential indicator of efficacy in this model.

Acknowledgements: S McLean is funded by a joint GSK-University of Bradford postgraduate studentship.

TA14

OBJECT-PLACE-CONTEXT RECOGNITION IN RATS: MODEL OF EPISODIC-LIKE MEMORY IN SCHIZOPHRENIA

Le Cozannet R, Fone KCF, Moran PM. Psychology, University of Nottingham, Nottingham NG7 2RD, lecozannet_romain@yahoo.fr

Episodic memory is the capacity to recall an event (what) in time (when) and in a specific context (where). People with schizophrenia have been shown to have deficits in episodic memory. There are a number of animal models of schizophrenia that induce memory deficits but none have been tested in tasks that simultaneously address the "what", "when" and "where" aspects that define episodic memory in humans. Glutamatergic antagonists such as phencyclidine (PCP) induce a range of schizophrenic-like symptoms in healthy volunteers, including episodic memory deficits. In rats, PCP induces memory deficits that are reversed by antipsychotic drugs. Isolation reared rats show behavioural and neurochemical alterations similar to several core deficits seen in schizophrenia, including memory. In the following study subchronic PCP and socially isolated rats were tested on an Object-Place-Context test of episodic memory where rats recognise objects under specific spatial, contextual and temporal conditions (Eacott and Norman 2004 JNEUROSCI 24(8):1948-1953).

Two animal models were used: the subchronic PCP model which consisted of administration of 5mg/kg i.p. twice daily for 7 days followed by 7 days withdrawal period and the isolation rearing model in which rats were housed in isolation from post natal day 24. The animals performed the object-place-context recognition task which followed 8 habituation sessions in each of two different contexts. Rats were tested twice in each context with two familiar objects A or B encountered previously (during a sample phase) in a different context-dependent location. These four conditions were replicated for each of 2 or 7 delays (2-120 min). Recognition memory was measured as greater exploration of the novel object than the familiar object. The novel object in this procedure is the one that is in a new location for a specific context as the rat is already familiar with the object.

First, these results confirmed a delay-dependent episodic-like memory in rats. Second, subchronic PCP-treated-rats but not isolated rats were impaired in this episodic memory task. Third, both PCP and isolated rats showed impairment of delay-induced reduction in total object exploration in the task, which reflects recognition of a specific object (Context-Object association) in a previously visited context.

These data suggest that this model is sensitive to glutamate antagonists as in humans and that it can identify highly specific memory impairments common to both PCP and social isolation rearing. This suggests that this may prove to be a sensitive preclinical model for episodic memory impairments in schizophrenia.

TA15

PHARMACOLOGICAL ATTENUATION OF THE MK-801-INDUCED DEFICIT IN WORKING MEMORY IN A RODENT 1-BACK TEST: FAILURE AND SUCCESS

Evenden JL, Ko T. Dept of Psychology, University of Delaware, 108 Wolf Hall, Newark, DE, 19716, USA, evendenj@udel.edu

A deficit in glutamatergic function in prefrontal cortex has been proposed to underlie the cognitive deficits seen in schizophrenia which can be modelled in rats by administration of NMDA antagonists such as MK801. Previous results have shown that repeated treatment with MK801 leads to a long lasting and stable deficit in choice accuracy (measure of working memory) in a 1-back task in rats, although the motoric effects of the drug show rapid tolerance.

Methods: Long-Evans rats were trained on the discrete-trial 1-back procedure. Either intra-cerebral cannulae were implanted directed at medial prefrontal cortex (mPFC), or once the effect of repeated systemic treatment with MK801 (MK, 0.15 mg/kg 15 min prior to testing) had stabilized, clozapine (CLZ) was added. Doses of 3.0, 4.5 and 6.0 mg/kg were administered 1 hour before testing, each for 10 successive days, in a stepwise ascending dose series.

Results: Although the highest dose of CLZ reduced the number of trials completed during the first session (MK (n=9): 69.6, MK+CLZ (n=8): 27.8, $p<0.05$), there was no effect of CLZ on the MK801-induced deficit in accuracy on that or any other day (first day: MK: 35.9%, MK+6.0 CLZ: 35.4%). When the MK801 administration was reduced at the end of the study a return to good performance was seen. A similar selective disruption of choice accuracy was seen after intra-mPFC administration of the NMDA antagonists MK801 (veh, 3 and 5 microg/side: 76.2%, 63.0% and 60.4%, respectively, $p<0.01$, n=9) and (RS)-CPP (veh or 100 microg/side: 75.7% and 65.3% respectively, $p<0.05$). These data show that the MK801-induced deficit in working memory is at least in part mediated by mPFC. The intra-mPFC MK801-induced deficit was attenuated by systemic administration of the 5 HT2A/2C antagonist, ritanserin (MK: 48.9%, MK+RIT: 69.0%, $p<0.05$, n=9).

Conclusions: The present data suggest that CLZ does not have an appropriate pharmacological profile of activity to reverse the selective deficit in working memory produced by repeated systemic NMDA blockade in the rat even though blockade of 5-HT2A/2C receptors appears to be sufficient to ameliorate the component mediated by mPFC. Clozapine has an atypical antipsychotic profile in schizophrenics, but, at best, it produces little improvement in the cognitive performance of such patients.

This research was carried out at and sponsored by CNS Discovery, AstraZeneca R & D Wilmington, Wilmington, DE, USA.

TA16

SOCIAL WITHDRAWAL INDUCED BY SUB-CHRONIC PCP IN FEMALE RATS, IMPROVEMENT BY ATYPICAL ANTIPSYCHOTICS VIA A 5-HT1A RECEPTOR MECHANISM: IMPLICATIONS FOR TREATMENT OF NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

Snigdha S, Neill JC. School of Pharmacy, University of Bradford, Bradford, ssnigdha@brad.a.uk

Introduction Schizophrenia consists of three separate symptom domains: positive, negative and cognitive. Negative symptoms include blunted affect, poverty of speech and social withdrawal. Sub-chronic phencyclidine (PCP) mimics certain aspects of schizophrenia symptomology in rats. However, there is a marked lack of validated animal models of negative symptoms. We are working towards establishment of such a model and have recently shown that atypical antipsychotics, risperidone and ziprasidone but not the classical agent haloperidol, can reverse the PCP-induced deficit in social behaviours in female rats (Snigdha and Neill. 2008 Behaviour Brain Research 187:489-94). The aim of the present study is to investigate involvement of 5-HT1A receptors in reversal of the PCP-induced deficits in this model. 5-HT1A receptors may play an important role in depression (Maes and Meltzer 1995 Fourth Generation of Progress Raven Press, 933-944) and some of the newer antipsychotics such as ziprasidone and aripiprazole act as partial agonists at this receptor (Rollema et al. 2000 Biological Psychiatry 48:229-237)

Methods Adult female hooded-Lister rats received vehicle (n=36) or PCP (n=22; 2mg/kg i.p.) twice daily for 7 days, followed by 7 days washout. On test days, PCP treated rats received acute treatment with aripiprazole (5mg/kg, s.c.) or the 5-HT1A receptor antagonist, WAY100635 (0.5mg/kg, i.p.) alone and in combination. All acute treatments were given 30 min prior to testing. For the test, pairs of unfamiliar weight matched rats receiving either acute doses of drugs described above or vehicle were placed in the test arena and social behaviours (following, sniffing, climbing over and under, exploration of inanimate object and avoiding) were recorded on video for subsequent blind scoring. Data were analysed by factorial ANOVA followed by un-paired t-test.

Results Sub-chronic PCP produced a robust and significant reduction in social sniffing and increase in avoiding behaviour ($p<0.01$-$p<0.001$). The PCP-induced deficits in social behaviours were significantly attenuated by acute treatment with aripiprazole ($p<0.01$-$p<0.001$), an effect that was abolished by pre-treatment with WAY 100635. Conclusion These findings confirm that sub-chronic PCP induces robust social behaviour deficits in female rats and shows that they are reversed by the novel antipsychotic, aripiprazole. These results suggest that the beneficial effects of drugs such as aripiprazole and ziprasidone on PCP-induced social behaviour deficits, a potential model of negative symptoms of schizophrenia, may be a consequence of modifications of the serotonergic system, in particular through an interaction with 5-HT1A receptors, a hypothesis supported by Bruins Slot et al. 2005, Neuropharmacology 49: 996-1006).

TA17

THE UNCOMPETITIVE GLUTAMATE NMDA RECEPTOR ANTAGONIST MEMANTINE IMPROVES POSTWEANING SOCIAL ISOLATION-INDUCED RECOGNITION MEMORY DEFICITS IN RATS

Jones CA, Brown AM, Auer DP, Fone KCF. Institute of Neuroscience; School of Biomedical Sciences, University of Nottingham, Queen's Medical Centre, Nottingham NG7 2UH, mbxcj@nottingham.ac.uk

Postweaning social isolation is used as a neurodevelopmental animal model of schizophrenia, which induces several behavioural deficits in adult rats resembling some of the positive, negative and cognitive symptoms seen in schizophrenic patients. Memantine is an uncompetitive NMDA receptor antagonist which is a clinically approved cognitive enhancer used in the treatment of advanced Alzheimer's disease.

This study evaluated the effect of memantine on the cognitive and behavioural deficits induced by postweaning social isolation to investigate whether glutamatergic dysfunction occurs in this paradigm.

Male Lister-Hooded rats obtained immediately after weaning on postnatal day (PND) 24-25 were either group housed (3-4 per cage; n=9) or socially isolated (n=18) for a period of 6 weeks during which they received minimal handling but maintained visual, auditory and olfactory interaction with littermates. On PND's 63, 70, 77 and 83 animals received either vehicle (2 ml/kg; i.p.) or memantine (15 mg/kg; i.p.) 20 mins prior to testing and novel cage induced locomotor activity (LMA), novel object recognition (NOR), prepulse inhibition (PPI) of acoustic startle and conditioned emotional response (CER) paradigms were evaluated respectively.

Social isolation induced LMA hyperactivity and NOR, PPI and CER deficits in vehicle treated animals compared to group housed controls. Memantine significantly ($p \leq 0.0001$ by one-way ANOVA followed by post-hoc Bonferroni test) suppressed the total LMA counts in 60 mins of socially isolated animals (216 ± 19) compared to group housed (419 ± 27) and isolation reared (534 ± 29) controls, but significantly reversed the isolation rearing induced NOR deficit ($p \leq 0.001$ by one-way ANOVA and post-hoc Bonferroni) without significantly impairing total exploratory behaviour during the recognition task. Group housed rats showed a positive discrimination ratio (DR; 0.7) in NOR, whilst socially isolated rats demonstrated significantly lower DR values (0.5) i.e. equivalent to the chance level of 50% – a deficit which was restored by memantine (DR = 0.6). Memantine failed to reverse either PPI or CER impairments at the dose tested.

These preliminary data show that acute administration of memantine can reverse postweaning social isolation-induced recognition memory deficits and suggests that glutamatergic dysfunction may contribute to the cognitive deficits seen in this neurodevelopmental animal model of schizophrenia.

The authors wish to acknowledge the BBSRC for supporting this study financially.

TA18

THE PREFERENTIAL DOPAMINE D3 VERSUS D2 RECEPTOR ANTAGONIST, S33138, REVERSES DELAY-DEPENDENT AND ISOLATION REARING-INDUCED DEFICITS IN NOVEL OBJECT DISCRIMINATION IN RATS

Watson DJG, Loiseau F, Millan MJ, Fone KCF & Marsden CA. Institute of Neuroscience, School of Biomedical Sciences,, University of Nottingham, Queen's Medical Centre, Nottingham, NG7 2UH, David.Watson@nottingham.ac.uk

Rats reared in social isolation from weaning display enduring behavioural changes, some of which are akin to those seen in schizophrenia (reviewed in Lapiz et al., 2003, Neurosci Behav Physiol, 33, 13). The preferential ("optimised") dopamine D_3 *versus* D_2 receptor antagonist, S33138, possesses antipsychotic properties in diverse rodent models and improves cognitive function both in rats and in primates (Millan et al., 2008, J Pharmacol Exp Ther, 324, 121). Accordingly, the present study examined the actions of S33138 in the isolation rearing model of schizophrenia. Potential pro-cognitive effects of S33138 were also investigated using a delay-dependent deficit in the novel object discrimination (NOD) task.

Twenty-seven male Lister Hooded rats were housed singularly from postnatal day 24. Nine rats from the same litters were group housed. Forty days after isolation, exploration of novel activity boxes was analysed for 1 hr by interruption of infra-red beams. One week later, NOD was assessed using a two hour inter-trial interval (for methods, see King et al., 2004, Neuropharmacol, 47, 195). Thirty minutes prior to both the exploration trial and NOD, isolated rats received either 0.16 or 0.63 mg/kg S33138 or saline (1 ml/kg) (s.c. n = 9 per group). Group-housed rats received saline (1 ml/kg). In a separate study, group-housed male Lister Hooded rats (200-230g, n = 12) NOD was assessed using a four hour inter-trial interval. Thirty minutes prior to the familiarisation trial, rats were dosed with 0.16, 0.63 or 2.5 mg/kg S33138 or saline (1 ml/kg) s.c. Each animal received every treatment in a pseudorandom order over the course of four weeks.

Isolation-rearing induced hyperlocomotor activity was only attenuated by the higher (0.63) dose of S33138 ($p<0.05$). Isolation-reared rats were impaired in the NOD task. This impairment was abolished by both doses of S33138 (both $p<0.01$). In a separate study, group-housed, saline-treated rats were unable to discriminate the novel from the familiar object following a four hour inter-trial interval. This impairment was significantly blocked by all doses of S33138 ($p<0.05$).

These data support the potential use of S33138 for the treatment of schizophrenia. Its improvement of cognitive performance likely reflects D_3 receptor blockade, while both D_3 and D_2 receptors may intervene in its inhibitory influence upon hyperlocomotion.

TB01

INITIAL INVESTIGATION OF THE SOCIAL RECOGNITION TEST IN MICE

Turnbull ZLL, MacSweeney, CP, Marston, HM. Pharmacology, Organon Labs Ltd part of Schering Plough Corp, Newhouse ML1 5SH, Z.Turnbull@organon.co.uk

The ability to recognise a familiar conspecific is the foundation for all mammalian social relationships. The social recognition procedure is both simple and ethologically relevant, it relies on a rodent's innate desire to investigate conspecifics. This test can be used to assess if a compound has enhancing or detrimental effects on short term memory in rodents. Although this test is well established in the rat, there is very little published data in mice. Therefore, the aim of the present study was to set up and validate the test in mice using thioperamide, GSK399885 and haloperidol.

Male C57/BL6 mice were individually housed for up to 10 days prior to testing. In the first trial, a stimulus animal (an ovariectomized female) was placed into the home cage of the test animal for 5 minutes. Time spent interacting with the conspecific was measured. After an appropriate inter-trial interval, the stimulus animal was again placed into the home cage of the test animal and the investigation time was recorded a second time. Aggressive or sexual behaviours are not included. A decrease in investigation time during the second trial indicates that the test animal still remembers the encounter with the stimulus animal.

A time-course experiment was first performed to establish a forgetting curve, namely the time point at which the test mouse displays a similar level of exploration during the first and second trials. Intertrial intervals of 60, 120 and 240 minutes and 24 hours were explored. With respect to recognition of a specific female the criteria was met at 240 minutes and above. The effects of handling and injections were then investigated. It was found that an injection prior to the first encounter increased the time required to forget the conspecific; however, this effect could be negated by prior handling of the animals. Finally, pharmacological validation was performed using the H3 receptor antagonist thioperamide, the 5-HT6 receptor antagonist GSK399885 and the antipsychotic agent haloperidol. Mice treated with thioperamide (0.30-5mg/kg) or GSK399885 (0.1-1mg/kg) spent significantly less time exploring the conspecific at 240 minutes, indicating an improvement in social memory. Haloperidol (0.003-0.03 mg/kg), on the other hand, had no effect on social memory at the doses tested.n=10mice/dose, analysed by paired t-test.

In conclusion, the social recognition test has been established in mice. Agents found to produce an improvement include the H3 receptor antagonist thioperamide and the 5-HT6 receptor antagonist GSK399885, haloperidol displayed no effect in the test.

TB02

VIGILANCE DECREMENT OBSERVATION IN THE RODENT CONTINUOUS PERFORMANCE TEST: FURTHER EVIDENCE OF TRANSLATIONAL VALIDITY

Young JW, Geyer, MA. Psychiatry, University of California, San Diego, 9500 Gilman Drive, La Jolla, 92093-0804, jaredyoung@ucsd.edu

Impaired attention/vigilance is commonly observed in neuropsychiatric patients including schizophrenia, Alzheimer's disease, Bipolar Disorder, and ADHD. Moreover, this cognitive deficiency may have causal roots in further cognitive decline in these patients, thus treatment development in attention/vigilance is paramount (Chudasama and Robbins, 2004, Psychopharmacology 174: 86-98). Attention/vigilance is commonly assessed in humans using the continuous performance test (CPT), requiring a response to signal events, and an inhibition of response to non-signal events, allowing the use of signal detection theory (SDT) to evaluate performance (Riccio et al., 2002, Arch Clin Neuropsychol 17: 235-272). There is a paucity of animal attentional paradigms that follow these task parameters however. The recently developed rodent (r)CPT uses these parameters and therefore consistent with human CPT, also allows the use of SDT to evaluate performance, providing performance measures that may be more sensitive to detecting paradigm/drug effects (Riccio et al., 2002, Arch Clin Neuropsychol 17: 235-272).

C57BL/6J (n=4) and DBA/2J (n=3) mice were trained to perform the rCPT consisting of signal and non-signal trials. Performance was then challenged with 250 (200 signal and 50 non-signal) trials, and binned by groups of 50 trials. SDT was used to generate a sensitivity index (SI) score per trial bin, which was compared across trial bins and between strains in a repeated measures ANOVA with strain as a between subject factor.

A significant genotype effect ($F(1,5)=21.3, p<0.05$), was observed, with C57BL/6J mice exhibiting superior performance compared to DBA/2J mice. An effect of trial bin ($F(4,20)=4.65$, $p<0.05$), was also observed, although no gene by trial bin interaction ($F(4,20)=1.7, p=0.24$) was observed. Post hoc analyses revealed that Bins 1 and 2 differed from bins 4 and 5 ($p<0.05$), with performance in the latter bins poorer than the former. Task parameters in the rCPT are analogous to human CPTs in which response to signal events, and inhibition of response to non-signal events, are required.

The data presented here demonstrate construct validity for the rCPT, with a vigilance decrement observed over time, consistent with the human CPT (Parasuraman, 1998, The attentive brain, MIT Press, Cambridge). Future studies will further evaluate the translational validity of the rCPT following a series of psychopharmacological challenges. Importantly, as the rCPT has been developed in mice, vigilance performance of transgenic animal models of neuropsychiatric disorders can be evaluated.

Supported by the National Institute of Mental Health (R01-MH071916; R01-MH42228), as well as a Stein Institute for Research in Aging Fellowship (JWY)

TB03

EFFECTS OF LESIONS OF THE SUBTHALAMIC NUCLEUS ON PERFORMANCE ON A PROGRESSIVE RATIO SCHEDULE

Bradshaw CM, Bezzina G, den Boon FS, Hampson CL, Body S, Cheung THC, Szabadi E, Anderson IM, Deakin JFW. Psychopharmacology Section, Division of Psychiatry, University of Nottingham, Queen's Medical Centre, Nottingham, NG7 2UH, c.m.bradshaw@nottingham.ac.uk

The subthalamic nucleus (STN), a major relay in the indirect striatofugal pathway, plays an important role in extrapyramidal motor control [Gerfen, 2004, In: Paxinos, The rat nervous system, 3rd edn., Amsterdam, Elsevier, pp.455-508]. Recent evidence indicates that it may also be involved in regulating the incentive value of food reinforcers [Baunez et al., 2005, Nature Neurosci. 8:484-489; Uslaner et al., 2005, J. Neurosci. 25:8407-8415]. We have examined the effect of lesions of the STN on performance on the progressive ratio (PR) schedule of reinforcement, analysed using a mathematical model [Killeen, 1994, Behav. Brain Sci. 17:105-172] which yields a quantitative index of reinforcer value. In PR schedules, the response requirement increases progressively for successive reinforcers. Response rate, R, in PR schedules is related to ratio size N according to a bitonic (inverted-U) function ($R = [1-(1-\beta)^N]/\delta - N/a$). The peak of the function ($1/\delta$) expresses the maximum response rate; the slope of the descending limb is 1/a, where a expresses the incentive value of the reinforcer [Killeen, 1994].

Rats received bilateral injections of quinolinic acid into the STN (0.1 M, 0.3 µl injections into each hemisphere) (n=16) or sham lesions (n=14). They were trained to steady state under the PR schedule using food-pellet reinforcement in daily 50-minute sessions. The experiment consisted of three phases: in phase 1 (90 sessions), the reinforcer was a single 45 mg pellet, in phase 2 (30 sessions), it was 2 pellets, and in phase 3 (30 sessions), it was again one pellet. Killeen's response-rate function was fitted to the data from each rat; the parameters of the equation were compared using ANOVA (group × phase; criterion, $p<0.05$).

In both groups, the value of a was higher in phase 2 (2-pellet condition) than in phases 1 and 3 (1-pellet condition). Across all three phases, the value of a was significantly greater in the STN-lesioned group (s, mean±SEM in phases 1, 2 and 3: 202±38, 308±33, 186±30) than in the sham-lesioned group (150±20, 205±25, 133±21). The value of δ (s) was significantly greater (signifying a lower peak response rate) in the STN-lesioned group (1.4±0.1, 1.5±0.1, 1.4±0.1) than in the sham-lesioned group (1.1±0.1, 1.1±0.1, 1.0±0.1). The results are consistent with the notion that destruction of the STN results in (1) an enhancement of the incentive value of food reinforcers (expressed as a), and (2) an impairment of motor performance (expressed as δ).

Supported by the Wellcome Trust.

TB04

THE EFFECT OF ACUTE PHENCYCLIDINE WITHDRAWAL, HALOPERIDOL AND CLOZAPINE ON PROGRESSIVE RATIO SCHEDULE PERFORMANCE

den Boon FS, Body S, Hampson CL, Bezzina G, Cheung THC, Bradshaw CM, Szabadi E, deBruin N. Psychopharmacology Section, Division of Psychiatry, University of Nottingham, Queen's Medical Centre, Nottingham, NG7 2UH, c.m.bradshaw@nottingham.ac.uk

It has been claimed that while conventional antipsychotics may exacerbate negative symptoms of schizophrenia (e.g. anhedonia, apathy), atypical antipsychotics may help to alleviate these symptoms [Corrigan et al., 2003, Schizophrenia Res 63:97-101]. One behavioural manifestation of anhedonia in animals is believed to be a reduction of the efficacy or 'value' of reinforcers. The claim that atypical antipsychotics may help to alleviate anhedonia therefore suggests that these drugs may enhance reinforcer value. Withdrawal from acute or chronic treatment with phencyclidine (PCP) induces a state of apathy and anhedonia in humans, and has been proposed as a means of inducing anhedonia in animals [Mouri et al., 2007, Neurochem. Int., 51:173-184]. We have examined the effects of antipsychotics and PCP-withdrawal on the performance of rats on the progressive ratio (PR) schedule of reinforcement, which allows quantitative assessment of reinforcer value. In PR schedules, the response requirement increases progressively for successive reinforcers. Response rate, R, in PR schedules is related to ratio size N according to a bitonic (inverted-U) function ($R = [1-(1-\beta)^N]/\delta - N/a$). The peak of the function ($1/\delta$) expresses the maximum response rate; the slope of the descending limb is 1/a, where a expresses reinforcer efficacy [Killeen,1994, Behav. Brain Sci. 17:105-172]. Rats (n=36) were trained to steady state (90 sessions) under a PR schedule using food-pellet reinforcement. Drugs were administered intraperitoneally (2.5 ml kg-1). PCP (6 mg kg-1, n=12) was administered 8 hours before testing, antipsychotics (clozapine 4, 8 mg kg-1, n=12; haloperidol 0.05, 0.1 mg kg-1, n=12) 30 minutes before testing. Killeen's response-rate function was fitted to the data from each rat; parameters were compared between active treatments and vehicle (ANOVA, Dunnett's test; criterion, $p<0.05$). Withdrawal from PCP (6 mg kg-1) significantly decreased a (s, mean±SEM: 113±12) compared to vehicle (165±22) and significantly increased δ (0.84±0.07) compared to vehicle (0.76±0.06). Treatment with clozapine (4, 8 mg kg-1) significantly increased a (840±139, 1043±322) compared to vehicle (283±79) and δ (1.86±0.14, 3.80±0.58) compared to vehicle (0.97±0.10). Treatment with haloperidol (0.05, 0.1 mg kg-1) significantly decreased a (156±54, 35±8) compared to vehicle (205±50). Acute withdrawal from PCP decreased a, an index of reinforcer efficacy. This is consistent with previous findings on the effect of PCP withdrawal on responding for brain stimulation reward [Spielewoy and Markou, 2003,. Neuropsychopharmac. 28:1106-1116]. The finding that clozapine increased, and haloperidol decreased a confirms previous findings with these drugs [Zhang et al., 2005, Psychopharmacology 179:489-497]. Acknowledgement. Supported by Solvay Pharmaceuticals.

TB05

EFFECT OF DISCONNECTING THE ORBITAL PREFRONTAL CORTEX FROM THE NUCLEUS ACCUMBENS CORE ON INTER-TEMPORAL CHOICE BEHAVIOUR

Bradshaw CM, Bezzina G, Body S, Cheung THC, Hampson CL, Szabadi E, Anderson IM, Deakin JFW. Psychopharmacology Section, Division of Psychiatry, University of Nottingham, Queen's Medical Centre, Nottingham, NG7 2UH, c.m.bradshaw@nottingham.ac.uk

Destruction of the orbital prefrontal cortex (OPFC) or the nucleus accumbens core (AcbC) in rats alters choice between two delayed food reinforcers [Kheramin et al., 2002, Psychopharmacology, 165:9-17; Bezzina et al., 2007, Psychopharmacology, 195:71-84]. Application of a quantitative model of inter-temporal choice ['multiplicative hyperbolic model', MHM: Ho et al., 1999, Psychopharmacology, 146:362-372] suggested that lesions of either structure increased the delay-dependent degradation of reinforcer value (delay discounting); destruction of the OPFC (but not the AcbC) also increased the relative value of the larger reinforcer. This experiment examined the effect of disconnecting the OPFC from the AcbC on inter-temporal choice.

Under isoflurane anaesthesia, rats received injections of the excitotoxin quinolinic acid into the OPFC of one hemisphere and the AcbC of the other (disconnection: n=14), severing of the anterior corpus callosum (callosotomy: n=15), a combined lesion (disconnection+callosotomy: n=13), or sham lesions (n=13). They were trained in a discrete-trials progressive delay schedule [Evenden and Ryan, 1996, Psychopharmacology, 146:413-421] to press levers A and B for a sucrose solution. Responses on A delivered 50 µl of the solution after a delay dA; responses on B delivered 100 µl after dB. dB increased across blocks of trials; dA was manipulated across phases of the experiment. The indifference delay, dB(50) (value of dB corresponding to 50% choice of B), was estimated for each rat in each phase, and linear indifference functions (dB(50) vs. dA) were derived. The slopes and intercepts of the functions were analysed by two-factor repeated-measures ANOVA (presence/absence of disconnection, presence/absence of callosotomy) followed by multiple comparisons using Dunnett's test (criterion: $p<0.05$). The linear indifference function provided a good description of the data from all four groups [$r2=0.865\pm0.022$]. The disconnection+callosotomy group showed a significantly lower intercept of the function (mean±SEM: 1.56±0.92 s) than the sham-lesioned group (5.59±1.31 s); the disconnection (3.36±1.17 s) and callosotomy (6.06±1.07 s) groups' intercepts did not differ significantly from that of the sham-lesioned group. The slope of the function did not differ significantly among the four groups. The effect of the disconnection+callosotomy lesion is similar to the effect of bilateral destruction of the AcbC [Bezzina et al., 2007]. According to MHM, a reduction of the intercept of the indifference function with no change in the slope is indicative of a change in the rate of delay discounting.

The present results thus suggest that OPFC-AcbC connections are involved in delay discounting of food reinforcers.

Supported by the Wellcome Trust.

TB06

OPPOSING EFFECTS OF 5-HT DEPLETION IN THE ORBITOFRONTAL CORTEX AND AMYGDALA ON PERSEVERATIVE RESPONDING

Man MS, Dalley JW, Roberts AC. Physiology, Development & Neuroscience, University of Cambridge, Downing Street, Cambridge, CB2 3DY, msm36@cam.ac.uk

Serotonin (5-hydroxytryptamine, 5-HT) has been implicated in aversive processing as well as in response inhibition. We have shown that 5-HT depletions of the orbitofrontal cortex (OFC) induce perseverative responding on a serial discrimination reversal task (Clarke et al, Cerebral Cortex 2007, 17:18-27) whilst other studies have implicated serotonin in the amygdala and striatum in aversive processing (Hariri et al, 2006, Biol. Psychiat. 59:888-897; Daw et al, 2002, Neural Networks, 15:603-616). However, the actions of 5-HT within the OFC and subcortical structures have not been directly compared. Thus, the present study investigated the effects of 5-HT depletions of the OFC and amygdala on an incongruent incentive discrimination task, a test of response inhibition.

Marmosets received infusions of 5,7-dihydroxytryptamine (5,7-DHT) into either the OFC or amygdala and were tested on a discrimination task involving choosing between two Perspex boxes containing high (marshmallows) or low (lab pellets) incentive food. Subjects had to inhibit their prepotent tendency to reach for the box containing high incentive food, and learn to choose instead the box containing low incentive food to receive "syrup bread" reward. 5-HT-lesioned OFC animals (n=2) made significantly more errors ($p=0.03$) to reach criterion compared to controls (n=4). This was due to increased perseverative responding to the high incentive food ($p=0.015$). In contrast, 5-HT-lesioned amygdala animals (n=3) were indistinguishable from controls in the total number of errors to criterion, despite significantly less perseverative errors ($p=0.05$). In vivo amygdala microdialysis revealed that, compared to controls, baseline extracellular 5-HT levels in amygdala lesioned animals were undetectable and potassium evoked increases in extracellular 5-HT were significantly blunted (95%). Post mortem tissue analysis showed mean 5-HT depletion of 73% and 50% in the OFC and amygdala of 5,7-DHT OFC and amygdala lesioned animals, respectively. These findings reveal opposing behavioural effects of 5-HT depletions within the OFC and amygdala. 5-HT OFC depletion impaired learning to inhibit a prepotent response due to increased perseverative responding, whereas 5-HT amygdala depletion reduced perseverative responding, without potentiating learning. These findings will be discussed with respect to the role of 5-HT in both OFC-mediated cognitive flexibility, and motivational aspects of amygdala function. These results have important implications for the role of OFC and amygdala 5-HT in compulsive disorders and depression. Supported by the Medical Research Council Programme Grant (MRC, G0401411) to ACR, and performed within the Behavioural and Clinical Neurosciences Institute supported by a joint Wellcome Trust and MRC UK consortium award.

TB07

ATTENUTATION OF THE EFFECTS OF D-AMPHETAMINE ON INTERVAL TIMING BEHAVIOUR BY 5-HT DEPLETION

Body S, Cheung THC, Hampson CL, den Boon FS, Bezzina G, Fone KCF, Bradshaw CM, Szabadi E. Psychopharmacology Section, Division of Psychiatry, University of Nottingham, Queen's Medical Centre, Nottingham, NG7 2UH, stephanie.body@nottingham.ac.uk

It has been proposed that dopaminergic neurotransmission plays a role in interval timing behaviour (Meck, 1996 Cognitive Brain Research 3:227-242). Interval timing in the free-operant psychophysical procedure (FOPP: Stubbs, 1976, J Exp Anal Behav 6:15-25) is sensitive to the dopamine-releasing agent d-amphetamine, the D2 dopamine receptor agonist quinpirole and the D1 receptor agonist 6-chloro-2,3,4,5-tetrahydro-1-phenyl-1H-3-benzepine (SKF81297) (Body et al., 2006, Psychopharmacology 189:331-343; Cheung et al., 2006 Psychopharmacology 185:378-388; Cheung et al., 2007, Psychopharmacology 193:423-436). Previous studies indicated that d-amphetamine's effect can be antagonised by selective D1 receptor and 5-HT2A receptor antagonists (Body et al., 2006). This experiment examined whether the effects of d-amphetamine, quinpirole and SKF-81297 are disrupted by destruction of the 5-HTergic pathways.

Under isoflurane anaesthesia, rats received injections of the neurotoxin 5,7-dihydroxytryptamine (4µg in 2µl phosphate-buffered 0.9% saline) into both the dorsal and median raphe nuclei (n=10), or sham lesions (n=13). Rats were trained under the FOPP to press levers A and B in 50-s trials in which reinforcement was provided intermittently for responding on A in the first half, and B in the second half of the trial. Percent responding on B (%B) was recorded in successive 5-s epochs of the trials; logistic functions were fitted to the data for derivation of timing indices (T50, time corresponding to %B=50%; Weber fraction). The effects of d-amphetamine (0.4 mg kg-1, i.p.), quinpirole (0.08 mg kg-1, i.p.) and SKF-81297 (0.8 mg kg-1, s.c.) were compared between lesioned and sham-lesioned animals (t-test; criterion, $p<0.05$. Concentrations of 5-HT and catecholamines in the brain were measured by high-performance liquid chromatography. Sham-lesioned group: T50 was reduced by d-amphetamine (mean±SEM: 11.40±1.3 s), quinpirole (9.45±0.96 s), and SKF81297 (7.18±1.19 s) compared to vehicle-alone treatment (15.01±1.82 s). None of the treatments affected the Weber fraction. Lesioned group: T50 was reduced by quinpirole (10.69±0.79 s) and SKF81297 (8.99±1.42 s), but not by d-amphetamine (13.91±1.50 s), compared to vehicle-alone treatment (14.55±1.11 s). The Weber fraction was increased by SKF81297 (0.56±0.07) compared to vehicle-alone treatment (0.29±0.03). Levels of 5-HT in the neocortex and striatum were reduced by >80% in the lesioned group; catecholamine levels were not affected.

The results suggest that the effect of d-amphetamine on performance in the FOPP is dependent upon an intact 5-HTergic system. This is consistent with previous evidence for a functional interaction between dopamine and 5-HT receptors in the effects of d-amphetamine on interval timing in this schedule (Body et al., 2006).

Supported by the BBSRC

TB08

PERFORMANCE OF HEAD-INJURED PATIENTS ON AN INTER-TEMPORAL CHOICE TASK: A QUANTITATIVE ANALYSIS

Ho M-Y, Lee S-S, Yeh P-Y, Yang Y-Y, Bradshaw CM. Institute of Clinical Behavioural Science, Chang Gung University, 259 Wen Hwa 1st Road, Kwei Shan, Tao Yuan County 333, myho@mail.cgu.edu.tw

The multiplicative hyperbolic model of inter-temporal choice [MHM: Ho et al., 1999, Psychopharmacology 146:362-372] provides a theoretical basis for quantifying choice between rewards that differ with respect to their sizes, delays and/or probabilities. The aim of the present study was to evaluate head-injured patients' sensitivity to delayed reinforcement and reward size using a quantitative paradigm based on MHM.

Twenty-eight healthy volunteers and twenty-six patients with frontal lobe injuries (11 with additional injuries to temporal or parietal regions) were recruited. They pressed two buttons (A and B) for monetary rewards. A produced a smaller reward (NT$=0.5) after a short delay, dA, and B a larger reward (NT$=1.0) after longer delays, dB. dA was manipulated across 5 blocks of 50 trials. Indifference delays, dB(50) (value of dB yielding 50% choice of B), were estimated for each participant in each block. The dB(50)s derived from all blocks for both groups were compared using ANOVA with repeated measures. A linear function of dB(50) vs dA was fitted to the data from each participant; the slopes and intercepts were compared between groups using independent t-tests (criterion, $p<0.05$).

The results showed that each participant's dB(50) increased linearly with dA [$F(4,208)=73.83$, $P<0.001$; r2s>0.90]. The dB(50)s for the head-injured group were significantly lower than those for the control group across most blocks [$F(1,52)=4.58$, $P<0.05$]. There was also a significant group × block interaction [$F(4,208)=4.35$, $P<0.05$]. The control group showed steeper slopes of the linear function (mean±SEM: 3.85±0.53) than those obtained from the patient group (2.31±0.44) [$t(52)=2.21$; $P<0.05$]; but the intercept in the patient group (0.52±0.36) was not significantly different from that in the control group (0.12±0.81) than [$t(52)<1$]. According to MHM, the linear relation between dB(50) and dA is determined by sensitivity to both reinforcement delay (K) and reinforcement quantity (Q), according to the equation, $dB(50)= dA.[(1+Q/qA)/(1+Q/qB)] + [(1+Q/qA)/(1+Q/qB) - 1]/K$ [Ho et al., 1999]. The flatter mean slope shown by the head-injured patients signifies a lower value of Q, suggesting that their sensitivity to reinforcement quantity might have been altered. Although the intercept did not differ significantly between the two groups, the estimated value of K for the patient group appeared to be larger than that for the control group based on the group mean slope and intercept [K= (slope-1)/intercept, Ho et al., 1999]. This suggests that the patient group is also less tolerant of delay of reinforcement.

The work was supported by the National Science Council, Taiwan (NSC96-2413-H-182-001).

TB09

A MEASURE OF TEMPORAL DISCOUNTING FOLLOWING TRAUMATIC BRAIN INJURY

McHugh L, Wood RL. Psychology, Swansea University, Singleton Park, Swansea, l.mchugh@swansea.ac.uk

The term *temporal discounting* refers to the tendency for some individuals to prefer smaller sooner rewards (SSRs) over larger later rewards (LLRs). Research has shown that decision making for SSR's or LLR's is not affected by real versus hypothetical rewards. The choice of an immediate smaller reward over a delayed larger reward is said to exemplify impulsivity whereas choice of the delayed larger reward reflects self control. A temporal discounting paradigm may therefore be a useful paradigm to explore impulsive decision making following traumatic brain injury (TBI). The current study employed a temporal discounting paradigm to compare decision making in a group of TBI patients with age and IQ matched controls. No external funding was provided for the research.

28 individuals participated (14 TBI patients and 14 controls). The TBI patients were recruited from a consecutive series of referrals to the Head Injury Clinic at Swansea University. Patients were included in the study if they had suffered a closed head injury, without previous history of head trauma, neurological disease or psychiatric disorder (including drug and/or alcohol abuse). All participants were between 18-65 years; with no history of learning difficulties, and free of perceptual, language, or motor disorders that might have affected their performance on the discounting task. Participants were asked to choose between a larger hypothetical monetary reward available at a specified time in the future and smaller hypothetical monetary reward available immediately. An example trial from the procedure is as follows: Would you prefer £60 now or £100 in one month. Each of the two groups demonstrated temporal discounting; that is, the subjective value of the reward decreased with increasing delay. However, the TBI group discounted significantly more than the controls ($p<.01$), suggesting that their decision making was more impulsive.

The results suggest that a temporal discounting paradigm might be used as a means of quantifying the degree of impulsivity affecting decision making after head trauma. The present data add to the self-control/impulsivity literature, by indicating that the amount of temporal discounting is higher in those suffering from TBI, implying that this will largely be a consequence of frontal dysfunction. Individuals who display impulsive decision making and behaviour are less able to evaluate the future consequences of their actions, therefore discounting procedures could potentially be used as part of a neurobehavioural assessment both for rehabilitation purposes and to predict psycho-social outcome.

TB10

ASSESSMENT OF COGNITIVE AFFECTIVE BIAS IN HEALTHY HUMAN VOLUNTEERS USING A NOVEL TRANSLATIONAL TONE DISCRIMINATION TASK

Robinson ESJ, Hardcastle C, Munafò MR. Physiology and Pharmacology, University of Bristol, University Walk, Bristol BS8 1TD, Emma.S.J.Robinson@bristol.ac.uk

In human research negative attentional bias and enhanced memory for negatively valenced information has been attributed to affective disorders such as depression and anxiety. These important features of the human psychiatric conditions have been largely overlooked in pre-clinical studies because of a lack of suitable translational methodology. In order to address this, we have undertaken a reverse translation approach. A cognitive affective bias (CAB) task was developed for rats based on an emotional go/no-go paradigm (Harding et al., 2005, Nature 427:312).

In this task, rats are trained to discriminate between two tones predicting reward or avoidance of punishment. Probe trials, analogous to ambiguous information, were introduced and response selection and latency quantified. Induction of a depressive phenotype resulted in a significant negative bias in responding in rats. To complete the reverse translation, we have now developed and tested an identical task using human volunteers. The computer-based task attributes 'reward' (money) and 'punishment' (burst of white noise) to two pure tones 400Hz apart. The subjects learnt to discriminate between the tones in order to receive a cash reward or to avoid punishment. After an initial training phase, probe tones of intermediate frequency were include in the task. The probe tones were equally distributed across the mid-point frequency and were assigned as reward or punishment based on their relative frequency.

At the end of testing, the STAI questionnaire was completed to provide a measure of baseline mood state. Response selection and response latency for each set of 'pure' tones and intermediate 'probe' tones were quantified. Analysis of the data examined, the response selection and latency for each of the tone frequencies and the slope of the line following linear regression analysis of % positive responding during probe trials. Results were then compared with mood score using a x-y Pearson correlation analysis. Analysis of an initial data set (9 healthy volunteers, ages 22-35, 5 female, 4 male, revealed a significant correlation between positive affect score (from the revised STAI) and response bias during probe tones ($p=0.026$, $r= 0.63$). A significant correlation was also found between STAI state anxiety score and response bias during probe tones ($p=0.036$, $r= 0.66$). These data provide an initial indication that a tone based discrimination task, pairing neutral cues with emotionally-relevant outcomes can be undertaken in both humans and rodents. The preliminary results suggest that responses to probe trials are sensitive to cognitive affective bias.

Funding: ESJR holds an RCUK Academic Fellowship supported by the British Pharmacological Society Integrative Pharmacology Fund.

TB11

THE ROLE OF ATTENTION AND EMOTION IN CONDITIONING

Austin A, Hogarth L, Duka T. Psychology, University of Sussex, Brighton BN1 9QH, aja20@sussex.ac.uk

Learning theories state that in order to maximise learning efficiency attention towards a stimulus is governed by how predictive that stimulus is of an outcome. However, attention can also be drawn to stimuli that have rewarding properties and withdrawn from stimuli with aversive properties. We examined the impact of the emotionality of stimuli on attentional processes that may occur independent of learning about the outcome. A computerised Pavlovian conditioning paradigm with either a negative reinforcer or a positive reinforcer was used to see if attention to stimuli, with different outcome contingencies, followed predictive rules or appeared to be influenced by the emotional qualities of the stimuli.

Thirty two participants (16 males) completed either the aversive or appetitive conditioning task whilst wearing an eye-tracker device for measuring eye movements. Participants were presented with picture pairs one of which predicted the outcome of the occurrence of the reinforcer and the other which was a neutral stimulus (contextual cue). The predictive stimuli provided differential information for the likelihood of a blast of 97db white noise or of a win of 10p to occur with one of the following contingencies: 100% (S+), 50% (S+/-), or 0% (S-). The measures of attention were dwell time, first fixation duration, and latency to first fixation. Mixed ANOVAs with reinforcer type as the between subjects factor and stimulus probability as the within subjects factor were applied to each of the attentional measures.

The dwell time for the noise S+ was greater than for the money S+($p<0.05$). First fixation duration was greater for the contextual cue when presented with the noise S+/-($p<0.05$) . This effect was not seen with the contextual cue when presented with the money S+/-. Across blocks of trials latency to first fixation increased for the money S- while it decreased for the noise S-($p<0.05$). The avoidance found for the noise S+/- but not for the money S+/- in first fixation duration suggests that the aversive qualities of a stimulus may lead to withdrawal of attention. The decrease of attention to the money S- and the increase of attention to the noise S- over time indicate that the noise S- acquiring positive emotional properties, thereby engaging attention. However, allocation of attention was greater for the noise S+ than for the money S+ implying that the predictive value of the stimulus may also control attention albeit in aversive more than in appetitive learning. ESRC funded.

TB12

PREGNANCY ADVERSELY AFFECTS COGNITIVE FUNCTION IN CERTAIN DOMAINS: EFFECTS OF TASK AND STAGE OF PREGNANCY

Farrar D, Neill JC, Tuffnell DJ, Marshall KM. School of Pharmacy, University of Bradford, Richmond Road, Bradford BD7 IDP, diane.farrar@bradfordhospitals.nhs.uk

Background: Few studies have attempted to perform an objective assessment of memory in pregnancy and results are equivocal. Female sex steroids influence learning and memory and the neurobiology of brain regions involved in memory processing such as hippocampus (see Cahill, (2006) Nature Reviews Neuroscience 7: 477-484 for review). Pregnancy allows overriding of regulatory feedback loops leading to substantial elevation of endogenous serum hormone levels. The aim of this investigation is to increase understanding of the effects of pregnancy and gonadal steroid hormone levels on cognitive ability.

Methods: Participants (n=40) are being tested pre-conceptually, each trimester and post-natally in a longitudinal study. Non-pregnant controls are tested using the same methodology. Demographic, mood and general health data are collected at each session. Verbal intellectual ability is assessed using the National Adult Reading Test. The Cambridge Neuropsychological Test Automated Battery (CANTAB), a non-invasive computer based task, is used to examine working memory, planning ability and attention. Plasma samples are obtained at each session for later steroid hormone analysis. Data were analysed using SPSS version 14 and found to be normally distributed using the Kolmogorov-Smirnov test. Independent samples *t*- test compared pregnant and control group mean scores for each test session outcome measure. The study received ethics approval and was funded by the University of Bradford and Bradford Teaching Hospitals.

Results: During the first trimester, pregnant participants showed a significant performance deficit in the delayed matching to sample-DMS- % correct all delays test, compared with controls: pregnant group 78% ±1.8, control 85% ± 1.5 ($p=0.003$) and DMS-probability of an error following an error, pregnant group 0.17 ±0.01, control group 0.07 ±0.02 ($p=0.03$). During the second trimester, pregnant participants showed a significant performance deficit in the spatial recognition memory task-% correct, pregnant group 73%±2.4, control group 84%±3.9, ($p=0.02$). There were no statistically significant differences between groups in the Stockings of Cambridge and Intra/extra dimensional shift tests, IQ, age or general wellbeing.

Conclusions: Initial data support the hypothesis that pregnancy adversely affects performance of certain cognitive tasks particularly in the first trimester, specifically simultaneous and short term visual working memory. The significant finding in terms of probability error, suggests a pregnancy related memory processing deficit. Specific first trimester deficits may have particular relevance for pathology induced in offspring following first trimester trauma (Khashan et al. (2008) Archives of General Psychiatry.65:146-152). On-going work is gathering data and correlating gonadal steroid hormone levels with cognitive performance in order to determine cognitive deficits in subsequent trimesters and post-partum and to explore the mechanism of these cognitive deficits.

TC01

MODULATION OF 5-HT NEURONAL ACTIVITY BY DHEA AND ITS METABOLITES

Gartside SE, Griffith NC, Kaura V, Ingram CD. Institute of Neuroscience, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, sasha.gartside@ncl.ac.uk

It is established that circulating levels of the steroid dehydroepiandrosterone (DHEA) decrease with age. Low DHEA levels have been associated with cognitive decline and anxiety and mood disorders and DHEA supplements are taken by many individuals. Neurosteroids, including DHEA, reportedly modulate GABAA receptor function. Here we examined the ability of DHEA and two of its metabolites – the sulphated conjugate DHEA-S and the androgen, androsterone (ADT) - to modulate the function of GABAA receptors regulating 5-HT neuronal firing in the dorsal raphe nucleus (DRN).

Slices of DRN from adult male hooded Lister rats were perfused continuously with phenylephrine (PE) (1 uM). Extracellular recordings of the firing activity of individual 5-HT neurones were made. The effects of DHEA, DHEA-S and ADT on basal firing rate and on the responses to the GABAA receptor agonists, 4,5,6,7-tetrahydrisoxazolo[5,4-c]pyridinyl-3-ol (THIP) and GABA, were determined. Drugs were applied via the perfusion with agonists applied for 2 min and neurosteroids applied for 5 min -3 min before and 2 min during reapplication of the agonist. Groups comprised between 4 and 19 neurones. Concentration-response data were analysed by ANOVA, between-group comparisons were made by paired t-test. Significance at the 5% level is reported. 5-HT neurones fired slowly (around 1Hz) and regularly. THIP (25 uM) and GABA (30 uM) rapidly and reversibly inhibited firing. DHEA (1-300 uM) caused a small concentration-dependent reduction in the inhibitory effect of THIP which was significant at 100 and 300 uM. DHEA (100uM) also significantly reduced the effect of GABA. DHEA-S (1-100 uM) caused a concentration-dependent reduction in the response to THIP which was significant at 1, 10 and 100 uM. DHEA-S (100uM) also significantly reduced the effect of GABA (30 uM). It was notable that DHEA-S was both more potent and more efficacious than DHEA. ADT (10 and 30 uM) enhanced the effect of THIP on 5-HT firing. Interestingly, whilst the effect of DHEA and DHEA-S was evident only during application of the drug, the effect of ADT was maximal 15 min following a 5 min application and lasted for at least 30 min. None of the steroids tested altered the basal firing rate.

The results indicate that DHEA and its metabolites can influence the GABAergic regulation of 5-HT neuronal firing and hence 5-HT neurotransmission in the forebrain. Given the putative roles of 5-HT in cognition, mood and anxiety regulation, our data suggest that endogenous and exogenous DHEA will impact on these brain functions.

TC02

IMPACT OF ASPIRIN PRE-TREATMENT ON NEUROENDOCRINE AND NEUROPSYCHOLOGICAL FUNCTION IN HEALTHY SUBJECTS

Menon A, Place S, Horton K, Corcoran C, Gallagher P, Carlile J, Watson S. University of Newcastle, School of Neurology, Neurobiology and Psychiatry,, Royal Victoria Infirmary(Leazes wing), Richardson road, Newcastle upon Tyne NE1 4LP, menon.anuradha@gmail.com

Major depressive disorder (MDD) is one of the leading contributors to global burden of disease, partly because of high rates of treatment non-response. Overactivity of the hypothalamic-pituitary-adrenal (HPA) axis predicts non-response and its normalisation during standard treatment appears to precede response. Antiglucocorticoid agents have efficacy as augmenting agents (Gallagher,P. et al Cochrane Database Syst Rev. 2008 Jan 23;(1):CD005168.), however, such agents are not available in routine care. There is a need to find safe,easily available drugs which normalise the HPA axis and thereby have utility in the treatment of MDD. In chronic stress arginine vasopressin (AVP), which acts via a prostaglandin (PG) dependent process, appears to become the dominant adrenocorticotropic hormone (ACTH) secretagogue. A single 600mg dose of the PG inhibitor aspirin has previously been shown to reduce ACTH and cortisol response to AVP challenge (Nye, E. et al. (1997) Journal of Clinical Endocrinology and Metabolism 82(3): 812-817.) Aspirin has also been shown to blunt anticipatory pre-exercise increase in ACTH and cortisol and to reduce post-exercise cortisol concentrations. Aspects of neuropsychological function have been shown to be dependent on HPA axis function and to be a sensitive proxy measure of treatment response. We hypothesise that aspirin will attenuate HPA axis function and cortisol dependent measures of neuropsychological performance. In a double-blind, within-subject placebo-controlled, random order, cross-over study design, we examined the impact of acute (600mg at 10am) and sub-chronic aspirin (300mg daily for 7 days) treatment in 18 healthy male subjects on waking salivary cortisol, plasma cortisol, ACTH response to ddAVP and on neuropsychological performance using backwards digit span (shown to be reduced in mood disorder patients and cortisol sensitive) and using control measures (Rey AVLT, verbal fluency) AVP challenge (100mcg ddAVP) produced a significant plasma cortisol and ACTH response which was not attenuated by aspirin pre-treatment. Salivary cortisol response was significantly attenuated by chronic aspirin treatment. Neuropsychological results showed a significant improvement in verbal working memory (backwards digit span) with aspirin pre-treatment(df 2.0, F 4.45 p value .025).Control measures were unaffected. 2 patients were excluded from the analysis as plasma salicylate levels were elevated in the placebo arm. Preliminary data suggests that aspirin attenuates some measures of HPA axis function and specifically enhances backwards digit span suggesting that further research into its potential use as an augmenting agent in TRD is warranted.

This study was funded by the RVI hospital trustees and the NTW Trust

TC03

OXYTOCIN ENHANCES POSITIVE VERSUS NEGATIVE EMOTIONAL INFORMATION PROCESSING IN HEALTHY MALE VOLUNTEERS

Di Simplicio M, Massey-Chase R, Cowen P, Harmer CJ. Department of Psychiatry, University of Oxford, Warneford Hospital, Warneford Lane, Oxford OX37JX, martina.disimplicio@psych.ox.ac.uk

Rationale: Animal studies have shown the role of oxytocin in affiliation and attachment and recent evidence suggests that oxytocin is also involved in human models of approach behaviour, possibly by modulating the processing of emotionally valenced stimuli. Although oxytocin administration has been reported to decrease neural responses to facial emotional information and to modulate trusting behaviour, the effects on a wider range of behavioral measures of basic emotional processing previously shown to be sensitive to antidepressant manipulation have not been examined.
Objective: The aim of this study was to investigate whether intranasally administered oxytocin affects the processing of positive and negative affective information in healthy male volunteers across tasks measuring attention, perception and memory.
Methods: Twenty-nine male healthy volunteers were randomly allocated to receive a single dose of oxytocin nasal spray (24 UI) or placebo. Fifty minutes later, participants completed a battery of psychological tests measuring emotional processing. Data were analysed using between-groups repeated measures analyses of variance with treatment group as between-subjects factor and facial expression or valence as within-subjects factor. Interpretation of significant interaction effects was aided by simple main effect analyses. The study was funded by a MRC grant.
Results: A single-dose of intranasally administered oxytocin slowed reaction time to correctly identify fearful facial expressions (emotion x intensity x group, $p=0.037$; emotion x intensity for fearful faces, $p=0.017$) and reduced the misclassification of positive or ambiguous facial expressions as negative ones (group x valence, $p=0.031$; T test positive/ambiguous to negative misclassifications, $p=0.010$.). Volunteers receiving oxytocin were also more likely to recall words describing positive characteristics, although this was predominantly seen on a task featuring non-self-relevant adjectives (group x valence, $p=0.023$). These effects occurred in the absence of significant differences in subjective ratings of mood and anxiety.
Conclusions: Oxytocin modulates emotion processing in healthy male volunteers. The present results could not be explained by effects on sedation, vigilance or face processing. Therefore, oxytocin may produce an emotional processing pattern which is less focused on potential negative threats, reducing the salience of ambiguous stimuli and leading to a more general increase in perception of positive social cues. Compared with previous reports of the effects of antidepressants on emotional processing tasks, the action of oxytocin appears more limited. However, it could be speculated that the neuropeptide could play a role in improving a more specific set of functions, in line with its emerging role in promoting affiliative and approach behaviour.

TC04

A MODEL OF MILD NEGATIVE AFFECT IN A NEW WORLD PRIMATE: A NEURAL AND PHARMACOLOGICAL INVESTIGATION

Mikheenko YP, Braesicke K, Johns ME, Man M, Roberts AC. Dept. of Physiology, Development and Neuroscience, and the Behavioural and Clinical Neurosciences Institute, University of Cambridge, Downing Street, Cambridge, CB2 3DY, ypm20@cam.ac.uk

Changes in autonomic activity are a core component of negative emotions, and the way such changes are regulated is an important indicator of a person's resilience to stress. Abnormal cardiovascular responses are linked to low trait resilience (Tugade and Fredrickson, 2004, J. Pers. Soc. Psychol., 86(2): 320-333) and affective disorders such as post-traumatic stress disorder and major depression. We have developed a model of mild negative emotionality in the marmoset (Callithrix jacchus) that can be used to probe the pharmacological and neural underpinnings of the cardiovascular changes during negative affect. Marmosets received Pavlovian conditioning in which a neutral stimulus (~80 dB sound, 20 s) predicted the onset of a burst of aversive loud noise (~110 dB, 0.2 s). Heart rate (HR) changes were monitored by radiotelemetry, and anxious behaviours were scored. Acquisition of conditioned responses in un-operated ($n = 3$) and amygdala-lesioned ($n = 2$) subjects was compared to an un-operated pseudoconditioned group ($n = 3$). The autonomic nervous system control of conditioned HR during extinction trials was investigated in two un-operated animals by intramuscular administration of a parasympathetic antagonist, atropine methyl nitrate, and a sympathetic antagonist, sotalol hydrochloride. All conditioned subjects acquired acceleratory HR responses to the predictive sound within 2 sessions (criterion: over a 15-trial session, HR during the sound is significantly above baseline, $P < 0.01$, one-sample t test), accompanied by anxious behaviours. Pseudoconditioned HR accelerations were less consistent, 2 out of 3 animals showing either no change (last session, $t = 0.52$, NS) or HR deceleration (last session, $P < 0.05$) after 5 sessions. Excitotoxic amygdala lesions impaired the acquisition of conditioned responses, animals failing to show significant HR acceleration after 5 sessions (last session, $t = 1.17$ and 0.52, NS). Conditioned HR was sensitive to both parasympathetic and sympathetic antagonist administration (one-way ANOVA, P's < 0.05). In conclusion, HR accelerations and anxious behaviours show that anticipation of aversive loud noise induces mild negative affect in marmosets, the acquisition of which is amygdala-dependent. Future studies will determine the role of prefrontal cortex and the monoamines in the regulation of negative emotion, which may provide insights into treating affective disorders. Supported by a Medical Research Programme Grant (G0401411) from the Medical Research Council UK (MRC) to ACR. YPM is supported by an MRC studentship. Work was carried out within the Behavioural and Clinical Neurosciences Institute supported by a consortium award from the Wellcome Trust and the MRC.

TC05

THE EFFECT OF ANTIPSYCHOTIC DRUG ADMINISTRATION ON HYPOTHALAMIC EXPRESSION OF NEURONAL NITRIC OXIDE SYNTHASE AND NEUROPEPTIDE Y IN THE MALE RAT

Zhang XR[1], Zhang ZJ[2], Reynolds GP[1]. [1]Div of Psychiatry and Neuroscience, Queen's Univ Belfast, 97 Lisburn Road, Belfast BT9 7BL, [2]Dept of Neurology, Afiliated Zhongda Hospital of Southeast University, China xzhang08@qub.ac.uk

Object: Antipsychotic drug-induced sexual dysfunction is a common and problematic side effect, which may diminish quality of life and lead to treatment non-compliance. It has been demonstrated that neuronal nitric oxide (nNOS) and neuropeptide Y (NPY) in the medial preoptic area (MPOA) of the hypothalamus have important roles in the regulation of sexual behaviour. We investigated the influences of administration of haloperidol, risperdone and quetiapine on expression of nNOS and NPY in MPOA. **Methods:** Four groups of 3-month-old male Sprague-Dawley rats (n=7 in each group) received intraperitoneal injection of haloperidol (0.5mg/kg), risperidone (0.25mg/kg), quetiapine (20mg/kg) or vehicle (saline) once daily for three weeks. Rats were anesthetized with 30mg/kg pentobarbital intraperitoneally 24 hours after the last drug injection, perfused with 4% paraformaldehyde and brains embedded into wax blocks. Immunostaining was used to identify nNOS and NPY expression. Immunopositive neuronal density and integrated optical density were measured in two sub-nuclei of MPOA: anterodorasal preoptic nucleus (ADP) and medial preoptic nucleus (MPN). Results were compared by one-way ANOVA with significance at $p<0.05$. **Results:** nNOS-immunopositive neuron density in ADP for each group expressed as mean (SD) in cells per mm^2, was: controls 87.7 (18.0); haloperidol 65.4 (15.4); risperidone 79.1 (13.4); quetiapine 89.2 (17.9), in which only haloperidol value was significantly reduced below control. There was no significant difference of neuron density in MPN between four groups. NNOS integrated optical density (relative values) in ADP was: controls 258.7 (63.9); haloperidol 113.2 (63.1); risperidone 143.7 (45.6); quetiapine 285.7 (104.9), in which changes of haloperidol and risperidone were statistically significant. The nNOS integrated optical density in MPN was significantly decreased by haloperidol 151.8 (102.6), but not by risperidone 172.5 (50.4) or quetiapine 170.7 (72.1), compared with the control group 256.2 (95.1). Neither immunopositive neuron density nor integrated optical density for NPY was significantly affected in the two sub-regions of MPOA by any antipsychotic drug. **Conclusions:** The expression of nNOS in the MPOA was affected to different extents by the long-term administration of risperidone and haloperidol, but not by quetiapine. These central effects might play a role in sexual dysfunction induced by certain antipsychotic drugs.

TC06

THE EFFECTS OF ANTIPSYCHOTICS ON ERECTILE FUNCTION, NITRIC OXIDE SYNTHASE ACTIVITY AND GENE EXPRESSION IN RAT PENILE TISSUES

Zhang XR[1], Zhang ZJ[2], Reynolds GP[1]. [1]Div of Psychiatry and Neuroscience, Queen's Univ Belfast, 97 Lisburn Road, Belfast BT9 7BL, [2]Dept of Neurology, Afiliated Zhongda Hospital of Southeast University, China xzhang08@qub.ac.uk

Objective: Antipsychotic drug treatment may be associated with common and problematic sexual dysfunction, especially impotence, which can diminish quality of life and lead to treatment noncompliance. The present study investigated the effect of haloperidol, risperidone and quetiapine on erectile function using the rat copulatory behaviour test. Nitric oxide synthase (NOS) is an important cellular modulator of erectile function. We also investigated the effect of antipsychotic drug administration on activity and gene expression of NOS in rat penile tissues. **Methods:** Twelve groups of Sprague Dawley rats (n=7 each) were orally treated by gavage with haloperidol (0.25, 0.5 or 1 mg/kg), risperidone (0.125, 0.25 or 0.5 mg/kg), quetiapine (10, 20 and 40 mg/kg) or vehicle (distilled water) in the corresponding control groups respectively once daily for three weeks. Their penile erectile behaviours were evaluated with the copulatory behavior test 10 hours after the last treatment. Animals were killed 24 hours after last treatment and NOS activity of the penile tissue was measured spectrophotometrically using a commercial kit based on the NO oxidation of oxyhaemoglobin to methaemoglobin, permitting determination of inducible NOS (iNOS) and constitutive NOS (cNOS) activities, the latter including endothelial NOS (eNOS) and neural NOS (nNOS). The mRNA of eNOS, nNOS and iNOS in the penile tissues were analyzed by relative quantitative real-time polymerase chain reaction. Mann-Whitney U-test was used for the analysis of copulatory behaviors between groups. Results of NOS activity and mRNA expression were compared by one-way ANOVA. Significance was set at $p<0.05$. **Results:** Mount and intromission frequency were significantly decreased in 1mg/kg haloperidol group after three weeks treatment compared with control group. 1 mg/kg haloperidol also significantly suppressed the 'hit ratio' (intromissions/mounts), which indicated erectile dysfunction. 0.5mg/kg risperidone significantly reduced mount and intromission frequency, however the 'hit ratio' showed no significant difference from control. There were no significant changes of sexual behaviour with lower doses of either haloperidol or risperidone. The activity of cNOS was significantly decreased below control only in the 1mg/kg haloperidol group. The expression of eNOS and nNOS mRNA were significantly reduced in penile tissues from the high dose haloperidol group. High dose risperidone also reduced the eNOS mRNA expression. No dose of haloperidol or risperidone had a significant effect on gene expression and activity of iNOS in penile tissue. Quetiapine significantly increased iNOS mRNA expression with 20 and 40mg/kg doses, while sexual behaviour and NOS activity were not influenced by any dose of quetiapine. **Discussion:** This study along with our previous work (Zhang X, et al. 2007 J Psychopharmacol. 21: 428-434) identified that the clinical sexual dysfunction following antipsychotic treatment could be modelled in the rat with appropriate drug dose and duration. This is the first study to indicate that the gene expression and activity of isoforms of NOS are differentially affected by chronic antipsychotic treatment in rat penile tissues. These preliminary results have important implications for enhancing our understanding of mechanisms by which antipsychotic drugs induce sexual dysfunction.

TC07

NEUROTROPHINS IN AUTISTIC SPECTRUM DISORDER, SCHIZOPHRENIA AND ATTENTION DEFICIT AND HYPERACTIVITY DISORDER

Hunnerkopf R, Forbes-Robertson S, Jans T, Romanos J, Klampfl K, Romanos M, Renner T, Irblich B, Coogan A, Dudley E, Haberhausen M, Martin B, Theissen FM, Gudererian F, Mehler-Wex C, Warnke A, Gerlach M, Thome J Academic Unit of Molecular Psychiatry, Institute of Life Sciences, Swansea University, Singleton Park, SA3 4EA Swansea, r.hunnerkopf@swansea.ac.uk

Introduction: Neurodevelopmental abnormalities have been implicated in the pathophysiology of psychiatric conditions, such as autistic spectrum disorder (ASD), schizophrenia or attention-deficit hyperactivity disorder (ADHD). During embryogenesis and in adult life, neurotrophins play a crucial role in the proliferation, migration, differentiation and survival of neurons in the CNS. Altered expression and/or function of these neurotrophic factors may cause neural maldevelopment, migrational deficits, disconnections and an impaired neuroplasticity. In fact, such structural abnormalities as well as altered levels of neurotrophins in the brain or periphery have been reported in ASD and schizophrenic patients. The aim of this ongoing study is to compare specific neurotrophin protein and mRNA levels in serum obtained from children and young adults with ASD, schizophrenia, ADHD and healthy controls, in order to clarify their role in the pathophysiology of these conditions and to identify potential diagnostic and prognostic biomarkers. The project is funded by the German research council.
Methods: Serum brain derived neurotrophic factor (BDNF) and neurotrophin NT3, NT4/5 levels of ASD (n=30), early-onset schizophrenia (n=6) and ADHD (n=5) patients as well as matched healthy controls (n=32) are measured using an enzyme-linked immunosorbent assay (ELISA). Neurotrophin mRNA expression will be assessed by quantitative reverse transcription PCR.
Results: Our results revealed a mean BDNF serum concentration ± SD of 19524 ± 2039 pg/ml in schizophrenic patients, 20492 ± 6259 pg/ml in the ASD group, 21100 ± 5008 pg/ml in ADHD patients, and 23179 ± 3894 pg/ml in healthy control subjects. A one-way-ANOVA showed significantly lower BDNF levels in patients compared to the control group ($P<0.05$).
Conclusions: These preliminary results may indicate that serum BDNF levels are significantly altered in patients with neuropsychiatric conditions. However, further studies in larger groups of patients are in progress including the analyses of protein and mRNA levels of additional neurotrophins, in order to corroborate and confirm our pilot data. Notwithstanding, elucidating the pathophysiological role of neurotrophins in psychiatric conditions could contribute to the identification of clinically useful biomarkers. Additionally, this line of research may contribute to the development of improved treatment strategies.

TC08

CHRONIC METHYLPHENIDATE AFFECTS BRAIN-DERIVED NEUROTROPHIC FACTOR PROTEIN LEVELS IN RAT HIPPOCAMPUS AND FRONTAL CORTEX

Banerjee PS, Stevenson CW, Boarder, MR, Zetterstrom TSC. Neuropharmacology, Leicester School of Pharmacy, The Gateway, Leicester, pbanerjee@dmu.ac.uk

Introduction: Despite the proven clinical efficacy of methylphenidate (MPH) for treatment of children diagnosed with attention deficit hyperactivity disorder (ADHD), the potential for its long-term neurophysiological consequences are constantly being questioned (Yano and Steiner (2007). Trends Pharmacol Sci, 28(11):588-96). Previously we have shown that acute administration leads to a significant down-regulation of brain-derived neurotrophic factor (BDNF) gene expression in rat hippocampus and frontal cortex (Fcx) (Banerjee & Zetterström (2007). J Psychopharmacol (suppl), 21(7), A19). Subsequently, we have also shown that BDNF down-regulation is sustained upon chronic administration of MPH (Banerjee & Zetterström (2008). Proc Br Pharmcol Soc, In press). Therefore, we sought to investigate whether this decrease is further translated to corresponding protein levels in the same brain regions 2 and 24 hours after chronic administration of MPH.
Method: 20 days old (PND20, 65-80g) male Sprague-Dawley rats were injected twice daily with MPH (2 mg/kg, i.p.) or saline (SAL) 1ml/kg for 15 days. The rats were killed at 2 and 24 hours after the last injection, brains were isolated and hippocampi and frontal cortices (cingulate cortex area) were dissected and prepared into samples for western blotting using standard protocol. Each sample from two different time points was probed for BDNF (17KDa) with rabbit polyclonal anti-BDNF antibody (1:1000, Santa-Cruz Biotech, CA). Resultant blots were subjected to densitometric analyses, using MCIDTM autoradiography, relative to their respective saline controls. Each experiment was repeated three times to maintain reliability of measurements. Data was statistically analysed using a two-way ANOVA followed by a Newman-Keuls post-hoc test.
Results: Data from MPH treated groups are expressed as percentage of their corresponding saline treated control (mean±SEM, n=6/group). BDNF protein levels were significantly decreased in both hippocampal (78%±8, $P<0.001$ vs saline control) and FCx (89%±3, $P<0.05$) regions at 24 hours after the last MPH injection. At the 2 hours time-point, BDNF protein was only significantly reduced in the FCx (79%±3, $P<0.001$).
Conclusion: Consistent with our previous study, measuring BDNF mRNA levels, we have here shown that chronic administration of MPH also significantly decreases the corresponding BDNF protein in the developing rat brain. Acknowledgement:
This work was supported by a PhD studentship from Leicester School of Pharmacy, DeMontfort University.

TC09

DEXAMETHASONE SUPRESSES INFLAMMATORY AND APOPTOTIC RESPONSES BUT NOT SEIZURE OR NEURONAL CELL LOSS IN RESPONSE TO KAINIC ACID

Gleeson LG, Harkin A School of Pharmacy, Trinity College Dublin, Westland Row, Dublin 2, gleesolc@tcd.ie

Excitotoxicity is implicated as a mechanism of neuronal cell death in a range of neurodegenerative disorders. Such toxicity can be induced experimentally by systemic administration of the glutamate kainate receptor agonist, kainic acid. Specifically, kainic acid induces seizures and neuronal cell loss in the hippocampus following systemic administration to rats. Inflammation and apoptosis are also reported to accompany kainic acid-induced neuronal injury in the hippocampus. The aim of the current study was to determine the time course of behavioural, inflammatory, apoptotic changes and neuronal cell loss following kainic acid administration to rats, and to determine if pre-treatment with the anti-inflammatory glucocorticoid, dexamethasone would elicit neuroprotective effects in this model.
Kainic acid (10 mg/kg) was administered to male Wistar rats (n=8) which were thereafter continually observed for seizure related behaviours. All animals receiving kainic acid showed seizures and related stereotyped behaviours within 3 hours. Rats were euthanized 4, 12 and 24 hours after kainic acid andα, TNF-βadministration, and expression of inflammatory cytokines (IL-1 , the microglial activation marker CD11b, and the apoptotic marker caspase)γIFN- 3 were determined in hippocampus by real time PCR. In addition, hippocampal neuronal cell loss was determined histologically by nissl staining. All data are expressed as mean with standard error and were analysed by ANOVA and Newman-Keuls post hoc test, where appropriate, to determine differences between the treatment groups ($P <$ wereγ and IFN-α, TNF-β0.05). Expression of IL-1 increased in the hippocampus 4, 12 and 24 hours post kainic acid administration respectively, compared to vehicle treated controls.
The increase in expression was accompanied by an increase in expression of the microglial γIFN- activation marker CD11b, the apoptotic marker caspase 3 and a reduction in nissl staining of viable hippocampal neurons, 24 hours post challenge. Pre-treatment with dexamethasone (1mg/kg), 1 hour prior to kainic acid administration, CD11b andγsignificantly attenuated the excitotoxin-induced increase in IFN- caspase 3 expression, but failed to influence kainic acid-induced seizures or hippocampal neuronal cell loss. In conclusion, whilst the inflammatory related changes may contribute to apoptosis, our data suggest that microglial activation expression do not account for kainic acid-induced neuronal loss, andγand IFN- therefore, alternative mechanisms such as necrosis are likely to account for the neurodegeneration observed in this model of excitoxicity.
Supported by the Irish Research Council for Science Engineering and Technology.

TC10

EARLY LIFE STRESS ALTERS INTER-HEMISPHERIC COMMUNICATION WITHIN THE ADULT MEDIAL PREFRONTAL CORTEX

Stevenson CW, Taxidis I, Coomber B, Marsden CA, Owen MR, Mason R. Leicester School of Pharmacy, De
Montfort University, The Gateway, Leicester LE1 9BH, cstevenson@dmu.ac.uk

Early life stress is an important environmental factor associated with the development of mental illness in adulthood. Early adverse events likely increase the susceptibility to develop psychiatric disease by enhancing the vulnerability to stressors later in life. Maternal separation (MS) in the rat models certain behavioural and physiological disturbances caused by early life stress, including enhanced stress reactivity. The medial prefrontal cortex (mPFC) mediates cognition, executive function and emotional regulation. As such, this region plays an integral role in modulating various stress responses. Moreover, evidence indicates that hemispheric specialisation in mPFC mediates adaptive coping responses to stressors. We have recently demonstrated that MS alters lateralised activation and hemispheric synchronisation of mPFC in adulthood (Stevenson et al. (2008) Soc Neurosci Abstracts 832.10), suggesting a possible mechanism by which MS enhances the vulnerability to stressors.
Here the effects of MS on inter-hemispheric communication in mPFC were examined further by assessing the direction of information flow between the left and right mPFC in response to FG-7142, a benzodiazepine receptor partial inverse agonist which mimics various stress responses. Rats were subjected to MS (6 hrs/day) or brief handling (15 mins/day) on post-natal days 2-14. In the adult males (n=5/group), in vivo electrophysiology was used to conduct acute recordings of local field potential (LFP) activity under isoflurane anaesthesia simultaneously in the left and right mPFC in response to FG-7142 (0-10 mg/kg, i.v.). Partial directed coherence was used to analyse the uni-directional (left-to-right or right-to-left) spread of the LFP signal between the mPFC hemispheres, allowing for a preliminary qualitative analysis of differences between the early rearing groups in response to FG-7142 at various frequency bands.
The early rearing groups showed frequency-specific differences in the directionality of LFP signal flow between the left and right mPFC. Whereas the spread of signal power from left-to-right mPFC was greater with MS, the spread of signal power from right-to-left mPFC was greater with handling. These early rearing group differences were observed only at lower (< 4 Hz) frequencies and were abolished by FG-7142 administration in a dose-dependent manner.
Taken together with previous findings, these results add to a growing body of evidence indicating that early life stress alters the hemispheric functional connectivity of the mPFC in adulthood. They also suggest a possible mechanism by which early life stress confers enhanced vulnerability to stressors later in life.
Supported by NARSAD (CWS), the EU (CWS, IT), and the MRC (MRO, RM).

TC11

SURINABANT INHIBITS THE EFFECTS OF THC IN A NOVEL THC-CHALLENGE TEST

Klumpers LE, Roy C, Poitiers F, Turpault S, van Gerven JMA CNS, Centre for Human Drug Research (CHDR), zernikedreef, 2333 cl leiden, lklumpers@chdr.nl

Cannabinoid receptor type 1 (CB-1) antagonists are being developed for treatment of obesity and associated risk factors, and for smoking cessation. Surinabant is a high affinity CB-1 receptor blocker in vitro. The aim of this study was to assess the magnitude of inhibition by surinabant of CNS effects and heart rate induced by Δ9-tetrahydrocannabinol (THC) in human. This was a double blind, placebo-controlled, randomized, six-treatment four-period six sequence incomplete balanced cross-over study.

Thirty healthy young male occasional cannabis users (< 1/week) were included. Single oral dose of surinabant (5, 20 or 60 mg) or placebo was administered followed 1.5 hours later by four increasing doses of THC (2, 4, 6 and 6 mg) or placebo inhaled at 1 h intervals. Pharmacodynamic (PD) measurements were: body sway, "alertness" factor from Bond and Lader visual analogue scales (VAS), item "feeling high", and composite factors "internal perception" and "external perception" from Bowdle VAS, and heart rate. PD parameters were analysed using a linear mixed effect model with treatment, period, time and treatment by time as fixed effects, subjects and subject by treatment as random effects and with baseline value as covariate. Surinabant 60 mg by itself did not show significant effects on any studied PD parameters.

Single doses of surinabant 20 and 60 mg were able to inhibit all CNS and cardio-vascular effects induced by THC in a similar range for both doses (e.g., inhibition rates on external perception, composite factor from Bowdle VAS were of 87.1% [95% CI 45.6;128.6] and 87.9% [95% CI 46.1;129.6] , respectively for 20 and 60 mg doses), whereas the 5 mg dose was not shown to be significantly active. The dose-related reversal of all THC-effects by surinabant, without any effect of its own at a high dose, suggests that this compound behaves as a neutral CB-1 receptor antagonist in humans.

This study was sponsored by Sanofi-Aventis.

TD01

OLFACTORY IDENTIFICATION FUNCTION AS A TREATMENT RESPONSE MARKER IN PATIENTS WITH ALZHEIMER'S DISEASE RECEIVING DONEPEZIL

Velayudhan L, Lovestone S. Section of Old Age Psychiatry, Box PO 70, Institute of Psychiatry, De Crespigny Park, London, SE5 8AF, Latha.Velayudhan@iop.kcl.ac.uk

Cholinesterase inhibitors (CI) are currently the only recognised treatment for patients with Alzheimer's disease (AD) with variable response rates. General olfactory dysfunction and impaired odour identification in particular is known in AD. The entorhinal cortex and the olfactory bulb are rich in acetylcholine, the neurotransmitters implicated in AD pathology and treatment. In view of the common anatomical substrate, we aimed to determine whether performance on olfaction test can be used as a clinical marker for monitoring the efficacy of donepezil (CI) in patients with AD.

Patients with mild to moderate AD, planned for donepezil treatment, were recruited during the period May'06 through Oct'07, from mental health for older adults (MHOA) services of the South London and Maudsley (SLaM) NHS Foundation Trust. Exclusion criteria were; previous psychiatric or neurological history, current cigarette smoking, upper respiratory tract infection and conditions known to affect olfactory functioning. Baseline assessments were done prior to commencing donepezil therapy, with Mini Mental State Examination (MMSE); Neuropsychiatric Inventory (NPI); Bristol Activities of Daily Living (ADL) and a "scratch 'n sniff" University of Pennsylvania Smell Identification Test (UPSIT). Following three months of treatment, Clinicians' Interview-Based Impression (CIBIC) was completed, in addition to repeating the baseline assessments. 'Treatment responders' were patients with increased UPSIT scores by two or more points from baseline. Statistical analyses were done using Chi-Square, student's t-test and Paired-samples T test (SPSS 15.0). Informed consent or assent as appropriate was taken. The Joint Institute of Psychiatry and SLaM ethics committee provided the ethics approval. The source of funding was through NIHR Specialist Biomedical Research Centre for Mental Health at the SLaM NHS Foundation Trust. 28 patients with AD agreed to participate and 25 patients successfully completed the follow-up assessments (21 women; baseline MMSE 20.8±2.7; age 82.2±5.8 yrs). Of these, 18 patients continued to have donepezil therapy at follow up.

The UPSIT scores for these patients improved from 15.1 to 17.1 ($t=-1.9$; $\rho=0.073$) with no change in other outcome measures. The 'treatment responders' group (n=12) had a mean UPSIT score change of 4.4±2.8 at follow-up, with a significant improvement overall, as shown in CIBIC ratings ($\rho=0.002$), and improved ADL scores ($t=2.6$; $\rho=0.023$). Conversely, the UPSIT scores dropped from 17.8 to 14.8 ($t=3.2$, $\rho=0.023$) in 'treatment non-responders' group (n=6), with no significant change in other measures.

In conclusion, smell identification function could be useful as a clinical measure to assess treatment response with donepezil therapy in patients with AD.

TD02

A PILOT STUDY OF VITAMIN E FOR THE TREATMENT OF ALZHEIMER'S DISEASE

Boston PF, Gopal YV. Longley Centre, Sheffield Care Trust, Norwood Grange Drive, Sheffield S5 7JT, paul.boston@sct.nhs.uk

Introduction: There has been longstanding interest in antioxidants for the treatment of Alzheimer's disease, as oxidative processes are important in the pathogenesis of this disorder. Vitamin E has antioxidant properties and has been studied as a preventative agent for Alzheimer's disease and for the treatment of mild cognitive impairment. However, there has been only one therapeutic trial in Alzheimer's disease. This showed a significant improvement in the primary outcome measures of time to the occurrence of death, institutionalisation, loss of the ability to perform basic activities of daily living or development of severe dementia. No improvement in that study was seen in cognitive scores. Patients with Alzheimer's disease are normally treated with cholinesterase inhibitors. We therefore set out to investigate whether vitamin E could improve both cognition and activities of daily living in patients with established Alzheimer's disease who were already stabilised on a cholinesterase inhibitor.

Methods: 10 patients with Alzheimer's disease (by ICD-10 criteria) of mild to moderate severity were entered to the study. Following baseline assessments, the patients underwent a 12 week assessment period without treatment. All patients then received 12 weeks' treatment with vitamin E suspension 500mg twice daily. MMSE, ADAS-Cog and Bristol Activities of Daily Living Scale (BADL) were recorded at baseline, after 12 weeks assessment and finally at 24 weeks, after 12 weeks treatment with vitamin E. A mixed models algorithm approach was used to analyse the data and, where appropriate, baseline values were included as a covariate in the analysis.

Results: A small improvement in score was observed on both the MMSE (an increase) and on the BADL (a decrease), during the treatment period, relative to the assessment period. However, the ADAS-Cog showed a small improvement (decrease) in score throughout the study which was slightly greater during the assessment period than during the treatment period. None of the observed differences reached statistical significance (mixed models algorithm $p> 0.05$).

Conclusions: Some inconsistency in the results of the outcome measures may be related to the relatively short treatment period of 12 weeks. However, the 95% confidence intervals for the differences between assessment and treatment periods indicate that the results were compatible with small clinical benefits of vitamin E, which might be shown in a larger study, preferably of longer duration.

Funding: Study was funded by Sheffield Care Trust (no external funding)

TD03

PILOT STUDY OF THE EFFICACY AND SAFETY OF A FLEXIBLE DOSE OF QUETIAPINE IN THE TREATMENT OF AGITATION AND OTHER BEHAVIOURAL AND PSYCHOLOGICAL DISTURBANCES IN ALZHEIMER'S DISEASE

Dale M, Higham S, Eves L, Baddeley S, Jepson C. MAC UK Neuroscience, Faraday Way, Blackpool, FY3 9QR, markdale@macukneuroscience.com

Atypical antipsychotics including quetiapine have a precaution for use in elderly demented patients due an increased risk of death. Quetiapine is an atypical antipsychotic which appears to be less likely to induce extra-pyramidal symptoms and may remain a treatment option for agitation and Behavioural and Psychological Symptoms of Dementia (BPSD) in Alzheimer's disease patients. This study assessed the tolerability, safety, and clinical benefit of quetiapine in Alzheimer's disease patients suffering from agitation.

Methods: Elderly patients (60 – 90 years old) with Alzheimer's disease, as defined by the Diagnostic and Statistical Manual of Mental Disorders, IV Edition, who had suffered from agitation for at least 6 4 on the irritability or aberrant motor behaviour scales≥weeks with scores of of the Neuropsychiatric Inventory (NPI) and a Mini-Mental State Examination (MMSE) score of 6 – 26 participated in this 36 week open label single centre study. Quetiapine was increased and adjusted daily (50-400 mg) according to tolerance and clinical response, and assessed safety and efficacy. Efficacy assessments were made using the Clinicians Global Impression (CGI), Cohen Mansfield Agitation Inventory (CMAI), MMSE and the NPI.

Results: Ten patients were included in the study (6 male and 4 female) with a mean age of 75.6 years. Overall, 7 (70%) patients completed treatment through 36 weeks. The only significant finding was an improvement over time between Baseline and the Final Visit on the NPI Delusions subscale ($F[2,12] = 4.079$, $p<0.045$), as assessed by a Single-factor repeated measures ANOVA. Two SAE were reported (increased agitation and fractured femur), although neither was assessed as causally related to the study medication. In 4 cases, ECGs were found to be abnormal in the final visit, compared with those recorded at Baseline although no patients reported cardiac symptoms.

Conclusion: In conclusion, quetiapine resulted in subtle improvements for neuropsychiatric behaviour, however due to slow recruitment insufficient subjects were entered into the study to allow meaningful interpretation of the data.

Funding was provided by AstraZeneca.

TE01

[11C](+)RX-821024: A NOVEL TRACER FOR IMAGING α2-ADRENOCEPTORS

Parker CA, Tyacke RJ, Rabiner EA, Salinas CA, Gunn RN, Richards SN, Rosalki J, Gee AD, Jakobsen S, Greedy B, Husbands SM, Slifstein M, Malizia A, Nutt DJ, Laruelle M. CPDM-Imaging, Clinical Imaging Centre, GlaxoSmithKline, Du Cane Road, London, W12 0NN, Christine.2.Parker@gsk.com

Introduction: a_2-Adrenoceptors (a_2-AR) have a heterogeneous distribution in the brain and are known to be involved in the pathophysiology of multiple CNS disorders e.g. depression. The development of a successful PET radioligand for a_2-AR would provide a unique tool to probe these targets, *in vivo*. This study investigated the utility of two enantiomeric forms of RX-821024 (RX; idazoxan derivative), as PET ligands for imaging a_2-AR in pig and baboon brain.

Methods: Both (+) and (-)RX were radiolabelled with C-11 and were evaluated in anaesthetised pig (n=2) and baboon (n=2). In *pig*, [^{11}C](+) and [^{11}C](-)RX PET scans were performed pre and post a blocking dose of the a_2-AR antagonist, yohimbine (2mg/Kg). In *baboon*, Subject 1 received baseline scans with both enantiomers; Subject 2 was scanned with [^{11}C](+)RX pre and post yohimbine (0.2mg/Kg). For all scans arterial blood samples were taken to generate input functions. Regional volumes of distribution (V_T) were estimated using a one and two tissue compartment model for the pig and baboon, respectively. Estimates of binding potential (BP_{ND}) were derived indirectly from V_T using the non-displaceable distribution volume estimated from the post yohimbine scans.

Results: In *pig*, [^{11}C](+)RX showed highest uptake in the striatum, thalamus and cortices (V_T~5.1; BP_{ND}~0.76) and lower uptake in the cerebellum (V_T~3.7; BP_{ND}~0.28), consistent with a_2-AR distribution. The [^{11}C](+)RX uptake was reduced to a homogeneous level following yohimbine (V_T~3.0). [^{11}C](-)RX brain uptake was homogeneous (V_T~2.9), unchanged following yohimbine (V_T~3.2) and was consistent with post yohimbine [^{11}C](+)RX data. These *in vivo* data are in agreement with *in vitro* data where (+)RX demonstrates ~100-fold higher affinity for a_2-AR compared to (-)RX (K_i's ~35 and 3125 nM, respectively). In *baboon*, homogeneous distribution was observed following [^{11}C](+)RX (V_T~3.5), with no change post yohimbine (V_T~3.5).

Conclusion: [^{11}C](+)RX showed good brain uptake in *pigs* and produced a a_2-AR specific binding signal as demonstrated by heterogeneous distribution, blocking studies with yohimbine and differences between the active and inactive enantiomers. However, the specific binding signal in the pig was low (BP_{ND}~0.76). This specific signal was not observed in *baboons*, presumably because the a_2-AR density may be lower in primate brain compared to pig brain. Thus, this scaffold holds promise for the development of a PET ligand, and analogues with higher affinities are currently being evaluated. CAP, EAR, CAS, RNG, SNR, JR, ADG, ML = GSK, CIC, London, UK; RJT, AM, DJN = Psychopharmacology Unit, Bristol, UK; SJ = Aarhus PET Centre, Denmark; BG, SMH = Dept Pharmacy, Bath University, UK; MS = Dept Psychiatry, Columbia University, NY, USA.

TE02

NORADRENERGIC RESPONSIVENESS IN GENERALIZED ANXIETY DISORDER: A SPECT STUDY

Kalk NJ, Melichar, JK, Holmes, RB, Hood,SD, Taylor, SD, Daglish, MRC, Parkin, VJ, Rees, MR, Lenox-Smith, A, Lingford-Hughes, ER, Nutt, DJ. Department of Psychopharmacology, Bristol University, Whitson Street, Bristol BS1 3NY, nicola.kalk@awp.nhs.uk

Generalized Anxiety Disorder (GAD) is characterised by chronic apprehension, motor tension and autonomic hyperactivity, suggesting a maladaptive stress response. While resting catecholamine studies failed to show a consistent abnormality in GAD, there is evidence of reduced peripheral responsiveness to noradrenergic stimulation or inhibition (Abelson: Arch Gen Psych 1991; 48:157-162). The suggested pathophysiology of GAD is of chronic noradrenergic release producing blunted noradrenergic responsiveness (Nutt: J Clin Psych. 2001; 62(S11) 22 -7). We aimed to investigate the effect of clonidine, an α2-agonist, on regional cerebral blood flow (rCBF) during a task which taxed the noradrenergic system – verbal fluency – in subjects with GAD and control subjects, and to investigate whether these paralleled changes in psychological and physical measures. Seven control subjects, ten subjects with untreated GAD and seven venlafaxine-treated subjects with GAD were subjected to 99mTc-HMPAO SPET scan performed on a SMV DST-Xli gamma camera using a split dose (300MBq:200 MBq) technique (Moffoot: Psychological Medicine 1994; 24, 53-61). Clonidine (10μg/kg) was infused over ten minutes prior to the second scan. Psychological measures and physiological measures were undertaken at various time points. Images were analysed using SPM5 (Wellcome Department of Cognitive Neurology 2005). Clonidine had a pronounced effect on physiological and psychological measures, including verbal fluency (Hood: CINP 2008). Pre-clonidine, there was a significant increase in rCBF in the right cerebellar hemisphere during verbal fluency in subjects with GAD relative to controls ($p=0.000$). There was no significant difference between treated and untreated groups of GAD subjects prior to clonidine. Following clonidine, there was a significant increase in perfusion in the left putamen following clonidine ($p=0.035$). Clonidine appeared to have a different effect on subjects with treated and untreated GAD. In subjects with untreated GAD, there were significant increases in rCBF in both the right dorsolateral prefrontal cortex ($p=0.010$) and in the left posterior cingulate gyrus ($p=0.033$). In subjects with treated GAD, there was an increase in rCBF in the left supplementary motor area ($p=0.003$). Preliminary analyses have not found any association between changes in rCBF and physiological or psychological data. There are differential effects of clonidine on rCBF in subjects with untreated, and treated GAD in comparison with control subjects. Rather than supporting a blanket hyposensitivity hypothesis, our data is consistent with theories regarding noradrenergic dysregulation in depression (Fu: Biological Psychiatry 2001; 49: 317–325), which suggest hyposensitivity of pre-synaptic alpha2 adrenoreceptors together with regional frontal hypersensitivity reflected in increased rCBF.

Sponsor: Wyeth

TE03

HYDROCORTISONE INDUCES, HIPPOCAMPAL AND LIMBIC/PARALIMBIC CEREBRAL PERFUSION CHANGES AS MEASURED BY HIGH FIELD MRI ARTERIAL SPIN LABELLING

Tyacke RJ, Holmes R, Reid A, Grant EJ, Henry B, Zelaya F, Reul JMHM, Lightman S, Williams SCR, Nutt DJ, Malizia AL. Psychopharmacology Unit, University of Bristol, Whitson Street, Bristol BS1 3NY, r.j.tyacke@bris.ac.uk

Acute stress has direct effects on regional brain function. This is mediated by corticosteroids released from the adrenal cortex that freely cross the blood-brain-barrier to cause their effect. In an attempt to study this effect in a human experimental model, the effects of an exogenous bolus of hydrocortisone (HCORT), a glucocorticoid receptor (GR) agonist, on regional brain function using the MRI technique of Arterial Spin Labelling (ASL) were investigated. It was hypothesised that the HCORT would cause changes in neuronal activity in areas associated with acute stress such as the hypothalamus, hippocampus and various cortico-limbic structures.

Twelve right-handed, healthy, male volunteers (ages 23-46yrs, mean age±SD, 34±7) were scanned (GE 3T Excite II) on two occasions. At approximately 16:00hrs volunteers were infused with either saline (placebo) or HCORT (7mg/kg, up to 500mg). Two ASL scans were collected one 15min before the infusion and one 95min after. For all this time, the subjects were lying down in the scanner. These provided a resting state cerebral blood flow map in true physiological units (ml/100g tissue/min). The resulting images were analysed using a region of interest analysis on regions selected a priori using the MarsBaR tool in SPM5 and compared using a paired t-test. Scans from two subjects were lost due to technical problems and the analysis is based on ten subjects. Globally there was a small decrease in regional cerebral blood flow with time in the scanner, which was not significant. On global comparison, there were many significant decreases in regional cerebral blood flow after HCORT. Significant reductions ($P < 0.05$) were seen in the right amygdala, left and right hippocampus, right caudate, left and right anterior cingulate, left and right inferior orbito-fontal cortex, left mid-frontal cortex and the left and right thalamus. Changes were seen in many of the areas predicted. However, there was no significant change in the hypothalamus. This may reflect the delay between the two scans, approximately 2hrs, and may indicate rapid hypothalamic adaptation to acute HCORT. ASL robustly measures changes in regional blood flow and would appear to be a viable method for understanding the role of corticosteroids on brain function.

We thank our collaborators and sponsors (Organon); S Lightman, JMHM Reul, HWLINE, University of Bristol, BS1 3NY, UK SCR Williams, F Zelaya, Centre for Neuroimaging Sciences, Institute of Psychiatry, London SE5 8AF, UK EJ Grant, B Henry, Department of Pharmacology, Organon, part of Schering-Plough Corporation, Newhouse, Lanarkshire, ML1 5SH, Scotland, UK

TE04

USING IN VIVO VOLTAMMETRY TO INVESTIGATE THE RELATIONSHIP BETWEEN NEURONAL ACTIVITY AND TISSUE OXYGEN IN THE RAT BARREL CORTEX

Li J, Gilmour G, Bannerman D, Tricklebank M, Lowry JP, McHugh S. Experimental Psychology, University of Oxford, South Parks Road, Oxford, lije@lilly.com

Neuronal activation induces changes in local extracellular oxygen (O_2) concentration determined by the balance between O_2 consumption and the delivery of O_2 via increased cerebral blood flow (CBF). Functional magnetic resonance imaging (fMRI) studies use the blood-oxygen-level-dependent (BOLD) signal as an indicator of neuronal activation. The uncoupling of CBF and O_2 metabolism remains under debate and controversy surrounds whether there is an 'initial dip' in the BOLD response corresponding to O_2 utilisation preceding an increase in regional CBF and an increase in O_2 concentration. The whisker-barrel sensory pathway in rodents is an ideal neural network for investigating neuronal activity due to its simple columnar spatial structure and its well defined neuronal circuitry. To resolve the issues of supply and demand of oxygen to active brain regions we investigated the relationship between evoked neuronal activity and extracellular O_2 concentration in the barrel cortex of anaesthetized rats using online voltammetric O_2 biosensors.

Electrical and mechanical whisker stimulations were administered and evoked field potentials (EFPs) and the O_2 signal were recorded simultaneously from double electrodes placed in the barrel cortex of urethane anaesthetized male Spague Dawley rats. Carbon paste electrodes were used to record O_2 via constant potential amperometry with a -650mV applied potential. Electrical stimulations (contralateral, 1.2mA, 0.3ms duration) and mechanical stimulations (a peizo-electric stimulator deflects whiskers up to 0.25mm) were administered every 10 seconds.

An initial short-lasting decrease in O_2 was seen about 30-70ms after the EFP following whisker stimulation, with mechanical stimulation producing a smaller oxygen 'dip' than electrical stimulation. The amplitude of the oxygen 'dip' was significantly correlated with the amplitude of the EFP in both stimulation conditions. The EFP and the oxygen dip amplitude were reduced by direct administration of a local anaesthetic to the whisker pad suggesting that the inhibition of neuronal transmission also blocks the oxygen response. A depth profile of the oxygen response showed that the direction of the oxygen change is laminar-specific with increases seen closer to the surface of the barrel cortex.

Oxygen voltammetry may prove a useful method of investigating the effects of neuronal activity on neurovascular and metabolic events in the rat, and can be advanced into conscious behaving animals. It has higher temporal resolution than the fMRI BOLD signal and other tissue oxygen recording techniques (Clark type electrodes, which involve O_2 diffusing across a membrane), giving us critical information about the coupling between cortical haemodynamics and neuronal electrical activity.

Funded by Lilly.

TE05

PAST DEPRESSION AND TRAIT RUMINATION MODULATE NEURAL RESPONSE TO TASK FAILURE

Pegg EJ, McKie S, Deakin JFW, Anderson IM, Elliott R. Neuroscience and Psychiatry Unit, University of Manchester, Oxford Road, Manchester M13 9PT, emma.pegg@manchester.ac.uk

Rumination is a risk factor for depression and has been shown to correlate with a sustained limbic response to emotional stimuli in depression. However, it is not clear whether this over-activity is state dependent, or a trait of those at risk for depression. We have previously shown that highly ruminative healthy participants recognise more words from a failed task, indicating over-processing of the stimuli due to rumination. Here we imaged responses to this task using fMRI, in control and remitted depressed participants. We hypothesised that, in response to failure on individual trials, activity would differ significantly between the groups and correlate with self-reported rumination, particularly in limbic areas. 36 currently non-depressed volunteers (24F) were enrolled. 15 (11F) had experienced at least one previous episode of major depression. Each volunteer completed the Ruminative Responses Scale (RRS) and underwent scanning using a 1.5T Philips Intera MRI scanner. During scanning they completed a word problem-solving task comprising 80 multiple-choice problems, of which only 60 were soluble. They believed that a score of over 75% correct was needed to pass. Feedback was provided after each trial and overall score presented at the end. Data were analysed using a random-effects multiple regression model in SPM5. Imaging results are reported as p (uncorrected) ≤ 0.001. Remitted volunteers had significantly higher mean RRS scores (53 (11.6) v 39.7 (7.6), $p<0.01$). There was no significant difference in accuracy between the groups ($p<0.05$). The mean correct score was 47±8.78. BOLD responses to negative feedback were subtracted from those to positive feedback. Remitted participants showed greater response to incorrect feedback in the anterior cingulate (BA24 & 32), caudate nucleus, medial and inferior frontal gyri (BA10 & 45) and parahippocampal gyrus (BA36). The parahippocampal gyrus and caudate nucleus differences remained significant controlling for RRS scores. Scans from both groups were combined and correlated with RRS scores, revealing a significant positive correlation in the anterior cingulate (BA32). Consistent with our hypotheses, remitted depressed volunteers showed greater neural response to failure in limbic areas. Activity in the parahippocampal gyrus and caudate was not modulated by trait rumination, while anterior cingulate responses did correlate with RRS scores. These findings lend support to theories that limbic over-activity in response to negative and emotional stimuli may underlie vulnerability to depression and may also be manifested behaviourally as rumination, even in non-depressed individuals. Funding: MRC Studentship, TIU Grant (University of Manchester) and NEWMOOD EU Integrated Programme LSHM-CT-2004-503474.

TE06

BLUNTED ANTERIOR CINGULATE RESPONSE TO INCONGRUOUS FEEDBACK FOLLOWING REMISSION FROM MAJOR DEPRESSION

Downey D, McKie S, Deakin JFW, Anderson IM, and Elliott R. Imaging Science and Biomedical Engineering, University of Manchester, Oxford Road, Manchester M13 9PT, darragh.downey@manchester.ac.uk

Behavioural studies have indicated performance deficits in depressed patients following feedback, especially negative feedback or perceived failure. Biases in emotional processing and error detection have also been reported. Some cognitive abnormalities found in depression may persist through remission and constitute a vulnerability factor for relapse. We designed a reward-related decision-making task based upon the game of Scissors, Paper, Stone (SPS), which incorporated congruent and incongruent feedback in order to assess whether information processing biases persist in volunteers who have recovered from depression.

16 control and 13 remitted depressed (RD) volunteers undertook a 16min choice selection fMRI task. Whole brain images were acquired on a 1.5T Philips-Intera scanner and analysed using SPM5. Participants undertook a modified version of SPS, playing sequences of predetermined outcomes against the computer, gaining 200 points for playing a winning hand and losing 100 for losing. Participants were unaware that the outcome was fixed. Games were divided into four '16 hand' sets whereby winning 7 hands retained the points accumulated in the set and losing 7 hands lost the accrued points. Blocks were divided into predetermined sets with 7 wins, 5 draws and 4 losses in winning sets and with the number of losses and wins reversed in losing sequences. Non-performance based information was presented as feedback in each set, independent of outcome. This feedback was encouraging or discouraging statements (e.g. good play or this isn't your best game). Winning and losing sets were identical in order and outcomes, differing only in the type of feedback presented. The greatest difference between RDs and controls occurred when feedback was given discordantly to actual performance. Decreases in anterior and posterior cingulate activity in RDs were found when performance and feedback were conflicting ($p<0.05$ FDR). There was no significant difference in decision making times between the groups. Discordant feedback is associated with an abnormal response in RD in well defined error processing and sensory association brain areas. The abnormality in the ACC suggests that RDs are not processing the discrepancy or not attributing the same classification to its experience. Decision making times were not different, suggesting that changes were due to differences in brain processing rather than attentional impairment. This functional processing difference may be due to deficiencies in error processing or performance assessment; alternatively RD participants may rely on externally derived cues more than never depressed controls to assess their performance. Work contributes to NEWMOOD EU Integrated Program LSHM-CT-2004-503474

TE07

UNEXPECTED AND EXPECTED REWARD AND PUNISHMENT ELICIT DIFFERENTIAL NEURAL ACTIVITY IN THE STRIATUM, AMYGDALA AND DORSAL RAPHE NUCLEUS

Robinson OJ, Sahakian BJ, Cools R. Department of Psychiatry, Behavioural and Clinical Neuroscience Institute, University of Cambridge, Addenbrooke's Hospital, Cambridge, CB2 2QQ, ojr23@cam.ac.uk

Adequate adaptation to our constantly changing environment requires the anticipation of biologically relevant events by learning signals of their occurrence, i.e. reward and punishment prediction. Reversal learning is the adaptation of this behaviour according to changing stimulus-reward or stimulus-punishment contingencies. Functional magnetic resonance imaging (fMRI) has demonstrated that reversal learning evokes neural activation in the ventrolateral prefrontal cortex and the ventral striatum (Cools et al., 2002). Here we extend this prior work by separately assessing neural mechanisms for reversals signalled by unexpected reward and unexpected punishment. 16 subjects completed the task in the fMRI scanner. BOLD response at stimulus outcome was examined in an event related design. Prior predictions of ventral striatum involvement in reward prediction and amygdala response in punishment prediction enabled anatomical region of interest (ROI) analysis. Whole-brain contrasts ($P(\text{uncorrected})=0.001$) replicated previous findings demonstrating that the ventral striatum and the ventromedial prefrontal cortex are more active when subjects switch responding (i.e. during unexpected vs expected feedback). We also revealed neural activation in the raphé nucleus during expected (non-switch) punishment evoked relative to expected reward. ROI analysis (paired sample t-tests between trail types; $p<0.05$) revealed increased neural activity in the ventral striatum during unexpected reward and decreased neural activity in the amygdala during unexpected punishment. Increased activity in the ventral striatum during unexpected reward is consistent with previous research implicating the ventral striatum in positive reward prediction errors and may correspond with psychopharmacological data from the same task showing improved reward based reversals relative to punishment based reversals under elevated dopamine (Cools et al. 2006). The increased neural activity in the raphé following expected punishment may also correspond with psychopharmacological data from the task showing that punishment prediction on non-switch trials is sensitive to manipulation of serotonin. The ventral striatum and raphé activations therefore concur with distinct dopaminergic and serotoninergic mechanisms of outcome-based switching and punishment-prediction respectively (Cools et al., 2006; 2007). The decreased amygdala activity during unexpected punishment suggests that amygdala activity may represent the negative reward prediction error (Seymour et. al., 2004). Taken together with the ventral striatum finding, this indicates that positive and negative prediction errors (unexpected reward and unexpected punishment or reward omission respectively) may be carried by different subcortical brain regions. These findings may have implications for our understanding of the neural basis of affective disorders such as mania and depression. Funded by the Cambridge BCNI, supported by a joint award from the Medical Research Council and the Wellcome Trust

TE08

REWARD-OUTCOME INSENSITIVITY FOLLOWING AMPHETAMINE SENSITIVITY IN HEALTHY HUMAN VOLUNTEERS

O'Daly O, Joyce D, Stephan K, Murray R, Shergill S. Centre for Neuroimaging Sciences, Clinical Neuroscience, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, spdpood@iop.kcl.ac.uk

Decision-making deficits are commonly observed in patients with schizophrenia and substance abusers. The dysregulation of normal mesolimbic dopamine function may to this failure to use reward-related information to appropriately guide behaviour. Amphetamine sensitisation is a well-established animal model of the neuroplastic mechanisms underlying the development of addiction and psychosis. Recent evidence suggests that sensitisation in humans is associated with enhanced drug-induced striatal dopamine release mirroring that seen in sensitised rodents. However, the neurofunctional consequences of amphetamine sensitisation in humans are unknown. Furthermore, it remains unclear to what degree sensitisation may impact on reward processing and decision-making mechanisms in humans.

Twenty-two subjects were assigned to receive either d-amphetamine (n=11) or placebo (n=11) using a dosage regimen previously shown to produce sensitisation. Sensitisation was assessed using Visual Analogue Scales and pulse and eye-blink rate. Subjects underwent fMRI scanning 2hrs post-administration on the first and final visit. During the scan, participants performed a gambling task where the probability of reward receipt was manipulated. Data were acquired on a GE 1.5T scanner with 43 slices of 3mm thickness (0.3mm gap) using a repetition time of 4 seconds. The data were pre-processed (realigned and unwarped, normalised to MNI space, and smoothed) using SPM2. Following repeated intermittent exposure we found that subjects receiving amphetamine reported enhanced amphetamine-like experiences (Addiction Research Center Inventory: Amphetamine-scale; $F(2.5, 49.8) = 4.2$ $p < 0.015$), and greater feelings of Vigour (POMS: Activity-Vigour; $F(2.8, 55.8) = 3.7$ $p< 0.018$) in response to their 4th dose compared to the first. Following repeated amphetamine exposure the normal relationship between probability of reward receipt and reaction times during task perfomance was reversed ($F(1.87,35.546) =6.321$, $p<0.005$). Sensitisation was associated with reduced decision-related neural activity in the ventrolateral prefrontal cortex (VLPFC) ($p<0.05$ corrected for multiple comparisons) and blunted anticipatory activity in the ventral striatum ($p<0.001$ uncorrected). While a large distributed network, including the striatum, parietal cortex, frontal cortices, showed a differential response to wins and losses in the placebo group and those on the first dose of amphetamine, this neural differentiation between positive and negative outcomes (Wins>Losses) was lost in the sensitised subjects ($p<0.001$ uncorrected). Our data show that sensitisation-related mechanisms can disrupt the normal link between reward contingencies, outcome-processing and decision-making and thus may play a role in the expression of outcome-insensitive behaviour seen in substances abusers and patients with schizophrenia.

The project was funded by the Psychiatry Research Fund at the Institute of Psychiatry, KCL.

TE09

THE NEURONAL BASIS OF IMPULSIVITY IN PATHOLOGICAL GAMBLERS, NON-PATHOLOGICAL GAMBLERS AND SUBSTANCE ABUSERS: EVIDENCE FOR DYSFUNCTION WITHIN THE ORBITOFRONTAL CORTEX

Hinvest N, Elliott R, McKie S, Anderson, IM. Department of Psychology, University of Bath, Bath, BA2 7AY, n.hinvest@bath.ac.uk

Choice behaviour is hypothesised to be influenced by the interaction between two systems; a "cognitive" (or "executive") system promoting deliberative self-controlled action which can override the "affective" (or "impulsive") system promoting immediately gratifying action (Brocas and Carillo, 2006; Lowenstein and O'Donoghue, 2004). Addiction disorders have been associated with hyperactivity of the impulsive system (Bickel et al, 2006). Substance abusers, alcohol abusers and pathological gamblers have reliably shown heightened levels of impulsivity (defined as choosing a smaller, immediate, reward over a larger, delayed, reward) compared to controls (for a review, see Reynolds, 2006). This increase in impulsivity is thought to motivate addiction-disordered individuals to seek immediate rewards (e.g. drug 'high') over delayed rewards (e.g. better health). This study investigated the neural basis of the heightened impulsivity exhibited by addiction-disordered individuals.
12 substance abusers, 10 pathological gamblers, 10 non-pathological gamblers and 12 controls were tested. Participants were given a behavioural delay discounting task providing real delays (0-24 seconds) and hypothetical small monetary rewards (£0.10 or £0.20) and then a FMRI delay discounting task providing small hypothetical monetary rewards (£1.00 or £2.00) and real delays (2-40 seconds). Using a repeated measures ANOVA, there was found to be no effect of group on the behavioural delay discounting task ($p>.05$). The FMRI data was analysed using an independent measures ANOVA. A subtraction analysis was performed in which forced choices (alternatives A and B the same) were subtracted from free choices (A = small sooner reward; B = large later reward). In all groups, free choice was associated with significantly increased BOLD signal within the orbitofrontal cortex (OFC), ventromedial prefrontal cortex and dorsolateral prefrontal cortex ($p<.001$, uncorrected).
Substance abusers, pathological gamblers and non-pathological gamblers all showed increased BOLD signal within a specific area of the right OFC (BA47) compared to controls ($p<.001$, uncorrected). The OFC has been associated with roles in stimulus valuation and goal-maintenance. Hyperactivity of the OFC may mask potential decision-making deficits in these groups, perhaps explaining why significantly different levels of impulsivity between groups were not found. Alternatively, it may represent a dysfunction inherent within addicted and non-addicted samples affecting impulsive choice. Our current study expands these findings by comparing the function of neural areas in pathological gamblers and controls associated with impulsive choice (involving choices that contain a larger range of rewards and delays) and underlying valuation of monetary rewards and losses. This research was funded by the Research in Gambling Trust.

TE10

NICOTINE REDUCES THE RELIABILITY OF BRAIN ACTIVATION IN NON-SMOKERS: AN FMRI STUDY.

Caceres A, Kumari V., Patel D., Michel T. M., Nwaigwe A., Anilkumar A. P., Mehta M. A., Williams S.C.R., Ettinger U Institute of Psychiatry, King's College Lodon, De Crespigny Park, Lonon, SE5 8AF, alejandro.caceres@iop.kcl.ac.uk

We present a novel method to assess individual differences in brain response to a pharmacological challenge using functional magnetic resonance imaging (fMRI). We apply this method to a study of the effects of nicotine on antisaccade-related BOLD activation patterns. The method formally assesses the changes in regional reliability of subject activations when nicotine is administered in the retesting session instead of placebo.
We compute voxel distributions of intra-class correlation coefficient (ICC) within the whole brain volume, task-related network and individual activated clusters. Reliability comparisons are given in term of the median values of such distributions; of particular interest are the comparisons relative to the whole brain distribution. The method is applied to a study comprising 13 smokers and 11 non-smokers who were each scanned on two occasions separated by one week. On each occasion scans were performed before and after subcutaneous injection of nicotine (12μg/kg) or saline placebo. The network reliability of non-smokers was reduced for retesting after nicotine compared with placebo (test for difference in the medians of ICC distributions, $z=-24.58, p<0.001$), whereas the network ICC for the smokers was unchanged by the drug condition ($z=-1.15, p=0.25$). Individual clusters tended to confirm this general pattern. However, for the left frontal eye field nicotine reduced reliability for non-smokers ($z=-49.16$, $p<0.001$), but increased it to highly significant values for the smokers ($z=31.09$, $p<0.001$). This method allows the determination of the parts of a task network where subjects respond differentially to a drug. Using nicotine we conclude that smokers' respond in a more predictable manner to the drug compared to non-smokers. However, these effects were not uniform across all the components of the network, particularly for the left frontal eye-field. We did not find significant differences in a simple class comparison between drug and placebo within each group. Therefore, this method offers additional information between conditions based on the variance structure of the data and may be useful in defining individual differences in drug modulatory effects.
This work was supported by funding from the Leverhulme Trust (ECF/2004/0370) and ESRC/MRC (PTA-037-27-0002).

TE11

THIS ABSTRACT HAS BEEN WITHDRAWN

TE12

GLUTAMATE AND PSYCHOSIS - AN EXCITOTOXIC PROCESS?

Stone JM, McLean MA, Lythgoe DJ, O'Gorman RL, Barker GJ, McGuire PK. Psychiatry, King's College London Institute of Psychiatry, De Crespigny Park, London SE5 8AF, james.stone@iop.kcl.ac.uk

Background: Magnetic Resonance Spectroscopy (MRS) is a non-invasive technique permitting analysis of brain chemistry using a standard MRI scanner. MRS studies of patients with schizophrenia often report reduced N-acetyl-aspartate (NAA) levels (thought to be a measure of neuronal integrity). MRS studies have also found elevated glutamine or glutamate plus glutamine in the anterior cingulate or medial frontal cortex of patients in the early stages of schizophrenia. Elevated glutamatergic transmission in cortical brain regions might lead to the grey matter changes associated with the illness through altered plasticity or excitotoxicity.
Methods: We compared 27 individuals with attenuated psychotic symptoms who were at ultra high risk for psychosis (UHR) with 27 healthy volunteers using MRS and volumetric MRI on a 3T scanner. MRS spectra were acquired from anterior cingulate (bilaterally), left thalamus and left hippocampus. LCModel was used to derive water-scaled glutamate, glutamine and NAA concentrations from MRS spectra, and these were then corrected for grey matter concentration. Differences in grey matter volume and correlations with glutamate and glutamine levels were compared using voxel-based morphometry (VBM) employing in-house software (XBAMM).
Results: UHR subjects had significantly reduced grey matter volume in a single voxel in medial frontal cortex including anterior cingulate. UHR subjects had reduced NAA (N=51; p=0.004) and glutamate (N=51; p=0.02) in thalamus. Reliable measurement of glutamine was possible in only 30% of anterior cingulate spectra, and in less than 10% of left thalamus and left hippocampus spectra. Despite this, a significant difference was still found between UHR subjects and controls, with elevated glutamine in anterior cingulate in UHR subjects (N=21; p=0.03). Thalamic NAA levels showed a negative correlation with anterior cingulate glutamine levels (n=21, r=-0.519, p=0.02). Levels of glutamine in anterior cingulate (uncorrected for grey matter) had an inverse correlation with grey matter volume in medial frontal cortex (n=21, p<0.01). Glutamate levels in thalamus correlated directly with temporal cortex grey matter volume, and inversely with caudate grey matter volume (n=52, p<0.01). Conclusions: These data suggest that brain glutamate function may be perturbed in people at high risk of developing psychosis, and that increasing glutamine levels in anterior cingulate are associate with a local reduction in grey matter volume, supporting the hypothesis of an underlying excitotoxic process. Future work will determine whether elevated levels of cortical glutamine at baseline predicts subsequent transition to psychosis.
This research was funded by an MRC Clinical Research Training Fellowship to Dr Stone.

TE13

META-ANALYSIS OF MAGNETIC RESONANCE IMAGING STUDIES IN BIPOLAR DISORDER AND SCHIZOPHRENIA

Arnone D[1], Cavanagh J[2], Gerber D[3], Lawrie SM[4], Ebmeier KP[5], McIntosh AM[4]. [1]Neurosci and Psychiatry Unit, Univ of Manchester, Manchester, UK [2]Div of Community Based Sci, Faculty of Medicine, Univ of Glasgow, Glasgow, UK [3]Gartnavel Royal Hospital, Glasgow, UK [4]Univ of Edinburgh, Royal Edinburgh Hospital, Edinburgh, UK [5]Univ Dept of Psychiatry, Oxford, UK danilo.arnone@manchester.ac.uk

Introduction Great interest has been devoted in studying brain structure of people with bipolar disorder (BD) and schizophrenia (SCH) in comparison to healthy controls (HC). However, a number of magnetic resonance imaging studies have compared these two conditions directly, sometimes in relation to HC. A number of meta-analyses and systematic reviews have described MRI studies of SCH or BD in comparison with HC. To our knowledge there has not been any meta-analysis comparing volumetric differences between BD, SCH and HC. The aim of this study was to test the hypothesis that volumetric differences exist between BD and SCH in specific brain areas consistent with the neuropathology of these conditions. Methods A systematic search was conducted from a comprehensive range of electronic database complemented by a manual search of bibliographic cross-referencing. Studies were included if they presented original data and were 1) published by March 2008, 2) compared subjects with SCH, BD and unrelated HC, 3) reported volumetric measures of brain areas according to SI units as mean and standard deviation. Statistical analysis was conducted using STATA 8.0 (StataCorp, College Station, Texas) supplemented by 'Metan' software downloadable from the Centre for Statistics in Medicine, Oxford, UK. Results Sixty three reports met inclusion criteria and were analysed using random effect analysis. Subjects with BD in comparison to HC showed whole brain volumetric reduction (N = 641 versus N = 723), estimate: - 0.15; 95% CI: - 0.3, - 0.02 with no significant heterogeneity or publication bias I^2: 0; Egger (p): 0.67). Frontal cortex volumes appeared significantly reduced in BD versus HC (N = 122 versus N = 97), estimate: - 0.42; 95% CI: - 0.70, - 0.15 with no significant heterogeneity or publication bias I^2: 0; Egger (p): 0.67. Finally, left and right lateral ventricles (LLV, RLV) were larger in BD (N = 157 versus N = 179), estimate: 0.27; 95% CI: -0.05, 0.49, with no significant heterogeneity or publication bias I^2: 0; Egger (p): 0.07. The LLV contributed to this difference more substantially (N = 348 versus N = 325), estimate: 0.18; 95% CI: 0.02, 0.33, I^2: 0; Egger (p): 0.6. In comparison to SCH, BD showed increased right amygdala volume (N = 115 versus N = 200), estimate: 0.47; 95% CI: 0.21, 0.73, I^2: 0; Egger (p): 0.59. Also lateral ventricles in BD appeared bilaterally smaller than in SCH (N = 126 versus N = 158). The estimate for the LLV was: -35; 95% CI: -0.59, -0.11, I^2: 0; Egger (p): 0.11 and for RLV: -26; 95% CI: -0.49, -0.02, I^2: 0; Egger (p): 0.06.
Conclusion Findings from this report suggest that BD in comparison with HC is associated with brain volumetric reduction particularly significant in the frontal cortex and with ventricular enlargement. In comparison with SCH, BD presents with a more preserved ventricular system and with an increased right amygdala volume. The latter finding might be more specific for schizophrenia. Source of funding DA is currently supported by the UK Medical Research Council.

TE14

META-ANALYSIS OF MAGNETIC RESONANCE IMAGING STUDIES IN VELOCARDIOFACIAL SYNDROME (VCFS)

Tan GMY[1], Arnone D[2], McIntosh AM[3] , Ebmeier KP[4] [1]Div of Psychological Medicine & Psychiatry, Inst of Psychiatry, London, UK [2]Neurosci and Psychiatry Unit, Univ of Manchester, Manchester, UK [3]Univ of Edinburgh, Royal Edinburgh Hospital, Edinburgh, UK [4]Univ Dept of Psychiatry, Oxford, UK, Giles.Tan@iop.kcl.ac.uk

Introduction Velocardiofacial syndrome (VCFS) is a common genetic disorder due to a micro deletion on chromosome 22q11. This region includes several risk-associated genetic variants, including COMT, and VCFS is associated with a substantially increased risk for schizophrenia. As such, VCFS may serve as a valuable model for clarifying the neuroanatomical changes associated with genetic risk for psychosis. Whilst structural brain abnormalities have been described in case-control studies of this disorder, sample sizes are small and the literature is in much need of meta-analytic review.
Methods A systematic and comprehensive literature search was conducted using a range of electronic databases and supplemented by a cited literature search. Studies were included if they presented original data and were 1) published by March 2008, 2) compared subjects with VCFS and healthy controls, 3) reported measures of brain areas according to SI units as mean and standard deviation (volumes or areas). Data extracted from the studies included diagnosis according to diagnostic criteria, demographic variables, (e.g. number, age, gender), IQ, and duration of illness. Statistical analysis was conducted using STATA 8.0 (StataCorp, College Station, Texas) supplemented by 'Metan' software downloadable from the Centre for Statistics in Medicine, Oxford, UK.
Results Twenty studies were retrieved. All measures were expressed in volumes a part from the corpus callosum (area). Subjects with VCFS showed a reduced total brain volume (N = 156 versus N = 138), (standardized effect size [ES] = 1.04, 95% CI: 1.40, -0.67), with no significant heterogeneity or publication bias (I^2: 1.04, p = 0.09; Egger p = 0.7). This reduction reflected on total hemisphere grey (ES= – 0.5, 95% CI: -0.79, -0.22; I^2: 0, p = 0.62; Egger p = 0.69) and white matter (ES= – 1.01, 95% CI: -1.41, -0.60; I^2: 0. 25, p = 0.9; Egger p = 0.03). Prefrontal, parieto-occipital and temporal cortices appeared to be particularly affected. A number of sub-cortical areas also showed decreased volumes including the hippocampus and putamen. In contrast, callosal areas were increased in VCFS whilst the ventricular system was not affected. Conclusion In relation to controls, subjects with VCFS present with an overall reduction in brain volumes but also specific abnormalities in multiple cortical brain regions and subcortical areas. These abnormalities might explain why VCFS is associated with a greatly increased risk of psychosis and other psychiatric disorders. Source of funding DA is currently supported by the UK Medical Research Council.

TE15

GRAY AND WHITE MATTER ALTERATION IN AMNESTIC TYPE MILD COGNITIVE IMPAIRMENT: A COMBINED OPTIMIZED VOXEL-BASED MORPHOMETRY AND DIFFUSION TENSOR IMAGING STUDY

Bai F, Zhang ZJ, Yu H, Wang L, Zhu WL, Zang YF，Zhu CZ，Shi YM, Yuan YG, Qian Y.
School of Clinical Med, Southeast University, China, Ding Jia Qiao 87#, Nanjing 210009, China baifeng515@126.com

Introduction: Structural investigations of mild cognitive impairment (MCI) have focused on the presence and distribution of gray matter abnormalities. Despite its popularity in studies of MCI have identified the expected extent gray matter abnormalities, there has not been a comprehensive optimized voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) investigations of whole-brain white matter in MCI.
Methods: The optimized VBM and voxel-based DTI were applied on the structural magnetic resonance images (MRI) to evaluate the differences of whole-brain gray matter and white matter changes between the amnestic type MCI (aMCI) subjects and normal aging controls. Twenty aMCI subjects and nineteen well-matched normal aging controls underwent imaging scans of MRI, and correlation was analyzed between gray matter atrophy and white matter alteration in aMCI subjects.
Results: Compared with the normal aging subjects, aMCI subjects were associated not only with abnormalities in gray matter of memory-related areas, such as parahippocampal gyrus, temporo-parietal areas and frontal areas (P<0.05, corrected), but also with concomitant abnormalities in cerebral white matter regions, such as the frontal lobe, temporal lobe, cingulate gyrus, corpus callosum and fusiform gyrus (P<0.001, uncorrected). In addition, white matter abnormalities of frontal lobe/ sub-gyral and corpus callosum were significant positive related to gray matter atrophy parahippocampal gyrus (P<0.001, uncorrected).
Conclusions: The cortico-cortical disconnection was confirmed by both optimized VBM and DTI structural MRI in the aMCI subjects. Furthermore, the study directly revealed that white matter alteration of frontal lobe/ sub-gyral and corpus callosum may be closely related to pathology in aMCI.
Acknowledgments: This research was partly supported by National Natural Science Foundation of China (No. 30370519), National Basic Research Program of China (973 Program) (No. 2007CB512308), National Hi-Tech Research and Development Program of China (863 Program) (No. 2007AA0200Z435), and Chinese-Finnish NEURO program from Natural Science Foundation of China (NSFC, No.30621130074).

TF01

ECSTASY/MDMA USE AND THE PROCEDURAL MEMORY CONSOLIDATION EFFECT OF SLEEP

Blagrove M, Seddon J, George SA, Jones KA, Stickgold R, Walker MP, Morgan MJ, Parrott AC. Psychology, Swansea University, Swansea SA2 8PP, m.t.blagrove@swansea.ac.uk

A period of sleep on the night after learning causes improvement in declarative and procedural memory, despite there being no intervening practice on the task (Maquet et al, 2003, Sleep and brain plasticity. Oxford U.P.; Stickgold, 2005, Nature, 437, 1272-1278; Walker, 2005, Behavioral and Brain Sciences, 28, 51-64). This effect is not due to reduced sleepiness, and is not found after a similar length of time spent awake (Walker et al, 2003, Nature, 425, 616-620). Ecstasy/MDMA affects serotonin and sleep. It was therefore hypothesized that the beneficial effect of post-learning sleep on a procedural memory task might be diminished by ecstasy use. This was tested using the Finger Tapping Task (FTT: Walker et al, 2002, Neuron, 35, 205-211), performance on which is improved by sleep.
Method Participants: Control participants who had never taken ecstasy and do not take illegal drugs (C: n=15, mean age=18.8yrs, 7 males); Ecstasy users who had taken ecstasy 2–3 days before the first FTT session (E3: n=15, age=20.6yrs, 9 males); Ecstasy users who had not taken ecstasy for at least 10 days before the first FTT session (E10: n=6, age=21.6yrs, 2 males). Procedure: Participants were tested on the FTT, which involves typing the numbers 4-1-3-2-4 on a keypad for 12 trials of 30 seconds each, with a break of 30 seconds between each trial. The first session occurred in the afternoon or early evening, with re-testing exactly 24 hours later. Participants also recorded their sleep times.
Results Mean sleep lengths did not differ between the groups on the night before the first (C=7.3hrs; E3=6.5hrs, E10=7.4hrs) or before the second (7.3hrs for all groups) FTT testing sessions. The groups did not differ on speed of finger tapping, nor number of errors, in the first FTT session. On the first 3 trials of the second session, compared to the last 3 trials of the previous day's session, each of the groups had a significantly increased speed of finger tapping (Wilcoxon matched-pairs test: C, p=.001; E3, p=.01; E10, p=.03) and a decrease in errors (Wilcoxon: C, p=.017; E3, n.s.; E10, n.s.). The groups did not differ significantly from each other on these changes.
Conclusions Recent and abstinent ecstasy users do not show deficits in the initial learning of the FTT motor skill, and do show the procedural memory consolidation effect of sleep that has been found in non-drug using individuals.
Acknowledgement: Study funded by ESRC award RES-000-22-2426

TF02

SUGGESTIBILITY IN ECSTASY AND CANNABIS USERS

Jones KA, Parrott AC, Blagrove MT. Psychology, Swansea University, Singleton Park, Swansea, SA2 8PP, 226746@swan.ac.uk

Introduction: Previous studies have examined memory deficits in ecstasy users, but suggestibility (i.e., the answering of leading questions about items in memory) has not been investigated in relation to ecstasy use.
Method: Recreational current ecstasy users (n= 15) with moderate lifetime usage were recruited, along with regular cannabis users (n= 15) and light alcohol drinking controls (n= 15). Subjects were assessed on a battery of tests including: immediate and delayed recall of a short story taken from the Gudjonsson Suggestibility Scale; Blagrove et al's (1995, Applied Cognitive Psychology, 9, 21-40) version of Baddeley's logical reasoning task, and yield and shift scores in answering leading questions on the Gudjonsson Suggestibility Scale (GSS). The GSS involves 15 leading questions and 5 non-leading (i.e., valid) questions about the story being presented, and then presented again after negative feedback was provided about the initial answers. Yield was defined as the number of times that a participant 'agreed' with a leading question (range 0-15). Shift was defined as the number of times a participant 'shifted' or changed their response following negative feedback (range 0- 20). Participants reported their confidence in answering each of the leading and non leading questions, before and after the negative feedback.
Results: ANOVAs showed that the three groups differed significantly on recall of the short story ($p<0.05$), in errors and confabulations made on the story recall ($p<0.01$) and in logical reasoning performance ($p<0.05$). Group comparisons showed that cannabis users had poorer recall of the short story than controls (Tukey $p<0.05$), and ecstasy users made significantly more errors on the story than controls (Tukey $p<0.01$). Ecstasy users had significantly poorer scores on logical reasoning than controls (Tukey $p<0.05$). ANOVAs showed no group differences in yield or shift, nor in confidence when answering leading questions, nor when answering non-suggestible questions.
Conclusions: In conclusion, ecstasy users made more mistakes than controls when recalling a short story and showed deficits in logical reasoning. However, despite these cognitive deficiencies, the ecstasy users did not give more suggestible answers when answering questions about the story than did controls, and were not less confident when answering such leading questions. This has implications for ecstasy users undergoing interrogation or questioning in the criminal justice system.
This research was funded by Department of Psychology research fund, Swansea University

TF03

SELF RATED AND BEHAVIOURAL MEASURES OF CREATIVITY IN ECSTASY AND CANNABIS USERS

Jones KA, Parrott AC, Blagrove MT. Psychology, Swansea University, Singleton Park, Swansea SA2 8PP, 226746@swan.ac.uk

Introduction: Increased creativity has often been cited by drug users as a reason for drug use. Our aim was to assess self rated and behavioural measures of creativity in ecstasy users, there having been no published research on this, and to compare scores on these creativity measures for ecstasy users with cannabis users and alcohol using controls.

Method: Ecstasy users (n = 15), cannabis users (n= 15) and controls (n= 15) were given three measures of creativity: Gough's trait self-report Creative Adjective Checklist (Gough, 1979, Journal of Personality and Social Psychology, 37, 1398-1405), the Consequences behavioural test of creativity (Christensen et al, 1953, Sheridan Supply, Beverly Hills), and a 5 point scale on which participants self rated their own creative performance on the Consequences test. The Consequences test involved participants being given 5 hypothetical scenarios and asked to generate as many consequences as possible in 2 minutes per scenario. The responses to each scenario were rated blindly by two independent judges to ascertain each participant's number of novel responses (those determined as occurring for less than 5% of all responses from the 45 participants and their total number of responses (fluency of ideas score). Subjects were only told that Consequences was a test of their creativity after the task was completed, and before self rating of Consequences performance occurred.

Results: Group differences were tested by one way ANOVAs and Tukey tests. The groups did not differ significantly on Gough's creative adjective checklist nor on fluency of ideas on the Consequences test. On the consequences test the three groups differed significantly on number of novel responses (ANOVA, $p<0.05$): cannabis users had significantly more novel responses than did controls (Tukey test $p<0.05$); ecstasy users also had more novel responses than controls but this was not significant. The three groups differed significantly on self assessment of consequences test performance (ANOVA, $p<0.05$), with ecstasy users and cannabis users giving higher self ratings of behavioural creativity than controls. However, Tukey test showed that these differences missed significance (ecstasy>control $p= .058$; cannabis>control, $p= .088$).

Conclusions: In conclusion, there is a trend for ecstasy users to perceive their responses on the consequences test as more creative than do cannabis users and non-drug users, but it is only the cannabis users who do produce significantly more novel and creative ideas than controls. This research was funded by Department of Psychology research fund, Swansea University

TF04

CHANGES IN ACTIVITY AND TEMPERATURE FAIL TO CORRELATE WITH 5-HT RELEASE FOLLOWING REPEATED MDMA ADMINISTRATION IN RATS

Rodsiri R, Marsden CA, Fone KCF, Green AR. School of Biomedical Sciences, University of Nottingham, Nottingham NG7 2UH, mbxrr@nottingham.ac.uk

Human binge use of repeated low doses of 3,4-methylenedioxymethamphetamine (MDMA/ ecstasy) may maintain the euphoric state while reducing tolerance (Parrott, 2005). However there is limited information from animal studies whether analogous repeated MDMA causes behavioural effects and long-term serotonergic neurotoxicity. In this study we determined the acute effects of repeated low doses of MDMA on body temperature, activity and 5-HT release in the rat by combining telemetry and microdialysis.

Male Lister hooded rats (100-130 g) were individually housed after i.p. implantation of a telemetry device. Two weeks later a microdialysis probe was implanted into the hippocampus. The following day either MDMA (3 or 6 mg/kg) or saline were given i.p. (n = 6/treatment) 3 times every 2 h and microdialysis samples collected with activity and body temperature monitored simultaneously using telemetry. Two-way ANOVA with treatment and time as main factors was used followed by Bonferroni posttest.

MDMA (3mg/kg) significantly decreased body temperature after each injection and this returned to normal 3 h after the last injection. The maximum decrease occurred 40 min after each injection ($p < 0.001$ after the first and second injections and $p < 0.05$ after the third injection). The higher dose of MDMA (6mg/kg) reduced body temperature after the first injection ($p < 0.001$) but then increased temperature to a maximum of +1 ^{o}C 2 h after the last injection. There was no significant difference in activity between saline and MDMA (3mg/kg) treated animals. In contrast the higher dose of MDMA (6mg/kg) induced hyperactivity after each injection with a prolonged increase after the final dose. Both doses of MDMA increased extraneuronal hippocampal 5-HT with a maximum release 1 h after each injection. The higher dose of MDMA (6mg/kg) produced greater release of 5-HT following the first injection (+556% from predrug basal) than the lower dose (+127% from predrug basal). After the second and the third injections increases in 5-HT release were similar for both doses (approximately +300% from basal).

The results indicate that repeated administration of the higher dose of MDMA causes hyperthermia and hyperactivity while the lower dose results in hypothermia and no effect on activity. Moreover there appears to be no correlation between changes in extracellular 5-HT and either activity or temperature following repeated low dose MDMA administration. The results indicate that factors other than 5-HT release (possibly dopamine release) are involved in the behavioural and physiological effects acute low doses of MDMA.

Funding: R Rodsiri is financially supported by Royal Thai Government.

TF05

A LETHAL COMBINATION OF CAFFEINE AND MDMA ("ECSTASY") IS REPRODUCED WITH D-AMPHETAMINE AND D-FENFLURAMINE

Vanattou-Saifoudine N, Harkin A. School of Pharmacy and Institute of Neuroscience, School of Pharmacy and Institute of Neuroscience, College Green, Dublin 2, vanatton@tcd.ie

Previously, we have reported that caffeine profoundly exacerbates the toxicity of 3,4 methylenedioxymethamphetamine (MDMA "ecstasy") in rats with increased lethality, hyperthermia, tachycardia and long-term serotonin loss in the central nervous system (McNamara et al., 2006 Neuropharmacology, 50(1):69-80; McNamara et al., 2007, Eur J Pharmacol. 555(2-3):194-8). As MDMA is known to induce the release of catecholamines and serotonin in the brain, we further investigated if caffeine's synergistic effects with MDMA can be generalised to d-amphetamine and/or d-fenfluramine, amphetamines with predominant actions on catecholamine and serotonin systems respectively. All drugs were administered by the i.p. route to male Sprague Dawley rats housed in groups of 4. Core body temperatures and behaviour were monitored for 1 hour prior (baseline) and 5 hours following drug administration. All data are expressed as mean with standard error and were analysed by ANOVA and Newman-Keuls post hoc test, where appropriate, to determine differences between the treatment groups ($P < 0.05$).

Co-administration of caffeine (10 mg/kg) and amphetamine (5 and 15 mg/kg), unlike MDMA (15 mg/kg) did not induce lethality or provoke synergistic hyperthermia. Caffeine, however, prolonged d-amphetamine induced locomotor activity and stereotypy. Similarly, co-administration of caffeine (10mg/kg) with d-fenfluramine (5mg/kg) did not produce hyperthermia. Instead fenfluramine induced a hypothermic response which was not influenced by the co-administration of caffeine. By contrast, co-administration of caffeine (10mg/kg) with a combination of d-amphetamine (1 and 2.5mg/kg) and d-fenfluramine (5 mg/kg) provoked an MDMA-like response characterised by lethality, hyperthermia and increased locomotor and stereotyped behaviour when compared to the d-amphetamine and d-fenfluramine combination treatment alone. We have previously reported that pre-treatment with the selective D1/5 receptor antagonist SCH 23390 (1mg/kg) blocks MDMA induced-hyperthermia and its exacerbation by caffeine. Similarly, pre-treatment with SCH 23390 blocks the synergistic hyperthermia evident following the co-administration of caffeine, d-amphetamine and d-fenfluramine.

Our results suggest that both dopamine and serotonin are important regulators of the toxicity associated with the co-administration of caffeine and MDMA which converge on a dopamine D1 receptor dependent pathway.

The authors acknowledge grant support from the Health Research Fund.

TF06

RECREATIONAL COCAINE USE: SCHIZOTYPY AND COGNITIVE PERFORMANCE

Soar K, Mason C. Psychology, University of East London, Romford Road, London, E15 4LZ, k.soar@uel.ac.uk

Background/aims: Recent evidence suggests that recreational cocaine use is on the increase, with the UK reporting one of the highest levels of use in the EU (EMCDDA, 2005). Most of research into the effects of cocaine is based on assessment of chronic cocaine-dependent users. To date very few studies have addressed the psychological and behavioural effects associated with non-dependent recreational cocaine use. These have suggested some indication of psychotic-like symptoms, and only two known studies have addressed the neuropsychological effects associated with recreational cocaine use. The current study aimed to assess whether recreational cocaine show neuropsychological deficits on a battery of tests, previously shown to be sensitive to cocaine dependent individuals and psychosis-prone individuals. Schizotypal traits were also measured.
Methodology: Recreational cocaine users (n=10) were compared with polydrug controls (n=9) and drug-naïve controls (n=8) on patterns of drug use, the General Health Questionnaire (GHQ-12), the Brief Schizotypal Personality Questionnaire (SPQ-B) and four neuropsychological tasks from the CANTAB: spatial working memory task (SWM), Intra/extra dimensional (IED), the Stocking of Cambridge (SOC) and the Rapid visual processing (RVP).
Results: One-way ANOVA's (and Tukey HSD post hoc tests where appropriate) revealed that recreational cocaine users produced significantly more errors on the IED ($p \leq 0.05$), and the RVP ($p \leq 0.05$) relative to polydrug and non-drug controls; however there were no significant group differences in the mean latency to complete both of these tasks. Recreational cocaine users reported significantly higher scores on the cognitive-perceptual and disorganised thinking SPQ-B subscales, as well as total SPQ-B scores compared to the drug-naïve controls ($p<0.02$), and higher levels on the disorganised thinking subscale compared to polydrug users ($p=0.02$).
Conclusions: The data showed that recreational cocaine users displayed impairments on tasks addressing sustained attention and attentional shifting (but not on tasks of spatial memory or planning) relative to non-cocaine users. The cocaine users also reported higher schizotypal trait expression. Collectively these results can be contextualised within models of dopamine neuromodulatory changes, and indicate that regular moderate recreational cocaine use may be sufficient to induce such psychobehavioural alterations.
This research was supported by internal UEL funds.

TF07

5-HT6 ANTAGONISM ATTENUATES CUE-CONDITIONED REINSTATEMENT OF COCAINE SEEKING BUT NOT COCAINE SELF ADMINISTRATION

van Gaalen MM, Schoffelmeer ANM, Bespalov AY, De Vries TJ. Neuroscience Research, GPRD, Abbott, Knollstrasse, Ludwigshafen, marcel.vangaalen@abbott.com

Re-exposure to cocaine-related cues elicits craving and relapse in human cocaine addicts even after months of abstinence. Similarly, in laboratory rats, cocaine-related cues reliably reinstate cocaine seeking after prolonged periods of withdrawal or extinction, thus providing a model to study mechanisms underlying the relapse to cocaine. The serotonergic system is known to mediate and/or modulate some of the effects of cocaine. In this study, we focus on the role of 5-HT6 receptors. These receptors are abundantly expressed in brain areas such as the nucleus accumbens, an area that is crucial involved in cocaine reinforcement and relapse. Nevertheless, a possible modulatory role of 5-HT6 receptors in these processes has not been investigated so far.
Male Wistar rats were trained to self-administer cocaine on a FR1 schedule for 10 one-hour long sessions (40 µg/kg/infusion, iv) followed by extinction training for 15 sessions. During reinstatement testing, the experimental conditions were similar to the conditions during training on an FR1-schedule, with the exceptions that 1) animals were not connected to the swivel and 2) responses did not result in cocaine infusions.
Here, we report that the 5-HT6 receptor antagonists SB 271046 and Ro-04-6790 significantly attenuate cue-induced cocaine seeking in rats at 3-10 and 30 mg/kg respectively ($n = 9$-10, $p<0.05$, ANOVA followed by Dunnet's post hoc test). Both 5-HT6 antagonists, however, do not affect cocaine self-administration at these doses ($n=8$-9, $p>0.05$, ANOVA).
This indicates that 5-HT6 receptor antagonists specifically attenuate the incentive motivation to seek cocaine, but not the primary reinforcing effects of cocaine or general operant behavior. Our data reveal an important role of the 5-HT6 receptor in neuronal processes underlying relapse to cocaine seeking and that targeting this receptor may offer a novel strategy in the treatment of cocaine addiction.
Funded by Abbott Laboratories

TF08

EFFECTS OF ACUTE AND CHRONIC KETAMINE ADMINISTRATION ON SEMANTIC PRIMING

Stefanovic A, Klaassen E, Freeman TP, Das RK, Brandner B, Cregg R, Nagaratnam M, Morgan C, Rossell SL, Bromley L, Curran HV. Sub-Department of Clinical Health Psychology, University College London, 1-19 Torrington Place, WC1E 7HB, ana.stefanovic@ucl.ac.uk

One of the main confounds in research on cognitive deficits in schizophrenia is not being able to clearly distinguish between direct effects of underlying psychopathology and the secondary changes that result indirectly from it (e.g. the effects of antipsychotic medication; Rossell and Stefanovic, 2007, Current Psychiatry Reviews Vol.3(2): pp. 137-145(9)). Acute ketamine (an NMDA receptor antagonist) administration has successfully been used to model schizophrenia symptoms, thus avoiding some of the limitations found in schizophrenia research. In addition, recreational users provide a window into the effects of chronic ketamine administration.
The current study investigated semantic memory deficits, considered to be one of the key deficits in schizophrenia, using both acute (Experiment 1) and chronic (Experiment 2) ketamine models. Along with explicit tasks (e.g. fluency tasks), semantic memory function was investigated implicitly, using a semantic priming lexical decision task. Acute effects of low (75 ng/ml) and high (150 ng/ml) ketamine doses were investigated using a placebo-controlled, double-blind independent group design with 16 participants in each group. In addition, 21 regular recreational ketamine users were compared to 19 ketamine-naïve polydrug controls. Stimulus onset asynchrony (SOA) and relatedness proportion (RP) were manipulated to create two separate conditions: an automatic (short SOA & low RP) and a strategic condition (long SOA & high RP).
The main finding in the Experiment 1 was that neither of the ketamine groups showed the expected increased semantic priming in the strategic condition compared to the automatic. This effect was seen clearly in the placebo group ($p=0.008$). In Experiment 2, there was more semantic priming overall in the chronic ketamine group compared to the polydrug group ($p=0.012$). There was more semantic priming ($p=0.002$) in the strategic condition than in the automatic overall. While the semantic priming seemed intact when processing was restrained to automatic levels, there was an indication of a failure to efficiently use conscious strategic mechanisms after acute ketamine administration. However, this impairment was almost absent in chronic users. While the acute ketamine results are consistent with the only previous study that investigated the effects of ketamine on semantic priming (Morgan et al., 2006, Biol Psychiatry Vol. 59(3): pp. 265-72), the previous study found pronounced impairments in chronic ketamine, while the current study did not. Reasons for these discrepancies (including task differences) and the implications of the current results in regard to schizophrenia are discussed.
Source of funding: internal

TF09

JOURNEY THROUGH THE K-HOLE: PHENOMENOLOGICAL ASPECTS OF KETAMINE USE IN FREQUENT, INFREQUENT AND EX-USERS

Muetzelfeldt L, Kamboj SK, Morgan CJA, Curran HV. Psychopharmacology Unit, Sub-Dept of Clinical Psychology, University College London, Gower Street, London, WC1E 6BT, l.muetzelfeldt@ucl.ac.uk

Introduction: Although recreational use of the dissociative anaesthetic drug ketamine continues to increase, little is known about the phenomenological and dependence-inducing aspects of its use. We therefore designed a structured interview to examine positive and negative effects, initiation experiences, concerns about long-term effects and beliefs about the benefits and drawbacks of stopping using the drug.
Methods: Ninety participants (30 frequent users, 30 infrequent 'recreational' users and 30 ex-users who had abstained from use for at least 3 months) were interviewed and completed a modified version of the CAGE. Reported drug use was verified by analyses of hair samples.
Results: The most appealing effects of the drug for two-thirds of the sample were "melting into the surroundings", "visual hallucinations", "out-of-body experiences" and "giggliness". Some users referred to being 'psychonauts' on ketamine - astronauts of the psyche. Unappealing effects included "decreased sociability" and "impaired memory". Frequent ketamine users expressed more concerns than the other groups about long-term effects on physical health. Almost a third of this group reported experiencing K-cramps, or severe gastric pains, and 20% reported ketamine induced cystitis or bladder problems. Ex-users had more concerns about mental health problems. In terms of beliefs around cessation of use, the benefits included "clearer thinking" and "more in control of my life", whereas drawbacks included "not as much fun going out/ increased boredom". Addiction was also a concern: the majority of frequent users reported using the drug without stopping until supplies ran out and their mean increase in dosage from initiation to current use was 600%. This group also scored significantly higher on two questions on the CAGE, indicating a propensity to addiction.
Conclusion: We have identified some of the aspects which ketamine users subjectively rated as appealing and unappealing effects of the drug. Additionally, we have identified concerns which different groups of users have surrounding their use - specifically health issues which seem uniquely related to ketamine use. Our findings suggest that heavy users appeared to be more concerned with long-term physical effects of the drug whereas ex-users cited mental health problems as a reason for stopping ketamine use. Furthermore, the increased dosage over time, CAGE scores, and use of the drug until supplies ran out suggest that ketamine dependence may be a cause for concern for frequent users of this drug.
This research was funded by an ESRC grant.

TF10

NICOTINE DEPENDENCE IN PSYCHIATRIC INPATIENTS UNDERGOING ALCOHOL OR DRUG DETOXIFICATION: MINIMAL IMPACT OF A BRIEF EDUCATIONAL INTERVENTION

Walters P, Bekoe OO, Sinclair JMA, Baldwin DS. Shaftesbury Clinic, SW London & St George's Mental Health Trust, 61Glenburnie Road, London, SW17 7DJ, pamela.walters@virgin.net

Introduction: Cigarette smoking is common in the general population, but substantially more common in patients with alcohol or drug dependence syndromes. Tobacco-related deaths are increased in substance-dependent patients, and smoking contributes to the excess mortality associated with opiate use. We wished to establish the prevalence of nicotine dependence among psychiatric inpatients undergoing detoxification from alcohol or drugs, and to evaluate the potential effectiveness of a simple brief educational intervention in adjusting attitudes towards cigarette smoking in this patient group.
Methods: All patients admitted electively to a single detoxification ward over 6 months were considered for study participation, exclusion criteria being limited to the presence of comorbid severe mental illness or failure to complete the planned admission period. Consenting patients were assessed prior to and immediately after a 50-minute group intervention, based on health promotion principles, with distribution of educational leaflets and ensuing group discussion. Baseline assessments included demographic and clinical characteristics, smoking history, use of ICD-10 criteria for diagnosing substance misuse, completion of the Fagerstrom Test for Nicotine Dependence (FTND). Attitudes towards smoking and smoking cessation were assessed using a Likert scale questionnaire, before and after intervention.
Results: 174 patients (128 men, 46 women: mean age 41 years) consented to participate in the study assessments: 130 were admitted for alcohol and 28 for opiate detoxification, the remainder for detoxification from both alcohol and drugs. 144 (82.8%) patients (108 men, 36 women) were current smokers and potentially suitable for intervention: 111 (77.1%) having at least medium dependence on nicotine, according to FTND criteria. Only 45 (31.3%) patients (37 men, 8 women) chose to undertake the brief intervention, which was not associated with significant change in any of the questionnaire items assessing attitudes and motivations towards smoking and smoking cessation.
Conclusions: Smoking and nicotine dependence are common among psychiatric inpatients admitted for detoxification from alcohol or drugs of abuse. A simple brief educational intervention had a low take-up rate and was ineffective in engendering positive change in attitudes towards smoking cessation, indicating that more complex interventions are needed to effect change in cigarette smoking in this patient group. Source of funding: No external funding was sought for this study.

TF11

THE EFFECTS OF NICOTINE ON A CONCURRENT SELECTIVE ATTENTION AND WORKING MEMORY TASK IN SMOKERS AND NON-SMOKERS

Nikolaou KN, Powell JH, De Fockert JW. Psychology, Goldsmiths University of London, Lewisham Way, London SE14 6NW, xwrisonoma@yahoo.com

Introduction: Selection in tasks that involve cognitive conflict has been shown to rely on the maintenance of stimulus priorities within working memory (WM), and therefore on WM capacity; decreasing WM capacity results in greater interference on a concurrent conflict task. "Cognitive conflict" has been associated with dopaminergic (DA) activity, and activations in the anterior cingulate. Nicotine acts on cholinergic and DA pathways to the anterior cingulate and prefrontal cortex, and has been shown to affect tasks that are sensitive to capacity limitations.
Aims: To test whether nicotine's effect on cognitive conflict on the flanker task, during the concurrent performance of a WM task, of varying load, is associated with true enhancement or with relief from abstinence-induced withdrawal symptoms. To test whether nicotine affects the interaction between WM and cognitive conflict.
Methods: Mixed factorial design with GROUP (abstinent smokers vs. non-smokers) and GUM (nicotine vs. placebo) as between- and within-groups factors, respectively. 22 smokers (AS) (10+ cigarettes/day) and 25 non-smokers (NS) (-20 cigarettes/life-time) met the inclusion criteria (No to: prescribed medication; pregnancy or breast-feeding; diabetes; epilepsy; any drug-use including alcohol for 20+ days in the month prior to their participation), and took part in the study. Smokers were 12-hour nicotine-abstinent, and all participants abstained from alcohol and any illicit drugs for 24 hours prior to each session. Smokers received 4mg of nicotine gum, while non-smokers received 2mg. Gum administration was conducted in a counterbalanced, double-blind fashion. The task involved the combination of a flanker task (congruent vs. incongruent condition) and a WM task of varying load (high vs. low).
Results: Differences in accuracy scores and reaction times were computed between the congruent and incongruent conditions of the flanker task (measures of cognitive conflict). GUM x GROUP interaction for both accuracy and reaction times [$F(1, 43) = 4.21$, $p < 0.05$ and $F(1, 43) = 7.54$, $p < 0.01$, respectively]. Nicotine, by comparison to placebo, improved AS's accuracy of selection in the presence of a distracter [$t(21) = 2.23$, $p < 0.05$], but had no effect in NS [$t(24) < 1$, ns]. Nicotine tended to impair speed of selection in NS [$t(24) = 1.81$, $p = 0.08$], but had no effect in AS [$t(24) = -1.11$, ns]. The interaction between cognitive conflict and WM load was unaffected by nicotine.
Conclusions: Findings suggest a relief from withdrawal effect of nicotine rather than a true enhancing effect. PhD bursary-Goldsmiths funding

TF12

ACUTE NICOTINE ABSTINENCE AND NICOTINE EXPOSURE ON TASTE PERCEPTION IN SMOKERS

Mullings EL, Donaldson LF, Melichar JK, & Munafò, MR. Experimental Psychology, University of Bristol, 12a Priory Road, Bristol, BS8 1TU, Emma.Mullings@bristol.ac.uk

Smoking cessation is associated with marked increase in body weight, and this contributes to relapse. We investigated the effects of acute abstinence from smoking and nicotine administration on taste, since modulation of taste is a likely mechanism by which eating behaviours may be altered in abstinent smokers helping to identify novel treatments for post cessation weight gain. Cigarette smokers (n = 48) who reported smoking within 1 hour of waking were recruited from the general population. Participants were randomised to abstain for 12 hours or smoke as normal prior to testing, confirmed by exhaled carbon monoxide monitoring, and to receive a nicotinised or de-nicotinised cigarette. Measures of threshold at which the taste could be detected on the tip of the tongue, using a range of solution concentrations presented in a pseudo-random order, and subjective ratings of intensity, for salt and sucrose tastes were collected pre- and post-cigarette. ANOVA of threshold data, with abstinence, cigarette and sex as between-subjects factors, and time as a within-subjects factor indicated a significant sex x cigarette x time interaction ($F [1, 38] = 5.09$, $p = 0.030$), reflecting relatively higher taste thresholds for both salt and sucrose solutions among female participants who had smoked a nicotinised cigarette compared with those who has smoked a denicotinised cigarette ($p = 0.032$), but not among males ($p = 0.15$).

There were no significant main effects or interaction terms involving the abstinence factor ($ps > 0.15$). Our results indicate that nicotine results in attenuation of the general increase in taste sensitivity following repeated tasting among female but not among male participants. This does not appear to be a withdrawal-relief phenomenon, as there were no significant main effects or interaction terms involving the abstinence factor.

These data suggest that the appetite suppressant properties of cigarette smoking may operate via modifications in taste thresholds, particularly among female smokers.

TF13

PATTERNS OF CHANGE IN WITHDRAWAL SYMPTOMS, DESIRE TO SMOKE, REWARD MOTIVATION, AND RESPONSE INHIBITION ACROSS THREE MONTHS OF SMOKING ABSTINENCE

Dawkins LE, Powell JH, Pickering A, Powell J, West R. Psychology, University of East London, Romford Road, London; E15 4LZ, l.e.dawkins@uel.ac.uk

Introduction: We have previously demonstrated that acute smoking abstinence is associated with lowered reward motivation and impaired response inhibition (Dawkins et al., 2007, Psychopharmacology: 190, 457-467). This prospective study explores whether these impairments, along with withdrawal-related symptoms, recover over three months of sustained abstinence.

Methods: 145 smokers completed a 12-hour abstinent baseline assessment and were then randomly allocated in a 3:1 ratio to quit or continue smoking. All were re-tested after 7 days, 1 month and 3 months on a number of indices previously demonstrated in this cohort of smokers to be sensitive to the effect of nicotine vs. acute abstinence: reward motivation (SHAPS, CARROT, Stroop); tasks of response inhibition (antisaccade task; CPT) and clinical indices of mood (HADS), withdrawal symptoms (MPSS) and desire to smoke. Successful quitters' (N = 33) scores were compared with those of continuing smokers (N = 38), who were tested after ad libitum smoking.

Results: ANOVA revealed that abstinence-related anhedonia (SHAPS) and diminished reward responsivity (CARROT) showed significant improvement ($p < 0.05$) and plateaued after a month of abstinence, at which point they did not differ from the scores of continuing smokers. Mood, withdrawal symptoms and desire to smoke all declined from acute abstinence to 1 month of cessation ($p < 0.02$) and by this point were equivalent, or lower than ($p < 0.05$), the levels reported by continuing smokers. Response inhibition (antisaccade accuracy and CPT motor errors) did not show improvement over 3 months of abstinence.

Conclusion: Appetitive processes and related affective states do appear to 'recover' in smokers who remain nicotine-free for 3 months whereas response inhibition does not. The lack of recovery in inhibitory control may mean that deficits in this domain constitute a long-term risk factor for relapse and should be a target for intervention.

Study funded by the US National Institute of Drug Abuse (NIDA)

TF14

SMOKING A SINGLE CIGARETTE DOES NOT ALTER SENSITIVITY TO PUNISHMENT

Butler K, Rusted J, Gard P, Jackson A. Pharmacy and Biomolecular Sciences, University of Brighton, Brighton, kab14@brighton.ac.uk

Evidence indicates that nicotine alters sensitivity to reward (Kenny & Markou, 2006, Neuropsychopharmacology, 31, 1203). However, variable results have been reported regarding the ability of nicotine or smoking to alter sensitivity to punishment (Cherek & Bennett, 1991, Behavioural Pharmacology, 2, 23; Morrison, 1969, Psychopharmacologia, 14, 221). This study aimed to further investigate the effects of smoking on responding to punishers, in two different tasks.

30 dependent smokers (mean age 23.07 years) scoring ≥ 5 on the Fagerstrom questionnaire (mean 6.27) were recruited. 15 were randomly allocated to a smoking condition and 15 to a non-smoking condition. Both groups were abstinent for at least 3 hours before testing. Participants completed smokerlyzer tests, personality and subjective questionnaires, a conflict-task and a probabilistic response-reversal task (PRR), both using point gain and loss as reward and punishment.

Results were analysed with ANOVA/Kruskal-Wallis and appropriate post-hoc t-tests. The smoking group had higher exhaled carbon monoxide levels immediately after smoking compared to the non-smoking group ($t(28) = 2.56$, $p = 0.016$) and this remained higher at the end of the experiment ($t(28) = 2.60$, $p = 0.015$). Nicotine-sensitive visual analogue scales (VAS) showed that the smoking group had higher ratings of buzzed/headrush ($t(20.73) = 3.41$, $p = 0.003$), dizzy ($t(14.26) = 3.48$, $p = 0.004$) and contented ($t(28) = 2.39$, $p = 0.024$) and lower ratings of impatience ($t(17.57) = -2.61$, $p = 0.018$) following smoking compared to the non-smoking group.

Smoking did not alter response to punishment (suppression ratio: $F(1, 28) = 0.62$, $p = 0.440$, lose-stay errors: $H(1) = 0.45$, $p = 0.516$, win-maintenance failures: $F(1, 28) = 0.77$, $p = 0.388$) or reward sensitivity (win-shift errors $H(1) = 0.02$, $p = 0.908$) on either of the behavioural tasks. Irrespective of smoking condition there was a correlation between PRR-win-shift errors and years smoking (spearman's: $r_s = 0.52$, $p = 0.003$).

The effect of smoking on both exhaled carbon monoxide levels and VAS indicates that nicotine was active during the experiment. There was no evidence for change in sensitivity to punishment assessed with a conflict-task and PRR that used point gain and loss as reward and punishment. Future research using more salient rewards and punishers such as money or cigarettes as opposed to these hypothetical gains and losses may be more sensitive in detecting an effect of nicotine on punishment processing and aversive motivational processes.

This study was supported by a University of Brighton Studentship.

TF15

EFFECTS OF ACUTE NICOTINE ADMINISTRATION ON RATINGS OF ATTRACTIVENESS OF FACIAL CUES

Attwood AS, Munafò MR. Experimental Psychology, University of Bristol, 12a Priory Road, Bristol BS8 1TU, Angela.Attwood@bristol.ac.uk

It has been suggested that one mechanism by which nicotine may exert an influence over behaviour is by enhancing the reinforcing properties of other stimuli. We therefore sought to test the hypothesis that nicotine enhances the hedonic impact of behaviours performed in the presence of nicotine, using ratings of facial attractiveness, as we considered these to have considerable ecological validity in the context of the social environment within which cigarette smoking takes place.
Male and female participants (n = 29) attended a single testing session, and were randomized to smoke either a nicotine-containing or denicotinised cigarette, after which they completed ratings of attractiveness of twenty male and twenty female faces. Participants were required to have abstained from smoking for 24 hours prior to testing, and the nicotine manipulation was conducted double-blind.
A three-way ANOVA with nicotine condition and participant sex as between-subject factors and target sex as a within-subject factor revealed a significant main effect of nicotine ($p = 0.04$). The nicotine group rated faces as significantly more attractive (M = 4.0, SD = 0.6) than the placebo group (M = 3.6, SD = 0.4).
Our data indicate that nicotine increases ratings of attractiveness of facial cues. We did not observe any evidence that these effects differed between males and females. Importantly, we also did not observe effects on subjective ratings of mood, indicating that the effects we observed on ratings of attractiveness may not have simply been a consequence of global hedonic effects, or a positivity bias in questionnaire responding, in the nicotine condition.
Funding source: personal budget grant

TF16

EFFECTS OF THE GLYCINE-SITE PARTIAL AGONIST D-CYCLOSERINE ON THE COGNITIVE AND SUBJECTIVE EFFECTS OF SMOKING

Nesic J[1], Duka T[2], Rusted J[2], Jackson A[1]. [1]University of Brighton, Brighton, BN2 4GJ, [2]University of Sussex, Brighton, BN1 9QGj.nesic@gmail.com

Previous studies suggest that some of the effects of nicotine may be mediated by enhanced glutamate release (e.g. Jackson *et al*, 2008. Neuropsychopharmacology, in press). This study in healthy human volunteers was designed to investigate whether the partial glycine-site agonist D-cycloserine (DCS) would modulate subjective and cognitive effects of limited smoking.
Forty-eight habitual smokers (mean 12.5 cigarettes per day), abstinent for a minimum of two hours (mean 8.6h) were randomly allocated to receive either placebo or 50mg DCS (capsules administered double-blind). Subjective responses to DCS and smoking were determined using nicotine-like effects Visual Analogue Scales (VAS) and the Questionnaire of Smoking Urges (QSU). All questionnaires were completed at baseline (pre-capsule), 90 minutes post-capsule and again after smoking half of a cigarette or remaining abstinent. Cognitive effects were evaluated only after smoking/remaining abstinent, using the Rapid Visual Information Processing (RVIP) test. Breath CO levels, blood pressure and heart rate were measured at all three time points. Results were analysed using ANOVA with appropriate post-hoc t-tests.
In the absence of smoking, DCS did not produce significant subjective effects other than the increase in Nic-VAS ratings of 'Stimulated' ($p<.05$). Partial smoking did not produce any cognitive effects although it significantly increased systolic blood pressure and the VAS ratings of 'Buzzed', 'Stimulated' and 'Relaxed' (p's<.05), and decreased both the positive and the negative reinforcement aspects of craving (QSU factors 1 and 2; p's<.001). DCS was effective in blocking the smoking-induced increase in 'Stimulated' and 'Relaxed' ratings which were seen in the placebo/smoking group ($p<.01$ and $p<.05$, respectively). In contrast, DCS promoted the effects of smoking on the RVIP, where the DCS/smoking group made significantly less false alarm responses compared to both the DCS/abstinent and the placebo/smoking groups ($p<.05$). Regardless of the smoking manipulation, subjects receiving DCS had significantly slower response times on the RVIP ($p<.05$). While DCS alone did not have any cardiovascular effects, diastolic blood pressure was significantly increased by smoking only in the DCS group ($p<.05$).
In conclusion, DCS alone had minimal subjective effects although it successfully blocked some of the subjective effects of smoking. In contrast, DCS potentiated the cognitive effects of smoking and, independently of smoking, slowed subjects' responding. In addition, DCS interacted with smoking in increasing diastolic blood pressure. These findings are consistent with the hypothesis that enhanced glutamate release may indeed underlie some of the effects of smoking.
This study was funded by Wellcome Trust Grant No.074354.

TF17

VALIDATION OF RAT BEHAVIOURAL MODELS FOR THE ASSESSMENT OF CANNABINOID ABUSE POTENTIAL

Barrow ER, Staveley S, O'Conner EC, Parker DT, Broad A, Mead AN. Drug Safety Research & Development, Pfizer Global Research and Development,, Sandwich, Kent, CT13 9NJ, elizabeth.barrow@pfizer.com

The assessment of abuse potential is a critical component of safety testing for novel CNS-active compounds. Regulatory guidance indicates that novel compounds should be compared, where possible, to a comparator from the same drug class. Therefore, to examine the abuse potential of novel cannabinoid drugs, we developed rat behavioural models with existing cannabinoid agonists. All data was initially analysed using ANOVA and the appropriate post-hoc tests applied. In self-administration studies, rats were trained to respond for 6µg/kg/infusion WIN 55,212-2 (WIN) during daily 1h sessions (n=13). A dose response function for WIN (0, 3, 6, and 12µg/kg/infusion) was determined following acquisition of responding under an FR2 reinforcement schedule. Rats successfully acquired selective responding for WIN during the training phase on 6µg/kg/infusion ($p<0.01$) and a dose-response relationship was observed. For drug discrimination experiments, rats were trained to discriminate CP-55,940 (0.05mg/kg) from vehicle under an FR10 schedule of reinforcement for food (n=11). Generalization tests were then performed with Δ9-THC (0.1-3mg/kg) to investigate whether the interoceptive cue induced by Δ9-THC is similar to that induced by the CP-55,940. At 1mg/kg and 3mg/kg, Δ9-THC fully generalized to CP-55,940 ($p<0.01$). For physical dependence and withdrawal studies, rats were chronically dosed for 14 days with CP-55,940 (0.26mg/kg/24h), *via* osmotic mini-pumps. During the first 48h of withdrawal, CP-55,940 treated rats demonstrated increased activity ($p<0.05$) together with a higher percentage loss of body weight ($p<0.01$) compared to vehicle animals. Sleep architecture analysis revealed a reduction in both total sleep and REM sleep during the withdrawal period. These data provide positive controls which permit the non-clinical abuse potential assessment of cannabinoids in the rat.

TF18

EXAMINING NICOTINE- AND CUE- MAINTAINED RESPONDING USING SECOND ORDER SCHEDULES OF NICOTINE REINFORCEMENT IN RATS

Wing VC, Shoaib M. Psychobiology Research Group, Insitute of Neuroscience, Newcastle University, Framlington Place, Newcastle upon Tyne, NE2 4HH, Victoria.Wing@ncl.ac.uk

Under a second order schedule of reinforcement responding is maintained by presentation of a stimulus which is intermittently reinforced by simultaneous presentation of the primary reinforcer. The aim of this study was to establish second order schedules of reinforcement and examine the relative contribution of nicotine and the conditioned stimulus (CS) towards responding.

Male hooded Lister rats were initially trained under a fixed ratio (FR) schedule, in which active lever pressing resulted in an infusion of nicotine (0.03mg/kg/inf) paired with a 5 sec period of light oscillation (CS). A [FR5' (FR5:S)] schedule was employed (n=6-8) thus every 5th lever press resulted in presentation of the CS and every 25th lever press produced both nicotine infusion and CS presentation. This schedule of nicotine reinforcement was able to maintain drug-seeking behaviour and subsequent extinction tests were conducted over successive sessions. A two-way ANOVA for repeated measures revealed a significant effect of the extinction test [$f(2,8)=18.554$, $p=0.01$] and session [$f(4,16)=5.195$, $p=0.07$]. Removal of both nicotine and cues and replacement of nicotine with saline resulted in significantly lower levels of active lever presses over the 5 sessions than removal of cues alone ($p=0.013$ and 0.008 respectively, LSD post-hoc tests). These results suggest that under a [FR5' (FR:5S)] schedule behaviour is primarily controlled by nicotine with little contribution from the CS. Subsequently, a [FI10' (FR3:S)] schedule of reinforcement was established (n=8); every 3rd active lever press resulted in presentation of the CS, which after a 10 minute fixed interval was accompanied by nicotine infusion. Over three successive sessions there was a significant effect of extinction test [$f(3,21)=11.465$, $p<0.001$] and session [$f(2,14)=14.734$, $p<0.001$]. Removal of nicotine, the CS, and both nicotine and the CS, all significantly reduced responding compared to baseline ($p=0.001$, 0.011 and 0.06 respectively, LSD post-hoc test). There were no significant differences in the level of extinction, suggesting under this schedule, nicotine and the CS are similarly important in maintaining responding. This study demonstrates nicotine self-administration can be maintained under a second order schedule of reinforcement and that the specific schedule employed determines the contribution of the primary reinforcer and CS towards responding. The models presented allow exploration of the neural substrates, such as the endocannabinoid system which has been implicated in the motivational effects of nicotine and nicotine-associated cues, underlying the control of behaviour by nicotine and the CS.

This project was funded by the University of Newcastle and Merck Sharpe and Dohme

TG01

NICOTINE ENHANCES ANTIDEPRESSANT-LIKE EFFECTS OF CITALOPRAM AND REBOXETINE IN THE MOUSE FORCED SWIM AND TAIL SUSPENSION TESTS

Andreasen JTA, Redrobe JP. Dept. of Affective Disorders, Neurosearch A/S, Pederstrupvej 93, DK-2750 Ballerup, JTA@Neurosearch.dk

Current literature suggests that nicotinic acetylcholine receptors (nAChRs) are involved in major depression. For example, depressed patients have a higher smoking rate than healthy subjects and nicotine improves mood in non-smoking depressed patients. In rodents, antidepressant-like effects of both nicotine and the non-selective nicotinic receptor antagonist mecamylamine have been reported. Moreover, nicotine increases the firing rate of serotonergic and noradrenergic neurons and facilitates serotonin and noradrenaline release. Thus, it is hypothesised that nicotine may enhance the behavioural effects of serotonin (e.g., citalopram) and/or noradrenaline (e.g., reboxetine) reuptake inhibitors.

Here, we tested if nicotine enhanced the activity of citalopram or reboxetine in the mouse forced swim test (mFST) and mouse tail suspension test (mTST). The potential for mecamylamine to augment antidepressant drug action was also investigated. Sub-threshold and threshold doses of citalopram (3 and 10 mg/kg) or reboxetine (3, 10 and 20 mg/kg) were tested alone and in combination with nicotine (0.3 and 1.0 mg/kg) and mecamylamine (1 and 3 mg/kg). Appropriate locomotor activity experiments were performed to rule out non-specific stimulant effects. Differences between groups were analyzed by two-way analysis of variance (ANOVA), with nicotine/mecamylamine and citalopram/reboxetine as categorical predictors and followed by Planned Comparisons of the predicted means.

Nicotine (1.0 mg/kg) enhanced the effect of 10 mg/kg citalopram ($P<0.01$, n=8) and 20 mg/kg reboxetine ($p<0.001$, n=8) in the mFST. Similarly, in the mTST nicotine (1.0 mg/kg) enhanced the effect of 3 ($p<0.05$, n=8) and 10 mg/kg citalopram ($p<0.01$, n=8) as well as 3 and 10 mg/kg reboxetine ($p<0.001$, n=8). No concomitant locomotor stimulation was observed at the tested dose combinations. Mecamylamine did not augment the effects of citalopram or reboxetine at the doses tested in the mFST or mTST.

The data showed that nicotine enhances the effects of both serotonin and noradrenaline reuptake inhibitors, indicating that stimulation of nAChRs may enhance antidepressant action. Results from the mecamylamine combination experiments suggest that a different mechanism may be involved in the reported antidepressant-like activity of this compound.

TG02

KYNEURENINE/ 5-HT AND NO METABOLITES IN THE HIPPOCAMPUS AND FRONTAL CORTEX OF RATS EXPOSED TO CHRONIC MILD STRESS 'CMS'. ROLES OF A NEURONAL NITRIC OXIDE SYNTHASE INHIBITOR AND PENTOXYPHYLLINE

Amin BMS, Aboul-fetouh SA, Shehata HH, Yassin NAZ and Abdel-tawab AM. Pharmacology, National Research Centre, Tahreer Street, Guiza, Greater Cairo, bsamamin@hotmail.com

Cumulative evidence revealed the involvement of kynurenine pathway in certain types of depressive illness. The present study aims at using 7-nitroindazole '7-IND' and pentoxyphylline 'PENT' for probing the role of neuronal nitric oxide synthase 'nNOS' and TNF-alpha, respectively, in modulating the balance between the two major limbs of the metabolic pathways of Trp: 5-HT and Kyn in the hippocampus and frontal cortex of rats exposed to the CMS animal model of depression.

Male Wistar rats (45 animals) were divided into 5 groups. Control, and 6 week CMS-exposed groups. CMS included unpredictable stresses (e.g. pairing, cage tilting, cold stress, reversal of light/dark cycle, noise, flickering light, food and/or water deprivation). Another 3 groups were exposed to CMS and administered imipramine 'IMIP' 20 mg/kg/day i.p., '7-IND' 40 mg/kg/day s.c. or 'PENT' 50 mg/kg/day i.p. for the last three CMS weeks. Rats were assessed for body weight and sucrose preference, as a marker of anhedonia, open-field and forced swimming tests. Trp, 5-HT, 5-HIAA, Kyn and total nitric oxide metabolites 'NOx' were assayed in brain homogenates. ANOVA tests were applied for comparisons.

The CMS-exposed rats showed a decrease in body weight and sucrose preference with time. These effects were ameliorated in the IMIP, 7-IND and PENT treated groups. Similar effects were observed with the open-field and forced swimming tests. As regards the neurochemical changes, compared to the control group, there was a significant ($p<0.0001$) increase in the molar ratios of Kyn/5-HT in the CMS group in the frontal cortex [8.98±0.86 vs. 4.454±0.83] and in the hippocampus ($p<0.004$) [10.48±2.22 vs. 3.61±0.58]. This ratio was significantly different in the frontal cortex in the IMIP, 7-IND and PENT groups (4.81±0.54, 3.37±0.8 and 2.7±0.66, respectively). While in the hippocampus, the difference was significant in the 7-IND and PENT groups (2.38±0.56, 4.84±1.31, respectively). Other Trp and Trp metabolites' changes were variably shown. A significant ($p<0.0001$) increase in NOx was detected in the CMS group in comparison to the control group in the frontal cortex [787.8±81.22 vs. 340.0±37.25 nmol/ g tissue weight, respectively] and in the hippocampus ($p<0.0001$) [610.9±42.19 vs. 255.4±4.481nmol/ g tissue weight, respectively]. This was significantly different in frontal cortex (362.5±29.10 and 277.4±22.33 nmol/ g tissue weight) and hippocampus (320.4±51.65 and 258.7±15.85 nmol/ g tissue weight) in the 7-IND and PENT groups, respectively.

In conclusion: there is a possible role of Kyn and NOx in the CMS animal model of depression, and a possibility for alternative pharmacological approaches to understand the neurobiology of depression.

TG03

COMPARISON OF STRESS-INDUCED ALTERATIONS IN HIPPOCAMPAL MGLUR7 MRNA IN TWO ANIMAL MODELS OF DEPRESSION
O'Mahony CM, Bravo J, Dinan TG, Cryan JF. Pharmacology and Therapeutics, University College Cork, CORK, montyomahony@hotmail.com

Glutamatergic neurotransmission has been strongly implicated in the pathophysiology of emotional disorders such as anxiety and major depression. mGlu receptors are involved in modulating the activity of this neurotransmission in the CNS. The mGlu receptor 7 is found presynaptically and because it is abundantly distributed it may contribute to an array of functions in the CNS. For example, mGluR7 is known to be expressed in the hippocampus, a region critically involved in the modulation of anxiety and depression-related behaviour. Mice deficient in mGluR7 have an antidepressant-like behaviour and altered stress response suggesting a key role of this receptor in depression (Cryan et al., 2003, European Journal of Neuroscience,17(11):2409-17.;Mitsukawa et al., 2006, Neuropsychopharmacology, 31(6):1112-22.). The aim of the present study was to examine and compare the expression of hippocampal mGluR7 in two stress-related animal models of depression. Maternal separation during the early postnatal period is acknowledged to be a stressful status, resulting in a disturbance of normal CNS development. In adulthood, these rats display a depressive phenotype in several behavioural paradigms, as well as neuroendocrine and monoamine abnormalities. Wistar Kyoto (WKY) rats are a genetically selected strain that have a marked elevation in anxiety. As with the MS rats, they also elicit behavioural and hormonal responses suggestive of a depressive phenotype.
In this study, mGluR7 was localised in the hippocampus using in situ hybridisation. The hippocampal regions analysed for the presence of mGluR7 mRNA were the CA1, CA3 and the dentate gyrus. Using this procedure we have compared mGluR7 expression in MS and non-MS Sprague Dawley (SD) rats. The expression of mGluR7 in the WKY rat strain was also assessed to allow a comparison of an environmental and genetic model of depression to be made.
Our data demonstrate distinct expression patterns of mGluR7 within hippocampal regions studied. However, maternal separation stress did not alter this expression pattern. Future studies will involve examination of other brain regions implicated in depression, such as the cortex and the amygdala, which may further elaborate a specific role for mGluR7 in depression.
J.F. Cryan and T.G. Dinan are funded by a Science Foundation Ireland (SFI) grant awarded to the Alimentary Pharmabiotic Centre (APC).

TG04

SAFETY OF INTRAVENOUSLY ADMINISTERED DESMOPRESSIN FOR HPA-AXIS CHARACTERIZATION IN HEALTHY VOLUNTEERS
Jacobs GE, Hulskotte EGJ, Burggraaf J, Zuurman HH, Elassais-Schaap J, Peeters PAM, van Gerven JMA, Ruigt G. Centre for Human Drug Research, Zernikedreef 10, 2333 CL Leiden, gjacobs@chdr.nl

Introduction: Arginine-vasopressin (AVP) is a physiological co-activator of the hypothalamus-pituitary-adrenal (HPA) axis together with corticotrophin release hormone (CRH) and is believed to play a role in various psychiatric diseases. Characterisation of AVP's neuroendocrine effects in healthy volunteers may serve to better delineate its supposed role in psychiatric illness. A synthetic analogue of AVP, desmopressin (dDAVP) is proposed to produce HPA-axis activation on the level of the pituitary. So far, systematic studies of the neuroendocrine effects and safety of intravenously (i.v.) administered dDAVP in healthy volunteers have been limited.
Methods: A randomized, double blind, placebo-controlled, three-way crossover study in 6 male and 6 female healthy volunteers. dDAVP was administered i.v. either as 10 µg bolus infusion over one minute or 30 µg incremental infusion over 60 minutes. Neuroendocrine effects (serum ACTH, cortisol and prolactin) were investigated. Safety in terms of hemostatic (von Willebrand factor (vWF)), cardiovascular (systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR)), anti-diuretic (serum and urine osmolarity) effects and adverse events (AE's) were assessed. Pharmacodynamic and safety endpoints were measured up to 8 hours post dosing and were analyzed by mixed model analyses of variance. **Results:** Neuroendocrine results are presented as estimated percentual difference from placebo, with 95% confidence intervals, mean maximal values, for bolus and incremental infusions respectively: mean ACTH increased by 26.1 (5.8/50.3) % (p=0.01) reaching 15.85ng/L and 30.9 (11.1/54.2) % (p=0.00) reaching maximally 15.02ng/L; mean cortisol increased by 18.9 (4.1/35.8) % (p=0.01) reaching maximally 160.22ng/mL and 17.7 (3.5/33.8) % (p=0.02) reaching 158.25ng/mL. Prolactin did not change during either dDAVP infusion. vWF increased with 64 (41/86) % and 104 (84/124) % during the bolus and incremental infusions respectively. Serum and urine osmolality remained unchanged. Effects on SBP, DBP and HR were not clinically significant and were comparable for both infusions. All adverse events were compatible with the side-effect profile of dDAVP (facial flushing and headache) and no SAE's occurred. **Conclusions:** Intravenous administration of these doses of dDAVP leads to small amounts of ACTH and serum cortisol release: dDAVP-induced ACTH release precede cortisol release with roughly 15 minutes which may be explained in terms of vasopressin receptor mediated HPA-axis activation on the level of the anterior pituitary. Administration of dDAVP in either administration mode was safe: serum and urine osmolality were uninfluenced and its effects on blood pressure were modest; acute increases in vWF were seen, which were not considered to be clinically significant in this healthy volunteer group.
This study was sponsored by NV Organon part of Schering-Plough Corporation.

TG05

FRACTIONATION OF SPATIAL MEMORY IMPAIRMENTS IN BIPOLAR DEPRESSION AND RELATIONSHIP WITH HPA AXIS FUNCTION
Gallagher P, Smith MS, Watson S, Young AH, Ferrier IN, Gray JM. School of Neurology, Neurobiology & Psychiatry,, Newcastle University, Leazes Wing, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, peter.gallagher@ncl.ac.uk

Objectives Recent studies have found evidence for dissociable cognitive processes within object location memory. Studies in patients with neurological damage suggest separable frontal and hippocampal processes. Patients with bipolar disorder (BD) show significant impairments in verbal memory and 'frontal' executive function with the latter persisting in euthymia, specifically the executive control of visuospatial working memory. The purpose of the present study was firstly to examine the performance of patients with BD and healthy comparison subjects using a computerised memory location paradigm in which positional processing can be separated from object–location binding. Secondly, because of the known effects of corticosteroids on the hippocampus, we sought to examine the relationship between cortisol levels and task processes. Methods Twenty-six outpatients fulfilling DSM-IV criteria for BD in a current depressive episode and 24 healthy comparison subjects completed the Object Relocation paradigm (Kessels RPC, et al. Behavior Research Methods, Instruments, & Computers 31:423-428;1999). Following an assessment of object identity and visuospatial construction, 3 task conditions were used: positional memory (POM)– requiring the position of identical objects to be remembered and reproduced; object-location binding (OLB)– requiring objects to be remembered and relocated to pre-marked positions; and a combined condition (COM)– integrating both processes, with object and position to be remembered. Secondary measures of visuo-spatial memory, verbal memory, attention and executive function were also administered. Basal salivary cortisol levels were measured prior to testing. Results Patients with BD were impaired in performance on all three conditions: OLB ($t49=2.77, p=0.008$; Cohen's $d=-0.73$), POM ($t49=4.32, p<0.0001$; $d=-1.04$) and COM ($t49=3.17, p=0.003$; $d=-0.82$). After using ANCOVA to control for an initial difference between the groups in visuospatial construction ($t49=3.34, p=0.002$; $d=-0.85$), and following correction for multiple comparisons, the only remaining significant difference was the impairment in POM ($F1,48=9.18, p=0.004$). Examination of the relationship between indices of the Object Relocation paradigm and secondary measures revealed differences in task processes between patients and controls. In the subset of participants with available samples, evening 8pm cortisol levels correlated with OLB error in patients (partial $r=0.49$, $N=12$, $p=0.038$) and with POM error in controls (partial $r=0.44$, $N=13$, $p=0.050$).
Conclusions This study demonstrates that bipolar patients when depressed manifest general deficits in visuo-spatial memory with substantial impairment in positional memory. Patients may be exhibiting deficits in fine grain co-ordinate spatial processing which increases reliance on categorical/verbal processes. It remains to be seen whether this deficit persists into euthymia and the relationship with more precise measures of basal HPA-axis function. Funding: Funding for this study was provided by the Stanley Medical Research Institute (SMRI) and the Medical Research Council (MRC)

TG06

DO ILLNESS AND TREATMENT BELIEFS INFLUENCE ADHERENCE TO MEDICATION IN PATIENTS WITH BIPOLAR AFFECTIVE DISORDER? A PRELIMINARY CROSS-SECTIONAL STUDY

Hou R, Peveler R, Cleak V. School of Medicine, University of Southampton, Southampton, UK. R.Hou@soton.ac.uk

Background: A high incidence of medication non-adherence has been found in bipolar affective disorder (BPAD), ranging from 12% to 64%. Non-adherence to prescribed medication is increasingly recognised as a critical issue in treating patients with BPAD. Research has highlighted the importance of patients' personal beliefs towards their illness and treatment in medication compliance in chronic illnesses. However, it is not yet known whether a similar pattern can be demonstrated in patients with BPAD. *Objectives:* The aim of this study was to investigate the impact of illness and medication beliefs on medication adherence in patients with BPAD and to understand how they interact with related demographic and clinical characteristics. *Methods:* Patients with BPAD were recruited from secondary care clinics and all gave written informed consent. Demographic and clinical data were collected from medical notes. Illness beliefs were assessed by the Revised Illness Perceptions Questionnaire (IPQ-R); treatment beliefs were measured by the Beliefs about Medications Questionnaire (BMQ); adherence to medication was measured using the self-report Morisky Questionnaire (MQ). 35 patients completed all these measures. A cut-off derived from the MQ score was used to dichotomise patients into probably adherent and non-adherent groups. Demographic characteristics, clinical features, illness and treatment beliefs of the two groups were compared using independent samples *t* test, χ^2 test or Mann-Whitney U test as appropriate. Multivariate analysis was conducted using backward logistic regression analysis with adherent and non-adherent as the dependent variable and candidate variables as covariates, selected by Likelihood Ratio test. *Results:* 19 (54%) patients were categorized as probably non-adherent, and 16 (46%) as probably adherent. Univariate tests revealed significant differences between groups with regard to age (p=0.02), number of medications (p=0.03), and the consequences subscale (P=0.05) and timeline subscale (P=0.02) of IPQ-R, indicating that being younger, having more medication prescribed and believing the illness to be less serious and shorter-lasting were associated with probable non-adherence. Multivariate logistic regression analysis demonstrated that in addition to age (odds ratio 1.216, 95% confidence interval 1.065 to 1.389, P=0.04) patients' beliefs about whether medicines are over-prescribed by clinicians (odds ratio 0.681, 95% confidence interval 0.476 to 0.974, P=0.05) was a significant predictor of adherence. *Conclusions:* This preliminary study indicated that age and treatment beliefs are major predictors of adherence to medication, while illness beliefs and the number of medications prescribed are also potential predictors. BPAD patients' treatment and illness beliefs may be suitable targets for modification in efforts to change adherence behaviour.

TG07

ARIPIPRAZOLE MONOTHERAPY IN ACUTE BIPOLAR I MANIA: RESPONDER ANALYSIS IN A RANDOMIZED, PLACEBO- AND HALOPERIDOL-CONTROLLED STUDY (CN138-162)

Landsberg W, Felter C, Dudley E. Bristol-Myers Squibb, Uxbridge Business Park, Sanderson Road, Uxbridge UB8 1DH, wally.landsberg@bms.com

Introduction: A randomized, double-blind study showed that aripiprazole monotherapy significantly improved symptoms in acutely manic patients after 3 weeks, with clinical improvements sustained to Week 12 and similar to haloperidol. This secondary analysis evaluated efficacy of aripiprazole at Week 12 in the subgroup of patients showing response at Week 3.

Patients and Methods: Patients with acute bipolar I mania (Young Mania Rating Scale [YMRS Total ≥20), manic or mixed, who required hospitalization were randomized (1:1:1) to double-blind aripiprazole (15–30 mg/day; n=167), placebo (n=153) or haloperidol (5–15 mg/day; n=165) for 3 weeks. Aripiprazole and haloperidol patients remained on blinded treatment for a further 9 weeks. Primary endpoint was the mean change from baseline in YMRS Total score at Week 3. The Week 3 responder sample were those randomized patients who were still in the study and showing response (YMRS Total improvement ≥50%) at Week 3, and had an efficacy evaluation thereafter. Changes in symptom scales in this population were assessed by an ANOVA model, controlling for treatment and baseline value.

Results: In the overall population, the mean change from baseline to Week 3 (LOCF) in YMRS Total score was significantly greater with aripiprazole (–12.0; p=0.039) and haloperidol (–12.8; p=0.005) versus placebo (–9.7). Improvements were maintained to Week 12 for aripiprazole (–17.2) and haloperidol (–17.8; LOCF). In the subgroup of Week 3 responders, the mean change in YMRS Total score from baseline to Week 12 was –24.8 for aripiprazole and –24.2 for haloperidol (diff: –0.63; 95% CI –2.06; +0.79). The response rate at Week 12 for the Week 3 responders in the aripiprazole group was 97.0% and similar to haloperidol (98.5%). The percentage of patients in the Week 3 responder sample who showed remission at Week 12 was the same for both groups (95.5%). The response rates on the CGI-BP change from preceding phase (mania) were also the same for both groups (80.6%). The mean change from baseline to Week 12 on the MADRS Total score and PANSS Total score were also similar. The three most commonly occurring adverse events with aripiprazole were insomnia, akathisia and extrapyramidal disorder. The three most common adverse events with haloperidol were akathisia, extrapyramidal disorder and muscle rigidity.

Conclusions: For patients who were responders at Week 3, the efficacy of aripiprazole and haloperidol were maintained similarly in both groups through to Week 12.

Study funded by Bristol-Myers Squibb and Otsuka.

TG08

A YMRS ITEM ANALYSIS OF ADJUNCTIVE ARIPIPRAZOLE VERSUS PLACEBO IN BIPOLAR MANIA PARTIALLY NON-RESPONSIVE TO VALPROATE/LITHIUM (CN138-134)

Sullivan G, Felter C, Dudley E School of Care Sciences, University of Glamorgan, Cardiff, Gary.Sullivan@nglam-tr.wales.nhs.uk

Introduction: A multicentre, randomized study demonstrated the efficacy and safety of adjunctive aripiprazole in the treatment of patients with bipolar I mania (manic/mixed) who were partially non-responsive to lithium or valproate monotherapy. This post-hoc analysis was conducted to assess the specific effects of aripiprazole across the 11-line items of the Young Mania Rating Scale (YMRS) scale.

Methods: Following screening, psychotropic washout and attainment of therapeutic levels of lithium (0.6–1.0 mmol/L) or valproate (50–125 µg/mL) (Phase 1), patients received open-label lithium or valproate monotherapy for 2 weeks (Phase 2). Partial non-responders (YMRS Total score ≥16 during Phase 1 and at the end of Phase 2, where any decrease between Phase 1 and 2 had to be ≤25%) were randomized (2:1) to double-blind adjunctive aripiprazole (15–30 mg/day; n=253) or placebo (n=131) for 6 weeks. Primary endpoint was mean change in YMRS Total score from baseline. Item analysis of the YMRS scores was conducted post-hoc. Mean changes from baseline to endpoint in the YMRS Total score and individual items were analysed by analysis of covariance (ANCOVA) using the last observation carried forward (LOCF) data set with baseline measurements as a covariate and study centre and treatment as main effects.

Results: Mean improvement from baseline in YMRS Total score at Week 6 (primary endpoint) was significantly greater with aripiprazole (–13.3 from baseline: 23.1) versus placebo (–10.7 from baseline: 22.7; p=0.002; LOCF). Significant improvements in YMRS Total scores with aripiprazole versus placebo occurred from Week 1 onwards (p<0.05). Double-blind treatment was completed by 85% and 79% of patients randomized to placebo and aripiprazole, respectively. Aripiprazole showed statistically significant improvements relative to placebo on 6 of the 11 items: elevated mood (–1.3 vs. –1.2; p=0.049), sexual interest (–1.0 vs. –0.7; p=0.006), irritability (–1.6 vs. –1.2; p=0.006), speech (–2.2 vs. –1.6; p<0.001), disruptive/aggressive behaviour (–1.2 vs. –0.8; p=0.006) and insight (–0.6 vs. –0.4; p=0.004). Adverse events occurring during the 6-week double-blind treatment period at an incidence ≥5% in either treatment group were akathisia, diarrhoea, headache, insomnia, nausea, and tremor.

Conclusions: In patients with acute manic or mixed episodes of bipolar I disorder who are partially non-responsive to lithium/valproate monotherapy, adjunctive aripiprazole is effective in ameliorating the common symptoms.

Study funded by Bristol-Myers Squibb and Otsuka.

TG09

SERUM BRAIN-DERIVED NEUROTROPHIC FACTOR LEVEL IN THE PATIENTS WITH SINGLE-EPISODE AND RECURRENT UNIPOLAR FORMS OF MAJOR DEPRESSION

Zhang ZJ[1], Zhang YM[1,2], Sha WW[2]. [1]Department of Neurology, Affiliated ZhongDa Hospital of Southeast University, Nanjing, China, zhijunzhang838@yahoo.com.cn. [2]Department of Psychiatry, Affiliated WuTaiShan Hospital of Yangzhou University, Yangzhou, China

Objective: Both clinical and pharmacological studies have implicated the important role of brain-derived neurotrophic factor (BDNF) for the development of depression. The present study investigated serum BDNF in the patients with a single depressive episode and recurrent unipolar forms of major depression during acute depressive states and treatment. We also investigated the role of BDNF as a risk factor for relapse of major depression.
Methods: 58 patients with single depressive episode, 80 recurrent depression patients and 80 normal control subjects were recruited in present studies. All the patients were evaluated with Life Event Scale and the Hamilton Depression Scale (HAMD). The serum BDNF of all patients was assayed by the ELISA method before and after 2, 4 and 8 weeks of antidepressant treatment, while the controls had serum BDNF determined once after recruitment. Results were compared by t-test or ANOVA as appropriate, with significance at $p<0.05$.
Result: There were significant decreases in total HAMD scores after 2-8 weeks treatment in both patients with single depressive episode and with recurrent depression. There were no significant differences between the two groups in total HAMD scores and their changes at any treatment time point. Serum BDNF was significant lower in untreated patients with single depressive episode compared to controls. The significant difference in those patients disappeared 2 weeks later due to an increase in BDNF during treatment. Serum BDNF in recurrent depression patients, before treatment and 2 weeks after treatment, was significantly lower than both controls and patients with single depressive episode. This significant difference could not been seen at 4 and 8 weeks of treatment. Compared with single depressive episode group, patients with recurrent depression suffered from more risk factors such as lower BDNF before treatment, more childhood trauma, more family-related issues and earlier age of onset.
Conclusion: The relative deficit in serum BDNF in recurrent depression might implicate the role of BDNF as a biological marker for recurrence and prognosis of major depression.

TG10

ELEVATED INFLAMMATION LEVELS IN DEPRESSED ADULTS WITH A HISTORY OF CHILDHOOD MALTREATMENT

Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A. Social, Genetic and Developmental Psychiatry, Institute of Psychiatry, DeCrespigny Park, London SE5 8AF, a.danese@iop.kcl.ac.uk

INTRODUCTION: The association between depression and inflammation is inconsistent across research samples. This study tested the hypothesis that a history of childhood maltreatment could identify a subgroup of depressed individuals with elevated inflammation levels, thus helping to explain previous inconsistencies.
METHODS: A representative birth cohort of 1,000 individuals was followed to age 32 years as part of the Dunedin Multidisciplinary Health and Development Study, a prospective longitudinal cohort study based in Dunedin, New Zealand. Study members were assessed for history of childhood maltreatment and current depression.
RESULTS: Inflammation was assessed by a clinically-relevant categorical measure of high-sensitivity C-reactive protein (hsCRP >3mg/L), and a dimensional inflammation factor indexing the shared variance of continuous measures of hsCRP, fibrinogen, and white blood cells. Although depression was associated with high hsCRP (RR=1.45; 95%CI=1.06;1.99), this association was significantly attenuated and no longer significant when the effect of childhood maltreatment was taken into account. Individuals with current depression and childhood maltreatment history were more likely to show high hsCRP levels than controls (N=27; RR=2.07; 95%CI=1.23;3.47). In contrast, individuals with current depression only showed a non-significant elevation in risk (N=109; RR=1.40; 95%CI=0.97;2.01). Results generalized to the inflammation factor. The elevated inflammation levels in depressed+maltreated individuals were not explained by correlated risk factors, such as depression recurrence, low socioeconomic status in childhood or adulthood, poor health, or smoking.
CONCLUSIONS: A history of childhood maltreatment contributes to the co-occurrence of depression and inflammation. Information about experiences of childhood maltreatment may help to identify depressed individuals with elevated inflammation levels and thus cardiovascular disease risk.

TG11

FUNCTIONAL POLYMORPHISMS IN THE INTERLEUKIN-6 AND IL-10 GENES AND PSYCHOPATHOLOGICAL SYMPTOMS IN PATIENTS WITH CHRONIC FATIGUE SYNDROME

Bull SJ, Pariante C, Huezo-Diaz P, Aitchison KJ, Cleare A. Stress, Psychiatry and Immunology, Institute of Psychiatry, 125 Coldharbour Lane, London SE5 9NU, s.bull@iop.kcl.ac.uk

The inflammatory response system (in particular high concentrations of interleukin-6 [IL-6])has been implicated in the pathophysiology of a number of psychopathological symptoms, including fatigue. Recently the immune dysfunction hypothesis of the pathogenesis of chronic fatigue syndrome (CFS) has gained increasing support, with many studies focusing on proinflammatory cytokines (e.g., IL-1, IL-6 and TNF-α) but there remains inconsistencies in the data; therefore the role of the inflammatory response system still needs to be elucidated. We have tested the association between symptoms of fatigue and current mental health in patients with CFS, and two functional polymorphisms (rs1800795 in the IL-6 gene and rs1800896 in the IL-10 gene) that participate in the regulation of the inflammatory response system, by dictating proinflammatory IL-6 and anti-inflammatory IL-10 secretion level.
146 Caucasian subjects were recruited at the CFS Unit at the Institute of Psychiatry, King's College London. At their initial consultation with a psychiatrist, subjects completed self report questionnaires to measure fatigue and their current mental health, using the Chalder Fatigue Questionnaire (CFQ) and General Health Questionnaire (GHQ) respectively. Genetic polymorphisms were determined using SNPlex, using DNA extracted from cheek swabs. Statistical analysis was conducted using one-way ANOVA, and LSD for post-hoc analysis. The IL-10 polymorphism was associated with significant differences in fatigue - mean CFQ score & (SD) for genotype: AA=26.9 (4.6), AG=24.7 (6.2), GG=27.7 (4.5); F=4.463, df=2, P=0.013. Post-hoc analysis revealed that heterozygous AG subjects were significantly less fatigued than homozygous GG (P=0.006) and AA (P=0.045) genotype subjects (high and low IL-10 expressers). The polymorphism was not associated with differential GHQ scores: AA=19.7 (SD=7.6), AG=18.4 (SD=8.0), GG=20.2 (SD=8.0); F=0.118, df=2, P=0.5. The IL-6 polymorphism was not associated with significant differences in fatigue or current mental health. Mean CFQ (SD): CC=24.7(5.7), GC=26.5 (5.2), GG=26.4 (5.5); F=1.1, df=2, P=0.3. GHQ scores(SD): CC=18.8(6.9), GC=18.6(8.1), GG=20.5 (8.4); F=0.862, df=2, P=0.4). The functional polymorphism (rs1800896) in the IL-10 gene is associated with differential fatigue in patients with CFS; intermediate IL-10 expressers were significantly less fatigued.

TG12

THE INTERACTION BETWEEN INTERFERON GAMMA RECEPTORS AND THE MAPK6/8 SIGNALLING PATHWAY IS ASSOCIATED WITH ANTIDEPRESSANT TREATMENT OUTCOME IN DEPRESSION

Janssen DGA, Jordan M, Schweizer A, Baxter A, Verster JC, Deckert J, Arolt V, Domschke K, Baune BT.Psychiatric Neuroscience Research Unit, School of Medicine, James Cook University, QLD 4811, Townsville, Australia, debbie.janssen@jcu.edu.au

There is emerging evidence that increased production of pro-inflammatory cytokines, such as interferon-gamma (IFN-g) contributes to depression, known as the hypothesis of cytokine-induced depression. The pathways by which antidepressants influence depression are not well understood. Cytokines may exert their effects via various signalling pathways one of which is the MAPK pathway activated by cytokine receptor stimulation. Little understanding has been gained (1) on genetic cytokine effects on treatment response and (2) on interactions between cytokine receptors and subsequent signalling pathways in relation to antidepressants. In this analysis we investigated the effects of genetic variants of the IFN-g receptors 1/2 and MAPK6/8 polymorphisms and their impact on antidepressant treatment response over 6 weeks in major depressive episode (MDE). In total, 340 patients with MDE were treated over 6 weeks with a variety of antidepressants (i.e., SSRIs; SNRIs). Genotypes of single nucleotide polymorphisms (SNP) were determined using high resolution melt (Rotor-Gene 6000) analysis. Association analyses between genotypes and treatment response as measured weekly with the Hamilton depression scale were performed applying ANOVA with repeated measures (post-hoc Bonferroni correction). All 8 investigated SNPs were in HWE. None of the SNPs was individually associated with treatment response. However, the co-existence between particular genetic variants of the IFN-g receptors 1/2 and MAPK8-SNPs predicted poorer treatment response. More specifically, the GG genotype of the MAPK8-SNP rs10857565 conferred a significantly worse treatment response as compared to the AG ($p=0.02$) and AA ($p=0.03$) genotypes among patients with the AG genotype of the IFN-g receptor 1 SNP (rs9376268). Interestingly, an IFN-g receptor 2 SNP (rs 2284553) interacted with the MAPK8-SNP (rs10857565) similarly: the GG genotype of the IFN-g receptor 2 SNP (rs2284553) combined with the GG genotype of the MAKP8-SNP (rs10857565) showed significantly ($p=0.043$) poorer treatment response as compared to those with the AG genotype of the same MAPK8-SNP. The findings for the IFN-g receptor 1 were pronounced in patients treated with the combination of Venlafaxine and Mirtazapine. Other antidepressants did not modify the findings on the IFN-g receptor 1. Furthermore, the reported results on IFN-g receptor 2 and MAPK8 were not modified by the type or combination of antidepressants. Results indicate that the interaction between genetic variants of the IFN-g receptors 1/2 and MAKP8-SNPs influence treatment response which is not largely modified by the type/combination of antidepressants. The MAPK8-SNP rs10857565 appears to play a prominent role in mediating antidepressant effects by influencing the IFN-g receptor 1/2 activity. This study was supported by internal funding.

TG13

POLYUNSATURATED FATTY ACIDS AND INTERFERON-INDUCED DEPRESSION

Su KP, Huang, SY, Peng CY, Liao KF, Lai HC, Huang CL, Cheng JC, Aitchison KJ, Pariante CM. Department of Psychological Medicine, Institute of Psychiatry at King's College London, 125 Coldharbour Lane, London SE5 9NU, cobolsu@gmail.com

Introduction: Major depressive episode is common in patients with chronic hepatitis C viral (HCV) infection receiving interferon (IFN)-α therapy. However, clinical and biological predictors for the development of IFN-α-induced depression are still lacking. Polyunsaturated fatty acids (PUFAs) have been reported to play an important role in cytokine-induced depression and sickness behaviours. Specifically, n-6 PUFA arachidonic acid (AA) enhances the basal inflammatory response, raises serum corticosterone concentrations, and induces anxiety behaviours in animals. In contract, n-3 PUFA diet, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), suppresses the prostaglandin E2 (PGE2) and attenuates cytokine-induced sickness and depression behaviour in animals. Furthermore, n-3 PUFAs have be reported to have antidepressant effects in clinical trials. This study examines whether 3 main PUFAs, DHA, EPA and AA, are either predictors or biomarkers of IFN-α-induced depression. Methods: Sixty-three HCV patients were recruited and assessed prospectively every 2 weeks for 24 week of IFN-α therapy. Depressive symptoms were assessed with the 21-item Beck Depression Inventory (BDI) and diagnosis of major depressive episode was made with the structured Mini-International Neuropsychiatric Interview (MINI). Patients who developed IFN-α-induced depression were defined as "case group," while the rest were defined as "control group." Blood samples were obtained at weeks 0, 2, 12, and 24 to examine the erythrocyte DHA, EPA and AA levels. Fatty acid level was analysed by thin-layer gas chromatography. Results: Patients who later developed IFN-α-induced depression (case group, 21/63) had lower DHA levels before starting IFN-α therapy than control group ($p=0.024$). This baseline difference in DHA was not due to difference between cases and controls in baseline depression (BDI score). Furthermore, there was a trend for a negative correlation ($r=-0.22$; $p=0.078$) between baseline DHA levels and the highest scores of BDI during IFN therapy in the whole group. The mixed model analyses showed significant effects of time for all three PUFAs, indicating that IFN-α therapy changed all PUFAs' levels, but there was no difference overall between cases and controls. Interestingly, there was a group effect for DHA, with levels being lower in cases than in controls across time ($p=0.037$).
Conclusions: Decreased erythrocytes DHA levels before starting IFN-α therapy predicted IFN-α-induced depression. There are three possible mechanisms leading to the lower DHA levels, including lower dietary intake of DHA, a higher calcium-independent PLA2 (iPLA2) activity, and/or genetic variations on the iPLA2. The results in this study indicates that DHA might play a role as a protective factor against IFN-α-induced depression, perhaps because of its anti-inflammatory properties. These findings also provide the rationale to conduct a clinical trial to test the prophylactic antidepressant treatment with n-3 PUFAs for IFN-α-induced depression.
Acknowledgement: The work was supported by the grant, 95-2320-B-039-037-MY3, from the National Science Council to Dr. K.-P. Su. Dr. C.M. Pariante is funded by the UK MRC, the NIHR South London and Maudsley NHS Foundation Trust, and the British Academy.

TG14

ERYTHROPOIETIN REDUCES NEURAL AND COGNITIVE PROCESSING OF THREAT-RELEVANT INFORMATION IN DEPRESSED INDIVIDUALS: PRELIMINARY FINDINGS

Miskowiak K, Favaron E, Hafizi S, Inkster B, Goodwin GM, Cowen PJ, Harmer CJ. Department of Psychiatry, University of Oxford, Warneford Hospital, Warneford Lane, Oxford OX3 7JX, kamilla.miskowiak@psych.ox.ac.uk

Erythropoietin (Epo) has neuroprotective and neurotrophic effects in animal models and may be an important therapeutic agent in the treatment of psychiatric disorder marked by neural dysfunction. We have previously demonstrated that Epo has antidepressant-like effects on emotional processing and improves mood in healthy volunteers. The current study therefore aimed to explore the effects of Epo on the cognitive and neural processing of emotional information in acutely depressed patients.
A single dose of Epo (40,000 IU) or saline was administered iv. to 19 acutely depressed individuals in a randomised, double-blind, parallel-group design. On day 3, we assessed neuronal responses to emotional IAPS pictures during fMRI and performance on a facial expression recognition task. Mood was assessed with clinical rating scales at baseline and on day 3, and a blood test was taken at these times to assess any effects of Epo on red cell mass.
Exploratory whole brain analysis showed that Epo reduced neuronal response in the occipital cortex to negative vs. neutral IAPS pictures 3 days after administration ($Z=2.0$, $P<0.05$, corrected). This was paired with reduced recognition of fearful facial expressions in Epo-treated patients after the scan (ANOVA with group and fear intensity: $F(9,153)=1.98$, $P=0.045$). Notably, these effects occurred in the absence of changes in mood ($Ps>0.1$) or haematological parameters ($Ps>0.4$), suggesting that they originated from direct neurobiological actions of Epo. These findings are similar to the effects of conventional antidepressants and opposite to the negative biases in depression.
The present findings highlight Epo as a new candidate antidepressant compound with the potential to influence emotional processing through putatively different neurochemical signalling mechanisms.
This study was supported by Lundbeckfonden, Denmark.

TG15

DECREASED AFFECTIVE REPRESENTATIONS OF CHOCOLATE IN THOSE AT RISK OF DEPRESSION COMPARED TO NORMAL HEALTHY VOLUNTEERS

McCabe C, Harmer CJ, Cowen P Psychiatry, Oxford Univ, Warneford Lane, Oxford OX37JX, ciara.mccabe@psych.ox.ac.uk

Anhedonia is an important diagnostic criterion for major depressive disorder (MDD) where patients report a loss of interest and pleasure in normally rewarding stimuli. This experiment aimed to investigate how the brain responds to both pleasant and unpleasant stimuli and to examine how this reward circuitry is affected by risk for depression.

We used fMRI to measure the response to the flavour and the sight of chocolate, and to their combination, and also an unpleasant flavour and picture in normal healthy volunteers compared to those recovered from depression. Subjective ratings of "pleasantness" "intensity" and "wanting" of each of the stimuli were also collected on each of the trials within the scanner.

SPM5 analyses showed that the sight of chocolate produced more activation in normal healthy volunteers in the midbrain (p=0.01 svc). Also there was increased ventral striatal activation to chocolate in the mouth in the normal healthy control group compared to the recovered depressed group (p=0.01 svc). Furthermore, a combination of a picture of chocolate with chocolate in the mouth produced a greater effect than the sum of the components (i.e. supralinearity) in the medial orbitofrontal cortex in the normal healthy volunteers compared to the recovered depressed group (p=0.013 svc). Despite no differences in subjective ratings between the two groups we found reduced activation in the reward related areas such as the ventral striatum and the medial orbitofrontal cortex in those recovered from depression compared to normal healthy never depressed volunteers. Understanding the mechanisms that underlie the pleasantness and unpleasantness of stimuli and how these mechanisms may be dysfunctional in those at risk of depression has implications for our understanding of the role of anhedonia as a trait vulnerability marker of depression.

This work has been sponsored by the Medical Research Council.

TH01

BEHAVIOURAL DIFFERENCES IN IMPULSIVITY AMONGST CHIPPERS AND REGULAR SMOKERS

Brooks DDS, Jackson A. School of Pharmacy and Biomolecular Sciences, University of Brighton, Moulsecoomb, Brighton BN2 4GJ, ddsb@bton.ac.uk

Chippers are anomalous group of smokers who do not appear to become dependent upon nicotine. Impulsivity is thought to be a major contributing factor in drug taking behaviour (Evenden 1999, Psychopharmacology 146, 348) and previous research has established regular smokers as more impulsive than non-smokers (Mitchell 1999, Psychopharmacology 146: 455). This study aimed to investigate potential differences between chippers and regular smokers, in response to smoking and in impulse control.

24 volunteers were recruited (12 chippers, and 12 regular smokers); participants attended two sessions, during one of these sessions they smoked a cigarette, and during the other they remained abstinent. Both groups were abstinent for at least three hours prior to each test session. Participants completed a smokerlyzer test, then either smoked or remained abstinent before completing two computer based behavioural tasks: Rapid Visual Information Processing (RVIP) and Stop-Signal (Stop). Subjects also completed a simple word recall test as a baseline measurement of cognition and the following questionnaires: Temperament and Character Inventory (TCI), Barratt Impulsivity Scale (BIS), Fagerstrom, Etter CD-12 and Alcohol Use Questonnaire (AUQ). Results were analysed using analysis of variance, followed by appropriate post hoc tests.

During the RVIP smokers total response time decreased after smoking compared with the chippers ($p = 0.046$). Chippers made fewer false alarms than regular smokers ($p = 0.02$). There were no differences in stop latencies between the two groups in the Stop task. There were no differences between the two groups in the TCI personality questionnaire and the total BIS scores; however chippers had higher scores for attentional impulsivity in the BIS ($p = 0.026$). Results from the Fagerstrom and Etter questionnaires indicated that regular smokers were more dependent on nicotine than chippers ($p = <0.001$). There were no significant differences in the word recall test and AUQ.

This study highlights the various constructs of impulsivity in the fact that different subjective and behavioural measures produced different results, when comparing impulsivity in chippers and regular smokers. Chippers reported higher scores for attentional impulsiveness, whilst in the objective RVIP task they behaved less impulsively than regular smokers. It could be therefore, that chippers exerted more self-control in this behavioural task because they perceived themselves as being more impulsive. There is no doubt that important personality and behavioural differences exist between chippers and regular smokers, and further studies are needed to elucidate the possible mechanisms that underpin these differences.

TH02

DELUSIONS AMONG RECREATIONAL KETAMINE USERS: MERE SUPERSTITION?

Freeman TP, Morgan CJA, Das R, Curran HV. Clinical Psychopharmacology Unit, Clinical Health Psychology, University College London, Gower Street, London WC1E 6BT, tompfreeman@googlemail.com

Ketamine, an NMDA-receptor antagonist, acutely induces a range of psychotic-like symptoms in healthy individuals. Recently, Muetzelfeldt et al. (2008, Drug and Alcohol Dependence, in press) found evidence of increased delusional beliefs among recreational users of the drug. Those findings were based on clinical structured interviews and self-report measures and have not yet been replicated using an objective assessment. Theoretically, delusion formation in psychosis has been linked to elevated levels of 'superstitious conditioning' or the erroneous association of outcomes with events, due to chaotic mesolimbic dopamine firing (Shaner, 1999, Medical Hypotheses, 52, 119), an abnormality shown to occur following repeated administration of an NMDA-receptor antagonist in rats (Jenstch et al., 1998, Neuropsychopharmacology, 19, 105). The present study aimed to objectively assess superstitious conditioning in ketamine users with a novel task, and to explore whether performance on this task is associated with levels of trait schizotypy, dissociation and paranormal beliefs. An independent groups design compared 19 ketamine users with 19 polydrug controls (matched for other drug use and premorbid IQ). In the superstitious conditioning task, participants were required to choose 2 out of 3 stimuli in order to score the most points. However, in each of the 72 trials the points were awarded randomly, not contingent on actual responses. The index of superstitious conditioning was the extent to which particular pairs were chosen more frequently than others. Participants also explicitly reported if they had noticed any stimulus 'patterns' in the task. Finally, they were assessed on measures of trait schizotypy, dissociation and paranormal beliefs. Ketamine users showed a greater range in pair choice ($p = 0.02$) and reported seeing more 'patterns' in the task ($p = 0.02$) than controls. Groups did not differ in trait dissociation or overall schizotypy scores. However, ketamine users scored higher on both paranormal beliefs ($p = 0.04$) and 'cognitive disorganisation' ($p = 0.04$). No correlations emerged between these scales and superstitious conditioning or ketamine use. This study replicated previous findings of delusions in ketamine users using a novel, objective measure. Ketamine users showed higher levels of superstitious conditioning than controls, alongside increased levels of cognitive disorganisation and paranormal beliefs. No associations were found between these measures. This might be due to individual differences in vulnerability to ketamine's psychotomimetic effects, difficulties in quantifying lifetime drug use, or pre-existing differences among ketamine users. Nevertheless, if clinically validated, our novel task assessing superstitious conditioning may have important practical applications.

TH03

THE EFFECTS OF CANNABIS USE ON AWAKENING SALIVARY CORTISOL IN FIRST EPISODE PSYCHOSIS

Hepgul N, Mondelli V, Aas M, DiForti M, Handley R, Marques T, Navari S, Taylor H, Dazzan P, Murray R, Pariante C. Division of Psychological Medicine and Psychiatry, Institute of Psychiatry, 125 Coldharbour Lane, London, SE5 9NU, nilay.hepgul@iop.kcl.ac.uk

Previous studies show an increase in hypothalamic-pituitary-adrenal (HPA) axis activity with acute administration of cannabis. However, long-term effects of cannabis on HPA axis activity have not been clarified. The aim of our study was to investigate effects of cannabis use on basal and dynamic HPA axis activity, as measured by cortisol levels at awakening and during the day, in first-episode psychosis. We recruited 36 first-episode psychosis patients and 24 controls as part of the "Genetics and Psychiatric Illness" (GAP) study. We collected salivary cortisol, at awakening, 15, 30, and 60 minutes after awakening, 12 pm and 8 pm on two consecutive days, along with cannabis use information using the Cannabis Experiences Questionnaire (Barkus et al, 2006). The sample was split into groups based on lifetime frequency of cannabis use. One patient group with low or no frequency of cannabis use (n=16, males=7, mean±SEM age= 31.9±2.0 years), one patient group with high frequency of cannabis use (n=20, males=18, age= 28.0±1.5 years) and a control group with low or no frequency of cannabis use (n=24, males=18, age= 27.8±1.1 years). The response to awakening was measured as Area Under the Curve with respect to increase (AUCi). A one-way ANOVA with post-hoc analyses was used to test differences in AUCi and cortisol at 12pm and 8pm among the groups. Results are shown as mean±SEM. The groups significantly differed in their cortisol response to the awakening ($F=5.8$, $p=0.005$). Post Hoc tests indicated patients with high frequency of cannabis use did not differ from controls (204.7±57.5 nmol min/l vs 277.1±50.1 nmol min/l, $p=0.3$) but showed higher cortisol response to awakening compared with patients with low frequency of cannabis use as indicated by higher AUCi (204.7±57.5 nmol min/l vs 23.4±44.2 nmol min/l, $p<0.05$). Patients with low frequency of cannabis use showed blunted cortisol response to awakening compared to controls ($p<0.001$). These differences were specific to the awakening response as no differences were found for cortisol levels at 12pm or 8pm ($p=0.2$ and $p=0.6$, respectively). Our findings show high lifetime frequency of cannabis use can restore the cortisol response to the awakening that has been found blunted in first-episode psychosis. This suggests cannabis may have a role in restoring the dynamic activity of the HPA axis in first-episode psychosis. This research is funded by NARSAD Mental Health Research Association, British Academy, and NIHR Biomedical Research Centre Institute of Psychiatry (Kings' College London).

TH04

BIDIRECTIONAL EFFECTS OF NMDA RECEPTOR ANTAGONISTS IN A CONCURRENT VI30-VI120 ASSAY IN MALE LH RATS

Jones WT, Shahabi S, Loomis S, Gilmour G. Psychiatry DHT, Eli Lilly & Company Ltd., Erl Wood Manor, Windlesham, Surrey. GU20 6PH, wendy.t.jones@student.manchester.ac.uk

N-methyl-D-aspartate receptor (NMDAR) antagonists receive great attention from pre-clinical researchers due to their inferred ability to model symptoms of schizophrenia in animals. Drugs within this class include PCP and ketamine, which are often used interchangeably in rodent behavioural assays such as locomotor activity assessment, pre pulse inhibition and other assays of cognitive ability. However, previous work within our lab suggests that such NMDAR antagonists are not in actuality as equivalent as was previously considered. The current study aimed to further differentiate the behavioural profiles of a range of these antagonists by assessing how readily rats can distinguish between different reward schedules and switch between them.

48 male Lister Hooded rats (>300g Harlan, UK) were trained to press levers to obtain pellets in standard operant boxes on an asymmetric concurrent variable interval schedule (VI30-VI120). For each animal, one lever always delivered pellets on a VI30 schedule, the other on a VI120 schedule. Animals were free to spontaneously switch between the two simultaneously available schedules. Compounds studied were the open-channel blockers MK-801, memantine, phencyclidine and ketamine, the NR2A subunit selective antagonist NVP AAM 077, the NR2B selective antagonists CP101, 606 and Ro 25,6981 and the competitive antagonist SDZ 220,581.

NMDAR antagonists expressed varied behavioural profiles in this assay, both between subunit selective antagonists and within the open channel blocker class. MK-801 (0.025-0.1mg/kg) and PCP (0.5-10mg/kg) initially increased response rate on both levers and changeover frequency, followed by a decrease at higher doses. Ketamine, memantine (both 2.5-10mg/kg) and NVP AAM 077 (5-20mg/kg) uniformly decreased responding on both levers and changeover frequency. CP 101,606 and Ro 25,6981 (both 2.5-10mg/kg) uniformly increased responding and changeover rate.

Following NMDAR antagonist administration, animals could still match their relative responding to each response schedule (i.e. respond less for reward on a VI120 versus a VI30 schedule). However, different NMDAR antagonists dose-dependently increased or decreased absolute responding on each schedule. From observing these very different effects of each antagonist, it is clear they should not be considered equivalent for the purpose of pre-clinical behavioural assays. Also, it appears difficult to readily map behavioural effects of NMDAR antagonists as a class onto concepts of positive and negative symptomatology in schizophrenia.

TH05

PCP IMPAIRS EPISODIC MEMORY IN FEMALE RATS: INVOLVEMENT OF 5-HT1A RECEPTORS

Kirun A, Grayson B, Neill JC. School of Pharmacy, Bradford university, Richmond road, Bradford BD7 1DP, a.kirun@bradford.ac.uk

Introduction We have previously shown that atypical but not classical antipsychotics can reverse a sub-chronic PCP -induced deficit in the novel object recognition task (NOR) (Grayson et al. 2007 Behav Brain Res 184 (1): 31-38); a model of episodic memory of particular relevance for cognitive deficit symptoms of schizophrenia. We are currently exploring the behavioural mechanism underlying the PCP deficit in this task (see Grayson et al, this meeting) however, the pharmacology of its effects remain unexplored. Many of the atypical antipsychotics have 5-HT_{1A} receptor partial agonist properties. The aim of this study was to investigate the role of 5-HT_{1A} receptors in mediation of the PCP-induced deficit in this task.

Methods: Adult female (n=50) hooded-Lister rats received either PCP, n=40 (2 mg/kg, i.p.) or vehicle n=10 (0.9% saline, 1 ml/kg i.p) twice daily for 7 days, followed by 7 days washout. Testing consisted of a 3min acquisition phase whereby rats explored two novel objects followed by a 1min inter-trial interval, followed by a 3min retention phase where rats explored a familiar and a novel object. Results are shown as time spent exploring the novel compared with familiar object. Rats were tested for their performance in NOR following treatment with the 5-HT_{1A} receptor partial agonist buspirone (0.03125-1.25 mg/kg, i.p. 30 min prior to testing and a combination of the selective 5-HT_{1A} receptor antagonist WAY100635 at 0.3 mg/kg i.p. with buspirone at 0.0625 mg/kg, i.p. 30 min prior to testing.

Results There was no significant difference in exploration time (s) of the two familiar objects in the acquisition phase in any group. PCP-treated rats could not differentiate between the novel and familiar object in the retention trial. Control rats treated with vehicle and sub-chronic PCP rats treated with buspirone (0.0625mg/kg), significantly ($p<0.005$ and $p<0.01$, respectively) differentiated between the novel and familiar object. Doses of 0.03125 and 1.25 mg/kg buspirone were without efficacy. Pre-treatment with WAY100635 (0.3 mg/kg) 30min prior to buspirone (0.0625 mg/kg) reversed the rats' ability to discriminate between the novel and familiar object in the retention phase.

Conclusion These data agree with our recent results showing that novel antipsychotics with partial agonist activity at 5-HT_{1A} receptors, such as aripiprazole attenuated the sub-chronic PCP induced NOR impairment (Neill et al. presented at serotonin club meeting, July 2008). These results implicate 5-HT_{1A} receptor mechanisms in the ability of some atypical antipsychotics, to improve aspects of cognition in schizophrenia (Li et al. 2004 Eur. J. Pharmacol. 493; 75-83)

TH06

TRAUMA, DEPRESSION AND RESILIENCE IN MOOD DISORDER SERVICE OUTPATIENTS

Lit P, Garner MJ, Carr C, Baldwin DS. Clinical Neuroscience Division, University of Southampton, RSH Hospital, Brintons Terrace, Southampton, SO14 0YG, pl404@soton.ac.uk

Introduction. Many people experience traumatic events but only a proportion develop post-traumatic symptoms. Risk factors for the development of post-traumatic symptoms have been identified, but factors protecting against the development of post-traumatic stress disorder (PTSD) have not been studied extensively: however 'resilience' may be an important determinant of successful adaptation to trauma.
Method. In patients attending a tertiary referral mood and anxiety disorders service, lifetime history of trauma was ascertained by the Davidson Trauma Questionnaire (DTQ), depressive and anxiety symptoms assessed by the Hospital Anxiety and Depression Scale (HADS), post-traumatic symptoms by the Davidson Trauma Scale (DTS), symptom-related disability with the Sheehan Disability Scale (SDS) and resilience by the Connor-Davidson Resilience (CD-RISC) Scale. The Clinical Global Impression of Severity (CGI-S) was completed at the end of the assessment.
Results. 71 patients (39 women, 32 men; mean age 48.0 years) completed the study: 28 had a single diagnosis and 43 co-morbid diagnoses. 12 patients had bipolar disorder, 34 unipolar depressive disorder, 20 an anxiety disorder, and 5 other disorders. 63 patients reported lifetime history of trauma: in 32, trauma type and individual response fulfilled the definition of trauma according to DSM-IV PTSD. Mean rating scale scores across the three major diagnostic groups (unipolar depression, bipolar disorder, anxiety disorder, respectively) were as follows: HADS, 21.9 vs. 18.3 vs. 21.6; DTS, 38.8 vs 38.1 vs 31.4; CD-RISC, 48.2. vs. 52.7 vs. 44.5; SDS, 17.0 vs. 12.0 vs.17.2; CGI-S, 3.1 vs. 3.5 vs. 3.5. Mean CD-RISC scores in patients with or without a lifetime history of trauma were 46.0 and 60.4 respectively ($p=0.05$, 95%CI 0.26 to 28.70, independent sample t-test). In patients with lifetime trauma, mean CD-RISC scores differed significantly between those with probable, possible, and no depression: 34.1 vs. 52.6 vs. 61.6, respectively, ($p<0.001$, oneway ANOVA test). Similarly, CD-RISC scores differed significantly between those with probable, possible and no anxiety: 39.3 vs. 53.0 vs. 63.0, respectively, ($p<0.001$, oneway ANOVA test).
Conclusion Patients reporting a lifetime history of trauma were less resilient that those reporting no trauma. In patients with lifetime trauma, resilience scores are lower in patients with greater severity of depression. In patients with lifetime trauma, resilience scores are also lower in patients with greater severity of anxiety. Source of funding: No funding was sought for this study.

TH07

EXAMINATION OF N- ACETYL-CYSTEINE ON BEHAVIOURAL ADAPTATION TO CHRONIC NICOTINE EXPOSURE

Oughton JB, Shoaib M. Psychobiology Research Laboratories, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, jamie.oughton@ncl.ac.uk

This study uses a novel context-dependent sensitisation procedure to examine the expression of the conditioned hyperactivity effects of nicotine in rats. There is evidence to suggest that N-acetyl-cysteine (NAC) may be effective in reducing cravings for a variety of abused substances, studies which utilise reinstatement of extinguished responding of drug-seeking behaviours. NAC is thought to restore extracellular glutamate levels which are lowered during periods of abstinence, to baseline levels. The present experiments aim to examine the effects of NAC on the conditioned and stimulant effects of nicotine in rats. Conditioning sessions were carried out for 14 days during which male Hooded Lister rats (n=6-8) received either nicotine or saline immediately before placing in a locomotor test chamber for 45 minutes (paired groups). A third group received saline before placing in the chamber but was administered nicotine at the end of the day (unpaired group). The stimulant effects of nicotine were measured in the locomotor chamber. Rats were pre-treated with 5, 20, 50 or 100 mg/kg IP NAC or vehicle 2.5 hours before a challenge with nicotine (0.4 mg/kg SC) or saline and immediately placed in the test chamber. Conditioning sessions were carried out during intervening days between the tests. Nicotine-paired rats displayed hyperactivity relative to saline-treated controls during tests in which saline was administered. In a dose-dependent manner, NAC pretreatment decreased the context-induced hyperactivity response expressed by the nicotine-paired group compared to the control groups as noted by the significant interaction between NAC dose and group [$F(2,8)= 2.217$, $P<0.037$]. This reduction was specific to the context-induced effect since the same doses of NAC failed to specifically modify nicotine-induced increases on activity [$F(2, 8)= 1.348$, n.s.]. The largest dose of NAC produced a non-specific reduction supressing activity in all groups [$F(1,7)= 1.241$, $P<0.002$]. These findings demonstrate that NAC can specifically reduce conditioned hyperactivity in a dose-dependent manner without modifying the expression of sensitised activity to nicotine. Therefore, NAC may have potential as a smoking cessation aid that may work by reducing cravings elicited by contextual environmental cues.
Research supported by Newcastle University.

TH08

A PRELIMINARY INVESTIGATION INTO SUB-CHRONIC PCP INDUCED DEFICITS IN THE 5-CHOICE SERIAL REACTION TIME TASK

Patel AI, Barnes SA, Neill JC. School of Pharmacy, University of Bradford, Richmond Road, Bradford, BD7 1DP, aipatel@bradford.ac.uk

Introduction. Cognitive dysfunction is now recognised to be core to the symptomology of schizophrenia. These cognitive impairments include attentional and executive function deficits. The 5-choice serial reaction time task (5-CSRTT) is now one of the most widely used tests to assess the attentional function in rodents (Robbins 2002 Psychopharmacology 163: 362-380). Along with measuring sustained attention, the 5-CSRTT can measure compulsive and impulsive behaviours, deemed to be under executive control. The sub-chronic PCP model of schizophrenia is a valid means of pharmacologically inducing schizophrenic-like symptoms in animal models, producing deficits in a number of aspects of cognitive function in our laboratory e.g. reversal learning (Abdul-Monim et al. 2006 Behav Brain Res 169: 263-273) episodic memory (Grayson et al. 2007 Behav Brain Res 184: 31-38) and attentional set shifting (McLean et al. 2008 Behav Brain Res 189: 152 - 158)
The aim of this study was to investigate the ability of sub-chronic PCP administration to induced deficits in the 5-CSRTT in female rats.
Methods Female hooded-Lister rats were trained in the 5-CSRTT to detect a brief stimulus (1 second) with a 5 second inter-trail interval-ITI and 5 second limited hold. Once rats had reached criteria (>80% correct, <20% omissions) rats were sub-chronically treated with either vehicle (0.9% saline, 1 ml/kg, i.p.) or PCP (2 mg/kg, i.p.) using our 7-days bi-daily dosing regime. Following the 7-days washout period, rats' performance in the 5-CSRTT paradigm was assessed using an independent t-test.
Results Initial results indicate the sub-chronic PCP administration has no significant effect to impair performance in the 5-CSRTT looking across various measures of cognitive performance; in particular there were no significant differences in response accuracy, premature responding or perseverative over-responding, when compared with the vehicle group.
Conclusion. The failure of sub-chronic PCP to induce deficits in the 5-CSRTT may be due to the task's dependence on prefrontal cortical function (Chudasama et al. 2003 Behav Brain Res 146: 105-119). Sub-chronic PCP treatment produces lasting deficits in tasks more dependent on hippocampal activation such as reversal learning and reduces parvalbumin immunohistochemistry in hippocampal rather than in cortical regions (Abdul-Monim et al. 2007 J Psychopharmacology 21: 198-205). However, acute PCP treatment may induce neurochemical changes in the prefrontal cortex (Idris et al. 2004 SFN abstract: Prog No 695.9 Online) thus resulting in impaired performance in this task (Amitai et al 2007 Psychopharmacology 193: 521-537).

TH09

CAN RIMONABANT REVERSE THE COGNITIVE DEFICITS PRODUCED BY REARING RATS IN ISOLATION FROM WEANING?

Pointon J, Kok JL, Cho WS, Maneepairoj P, Fone KCF, Marsden CA. School of Biomedical Sciences, University of Nottingham, Clifton Boulevard, Nottingham NG7 2UH, mzyzjlp@nottingham.ac.uk

Introduction. Cognitive deficits are a key feature of schizophrenia that have persistent, detrimental effects on patients' lives and are not well managed by current antipsychotic drugs. A better understanding of the neurobiological basis of these cognitive defects would aid development of new treatments. Rearing rats in isolation from weaning produces robust, irreversible neurochemical and behavioural changes similar to those seen in schizophrenia (Bianchi et al., 2006, Eur. J. Neurosci., 24, 2894-2902). Since illicit cannabinoid use has been associated with psychotic symptoms and cognitive deficits (Moore et al., 2007, Lancet, 370, 319-328), the potential role of the endocannabinoid system as a target to modify cognitive function is worthy of investigation. This study investigates whether the CB_1 receptor antagonist, rimonabant, can reverse the cognitive deficits induced by isolation rearing.
Methods. 32 male Lister-hooded rat pups (25-28 days old) were group (n=4/cage) or isolation housed for 40 days. Isolates were randomly assigned to 3 treatment groups (n=8/group) to receive either vehicle or rimonabant (2mg/kg or 5mg/kg i.p.) on behavioural test days while group-housed rats all received vehicle. Locomotor activity (LMA) in a novel arena was measured prior to the start of drug treatment. The effects of housing and rimonabant on novel object recognition (NOR), over two trials with a 2hr inter-trial period, and prepulse inhibition of acoustic startle (PPI) were subsequently measured at one-week intervals.
Results. All isolates where hyperactive in the LMA task compared to group reared rats such that there was a main effect of time (ANOVA $F_{(11,336)} = 55.63$, $p<0.0001$), housing ($F_{(3,336)} = 18.86$, $p<0.0001$) and significant time x housing interaction ($F_{(3,336)} = 1.554$, $p= 0.0299$), demonstrating the effectiveness of the isolation protocol.
Vehicle treated isolates showed significant impairment of both NOR and PPI compared to group housed rats. The higher (5mg/kg) but not the lower dose of rimonabant reversed the isolation-induced deficit in NOR (exploration time of novel vs. familiar object, being $p<0.01$ Student's t-test in isolates), a measure of non-spatial working memory, but had no effect on the inhibition of PPI produced by isolation rearing.
Conclusions. The results suggest that rimonabant can reverse a cognitive deficit in NOR induced by isolation rearing, but can not alter the deficit in sensory processing measured by PPI. Further studies are required to determine whether the effects of rimonabant are due to a general improvement in cognition or limited to specific types of episodic memory. Furthermore, alterations in the endogenous endocannabinoid system may contribute to the cognitive deficits seen with isolation rearing. Rimonabant, used in conjunction with current antipsychotic drugs, might be useful in the management of cognitive symptoms in schizophrenia.

TH10

CORTISOL LEVELS AND EMOTIONAL PROCESSING IN ADULTS EXPOSED TO POSTNATAL DEPRESSION IN INFANCY

Potter JL, Harmer CJ. Department of Psychiatry, Warneford Hospital, Oxford, OX3 7JX, jessica.potter@univ.ox.ac.uk

Introduction. Halligan et al (2004, Biol Psychiatry, 55, 376-81) have demonstrated that infants exposed to postnatal depression (PND) have elevated morning cortisol levels when tested in early adolescence. The current study investigated whether this association would endure into adulthood in a population of undergraduate participants who had also been exposed to PND in infancy. Previous work was extended by conducting tests of emotional processing.
Method. Performance of the PND experimental group (n=13) was compared with two control groups: participants that had been exposed to the same duration of maternal depression but outside of the first year of life (n=14) and participants whose mothers had never had depression (n=16). This categorization was achieved via a posted questionnaire to the mother and all undergraduate participants were screened for current or previous psychological disorders. Participants completed emotional processing tasks (emotional categorization, facial expression recognition and emotional memory) and provided morning salivary cortisol samples at awakening and 15 and 30 minutes thereafter. Group matching criteria included gender, age, IQ, state and trait anxiety and current mood state.
Results. The data were analysed using mixed ANOVAs and it was found that the PND group did not show negative biases on emotional processing tasks, however, they did display slower reaction times on an emotional categorization task ($p<.05$). The PND group also showed elevated cortisol levels relative to participants who had been exposed to depressed mothers outside of the first year of life.
Conclusions. Exposure to a depressed mother within the first year of life, as opposed to a later exposure, was associated with higher cortisol levels suggesting an important role for the timing of the exposure to a depressed mother. Additionally, the experimental group showed an emotional categorization impairment, similar to that previously described in volunteers at high risk of depression (Mannie et al., 2007), and which may reflect a difficulty in using mood as information.

TH11

MEASUREMENT OF SUBJECTIVE AND OBSERVED MOOD CHANGE WITH ACUTE DEEP BRAIN STIMULATION IN TREATMENT RESISTANT DEPRESSION

Wood B, Tyacke RJ, Patel NK, Malizia AL. Psychopharmacology, DHB, University of Bristol, Whitson Street, Bristol, bw4632@bristol.ac.uk

Deep brain stimulation (DBS) of specific brain areas is emerging as a possible treatment for psychiatric disorders resistant to medicines. Early reports of acute stimulation of the subgenual cingulate cortex (BA25) described rapid changes in patients verbal affective report with specific contact stimulations (Mayberg et al, 2005 Neuron;45:651-60). We tested three subjects with various acute combinations of contacts (110, 73 and 70 respectively) over 2 – 4 days in a double blind DBS study comparing stimulation of BA25 and ventral anterior capsule/nucleus accumbens. Here we report the use of observed reports (comprising observed behaviour and evaluation of unguided speech), subjective questionnaires (Profile of Mood States Short Version- POMS SV) and visual analogue scales (VAS; Sad, Elated, Motivated, Irritated, Anxious) in describing subjective experiences during 5 minutes of acute DBS. In addition an independent observer rated the overall affect during the stimulation using a five-point scale (-2 to 2). For one subject, heart rate and heart rate variability were also available.
Results. Each patient had a different pattern of response. Observed ratings recorded definite changes in 1%, 16% and 21% of stimulations with 60% of these being a worsening of mood. POMS-SV fatigue, confusion and vigor showed little variation across stimulations or patients. POMS-SV anger and tension were not sensitive to change in two and one patients respectively. POMS-SV depression varied in all three with a standard deviation of 7 – 15% of the mean. VAS describing sad, elated and motivated showed little variation. VAS "irritable" was close to floor in two patients. VAS "anxious" varied with a standard deviation of 3 – 15% of the mean. For one patient the observed score was highly correlated with relevant VAS and POMS measures: tension (Spearman's rho -0.76; $p<0.0001$), anger (-0.72; $p<0.0001$), depression (-0.7; $p<0.0001$), anxiety (-0.7; $p<0.0001$) and irritability (-0.54; $p=0.0001$). For one patient the observed score was significantly correlated with depression POMS-SV (-0.32). VAS irritable and POMS-SV anger were correlated in two patients (0.67 and 0.57; $p<0.0001$ and $p = 0.0002$ respectively). In only one patient was VAS anxious highly correlated to POMS-SV tension (0.87, $p<0.0001$). The one patient, who had cardiovascular measures, heart rate was significantly higher during periods of observed worsening of mood (t test; $p=0.02$) but there was no difference in heart rate variability.
Conclusions. Acute mood effects of DBS are observable and measurable. It is not known whether these have any long term prognostic significance.

TH12

THE ANGIOTENSIN-CONVERTING ENZYME INHIBITOR, CAPTOPRIL, PREVENTS THE HYPERACTIVITY OF NK1R-/- MICE

Yee P, Yan TC, Hunt SP, Stanford SC. Pharmacology, University College London, Gower Street, London WC1E 6BT, philyee01@hotmail.com

Introduction: We have previously reported locomotor hyperactivity in mice with functional ablation of the substance P-preferring (NK1) receptor gene (NK1R-/-) (Fisher et al. (2007) Eur J Neurosci, 25, 1195-1204). This hyperactivity is prevented by d- amphetamine or methylphenidate, which are first-line treatments for Attention-Deficit Hyperactivity Disorder (ADHD: Yan et al. (2007) Soc Neurosci Abstract 386.1). These findings suggest that NK1R-/- mice offer a mouse model of ADHD and that activation of NK1R could relieve this disorder. Substance P is hydrolysed by angiotensin-converting enzyme (ACE). It follows that ACE inhibitors, such as captopril, could be a novel treatment for ADHD. Here, we carried out a pilot experiment to test whether captopril modified the locomotor activity of mice and, if so, whether its actions depended on functional NK1R.
Methods: Male NK1R+/+ and NK1R-/- mice were used (25~35g; 129/Sv X C57BL/6 crossed with an outbred MF1 strain). Mice were randomly assigned for intraperitoneal administration of captopril (10 mg/kg) or saline (10 ml/kg). Their behaviour in a light/dark exploration box was monitored 30 min later (N = 5~6 / group; as in: Herpfer et al. (2005) Neuropharmacology, 48, 706-19), recorded digitally (for 30 min) and scored blind. Data were analysed by 2-way ANOVA, followed by the Bonferroni post hoc test. $P < 0.05$ was the criterion for statistical significance.
Results: As before, the drug-free NK1R-/- mice were hyperactive, compared with wild-types ($P<0.001$). The effect of captopril on animals' locomotor activity depended on genotype (Genotype * Drug interaction: $F1,18=6.8$; $P<0.05$). Thus, this ACE inhibitor prevented the hyperactivity of NK1R-/- mice ($P<0.05$) but did not affect the motor behaviour of NK1R+/+ mice.
Conclusion: The prevention of hyperactivity of NK1R-/- mice given captopril mimics the effects of d- amphetamine and methylphenidate. This suggests that captopril could be an alternative treatment for ADHD. However, because expression of NK1R is disrupted in NK1R-/- mice, this effect of captopril cannot be mediated by activation of NK1R and is unlikely to rest on inhibition of metabolism of substance P. This suggests that there are adaptive changes in NK1R-/- mice, which increase their sensitivity to captopril at sites that influence motor function (e.g. the dopamine system (van den Buuse et al, 2005 Neurosci Lett, 380, 6-11)). Importantly, the lack of effect of captopril in NK1R+/+ (wildtype) mice reflects the absence of adverse motor side effects in humans treated with this drug.
[This work was sponsored by UCL Business]

SO1

OBJECT-PLACE-CONTEXT RECOGNITION IN RATS: MODEL OF EPISODIC-LIKE MEMORY IN SCHIZOPHRENIA

Le Cozannet R, Fone KCF, Moran PM. Psychology, University of Nottingham, Nottingham NG7 2RD, lecozannet_romain@yahoo.fr

Episodic memory is the capacity to recall an event (what) in time (when) and in a specific context (where). People with schizophrenia have been shown to have deficits in episodic memory. There are a number of animal models of schizophrenia that induce memory deficits but none have been tested in tasks that simultaneously address the "what", "when" and "where" aspects that define episodic memory in humans. Glutamatergic antagonists such as phencyclidine (PCP) induce a range of schizophrenic-like symptoms in healthy volunteers, including episodic memory deficits. In rats, PCP induces memory deficits that are reversed by antipsychotic drugs. Isolation reared rats show behavioural and neurochemical alterations similar to several core deficits seen in schizophrenia, including memory. In the following study subchronic PCP and socially isolated rats were tested on an Object-Place-Context test of episodic memory where rats recognise objects under specific spatial, contextual and temporal conditions (Eacott and Norman 2004 JNEUROSCI 24(8):1948-1953).
Two animal models were used: the subchronic PCP model which consisted of administration of 5mg/kg i.p. twice daily for 7 days followed by 7 days withdrawal period and the isolation rearing model in which rats were housed in isolation from post natal day 24. The animals performed the object-place-context recognition task which followed 8 habituation sessions in each of two different contexts. Rats were tested twice in each context with two familiar objects A or B encountered previously (during a sample phase) in a different context-dependent location. These four conditions were replicated for each of 2 or 7 delays (2-120 min). Recognition memory was measured as greater exploration of the novel object than the familiar object. The novel object in this procedure is the one that is in a new location for a specific context as the rat is already familiar with the object.
First, these results confirmed a delay-dependent episodic-like memory in rats. Second, subchronic PCP-treated-rats but not isolated rats were impaired in this episodic memory task. Third, both PCP and isolated rats showed impairment of delay-induced reduction in total object exploration in the task, which reflects recognition of a specific object (Context-Object association) in a previously visited context.
These data suggest that this model is sensitive to glutamate antagonists as in humans and that it can identify highly specific memory impairments common to both PCP and social isolation rearing. This suggests that this may prove to be a sensitive preclinical model for episodic memory impairments in schizophrenia.

SO2

CB1 RECEPTOR MEDIATED DISRUPTION OF SENSORY GATING IN THE RAT HIPPOCAMPUS AND MEDIAL PREFRONTAL CORTEX

Dissanayake WDN, Zachariou M, Marsden CA & Mason R. School of Biomedical Sciences, University of Nottingham, Derby Road, Nottingham NG7 2UH, dilshani2003@yahoo.co.uk

Sensory gating, assessed using an auditory conditioning-test paradigm which measures the reduction in the auditory evoked response (AER) produced by a test stimulus following an initial conditioning stimulus (Bickford et al., 1990, Biol. Psychiatry 27:183-192), is found to be disrupted in schizophrenic patients (Cadenhead et al., 2000, Am. J. Psychiatry 157:55-59). Dysregulation of the endocannabinoid system has been suggested to be involved in the pathogenesis of schizophrenia (Emrich et al., 1997, Pharmco. Biochem & Behav. 56:803-807). This study examined the effects of the non-selective cannabinoid agonist, WIN55,212-2, on auditory gating in CA3 region of the rat hippocampus and medial prefrontal cortex (mPFC).
Local field potential (LFP) activity was recorded using multielectrode arrays in the CA3 and mPFC in isoflurane-N_2O:O_2 anaesthetised adult male Lister hooded rats (n=12). Paired auditory stimuli (3 kHz tones, 10ms duration, 90dB intensity, 0.5s inter-stimuli interval, 10s inter-trial interval) were presented binaurally over 128 trials. The effect of a single dose of WIN55,212-2 (1.2mg/kg, i.p; n=6) on the Test/Condition-evoked (T/C) N2 LFP wave amplitude ratio was assessed, 15 and 45min after drug administration. T/C values <50% were indicative of gating. One way analysis of variance (ANOVA) for repeated measures with post hoc Tukey t test was used to compare the basal and the drug induced changes and $P<0.05$ was considered statistically significant.
Sensory gating of the N2 wave was observed in both CA3 (T/C=28±5%; mean±s.e.m) and mPFC (T/C=43±5%) prior to drug administration. WIN55,212-2 disrupted auditory gating in CA3, both 15 min (T/C=94±6%; $P<0.01$) and 45 min (T/C=92±5%; $P<0.001$) after drug administration. Disruption of auditory gating was also observed in mPFC, 15 min (T/C=93±22%; $P>0.05$) and 45 min (T/C=177±42%; $P<0.01$) after WIN55,212-2 administration. In rats pre-treated with the CB1 receptor antagonist SR141716A (1mg/kg, i.p; n=6), there were no significant changes in T/C% ($P>0.05$) in CA3 or mPFC at 15 min or 45 min after WIN55,212-2 administration.
This study demonstrates that cannabinoid receptor activation disrupts auditory gating in both CA3 region of the hippocampus and mPFC, with deficits similar to those seen following phencyclidine administration (Adler et al., 1986, Biol. Psychiatry 21: 787-98). Prevention of WIN55,212-2 induced disruption of gating by CB1 antagonism suggests that the effects of WIN55,212-2 on gating in both CA3 and mPFC were mediated via CB1 receptors.
Acknowledgments: Government of Sri Lanka and the International Office of the University of Nottingham for funding.

SO3

BEHAVIOURAL AND NEUROCHEMICAL EVALUATION OF THE DDY/DAO- MUTANT MOUSE – A POTENTIAL ANIMAL MODEL FOR SCHIZOPHRENIA

Storey JD, Waters K, Thompson R, Simmons C, Reavill C, Bull S, Kew JN, Konno R, Woolley ML, Dawson LA GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, CM19 5AW, james.d.storey@gsk.com

N-methyl-D-aspartate (NMDA) receptor antagonists, such as phencyclidine (PCP), induce psychotic-like symptoms in healthy individuals and exacerbate the symptoms of schizophrenic patients, suggesting that NMDA receptor hypofunction is implicated in the pathophysiology of schizophrenia. D-serine is a co-agonist at the NMDA receptor, and is catabolised by the enzyme D-amino acid oxidase (DAO). Therefore, it is hypothesized that inhibition of this enzyme may lead to enhanced activation of the NMDA receptor, and provide a novel target for the treatment of schizophrenia. The present study describes the behavioural and neurochemical phenotype of a strain of mice, ddY/DAO$^-$, which lack DAO activity, due to a single point mutation in the DAO gene.

Mice were tested in the laboratory animal behaviour observation, recognition and analysis system (LABORAS®) and for pre pulse inhibition (PPI), a measure of sensory gating. The neurochemical effects of this deletion were investigated by measuring *ex vivo* levels of both D-serine and L-serine from brain tissue and blood serum by high performance liquid chromatography (HPLC) coupled with tandem mass spectrometry (MS-MS).

The ddY/DAO$^-$ mice showed increased locomotor activity and reduced grooming behaviour, when compared with their wildtype (WT) controls. When challenged with PCP (3 mg/kg), the ddY/DAO$^-$ mice exhibited an augmentation of the PCP-induced hyperactivity response. When assessed for sensory motor gating, whilst demonstrating a reduction in mean startle amplitude, ddY/DAO$^-$ mice performed equivalently to WT controls for PPI. Neurochemical evaluation showed the ddY/DAO$^-$ mice to have elevated levels D-serine (but not L-serine) in both the serum and cerebellum (consistent with these mice having no active DAO enzyme), and elevated tissue levels of dopamine, DOPAC, aspartate and glutamate in the nucleus accumbens.

These data demonstrate a clear phenotype relating to the loss of DAO activity. Elevations in serum and cerebellar D-serine levels confirm the null mutant genotype of these animals, and the augmentation of the behavioural response to PCP confirms the interaction at the level of the NMDA receptor. Collectively these studies provide further evidence that inhibition of the DAO enzyme enhances NMDA receptor function, and may therefore be beneficial in the treatment of schizophrenia.

SO4

SOCIAL WITHDRAWAL INDUCED BY SUB-CHRONIC PCP IN FEMALE RATS, IMPROVEMENT BY ATYPICAL ANTIPSYCHOTICS VIA A 5-HT1A RECEPTOR MECHANISM: IMPLICATIONS FOR TREATMENT OF NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

Snigdha S, Neill JC. School of Pharmacy, University of Bradford, Bradford, ssnigdha@brad.a.uk

Introduction Schizophrenia consists of three separate symptom domains: positive, negative and cognitive. Negative symptoms include blunted affect, poverty of speech and social withdrawal. Sub-chronic phencyclidine (PCP) mimics certain aspects of schizophrenia symptomology in rats. However, there is a marked lack of validated animal models of negative symptoms. We are working towards establishment of such a model and have recently shown that atypical antipsychotics, risperidone and ziprasidone but not the classical agent haloperidol, can reverse the PCP-induced deficit in social behaviours in female rats (Snigdha and Neill. 2008 Behaviour Brain Research 187:489-94). The aim of the present study is to investigate involvement of 5-HT1A receptors in reversal of the PCP-induced deficits in this model. 5-HT1A receptors may play an important role in depression (Maes and Meltzer 1995 Fourth Generation of Progress Raven Press, 933-944) and some of the newer antipsychotics such as ziprasidone and aripiprazole act as partial agonists at this receptor (Rollema et al. 2000 Biological Psychiatry 48:229-237)

Methods Adult female hooded-Lister rats received vehicle (n=36) or PCP (n=22; 2mg/kg i.p.) twice daily for 7 days, followed by 7 days washout. On test days, PCP treated rats received acute treatment with aripiprazole (5mg/kg, s.c.) or the 5-HT1A receptor antagonist, WAY100635 (0.5mg/kg, i.p.) alone and in combination. All acute treatments were given 30 min prior to testing. For the test, pairs of unfamiliar weight matched rats receiving either acute doses of drugs described above or vehicle were placed in the test arena and social behaviours (following, sniffing, climbing over and under, exploration of inanimate object and avoiding) were recorded on video for subsequent blind scoring. Data were analysed by factorial ANOVA followed by un-paired t-test.

Results Sub-chronic PCP produced a robust and significant reduction in social sniffing and increase in avoiding behaviour ($p<0.01$-$p<0.001$). The PCP-induced deficits in social behaviours were significantly attenuated by acute treatment with aripiprazole ($p<0.01$-$p<0.001$), an effect that was abolished by pre-treatment with WAY 100635. Conclusion These findings confirm that sub-chronic PCP induces robust social behaviour deficits in female rats and shows that they are reversed by the novel antipsychotic, aripiprazole. These results suggest that the beneficial effects of drugs such as aripiprazole and ziprasidone on PCP-induced social behaviour deficits, a potential model of negative symptoms of schizophrenia, may be a consequence of modifications of the serotonergic system, in particular through an interaction with 5-HT1A receptors, a hypothesis supported by Bruins Slot et al. 2005, Neuropharmacology 49: 996-1006).

SO5

RECLASSIFYING PSYCHOACTIVE SUBSTANCES ON THE BASIS OF THEIR ACTUAL HARMS: AN INTERNET SURVEY OF DRUG USERS

Morgan CJA, Muetzelfeldt L, Curran HV. Clinical Psychopharmacology Unit, University College London, Gower St, LONDON WC1E 6BT, c.morgan@ucl.ac.uk

Introduction: The extent of worldwide psychoactive substance use is estimated at 2 billion alcohol users, 1.3 billion smokers and 185 million drug users. However much controversy and confusion exists concerning the actual harms associated with the use of these substances. Nutt et al (2007) published a 'rational' scale used by two groups of experts to assess these harms. Drug users were not included in these expert panels despite their unique perspective on the harms of psychoactive substances. This survey aimed to assess drug users' views on the harms of drugs using the rational scale developed by Nutt et al. As users' choice of which drug to take is likely to be based on a risk/benefit analysis, we additionally assessed the perceived benefits of taking psychoactive substances.

Method: The survey was hosted on www.nationaldrugsurvey.org. All participants were required to be over 18 years old and residents of the U.K. The respondents completed a section detailing their experience of the 20 substances included in the original survey with the addition of crack cocaine. Only respondents with direct experience of the drugs rated their perceived harms. There were nine scales of harm under three sub-headings: physical harms, dependence-related harms and social harms. Each drug was rated on a four point scale, from no risk to extreme risk. The acute and chronic benefits of each drug were also rated on a similar four point scale.

Results: 1501 users completed the survey. Users rated heroin as the most harmful drug, followed by crack cocaine, cocaine, street methadone and alcohol. There was no correlation between classification under the Misuse of Drugs Act and ranking of harms by users (Kendall's rank correlation 0.234; $p=0.18$). Despite being unclassified drugs; alcohol, solvents and tobacco were all rated within the top ten most harmful drugs. There was a high correlation overall between users rankings and the experts rankings from Nutt et al.'s study ($r = 0.896$, $p<0.001$). Ecstasy, cannabis and LSD were rated consistently highly on both acute and chronic benefits.

Conclusions: The results of this study suggest that users are relatively well informed about the harms associated with the drugs they are using. They also imply that the current legal classification system of psychoactive substances may be in need of an overhaul as Class A substances such as Ecstasy and LSD are both rated as relatively low on harms by experts and users and high on benefits.

This project was funded internally.

SO6

DELTA-9-TETRAHYDROCANNIBINOL INDUCED PSYCHOSIS AS RATED BY SELF AND OTHER

Morrison PD, Murray RM, Kapur S. Psychological Medicine, Institute of Psychiatry, De Crespigny Park, London, paul.morrison@iop.kcl.ac.uk

The use of high potency THC amongst young people in the West has become a public health concern. Sinsemilla, characterised by high Δ9-tetrahdrocannibinol (THC) but negligible cannabidiol (CBD) concentration, is now the most prevalent form of cannabis in England. Cannabis is one of the first consistently identified risk factors for schizophrenia (Arseneault L. et al. (2004) Br J Psychiatry 184: 110-117). Here we report the acute psychotogenic effects of pure-synthetic THC in a sample of 22 healthy male volunteers. Previous work utilised The Positive & Negative Syndrome Scale (PANSS), an investigator-rated scale, to measure THC-psychosis (D'Souza CD. et al (2004) Neuropsychopharmacology 29: 1558-72). To control for possible observer bias, we have incorporated a participant-rated scale: The Community Assessment of Psychic Experiences (CAPE), (Stefanis NC. et al (2002) Psychological Medicine 32: 347-58). We hypothesized that investigator-rated THC-psychosis and participant-rated THC psychosis would show agreement. The local ethics committee approved all protocols. Participants were recruited from King's College London by email advertisement. Exclusion criteria included personal or family history of major mental illness and personal drug/alcohol dependence. Participants were required to be over 21 and be willing to give fully informed consent. Synthetic THC (2.5mg) was administered intravenously (IV) over 5 minutes, in a double-blind, placebo controlled manner. Psychotic responses were assessed using The PANSS and CAPE at 30, 80 and 120 minutes post injection. Within group differences in psychopathology were investigated using Friedman's test. Scores on the PANSS positive subscale increased from baseline following THC but not placebo administration ($\chi 2=62$, $p<0.001$). At 30 minutes post THC, PANSS-positive scores had increased by a mean of 3.7 points (range 0-17), returning to baseline levels by 120 minutes. Similarly, participant-rated positive psychotic symptoms as measured by The CAPE-state increased from baseline following THC but not placebo administration ($\chi 2=20$, $p=0.005$). Investigator-rated (PANSS) and participant-rated (CAPE-state) positive psychotic scores post-THC administration were correlated (Kendall's tau=0.50, $p<0.001$). Synthetic intravenous Δ9-tetrahdrocannibinol was shown to elicit positive psychotic symptoms in a proportion of healthy individuals. This held whether subjects rated themselves or were rated by a blinded psychiatrist. These findings add to a growing body of evidence that THC confers risk for acute and chronic psychoses. This study was funded by The Psychiatric Research Trust.

SO7

CHANGES IN ACTIVITY AND TEMPERATURE FAIL TO CORRELATE WITH 5-HT RELEASE FOLLOWING REPEATED MDMA ADMINISTRATION IN RATS

Rodsiri R, Marsden CA, Fone KCF, Green AR. School of Biomedical Sciences, University of Nottingham, Nottingham NG7 2UH, mbxrr@nottingham.ac.uk

Human binge use of repeated low doses of 3,4-methylenedioxymethamphetamine (MDMA/ ecstasy) may maintain the euphoric state while reducing tolerance (Parrott, 2005). However there is limited information from animal studies whether analogous repeated MDMA causes behavioural effects and long-term serotonergic neurotoxicity. In this study we determined the acute effects of repeated low doses of MDMA on body temperature, activity and 5-HT release in the rat by combining telemetry and microdialysis. Male Lister hooded rats (100-130 g) were individually housed after i.p. implantation of a telemetry device. Two weeks later a microdialysis probe was implanted into the hippocampus. The following day either MDMA (3 or 6 mg/kg) or saline were given i.p. (n = 6/treatment) 3 times every 2 h and microdialysis samples collected with activity and body temperature monitored simultaneously using telemetry. Two-way ANOVA with treatment and time as main factors was used followed by Bonferroni posttest. MDMA (3mg/kg) significantly decreased body temperature after each injection and this returned to normal 3 h after the last injection. The maximum decrease occurred 40 min after each injection ($p < 0.001$ after the first and second injections and $p < 0.05$ after the third injection). The higher dose of MDMA (6mg/kg) reduced body temperature after the first injection ($p < 0.001$) but then increased temperature to a maximum of +1 ^{o}C 2 h after the last injection. There was no significant difference in activity between saline and MDMA (3mg/kg) treated animals. In contrast the higher dose of MDMA (6mg/kg) induced hyperactivity after each injection with a prolonged increase after the final dose. Both doses of MDMA increased extraneuronal hippocampal 5-HT with a maximum release 1 h after each injection. The higher dose of MDMA (6mg/kg) produced greater release of 5-HT following the first injection (+556% from predrug basal) than the lower dose (+127% from predrug basal). After the second and the third injections increases in 5-HT release were similar for both doses (approximately +300% from basal). The results indicate that repeated administration of the higher dose of MDMA causes hyperthermia and hyperactivity while the lower dose results in hypothermia and no effect on activity. Moreover there appears to be no correlation between changes in extracellular 5-HT and either activity or temperature following repeated low dose MDMA administration. The results indicate that factors other than 5-HT release (possibly dopamine release) are involved in the behavioural and physiological effects acute low doses of MDMA. Funding: R Rodsiri is financially supported by Royal Thai Government.

SO8

EFFECTS OF ACUTE ALCOHOL CONSUMPTION ON THE PROCESSING OF PERCEPTUAL CUES OF EMOTIONAL EXPRESSION

Ataya AA, Attwood. A, Benton C, Penton-Voak I, Munafò M. Department of Experimental Psychology, University of Bristol, 12a Priory Road, Bristol, BS8 ITU, aa6613@bris.ac.uk

Introduction: The mechanisms underlying the relationship between alcohol and aggression are not particularly well understood. Alcohol may facilitate aggression via alterations in the processing of the emotional content of facial cues. Studies have reported impairments in the processing of emotional facial cues in alcohol dependent participants (Townshend & Duka 2003). Recently, studies have shown modified processing of emotional facial cues after acute doses of alcohol in non-dependent social drinkers (Kano et al. 2003). The studies reported here further explore these effects using adapted psychophysical tasks in order to measure threshold sensitivity and categorization of emotional expressions, and examining the effects of alcohol dose and expectancy. The effect of alcohol dose on the processing of facial cues in male and female social drinkers was also examined. Both studies were funded by the Alcohol Education and Research Council (AERC) Method: Study 1 (n = 100) was a between-subjects balanced placebo design, in which participants attended one session (0.0 or 0.4 g/kg alcohol) and were randomly allocated to one of four groups; received alcohol/told alcohol, received alcohol/told placebo, received placebo/told alcohol, received placebo/told placebo. A psychophysical task in which two faces were presented for each trial (neutral vs emotional) was employed, and participants were required to identify the emotional face. This task enables identification of perceptual sensitivity to small changes in facial emotional expressions. Sad, happy and angry emotional expressions were tested in male and female target faces. Study 2 (n = 96) employed a similar design to Study 1 however a miscategorisation task was used. A target face was presented consisting of a morph between two emotional exemplars (e.g., happy and angry face) and participants were asked to identify the emotion of the face (i.e., happy or angry). This task was run separately for angry-happy and angry-disgusted facial morphs. Results: : Data were analyzed within 2x2x2x2 mixed model ANOVAs with drink (alcohol, placebo), expectancy (told alcohol, told placebo) and participant sex (male, female) as between subject factors and target sex (male, female) as a within-subjects factor. Emotion was also included as a within-subjects factor compromising there levels for Study 1 (happy, angry, sad) and two levels for Study 2 (angry-happy, angry-disgusted).Study one revealed a near significant emotion by drink interaction ($F [2, 178] = 2.94$, $p = 0.055$), with higher thresholds after alcohol for sad, but not happy or angry, emotional expressions .Study two indicated a significant emotion x target sex x alcohol interaction ($F [1, 72] = 5.52$, $p = 0.02$), with participants showing a bias towards categorisation of disgusted faces as angry after alcohol but not after placebo consumption. There were no effects of alcohol on the angry-happy categorisation condition (ps > 0.05) Conclusions: These data suggest that alcohol may differentially affect processing of different emotional expressions. In study one, after alcohol consumption, participants showed reduced sensitivity to recognising sad emotion in faces compared to placebo, but no effects were found for angry or happy emotions. Study two showed that alcohol may lead to individuals miscategorising negative (disgusted), but not positive (happy), faces as angry, which has implications for real world situations in which a negative facial expression may be erroneously perceived as provocative. However these miscategorisation effects were obtained in male, but not female, targets, possibly due to greater expectancy of alcohol-related aggression in men.

SO9

CHRONIC ROACCUTANE TREATMENT ALTERS SEROTONERGIC GENE EXPRESSION IN RAT RAPHE NUCLEI IN VIVO

Trent S, Bailey, SJ. Pharmacy & Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, s.trent@bath.ac.uk

Vitamin A and its derivatives (retinoids) play a host of roles in adult brain function (Lane & Bailey, 2005 Prog Neurobiol 75: 275). Roaccutane (13-*cis* retinoic acid, 13-*cis* RA) is a synthetic retinoid widely used for the treatment of severe cystic acne. However, its use is associated with adverse psychiatric events including depression, suicidal ideation and completed suicide (Hull & D'Arcy, 2003 , Am J Clin Dermatol 4:493). Previous work has shown that 13-*cis* RA induces depression-related behaviour in mice (O'Reilly et al, 2006, Neuropsychopharmacol 31: 1919) and increases the expression of the serotonin transporter (SERT) and the serotonin 1A receptor (5-HT1AR) protein *in vitro* (O'Reilly et al, 2007 Exp Biol Med 232: 1195). Retinoids mediate their effects by binding to nuclear retinoic acid receptors (RARs), which in turn regulate gene expression. The objective of this study was to determine whether chronic treatment with 13-*cis* RA *in vivo* alters the expression of the serotonergic genes tryptophan hydroxylase (TPH2), SERT and 5-HT1AR. Adult male Wistar rats were treated with either 1mg/kg 13-*cis* RA or 1ml/kg of vehicle (0.9% w/v saline:DMSO, 1:1 v/v) daily (ip) for 6 weeks (n=3 per group). At the end of treatment, brains were removed; the raphe nuclei dissected and total RNA extracted using Trizol. Expression of the genes of interest in rat raphe tissue and amplicon specificity were confirmed using one-step RT-PCR. Quantitative real-time RT-PCR with the threshold cycle method ($2^{-\Delta\Delta Ct}$) was used to determine the expression of the target gene mRNAs in treated raphe tissue relative to vehicle treated controls. In each case, gene expression was normalized to that of a housekeeping gene (rRNA). RARα and the dopamine D2 receptor were used as positive controls and expression in treated animals increased by 7.8 fold (± 4.5) and 27.1 fold (± 22.5) respectively. Although the expression of the 5-HT1AR was not changed (1.5 ± 0.6 fold) , the expression of SERT and TPH2 was significantly increased following 13-*cis* RA administration (6.4 ± 2.9 and 43.4 ± 24.3 fold respectively). Here we report for the first time a marked increase in the expression of TPH2 and SERT in rat raphe tissue following chronic 13-*cis* RA administration. Altered expression of TPH2 and SERT has been reported in depressed patients. The changes we see with 13-*cis* RA treatment may reflect pro-depressive changes in serotonergic neurotransmission.
ST is funded by a BBSRC studentship.

SO10

SELECTIVE SEROTONIN REUPTAKE INHIBITOR-REMITTED PATIENTS WITH GENERALISED ANXIETY DISORDER DO NOT SHOW AN INCREASE IN SYMPTOMS FOLLOWING ACUTE TRYPTOPHAN DEPLETION

Hince DA, Hood SD, Robinson H, Rich A, Potokar J, Davies SJC, Argyropoulos S, Nash J, Morris K, Potter J, Forward S, Morris L, Nutt DJ. Psychiatry and Clinical Neuroscience, University of Western Australia, 35 Stirling Hwy, Nedlands, Perth, 6009, dana.hince@uwa.edu.au

Selective serotonin reuptake inhibitors (SSRIs) are effective treatments for all DSM-IV defined anxiety disorders. Acute tryptophan depletion (ATD) is a dietary technique that transiently reduces plasma tryptophan levels, and brain serotonin synthesis. ATD increases the likelihood of a recurrence of anxiety-related symptoms in SSRI-remitted individuals with Panic Disorder (Bell et al., J Psychopharmacol. 2002;16(1):5-14) and Social Anxiety Disorder (Argyropoulos et al., Biol Psychiatry. 2004;1;56(7):503-9), following a disorder-specific provocation. This is consistent with the hypothesis that synaptic serotonin availability is important for SSRI efficacy. It is not known whether this is also the case for Generalised Anxiety Disorder (GAD). The effect of ATD on anxiety symptoms is most robustly shown when paired with a disorder-specific provocation. Inhalation of 7.5% CO2 induces symptoms in volunteers that are similar to that seen in generalised anxiety (Bailey et al., Depress Anxiety. 2005;21(1):18-25), and these responses are attenuated following 21 day treatment with paroxetine (Bailey et al., J Psychopharmacol. 2007;21(1):42-9).
We combined 7.5% CO2 inhalation and ATD to assess the effect of reduced serotonin availability in SSRI-remitted GAD SSRI–remitted patients with DSM-IV diagnosed GAD (n = 13; 6 males) were included in the study. Participants were tested twice separated by at least one week. On one occasion, an amino acid drink not containing tryptophan was consumed (depletion day). A similar drink, additionally containing tryptophan was taken on the alternate (control) day. The order of depletion was randomised and double-blind. Five hours post-drink, participants inhaled either 7.5% CO2 or air for 12-20 min, followed by the other gas. Gas order was only known to the researcher. Psychological responses were measured using the Spielberger State Anxiety Inventory (SSAI) and GAD-symptom Visual Analogue Scales (VASs) (worry, tension). Difference score data (baseline - CO2 or air scores) were analysed using repeated measures ANOVA. Inhalation of 7.5% CO2 significantly increased SSAI ($p<0.01$), VAS-worry ($p<0.01$), and VAS-tense ($p<0.001$) compared with air, irrespective of depletion condition. ATD did not alter the response to challenge on these measures (depletion x challenge interaction, all $F<1$) despite the substantial reduction in free tryptophan: large neutral amino acid ratio (depletion day: - 94% v control day: + 6%). Although SSRIs effectively treat GAD, these results suggest the mechanism of action is different to that in Panic and Social Anxiety Disorders. Successful SSRI treatment of GAD may involve long term receptor changes or alterations in other neurotransmitter systems downstream of serotonin.
Funding: Raine Medical Research Foundation Priming Grant, Perth and Wellcome Trust Project Grant, Bristol.

SO11

DECREASED AFFECTIVE REPRESENTATIONS OF CHOCOLATE IN THOSE AT RISK OF DEPRESSION COMPARED TO NORMAL HEALTHY VOLUNTEERS

McCabe C, Harmer CJ, Cowen P Psychiatry, Oxford Univ, Warneford Lane, Oxford OX37JX, ciara.mccabe@psych.ox.ac.uk

Anhedonia is an important diagnostic criterion for major depressive disorder (MDD) where patients report a loss of interest and pleasure in normally rewarding stimuli. This experiment aimed to investigate how the brain responds to both pleasant and unpleasant stimuli and to examine how this reward circuitry is affected by risk for depression.
We used fMRI to measure the response to the flavour and the sight of chocolate, and to their combination, and also an unpleasant flavour and picture in normal healthy volunteers compared to those recovered from depression. Subjective ratings of "pleasantness" "intensity" and "wanting" of each of the stimuli were also collected on each of the trials within the scanner.
SPM5 analyses showed that the sight of chocolate produced more activation in normal healthy volunteers in the midbrain ($p=0.01$ svc). Also there was increased ventral striatal activation to chocolate in the mouth in the normal healthy control group compared to the recovered depressed group ($p=0.01$ svc). Furthermore, a combination of a picture of chocolate with chocolate in the mouth produced a greater effect than the sum of the components (i.e. supralinearity) in the medial orbitofrontal cortex in the normal healthy volunteers compared to the recovered depressed group ($p=0.013$ svc). Despite no differences in subjective ratings between the two groups we found reduced activation in the reward related areas such as the ventral striatum and the medial orbitofrontal cortex in those recovered from depression compared to normal healthy never depressed volunteers. Understanding the mechanisms that underlie the pleasantness and unpleasantness of stimuli and how these mechanisms may be dysfunctional in those at risk of depression has implications for our understanding of the role of anhedonia as a trait vulnerability marker of depression.
This work has been sponsored by the Medical Research Council.

SO12

COMPARISON OF STRESS-INDUCED ALTERATIONS IN HIPPOCAMPAL MGLUR7 MRNA IN TWO ANIMAL MODELS OF DEPRESSION
O'Mahony CM, Bravo J, Dinan TG, Cryan JF. Pharmacology and Therapeutics, University College Cork, CORK, montyomahony@hotmail.com

Glutamatergic neurotransmission has been strongly implicated in the pathophysiology of emotional disorders such as anxiety and major depression. mGlu receptors are involved in modulating the activity of this neurotransmission in the CNS. The mGlu receptor 7 is found presynaptically and because it is abundantly distributed it may contribute to an array of functions in the CNS. For example, mGluR7 is known to be expressed in the hippocampus, a region critically involved in the modulation of anxiety and depression-related behaviour. Mice deficient in mGluR7 have an antidepressant-like behaviour and altered stress response suggesting a key role of this receptor in depression (Cryan et al., 2003, European Journal of Neuroscience,17(11):2409-17.;Mitsukawa et al., 2006, Neuropsychopharmacology, 31(6):1112-22.). The aim of the present study was to examine and compare the expression of hippocampal mGluR7 in two stress-related animal models of depression. Maternal separation during the early postnatal period is acknowledged to be a stressful status, resulting in a disturbance of normal CNS development. In adulthood, these rats display a depressive phenotype in several behavioural paradigms, as well as neuroendocrine and monoamine abnormalities. Wistar Kyoto (WKY) rats are a genetically selected strain that have a marked elevation in anxiety. As with the MS rats, they also elicit behavioural and hormonal responses suggestive of a depressive phenotype.
In this study, mGluR7 was localised in the hippocampus using in situ hybridisation. The hippocampal regions analysed for the presence of mGluR7 mRNA were the CA1, CA3 and the dentate gyrus. Using this procedure we have compared mGluR7 expression in MS and non-MS Sprague Dawley (SD) rats. The expression of mGluR7 in the WKY rat strain was also assessed to allow a comparison of an environmental and genetic model of depression to be made.
Our data demonstrate distinct expression patterns of mGluR7 within hippocampal regions studied. However, maternal separation stress did not alter this expression pattern. Future studies will involve examination of other brain regions implicated in depression, such as the cortex and the amygdala, which may further elaborate a specific role for mGluR7 in depression.
J.F. Cryan and T.G. Dinan are funded by a Science Foundation Ireland (SFI) grant awarded to the Alimentary Pharmabiotic Centre (APC).

PW01

GALANTAMINE-INDUCED IMPROVEMENTS IN COGNITIVE FUNCTION ARE NOT RELATED TO ALTERATIONS IN ALPH4BETA2 NICOTINIC RECEPTORS IN EARLY ALZHEIMER'S DISEASE AS MEASURED IN VIVO BY 2-[18F]FLUORO-A-85380 PET
Nathan PJ, Ellisa JR, Villemagne VL, Mulligan RS, Saunder T, Young K, Smith CL, Welch J, Woodward M, Wesnes KA, Savage G, Rowe CC. Brain Mapping Unit, Department of Psychiatry, University of Cambridge, Hills Road, Cambridge CB2 2GG, pn254@cam.ac.uk

The nicotinic acetylcholine receptor (nAChR) system plays a regulatory role in a number of cognitive processes. Cholinesterase inhibitors (i.e. galantamine) that potentiate cholinergic neurotransmission, improve cognitive function in Alzheimer's disease (AD), however the relationship between these effects and associated changes in nAChRs are yet to be established *in vivo*. 2-[^{18}F]Fluoro-A-85380 (2-FA) binds to nAChRs and with PET imaging provides a composite measure of receptor density and ligand affinity. This study aimed to; 1) quantify nAChRs *in vivo* in 15 drug naïve patients with mild AD before and after chronic treatment with galantamine, using 2-FA and PET, and 2) examine the relationship between treatment-induced changes in nAChRs and improvements in cognitive function.
Participants were non-smokers, and underwent extensive cognitive testing and a PET scan after injection of ~ 200MBq of 2-FA on two occasions (before and after 8-weeks, galantamine treatment (16mg/d)). A 3-day washout period preceded the second scan. Brain regional 2-FA binding was assessed through a simplified estimation of Distribution Volume (DV_S).
Performance on global measures of cognition significantly improved following galantamine treatment ($p < .05$). This improvement extended to specific cognitive measures of language and verbal learning. No significant differences in nAChR DV_S before and after galantamine treatment were found ($p > .05$). The treatment-induced improvement in cognition was not correlated with regional or global nAChR DV_S, suggesting that changes in nAChRs may not be responsible for the improvements in cognition following galantamine in patients with mild AD.
Source of funding: Austin Hospital Medical Research Fund.

PW02

ADVANCES IN UNDERSTANDING THE NEURAL, NEUROCHEMICAL AND MOLECULAR BASIS OF IMPULSIVITY.
Winstanley CA Psychology, University of British Columbia, 2136 West Mall, Vancouver, cwinstanley@psych.ubc.ca

Introduction: Impulsivity is a characteristic of human behaviour that can be both beneficial and detrimental to our everyday lives. High levels of impulsivity are socially unacceptable, and are associated with a number of psychiatric disorders including attention-deficit hyperactivity disorder, bipolar disorder, personality disorders and pathological gambling. Impulsivity can also contribute to the generation and maintenance of drug addiction. Understanding the neurobiological basis of impulsivity could therefore offer valuable insight into these disorders and stimulate the development of novel treatments. However, it is increasingly recognised that impulsivity is a non-unitary construct incorporating aspects of motor disinhibition and maladaptive decision-making. Through modeling these different aspects of impulsivity in laboratory rats, it has proved possible to understand more about the neurobiological basis of impulsive behaviour.
Methods: The effects of selective brain lesions, pharmacological challenges and molecular manipulations have been explored on performance of tasks such as the five-choice serial reaction time task and the delay-discounting paradigm. Novel behavioural tasks are also in development to provide insight into the neurobiological basis of gambling.
Results: Different forms of impulsivity in rodents are regulated by overlapping yet distinct neural circuitry, incorporating regions of the striatum, amygdala, thalamus and prefrontal cortices. There is some evidence to suggest that competing neural circuits act to promote impulsive or self-controlled choice. The precise role that an individual area plays in a specific aspect of impulsivity likely reflects the contributions made by these regions to other aspects of goal-directed behavior, and also their functional neurochemical regulation by monoamines such as dopamine and serotonin. Recent work exploring the molecular basis of impulsivity and addiction may also shed some light on the molecular footprint of drugs which modulate impulse control in terms of kinase and transcription factor activation.
Conclusions: Improving our understanding of how key nodes in impulsivity circuitry are modulated by different neurotransmitter systems may explain why types of impulsive action and impulsive choice can be differentially affected by certain drugs. Such information can improve the treatment of impulse control disorders by recognising that the symptom profile of the patient can affect their response to certain pharmacotherapies.

PW03

AETIOLOGY AND CLINICAL RELEVANCE OF HPA AXIS DYSFUNCTION IN CHRONIC FATIGUE SYNDROME
Cleare AJ Department of Psychological Medicine, Institute of Psychiatry, 103 Denmark Hill, SE5 8AZ, a.cleare@iop.kcl.ac.uk

Chronic Fatigue Syndrome (CFS) is a common and disabling problem; whilst most likely of biopsychosocial origin, the nature of the pathophysiological components remain unclear. Dr Cleare has researched extensively on the contribution of biological factors to the aetiology and treatment of Chronic Fatigue Syndrome, and in this presentation focuses on the Hypothalamo-Pituitary-Adrenal (HPA) axis. The core deficit found in CFS is reduced cortisol output in at least some patients. Our RCT of low dose hydrocortisone replacement therapy demonstrated reduced fatigue on active treatment suggesting that low cortisol is a maintaining factor linked to symptom production or persistence. There is evidence for heightened negative feedback and glucocorticoid receptor function, and for impaired ACTH and cortisol responses to a variety of challenges. However, there is no evidence for a specific or uniform dysfunction of the HPA axis. Given the many factors that may impinge on the HPA axis in CFS, such as inactivity, sleep disturbance, psychiatric comorbidity, medication, weight changes and ongoing stress, it seems likely that HPA axis disturbance is heterogeneous and of multifactorial aetiology in CFS. This is supported by our prospective cohort studies of post operative and glandular fever patients that do not find HPA axis changes early on in the development of fatigue states, whereas we do find HPA axis changes after several years of illness. It is likely that HPA axis changes occur late in the course of illness secondary to these other factors in CFS, raising the possibility that addressing these factors could act to normalize HPA axis function and remove its influence in symptom maintenance. We have recently studied 103 patients with CFS undergoing CBT, and found that cognitive behavioural therapy, which reverses many of these factors, can indeed increase cortisol levels. We suggest that for most patients CBT is a likely to prove a safer and more enduring method to reverse HPA dysfunction in CFS than steroid replacement therapy. Also of note was that CBT proved less effective in those who had a more disturbed HPA axis function prior to therapy, suggesting that longer or modified therapy, or alternative treatment methods, may be necessary in these patients.

PD01

TARGETED DELETION OF THE GABRA2 GENE ENCODING α2-SUBUNITS OF GABAA RECEPTORS FACILITATES PERFORMANCE OF A CONDITIONED EMOTIONAL RESPONSE, AND ABOLISHES ANXIOLYTIC EFFECTS OF BENZODIAZEPINES AND BARBITURATES
Dixon CI, King SL, Stephens DN Psychology, University of Sussex, Brighton, BN1 9QG, c.i.dixon@sussex.ac.uk

GABAA receptors containing 2-subunits are heavily represented in brain areas associated with conditionedα anxiety, particularly the amygdala complex. Mice with point-mutated α2 GABAA receptor subunits (rendering them benzodiazepine (BZ) insensitive) are resistant to BZ anxiolytic-like effects in the conditioned emotional response (CER) test, but show normal anxiolytic effects of a barbiturate. We investigated the consequence of deleting the α2-subunit on acquisition of the CER, and on the anxiolytic efficacy of a BZ, diazepam, and a barbiturate, pentobarbital. α2 knockout (KO) and wildtype (WT) mice (n = 10) were trained in a CER task, in which lever-pressing for food was suppressed during the presentation of a compound light/tone conditioned stimulus (CS+) that predicted footshock. The amplitude of the footshock increased every 3 sessions until sufficient suppression of lever pressing in response to the CS+ was evident. The ability of diazepam (WT n = 7; KO n = 8) and of pentobarbital (WT n = 8; KO n = 7) to reduce suppression during the CS+ was interpreted as an anxiolytic response. All data were analysed using two-way, mixed design ANOVAs. There were no differences between the genotypes in shock sensitivity, as assessed by their flinch α2 KO mice showed a greater suppression of lever pressing ,responses. However, than WT littermates in the presence of the CS+ at shock levels between 0.25 and 0.45 mA (significant shock level by genotype interaction, $p < 0.01$) Diazepam (0, 0.5, 1 and 2 mg/kg) exerted a dose-dependent anxiolytic-like effect in WT mice, reaching significance at 2 mg/kg, but no such effect was seen in KO mice (significant dose by genotype interaction, $p< 0.05$). Similarly, although pentobarbital (20mg/kg) reduced the ability of the CS+ to lower lever-pressing rates in WT mice, this effect was not seen in the KO (significant dose by genotype interaction, $p < 0.05$). These findings suggest that α2-containing GABAA receptors mediate the anxiolytic effects of barbiturates, as well as benzodiazepines, and that they may be involved in neuronal circuits underlying conditioned anxiety.
Thanks to BBSRC and British Pharmacological Society for support.

PD02

ENDOCANNABINOID MODULATION OF CONDITIONED FEAR IN THE PRESENCE AND ABSENCE OF NOCICEPTIVE TONE
Roche M, Finn DP. Department of Pharmacology & Therapeutics, NCBES Neuroscience Cluster and Centre for Pain Research, National University of Ireland, Galway. michelle.roche@nuigalway.ie

The endocannabinoid system is comprised of cannabinoid receptors (CB_1 and CB_2), endogenous ligands for these receptors (endocannabinoids) and metabolising enzymes (e.g. fatty acid amide hydrolase). Evidence demonstrates an important role for the endocannabinoid system in the acquisition, expression and extinction of conditioned aversive behaviour. Pharmacological blockade or genetic deletion of the CB_1 receptor attenuates extinction of contextually-induced freezing in rodents (Marsicano et al., 2002 Nature 418, 530–534). In addition, systemic administration of the CB_1 receptor antagonist rimonabant (SR141716A) attenuates short-term extinction of contextually-induced freezing and 22KHz ultrasonic vocalisation, potentiates formalin-induced reductions in fear behaviours and abolishes fear-conditioned analgesia (Finn et al., 2004 Eur J Neurosci 20, 848–852). The focus of our studies at present involves investigating the role of the endocannabinoid system in various supra-spinal sites in the expression of contextually-induced aversive behaviour and analgesia association with conditioned contextual fear (fear-conditioned analgesia) in rats. The basolateral amygdala (BLA) and periaquaductal grey (PAG) are critical regions involved in modulating fear and pain behaviour. Both expression and extinction of conditioned fear is accompanied by increased levels of the endocannabinoids in the BLA[1] and cannabinoids in the PAG are involved in modulating aversive responding (Finn et al., 2003 Neuropharmacology 45, 594–604) and unconditioned stress-induced analgesia (Hohmann et al., 2005 Nature 435, 1108–1112). We have demonstrated that unilateral intra-BLA administration of rimonabant attenuates the short-term extinction of contextually-induced fear behaviour, an effect accompanied by dopamine alterations in the PAG and hippocampus (Roche et al., 2007 Eur J Neurosci 26, 2643–2653). In addition, administration of rimonabant, uni- or bi-laterally, into the BLA attenuates formalin-evoked decreases in freezing and ultrasonic vocalisation in early part of the fear expression trial. Furthermore, intra-BLA administration of rimonabant does not alter fear-conditioned analgesia but reduces formalin-induced nociceptive behaviour. Administration of rimonabant into the dorsal PAG does not alter fear-related behaviour but reduces formalin-evoked nociception. In contrast, intra-PAG administration of the fatty acid amide hydrolase inhibitor, URB597 enhances the duration of contextually-induced freezing and ultrasound emission in the absence but not presence of nociceptive tone. In conclusion, the present findings demonstrate an important role for the endocannabinoid system in the endogenous fear and analgesic systems and provide some insights into potential sites and mechanisms involved. These results may have implications for the understanding and treatment of conditions associated with anxiety and pain co-morbidity.
Work supported by Irish Health Research Board

PD03

EFFECTS OF 7.5% CO_2 INHALATION ON PROCESSING OF FACIAL CUES OF EMOTIONAL EXPRESSION

Cooper RM[1], Munafò MR[1], Bailey JE[2], Diaper A[2], Benton CP[1], Penton-Voak IS[1], Nutt DJ[2]
1. Department of Experimental Psychology, University of Bristol, 12a Priory Road, Bristol BS8 1TU, United Kingdom. 2. Psychopharmacology Unit, University of Bristol, Dorothy Hodgkin Building, Whitson Street, Bristol BS1 3NY, United Kingdom.

Theoretical accounts suggest that a core cognitive feature of anxiety is increased vigilance to threat-related stimuli, and that this is a key factor in the etiology and maintenance of anxiety disorders. This has, however, seldom been investigated experimentally. We therefore sought to investigate the cognitive impact of experimentally-induced anxiety, by means of an unconditioned 7.5% CO2 challenge, on attentional bias for positive and negative facial cues of emotional expression. Male and female participants (n = 20) attended a single testing session, and completed a visual probe task to assess attentional bias for fearful and happy facial expressions. The order of presentation of CO2 and air was randomized across participants. A 2 × 2 × 2 × 2 mixed-model ANOVA of visual probe reaction time data indicated a difference in attentional bias score for fearful ($p = 0.014$) but not happy ($p = 0.91$) cues in the CO2 condition compared with air, reflecting increased avoidance of fearful cues in the CO2 condition. Our data suggest that experimentally-induced anxiety results in an allocation of visual attention away from threat-related material (i.e., avoidance). The subjective effects produced by the inhalation of 7.5% CO_2 in this study are comparable with other findings from our group. This is the first demonstration that an unconditioned anxiety-provoking stimulus can lead to a change in the cognitive processing of threat-related material. These data are discussed in the context of current theoretical models of cognition and anxiety.

PD04

ROLE OF SEROTONIN IN THE ASSOCIATION OF PANIC DISORDER AND HYPERTENSION – BUILDING A MODEL THROUGH CLINICAL AND BIOLOGICAL STUDIES

Davies SJC, Lowry CA, Nutt DJ. Psychopharmacology Unit, University of Bristol, Dorothy Hodgkin Building, Whitson Street, Bristol BS1 3NY Simon.Davies@bristol.ac.uk

An association between panic disorder and hypertension has been reported by ourselves (Davies 1999) and others (Weissman 1990). Using information derived from clinical and biological studies, with reference to emerging preclinical data, we have constructed a model illustrating neurochemical mechanisms and neuroanatomical pathways potentially involved in this association.
Increased catecholamine spillover from key organs (Wilkinson 1998, Esler 1988) and reduced heart rate variability, both of which are indices of autonomic dysfunction, have been reported in both hypertension and panic disorder. On factor analysis of panic attack symptoms experienced by hypertensives and normotensives a dominant autonomic symptom factor was found, which was significantly associated with hypertension on regression analysis (Davies 2008).
The neurotransmitter serotonin may underlie this autonomic dysfunction. Serotonin promoting antidepressants, recognised treatment for panic disorder, have cardioprotective effects in depressed patients with heart disease and lowered blood pressure significantly in hypertensives with panic disorder (Polyak 2001). Tryptophan depletion in patients with treated panic disorder led to significantly greater blood pressure and psychological responses to stress challenges than under non-depleted conditions, confirming serotonin's role in buffering blood pressure responses to stress in panic disorder (Davies 2006).
The model incorporates evidence that stimulation of the rat midbrain ventrolateral periaqueductal gray (VLPAG) induces hypotension and sympathoinhibition, preventable by blockade of 5-HT1A receptors in the RVLM, a brainstem region involved in stress-induced sympathoexcitatory responses (Johnson 2004). Thus, serotonergic neurons within the VLPAG may moderate the activity of RVLM neurones, including C1 adrenergic neurones. Consistent with this, injections of serotonin or 5-HT1A receptor agonists in the RVLM region inhibited pre-existing hypertension in rats (Bago 1999). Some serotonergic neurons within the VLPAG are thought to project to the dorsal periaqueductal gray which may account for effects of serotonin moderating agents on behavioural aspects of panic disorder in addition to those on the stress induced autonomic responses mediated via the RVLM. Deficits in serotonergic neurotransmission in VLPAG neurons could therefore be implicated in the association of hypertension and panic disorder. We propose that neural systems underlying hypertension and behavioural and autonomic components of panic responses converge at the level of the brainstem and that these brainstem structures are under inhibitory control by serotonergic neurons in the VLPAG, which serve as an important sympathomotor control system.

GL1

MATERNAL CARE, GENE EXPRESSION AND EPIGENETIC PROGRAMMING OF NEUROENDOCRINE SYSTEMS

Meaney MJ Sackler Program for Epigenetics & Psychbiology, McGill University, LaSalle Blvd, Montreal Quebec Canada H4H 1R3, michael.meaney@mcgill.ca

Maternal care alters the development of adaptive behavioral and endocrine responses to stress in the rat; an example of maternally-regulated, phenotypic plasticity. The mechanisms for these 'maternal effects' involve stable changes in the expression of genes in brain regions that mediate stress reactivity as well as regions involved in the processing of information related to the stressor. Notable are the effects on systems that regulate central corticotrophin-releasing factor (CRF) synthesis and release from the hypothalamus and amygdala. The adult offspring of mothers that exhibit increased pup licking/grooming (LG) show increased glucocorticoid receptor mRNA throughout the hippocampus. The differences in glucocorticoid receptor expression are associated with effects at the level of both negative feedback inhibition and HPA responses to stress; the offspring of High LG dams show increased hippocampal glucocorticoid receptor expression, enhanced negative feedback regulation and more modest HPA responses to stress. These findings suggest that maternal care acts to 'program' HPA responses in the offspring through effects on systems that regulate CRF activity. Adoption studies reveal direct effects of maternal care. Recent studies focus on the mechanisms for these effects by examining DNA methylation within a brain-specific glucocorticoid receptor gene promoter. These studies reveal sustained effects of maternal behavior on the cytosine methylation of the consensus binding sequences for specific transcription factors that regulate glucocorticoid receptor gene expression. Pharmacological manipulations that reverse the maternal effect on cytosine methylation of the glucocorticoid receptor promoter eliminate the effect at the level of both glucocorticoid receptor expression and HPA responses to stress. These findings suggest that differential methylation mediates the sustained effects of maternal care on glucocorticoid receptor gene expression. The maternal effect on DNA methylation appears to involve an active demethylation process at specific CpG dinucleotides that is targeted by intracellular processes sensitive to the tactile stimulation associated with pup licking. Such a process may reveal experience-dependent plasticity in the chemistry of the DNA and chromatin structure

Journal of Psychopharmacology

Notes for Contributors

Publication statement

Papers submitted to this Journal for publication are considered on condition that they have been neither submitted elsewhere, nor published elsewhere other than in abstract form. The Editors do not enter into correspondence about papers considered unsuitable for publication; their decision is final.

Copyright. The author must assign copyright to the British Association for Psychopharmacology on acceptance of the paper for publication. All authors of a multi-authored paper are required to sign the assignment of copyright form. Those who are unable to assign their copyright will be sent an appropriate version of the assignment form. The author(s)' freedom to re-use their material in other works they are writing or editing is not impeded by the assignment of their copyright.

On acceptance of manuscripts for publication, all authors will be required to sign a Certification of Authorship form and a Conflict of Interest statement. This will be forwarded for signature on acceptance, together with the assignment of copyright form. Publication cannot be guaranteed until these completed forms have been received.

Submission of manuscripts

All submissions should be made online at the *Journal of Psychopharmacology* SAGETrack website http://mc.manuscriptcentral.com/jop. Please log onto the website. If you are a new user, you will first need to create an account. This is a three-step system that takes a matter of minutes to set up. Log-in information is sent via email immediately upon completion. Full instructions for uploading the manuscript are provided on the website. If you have already created an account but have forgotten your details type your email address in the 'Password Help' to recieve an emailed reminder.

Submissions should be made via the Author Center and the 'Click here to Submit a New Manuscript' option. For questions and a user guide, please use the 'Get Help Now' button at the top right of every screen. Further help is available through ScholarOne's® Manuscript Central™ customer support at +1 434 817 2040 x 167. If you would like to discuss your paper prior to submission, please email: j-psychopharm@bristol.ac.uk

Please ensure that your Microsoft Word or RTF document does NOT include a title page, an abstract, or page numbers: the *Journal of Psychopharmacology* SAGETrack system will generate them for you, and then convert your manuscript to PDF for peer review. Furthermore, it is imperative that authors remove from their submissions any information that will identify them or their affiliations to reviewers. All correspondence, including notification of the Editor's decision and requests for revisions, will be by email.

Publication categories

The Journal considers the following kinds of article for publication:

1. Original research reports, describing new experimental findings:
   (a) Full papers
   (b) Short reports requiring rapid dissemination
2. Review articles
   (a) General reviews that provide a synthesis of an area of psychopharmacology;
   (b) Perspectives – brief overviews, which are 4–6 printed pages in length including references, that address important new areas of general interest;
   (c) Critiques – focused and provocative reviews that are followed by a number of invited commentaries, with a concluding reply from the main author.
3. Letters to the Editors. Readers' letters should address issues raised by published articles or should report significant new findings that merit rapid dissemination. The decision to publish is made by the Editors, in order to ensure a timely appearance in print.
4. Book Reviews – to obtain an up-to-date list of books for review, please email: J-Pyschopharm@bristol.ac.uk

Manuscript presentation

Journal of Psychopharmacology subscribes predominantly to the editorial preferences expressed in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals issued by the International Committee of Medical Journal Editors. Articles submitted for publication in Journal of Psychopharmacology should be typed on one side of the sheet only, in double spacing throughout (this includes notes and references) and with generous margins all round. Each page should be numbered and identified with a shortened version of the title.

ELEMENTS WITHIN THE MANUSCRIPT

Cover sheet. Preface your paper with a cover sheet that carries the title, authors' names, addresses and affiliations; plus telephone, fax and email numbers for the corresponding author. Unless there are instructions to the contrary, the corresponding author will receive the article offprints and the voucher copies of the printed journal (see below). On this or the next following page list sources of support in the form of grants, equipment, drugs, or all of these, and any disclaimers.

Covering letter. Please attach to every submission a letter confirming that all authors have agreed to the submission and that the article is not currently being considered for publication by any other print or electronic journal.

Abstract. Provide an abstract of 150–250 words. The abstract should state the purposes of the study or investigation, basic procedures, main findings and the principal conclusions. Emphasize new and important aspects of the study or observations.

Key words or key word phrases, to accompany the abstract should not exceed 10. They should, if possible, be drawn from the MeSH list of Index Medicus and be chosen with a view to useful cross-indexing of the article.

Text. Subdivide your article with appropriate headings. Use no more than three levels of subdivision. For observational and experimental articles the first level will usually consist of the standard heads: Introduction, Methods and Materials, Results and Discussion. Other types of articles will benefit from less formulaic formats.

Acknowledgements. Between the end of the text and the start of the References section, please acknowledge sources of financial and material support, and those who have contributed intellectually, with their consent. Please refer to the Journal's Conflict of Interest statement.

References. Authors should be cited using the name and date convention, in date order: (Prewett and Green, 1989; Becker, 1992; Marlowe et al., 1994, Table 2). List authors up to two; for three or more use the name of the first author plus et al. References should have been checked against the original documents, and must be carefully crosschecked to ensure the text citation matches that in the reference list. Style of presentation in the reference list should follow the general pattern given below (for further examples see the Journal texts). Journal abbreviations should conform with the style adopted in the *Cumulated Index Medicus*.

Journal references:
Rickels K, Schweizer E, Clary C, Fox I, Weise C (1994) Nefazdone and imipramine in major depression: a placebo-controlled trial, Br J Psychiatry 164: 802–805

Book references:
Eysenck M W (1992) The nature of anxiety. In Gale A, Eysenck M W (eds), Handbook of individual differences: biological perspectives. John Wiley, Chichester
Maxwell S, Delaney H (1990) Designing experiments and analysing data: a model comparison perspective. Wadsworth, Belmont, CA

Tables should be typed on separate sheets. They must all be cited in the text, carry brief but complete titles, and be numbered consecutively with Arabic numerals. Keep rules (horizontal only) to a minimum.

Figures should be used with discretion to clarify (not duplicate) the text. They should be cited in the text, using Arabic numerals, and their approximate location in the paper clearly indicated [Figure 1 near here]. Please supply artwork electronically wherever possible. They should, for preference, be supplied at reproduction size (single- or double-column width), and lettering should be no smaller than 8 pt type. Computer-generated artwork must be submitted as laser printed output at a resolution of 600 dots per inch. Avoid the use of computer-generated tints; substitute hatching in their place. Photographs should be supplied as sharp black and white glossy prints, not laser output photos. Where possible artwork should also be supplied on disk as EPS, TIF or nature drawing package format.

Figures (both photographs and artwork) should be identified lightly on a label attached to the back of the original, and clearly on a set of accompanying photocopies, with an arrow to indicate the top edge of the figure. Do not write directly on the back of any photograph or figure, do not attach paper clips or in any other way distort or scratch the image area. Photomicrographs should have internal scale markers; any symbols, arrows or letters used should be clearly visible against the background. Legends should be explanatory but succinct. They should carry the Arabic numerals applicable to the figures, and be provided as a separate typed (double-spaced) list at the end of the paper, along with the figures themselves. Artwork can be printed in colour at the cost of £300 per page.

ELEMENTS OF OVERALL MANUSCRIPT STYLE

Units of measurement. Express these in SI and metric units; older conventional units may be added in parentheses. *Nomenclature*. Use the generic or chemical name of any drug, in lower case; the specific trade name (capitalized) may be given in parentheses after the first text reference.

Abbreviations and symbols. Use standard abbreviations, and define them in full in the first instance unless they are standard units of measurement. Avoid any use of abbreviations in the article title and abstract.

Disks. After final approval for publication, authors will be required to submit the accepted version on disk. These should be Apple Mac or IBM-compatible. The final version of the hardcopy and the file on disk must be the same.

Ethics. When reporting experiments on human subjects, indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) or with the Declaration of Helsinki 1975, revised Hong Kong 1989. Do not use patients' names, initials or hospital numbers, especially in illustrative material. When reporting experiments on animals, indicate whether the institution's or the National Research Council's guide for, or any national law on, the care and use of laboratory animals was followed.

Permissions. Authors must obtain written permission from the copyright holder (original author or publisher) to include in their paper any previously published material. Credit should follow the style and location requested by the copyright holder.

On publication

Access to 25 free e-prints will be provided; the corresponding author will receive five complimentary copies of the journal.

OnlineFirst

OnlineFirst articles are the definitive final version, and are fully searchable and citable using their DOI. When you cite an Online first article, give the paper's DOI at the end of the citation. For example,
Author(s) J Psychopharmacol OnlineFirst, day month year (doi:10.1177/0269881 106066333).
After print publication, you should give the DOI as well as the print citation, to enable readers to find the paper in print as well as online.

Journal of Psychopharmacology

Abstract Supplement to Volume 22 No 5 July 2008

Sage Science Press
www.bap.org.uk
http://jop.sagepub.com