These papers were presented at the Summer Meeting of the

BRITISH ASSOCIATION FOR PSYCHOPHARMACOLOGY

28 – 31 July, Harrogate, UK

Indemnity

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S01

SOCIAL BEHAVIOUR AND TOP-DOWN CONTROL IN AUTISM

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Introduction: Autism spectrum condition is characterised by difficulties in social interaction and communication. In recent years, there has been a major focus on the role of mirror neurons in autism and the possibility that imitation behaviour provides a marker of mirror neuron function. Here, I present data arguing against this thesis.

Method: I will review brain imaging and behavioural studies showing that mirror neuron systems are intact in autism. These include a systematic review of neuroimaging studies and new behavioural studies of imitation in children with autism. Results: The systematic review reveals no evidence that mirror neuron systems are abnormal in autism. The behavioural studies show that children with autism can imitate goal directed actions but do not overimitate actions in order to affiliate with other people.

Conclusions: These data suggest that brain and cognitive systems for top-down control of social responding are abnormal in autism. There are also important links between top-down control and social motivation. This new model of autism can help to move the field forwards.

S02

PRENATAL VALPROATE AS A RODENT MODEL FOR AUTISM

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Social dysfunction represents a key feature in several psychiatric disorders, including autism, schizophrenia, depression and drug dependence. Unfortunately this most debilitating human behavioural disorder remains largely untreated by current medication. Social interaction is performed by all species of the animal kingdom and their complex social interactions are an essential part of survival of the organism. It is thus imperative for the development of effective drug treatments of social dysfunctions that we study social behaviour across species, which can later be translated to the human condition. Recent data from our team suggest that prenatal exposure of valproate (VPA) could provide an animal model for autism and or reduced social interaction. In the clinic, it is well known that prenatal exposure to the antiepileptic drug VPA is associated with a high risk factor for cognitive dysfunction in the offspring, which may include autism spectrum disorder. In our model, pregnant rats received a sub-chronic daily administration of VPA at 20 or 100mg/kg from day 9 until the end of pregnancy. This model is thus designed to mimic the human clinical condition with VPA administered chronically to pregnant women with epilepsy. Our model differs from the original VPA model in which only one single high neurotoxic dose of VPA (600mg/kg) is injected at day 12.5 of pregnancy. This model shows reduced numbers of neurones and various behavioural changes. In contrast, we observe increases in neuronal cortical cell numbers in the offspring, a finding we suggest may be related to the stimulatory trophic effect of GABA on the migration of early embryonic cells in the fetal brain tissue. Our finding of increased cell number is consistent with the results of Courchesne et al (Courchesne E, et al. Neuron number and size in prefrontal cortex of children with autism. JAMA. 2011;306(18):2001-2010) reporting an abnormal excess of neurones in the prefrontal cortex of autistic males. In our model, we also observe decreased juvenile play behavior in young, male VPA rats, consistent with the social deficit observed in human autism. These VPA-rats had a marked decrease in the level of striatal serotonin, a finding consistent with the involvement of serotonin in social play behavior. The adult VPA rats showed enhanced performance in the object recognition test. These findings and our latest results on the receptor binding profile of the essential social neurotransmitters oxytocin and vasopressin will be presented.

S03

THE NEUROBIOLOGY OF SOCIAL PLAY BEHAVIOR IN RATS

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In between weaning and puberty, the young of all mammalian species, including humans, display a characteristic form of social interaction known as social play behaviour or rough-and-tumble play. This form of social behaviour is highly rewarding and essential for the development of social and cognitive skills. Indeed, social traumas in early life greatly enhance the risk for later psychopathology. Conversely, social play is known to be impaired in child and adolescent psychiatric disorders, including autism and early-onset schizophrenia. Despite its abundance and importance, however, the neural underpinnings of social play are incompletely understood. Recent pharmacological analysis of the neurotransmitter systems involved has revealed an important role for interacting opioid, cannabinoid and dopaminergic neurotransmission in the modulation of social play behaviour. This is in keeping with the rewarding properties of social play, as these neurotransmitter systems have been widely implicated in the positive emotional properties of food, sex and drugs. Investigation of the brain regions involved has identified the nucleus accumbens and basolateral amygdala, respectively, as important sites of action for opioids and endocannabinoids on social play. On the other hand, psychostimulant drugs, such as amphetamine and methylphenidate, reduce social play through stimulation of alpha2-adrenoceptors. These effects are exerted through the anterior cingulate cortex, amygdala and habenula. Consistent with a role for corticostriatal mechanisms in social play, pharmacological inactivation of medial prefrontal cortex, dorsomedial striatum and nucleus accumbens core alters social play behaviour. Last, our recent work has indicated that the positive subjective (‘pleasurable’) and incentive motivational properties of social play can be pharmacologically dissociated. In conclusion, there is emerging evidence to indicate that social play behaviour is modulated through opioid, cannabinoid and monoamine neurotransmission within limbic corticostriatal mechanisms that are involved in reward, motivation and cognitive control over behaviour. Identifying the neural underpinnings of social play behaviour will increase our understanding of normal social development as well as of the etiology of child and adolescent psychiatric disorders.
BDNF-TRKB SIGNALING IN STRIATAL ENKEPHALINERGIC NEURONS CONTROLS INHIBITION OF LOCOMOTOR BEHAVIOUR

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Huntington’s disease (HD) is a progressive neurodegenerative disorder caused by an expansion of the polyglutamine repeat at the huntingtin N-terminus, and is characterized by progressive motor impairment and cognitive dysfunction. This is due to the fact that the disease firstly causes degeneration of cells in the basal ganglia, which controls movement, emotion, and cognitive ability. In fact, although huntingtin (htt) mutation is widely expressed, the medium-sized spiny striatal neurons (MSN) undergo selective degeneration. In particular, the subpopulation expressing enkephalin and the D2 dopamine receptor, originating the indirect pathway (Gerfen CR (1992), Trends Neurosci 15: 133-139), are the first to be affected (Richfield et al., (1995), Ann Neurol 38: 852-861). Brain derived neurotrophic factor (BDNF) is believed to play a pivotal role in HD pathogenesis by changes in cortical Bdnf expression levels, and/or anterograde transport induced by mutant htt leading to preferential striatal neurons vulnerability (Altar et al. (1997), Nature 389, 856-860). Zuccato & Cattaneo (2007), Proc Neurobiol 81, 294-330). However, since ablation or alteration of Bdnf levels affects first of all cortical physiology (Kuhn, A. et al. Hum Mol Genet. (2007). 16, 1845-1861), this confounds the action of Bdnf anterogradely transported from the cortex to other regions of the brain, such as its striatal targets. Therefore, to address the physiological role of BDNF/TrkB signaling in striatal MSNs we have selectively removed TrkB from enkephalergic striatal target by generating a new BAC transgenic Cre-mouse line carrying Cre recombinase under the control of the Preproenkephalin promoter. Mutants show that BDNF is not required for survival and/or morphology of MSNs. Selective deletion of BDNF/TrkB signaling in neurons of the indirect pathway induces decreased expression of enkephalin, spontaneous and drug-induced hyperlocomotion. These data suggest that BDNF/TrkB signaling in striatal enkephalergic neurons controls inhibition of locomotor behaviour exerted by the indirect pathway MSNs. Therefore, these findings are highly relevant as they uncover a unique function of BDNF/TrkB signaling in striatal neurons controlling motor behavior, and clearly establish that altered BDNF/TrkB signaling in these neurons has no effect on survival and/or maintenance of these neurons. Sources of financial sponsorship This work was supported in part by grants from the European Union (EU FP6 MEMORIES, 037831; EU FP6 StemStroke, 037526) to LM; (EU FP7- Thematic priority HEALTH, 222918), Grants from Programmi di Ricerca Scientifica di Rilevante Interesse Nazionale PRIN2008, and Progetti Finalizzati Multicentrici Programma Neuroscienze Compagnia di San Paolo to PC.

BDNF INTERACTS WITH IMMATURE NEURONS IN THE HIPPOCAMPUS DURING MEMORY AND PATTERN SEPARATION

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Successful memory involves not only remembering information over time but also keeping memories distinct and less confusable. The computational process for making representations for similar input patterns more distinct from each other has been referred to as ‘pattern separation’. Although adult-born immature neurons have been implicated in pattern separation, the precise role of these neurons and associated molecules in the processing of pattern-separated memories is unknown. Using a new paradigm that allowed us to manipulate the load for pattern separation and to study the effects of manipulations at different stages of memory, we provide experimental evidence that BDNF-dependent pattern separation occurs in the dentate gyrus during the encoding/consolidation, but not the retrieval stage of memory. We also found that BDNF may be expressed on an “as-needed” basis for pattern separation and we finally show that, in the service of consolidation of pattern-separated memories, BDNF acts on immature neurons and requires the activation of NMDA receptors.
S07

EFFECT OF THE BDNF VAL66MET POLYMORPHISM ON SYNAPTIC AND COGNITIVE FUNCTION IN HEALTHY SUBJECTS

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Introduction: Clinical trials in Alzheimer’s disease (AD) are extremely challenging. Its slow progression and huge patient heterogeneity require lengthy studies with a large number of patients. Lack of sensitive and reliable biomarkers for its core pathophysiology makes it difficult to track disease progression and drug efficacy. Increasing evidence suggests that synaptic dysfunction is a key pathophysiological hallmark for AD. Success of a “synaptogenic” therapy depends on whether synaptic dysfunction and repair/regeneration can be measured in clinical studies. In this context, the discovery of the val66met polymorphism in the human brain-derived neurotropic factor (BDNF) gene provides a unique opportunity. Cellular, imaging and behavior studies have revealed that the BDNF-met allele is associated with a decrease in activity-dependent BDNF secretion, leading to impairments in synaptic plasticity and synaptogenesis, as well as various cognitive processes including episodic memory. Assuming that a reduction in BDNF secretion in BDNF-met carriers leads to proportional impairment in synaptic function in the brain, we systematically compared a number of “synaptic” and cognitive markers in individuals carrying val/val, val/met, met/met genotypes.

Methods: 60 healthy subjects (20 val/val; 20 val/met and 20 met/met) were recruited from GSK clinical unit and Cambridge Biorepository databases. Synaptic activity and cognition were quantified using Imaging (electrophysiology (resting EEG and Event Related Potentials; ERPs), functional Magnetic Resonance Imaging; fMRI) and behavioural (CANTAB neuropsychological tests, fear learning and motor learning tasks) methods. The study was conducted at the GSK Clinical Unit Cambridge (CUC).

Results: A number of BDNF sensitive markers of synaptic activity were identified. Compared to val homozygotes, met carriers (val/met and met/met) showed evidence of “inefficient” synaptic activity as demonstrated by impaired EEG activity (i.e. decreased delta/theta power and phase synchrony) during cognitive processing in an error related negativity task of executive function (all p<0.05), increased frontal, central, temporal and parieto-occipital relative slow wave EEG power in the theta frequency (all p<0.05), and increased hippocampal (p=0.05) and inferior frontal (p= 0.004) and parietal (p=0.009) cortical activation during retrieval of an episodic memory task. There was no evidence for a met load effect on any of the markers examined.

Conclusion: Using the BDNF val66met polymorphism, we have identified several electrophysiological and functional imaging biomarkers that could sensitively measure synaptic changes in the human brain, using relatively small number of subjects. These endpoints may potentially be used in early Phase 1 or 2 clinical trials in pre-clinical AD to monitor drug effects on synaptic activity or cognitive function. This study was funded by GlaxoSmithKline Pharmaceuticals.

S08

MODULATION OF AB AMYLOID-RELATED COGNITIVE DECLINE BY BRAIN-DERIVED NEUROTROPHIC FACTOR VAL66MET POLYMORPHISM IN PRECLINICAL ALZHEIMER’S DISEASE

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Background: Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism has previously been implicated in Alzheimer’s disease (AD)-related cognitive impairment. We aimed to determine whether BDNF Val66Met moderates Aβ amyloid-related cognitive decline, reduction in hippocampal volume, and Aβ amyloid accumulation in healthy older adults.

Methods: Healthy older adults (n=165) enrolled in the Australian Imaging, Biomarkers and Lifestyle (AIBL) study underwent positron emission tomography (PET) neuroimaging for Aβ amyloid using Pittsburgh Compound B (PiB), BDNF genotyping, and cognitive assessment at baseline, 18- and 36-months. Linear mixed models determined rates of change in cognition, hippocampal volume and Aβ amyloid accumulation over 36 months.

Results: In healthy older adults with high Aβ amyloid, Met carriers showed significant and moderate-to-large decline in episodic memory, executive function, and language, and greater reductions in hippocampal volume over 36 months compared to Val/Val homozygotes. BDNF Val66Met was not associated with rates of change in cognition or hippocampal volume in participants with low Aβ amyloid. BDNF Val66Met was not associated with levels of Aβ amyloid in participants with high or low Aβ amyloid levels at baseline. Similarly, BDNF Val66Met was not associated with rates of Aβ amyloid accumulation in participants with high or low Aβ amyloid levels at baseline.

Conclusions: BDNF Val66Met moderated the association between high Aβ amyloid and cognitive decline and hippocampal atrophy in healthy older adults. High Aβ amyloid levels coupled with Met carriage may be useful prognostic markers of accelerated cognitive decline and hippocampal degeneration in individuals in the preclinical stage of AD.

S09

WHERE IS THE ROOM FOR IMPROVEMENT IN THE DRUG TREATMENT OF ANXIETY DISORDERS?

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Anxiety disorders are amongst the most prevalent medical disorders and tend to have a chronic or frequently recurrent course. They can be very incapacitating, are often not diagnosed and form a huge burden for society (Witchen et al. 2011). The anxiety disorders are a heterogeneous group, involving the common anxiety disorders panic disorder, social phobia, specific phobia and generalized anxiety disorder, but also posttraumatic stress disorder and obsessive compulsive disorder. Current standard treatments for anxiety disorders consist of psychotherapy, especially forms of cognitive behavioural therapy, and/or pharmacotherapy. The efficacy of pharmacotherapies has been demonstrated in RCTs and subsequent meta-analyses, and they have been incorporated in the current evidence-based guidelines. In this presentation I will first discuss some key-aspects of the current state of affairs with regard to efficacy and tolerability in the acute and in the maintenance phase, and when data are available, the effectiveness and tolerability of (drug) treatment of anxiety disorders in routine clinical practice. The available data suggest limited efficacy and tolerability of current pharmacotherapies: the proportion of patients with full remission on drug treatment is still modest and many patients will relapse while on maintenance treatment. Also, many patients will experience side effects, often leading to early discontinuation or discontinuation during the maintenance phase. Finally, there is still a paucity of thoroughly investigated treatment algorithms. I will subsequently discuss what clinicians and patients would probably consider essential properties for an ‘ideal’ drug for the treatment of anxiety disorders and how several current research efforts try to address some of these topics. More clinically oriented research, for instance, is trying to identify existing drugs with an earlier onset of action, studying response prediction (involving both genetic as well as clinical variables), optimal treatment algorithms, and the emerging concept of staging and subtyping of anxiety disorders. Hopefully, experimental medicine approaches will eventually benefit from strategies trying to develop new classifications of psychopathology based on the increasing insights in the underlying neurobiological mechanisms at the cellular and the system level.

N.J.A. van der Wee received speaking fees from Eli Lilly and Wyeth and served on advisory panels of Eli Lilly, Pfizer, Wyeth and Servier.
S10

WHAT HAS EXPERIMENTAL MEDICINE EVER DONE FOR US?

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In the last 25-30 years both academia and industry have invested heavily in biomedical research, much of it directly aimed at elucidating the mechanisms underlying brain function. Consequently, our knowledge of brain systems and functions has increased vastly, new experimental techniques have been developed and a wealth of new drug targets aimed at improving the treatment of psychiatric disorders has been produced. However, deciding whether to progress compounds modulating these new targets from the preclinical to clinical arena is laden with risk. This is particularly true of compounds developed to treat CNS disorders. Approximately 50% of compounds that have promising profiles in animals fail in initial clinical trials, either for lack of efficacy or an unfavourable safety profile. One of the emerging roles of human experimental medicine is to reduce this failure rate by bridging the gap between pre-clinical CNS models and expensive patient studies. These healthy volunteer models often combined novel behavioural measures with functional magnetic resonance imaging (fMRI) to elucidate the mechanism of action of novel compounds developed to treat anxiety, depression and schizophrenia. These exciting developments in experimental medicine models is enabling rapid, accurate and reliable decision making about which compounds to progress into patient trials. An example of this approach is the 7.5% carbon dioxide (CO2) challenge assay that has been proposed as a human model of generalised anxiety disorder (GAD) that reliably reproduces GAD symptoms in healthy volunteers. In this model a number of benzodiazepines, such as lorazepam, reliably reduce these symptoms, but it has also been shown that a novel CRF1 receptor antagonist R317573, was also effective in this model (Bailey et al., J Psychopharmacol., 2011; 25:1199-1206). More recently healthy volunteers with particular behavioural phenotypes relevant to the psychiatric disease of interest have been recruited rapidly through social networking sites. These healthy volunteers can enhance the signal to noise ratio between placebo and drug treated groups allowing for lower recruitment and greater precision in identifying the symptoms that best respond to drug treatment. Thus experimental medicine methods are not only reducing the risk in developing new treatments for psychiatric disorders, they are also providing new tools to explore novel therapeutic targets. This work was supported by the P1vital CNS Experimental Medicine Consortium.

S11

WHAT DO STUDIES OF COGNITIVE BIAS MODIFICATION REVEAL?

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A range of psychiatric disorders are associated with information processing biases (known as cognitive biases). Anxiety, in particular, is associated with heightened sensitivity to threat. This is indexed by attentional biases (i.e., the preferential processing of, and allocation of attention to, threatening stimuli), and interpretive biases (i.e., the interpretation of ambiguous stimuli as threatening). Until recently, the causal nature of these biases was unclear. However, recent work has shown that the experimental manipulation of these biases can modify emotional responding to provocation challenges. These techniques are collectively known as cognitive bias modification, and they both serve to establish the causal basis of these biases, and offer potential new therapeutic interventions. We have recently begun to investigate the experimental manipulation of biases in the recognition of emotion in ambiguous facial expressions. In a series of experiments, we explored the relationship between these biases and aggressive thoughts and behaviour, both in healthy adults and in adolescent youth at high risk of criminal offending and delinquency. We showed that it is possible to experimentally modify these biases to encourage the perception of happiness over anger in ambiguous expressions. This change in perception results in a decrease in self-reported anger and aggression in healthy adults and high-risk youth, respectively, and also in independently rated aggressive behaviour in high-risk youth. We obtained similar effects on mood using two different techniques to modify biases in emotion perception (feedback-based training and visual adaptation). These studies provide strong evidence that emotion processing plays a causal role in anger and the maintenance of aggressive behaviour. In a subsequent experiment, we investigated the effects of emotion recognition training on depressive symptoms and mood in young adults reporting high levels of depressive symptoms (ISRCTN 02532638). We experimentally modified emotion recognition biases to encourage the perception of happiness over sadness in ambiguous expressions. Those in the intervention condition had lower depressive symptoms and negative mood at 2-week follow-up, but there was no statistical evidence for a difference. There was some evidence for increased positive mood. We are currently attempting to replicate and extend these findings (ISRCTN 17767674 and 50125738). Recently, we have begun to explore the emotion recognition biases in anxiety, using expressions that range from happy to angry. Preliminary data from these studies will be presented.

S12

HOW GOOD IS THE 7.5% CO2 INHALATION MODEL OF GENERALIZED ANXIETY DISORDER?

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Generalized Anxiety Disorder (GAD) is typically a severe and long-lasting condition characterized by excessive anxiety and worry that is difficult control, poor concentration and restlessness. There is a need to improve upon current treatments for anxiety through developing valid experimental human models of anxiety which allow us to more effectively evaluate novel pharmacological and psychological treatments (and mechanisms of action) in healthy volunteers, prior to evaluation in patient populations. Inhalation of air ‘enriched’ with 7.5% carbon dioxide (CO2) increases self-report anxiety (worry, tension) and autonomic arousal (heart rate, blood pressure) and provides a novel experimental model of generalized anxiety in healthy humans. Growing evidence from quantitative and qualitative methods suggests that 7.5% CO2 challenge can provoke core symptoms of GAD in healthy individuals. Recent work in our group shows that the CO2 model can also induce dysfunction in neuropsychological mechanisms that are compromised in (unchallenged) anxious populations e.g. poor attention control, hyper-vigilance and selective processing of environmental threat. Importantly, the comparable effects of CO2 challenge (in low anxious individuals) and trait anxiety on cognition and emotion processing appear to be independent of elevated state anxiety. Thus CO2 inhalation may directly challenge neuropsychological mechanisms that characterise generalized trait anxiety rather than transient state anxiety. Although not all evidence is consistent, pharmacological agents that are effective in the management of anxiety symptoms can attenuate subjective response to 7.5% CO2 challenge in healthy volunteers. Benzodiazepines, SSRIs and SNRI's have shown some efficacy, and novel psychological interventions for anxiety (e.g. cognitive bias modification, guided attention training) have shown positive results in initial studies. CO2 challenge readily translates into animal paradigms. Initial evidence in rodents suggests the amygdala as an important chemosensor that directly detects increasing CO2 concentrations (via acid-sensing ion channels) to provoke fear behaviours that are consistent with the anxiety phenotype (Ziemann et al. 2009, Cell 139: 1012-1021). However evidence that individuals with bilateral amygdala damage can still experience fear with CO2 challenge (Feinstein et al. 2013, Nature Neuroscience 16: 270-272) suggests additional mechanisms mediate the anxiety response in humans. In sum, research to date suggests that the 7.5% CO2 model provides a promising unconditioned, cross-species translational tool with which to challenge (and evaluate novel treatments that aim to resolve) subjective, autonomic and neurocognitive processes that underlie anxious behaviour in humans and which characterize the generalized anxiety phenotype. MRC research grant MR/J011754/1 awarded to Garner, Baldwin, Lynch & Munafo.
LISTENING TO DOPAMINE NEURONS USING IN VIVO ELECTROPHYSIOLOGY

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Midbrain dopamine neurons can fire either single action potentials or brief bursts of action potentials. Both types of firing occur spontaneously, and in response to a range of stimuli, including rewards and punishments. Monitoring this activity in vivo is typically accomplished with extracellular microelectrodes. In this talk, I will discuss methods to address these questions, we have used fast-scan cyclic voltammetry at chronically-implanted electrodes in behaving rodents to monitor real-time dopamine transmission in the nucleus accumbens core region while rats learned and performed a series of cost-benefit decision making tasks. Each session consisted of repeated blocks of “forced” trials, where only one option was presented, and “choice” trials, where both options were available and rats could choose between them. In all the experiments, the rats learned that one option was always associated with a fixed number of lever presses and a fixed reward size (e.g., 16 presses for 1 reward) whereas the alternative required a different number of lever presses and/or gave a different quantity of reward. The cost-benefit values of the options changed across conditions, meaning that the rats consistently had to re-learn the precise effort and reward values associated with each alternative and update their behavior.

Results: I will discuss evidence that dopamine at option onset (a) preferentially represents the known benefits and not the costs of a course of action in static environments, (b) reflects the relative value of one option over another in changing environments, and yet (c) does not appear to play any direct role in selecting one course of action over another.

Conclusion: Phasic dopamine transmission may provide an important opportunistic bias to motivate responding to rewarding options, particularly when the environment unexpectedly improves.

THE IMPACT OF DOPAMINERGIC MODULATORS ON COGNITION

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Catechol-O-methyltransferase (COMT) regulates dopamine levels in the prefrontal cortex. A common, functional polymorphism (Val158Met) in the COMT gene alters its enzyme activity and, therefore, prefrontal dopamine function. COMT activity can also be reduced pharmacologically, using the brain-penetrant COMT inhibitor tolcapone. Both the Val158Met polymorphism and tolcapone have previously been linked with differences in cognitive function and prefrontal BOLD response, determined using fMRI. We examined the separate and interactive effects of COMT genotype and tolcapone on cognitive function and brain activation. Healthy, male COMT Val vs Met homozygotes were administered 200mg tolcapone or placebo in a double-blind, between-subjects design (n’s = 16-18 for each drug + genotype combination). They performed tests of working memory, risk aversion and emotional processing. Neural activation was measured using magnetoencephalography, and structural and functional resting state MRI scans. We found interactive effects of genotype and drug on working memory performance and risk aversion: in those given placebo, Met homozygotes performed better on the working memory task and were more risk averse than Val homozygotes, but this difference was reversed in those given tolcapone. We also found separate and interactive effects of genotype and drug on neural activation. We showed that COMT inhibition was beneficial to working memory performance in Val homozygotes, who presumably have suboptimal prefrontal dopamine levels, but detrimental in Met homozygotes, who presumably have optimal levels. These findings are consistent with the ‘inverted U’ relationship between dopamine and working memory. Furthermore, we demonstrate a similar relationship between COMT activity and risk aversion, indicating that an inverted-U function may also apply to this cognitive domain. Finally, COMT activity also impacted on brain activation, suggesting mechanisms for links between COMT activity and behavioural performance. Our findings demonstrate how genetic and pharmacological agents can alter behavioural performance in lawful and predictable ways, and indicate that COMT activity provides a window into central dopamine function in humans.
S16

NEUROIMAGING OF DOPAMINE FUNCTION IN THE HUMAN BRAIN
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Neuroimaging provides a direct way of studying brain dopamine function in humans in vivo. Research in this area has provided new information on the normal role of dopamine, and how alterations in dopamine function may contribute to CNS disorders. Dopamine dysfunction is particularly important in psychosis, and studies on this disorder illustrate the range of different neuroimaging approaches that can be employed. Dopamine synthesis capacity can be measured using 18F-Dopa, a radio-labelled precursor of dopamine that is taken up by dopaminergic neurons in proportion to the local level of dopamine synthesis. The distribution and uptake of the tracer can then be measured using positron emission tomography (PET). In patients with psychosis, dopamine synthesis capacity is increased in the striatum and in the midbrain. Although on average, dopamine synthesis capacity is increased in psychosis, recent evidence suggests that in a subgroup of patients who do not respond to antipsychotic treatment, it may be relatively normal. The intrasynaptic release of dopamine (eg following administration of amphetamine) can be assessed by using PET or SPET (single photon emission tomography) to measure the displacement of radiolabelled tracers that bind to D2 receptors. In patients with psychosis, the release of dopamine in response to a stimulus is greater than that in controls. Dopamine function can also be assessed less directly using MRI-based techniques. The neural and vascular responses to an acute pharmacological challenge or a period of treatment with a dopaminergic drug can be measured using functional MRI and Arterial Spin Labeling (ASL), respectively. For example, functional MRI studies have shown that the acute induction of psychotic symptoms by 69-THC (the main psychoactive constituent of cannabis) may be mediated by its effect on striatal activation. Studies with ASL indicate that single doses of antipsychotics in volunteers alter blood flow in the striatum and the prefrontal, cingulate and medial temporal cortex. Functional MRI has also been used to examine the correlates of variations in genes that code for proteins that influence dopamine transmission, such as COMT and DAT. Comparison of subjects with different variants of these genes have shown how they influence regional brain activation, and how this may be altered in patients with psychosis.

S17

AN INTRODUCTION TO COMPUTATIONAL MODELLING FOR PSYCHOPHARMACOLOGISTS
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This talk will serve as a tutorial introduction to computational modelling for psychopharmacological experiments, focussing mainly on Bayesian analyses of behaviour with some applications to fMRI data. The aim of the tutorial is to give participants an intuitive overview over the central concepts necessary to build, fit and validate computational models. The tutorial will first introduce graphical models as a way to guide intuition in building models. It will then use reinforcement learning as an example because it unifies a large number of decision-making experiments. The best-known examples of reinforcement learning models centre around accounts of dopamine as signalling a prediction-error, and we will start from this to describe a sequence of models aimed at disentangling instrumental and Pavlovian response contingencies and learning. Next, the tutorial will give a detailed account of how to find maximum likelihood and maximum a posteriori parameter estimates, and discuss their advantages and disadvantages. We will explain how the likelihoods involved in fitting a model can be straightforwardly used to generate surrogate data. By examining aspects of the surrogate data and comparing it to the true data, the ability of models to really account for the effects seen in the raw data can be ascertained, and models can be improved in a specific and directed manner. Because continuously improving a model by increasing the match to the data can lead to overfitting, this will naturally lead on to a discussion about model comparison. The talk will spend some time describing the conceptual components of model comparison, and various ways to use (nested) model comparison to test specific hypotheses; to control for confounding effects; and to test for group differences. The talk will close with pointers towards model-based fMRI analysis, classification and uncertainty-weighted regression.

S18

CATECHOLAMINERGIC DISTURBANCES AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER
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Introduction: Substantial evidence suggests that attention-deficit/hyperactivity disorder (ADHD) involves disturbances in catecholaminergic function. However, the precise nature of these disturbances, and the detailed causal pathways linking them to the symptoms of the disorder, remain unknown.

Methods: We have developed neurocomputational models of the functions of the catecholamines that bridge from the neurochemical to the behavioral level, and we have used those models to explore the nature of the abnormalities that may underlie ADHD.

Results: We have found that reducing tonic and phasic catecholaminergic levels in the models causes them to exhibit the same behavioral phenotype that patients with ADHD do, suggesting that ADHD may be caused by catecholaminergic deficits. The models with reduced tonic and phasic catecholaminergic levels also exhibit characteristic abnormalities in functional connectivity between brain areas. Using fMRI, we confirmed that unmedicated patients with ADHD exhibit these same abnormalities that were predicted by the models. Furthermore, as also predicted by the models, those abnormalities were ameliorated by stimulant medication.

Conclusions: These results suggest that ADHD may involve low tonic and low phasic catecholamine levels. Furthermore, the models shed light on the causal pathway linking such changes at the neurochemical level to changes in systems-level brain function and, ultimately, in behavior.

This work was funded, in part, by the Klingenstein Third Generation Foundation and by the New York State Psychiatric Institute/Research Foundation for Mental Hygiene.
S19
IMAGING COMPETITION MECHANISMS IN LIVING HUMANS
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Recent advances in modelling and imaging have allowed more mechanistic questions to be investigated in human neuroscience. I will give an example in prefrontal cortex, where we have used computational models to relate data from neurochemistry through physiology in macaque monkeys to bulk human imaging responses. This approach helps to bridge the different levels of systems neuroscience, and may allow more mechanistic understandings of the relationships between computations, physiological responses and behaviour.

S20
ABNORMAL VALUATION IN DEPRESSION, SCHIZOPHRENIA AND ADDICTION
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The limitations of current diagnostic classifications in psychiatry have been much discussed, particularly with the release of the latest version of the Diagnostic and Statistical Manual of Mental Disorders. The idea behind biologically orientated research into psychiatric disorders is that the brain supports mental function and some of the most effective psychiatric treatments act on the brain. However, in seeking a more objective type of classification based on brain mechanisms and better understanding of therapeutic mechanisms, psychiatry and psychopharmacology face a huge explanatory gap; between molecular and clinical levels of understanding. Currently we do not know why any patient with depression responds to serotonergic reuptake inhibitors or why any patient with schizophrenia responds to D2 receptor blocking drugs. Consequently, when patients are treatment resistant, there is no mechanistic framework to guide further interventions and research. Computational psychiatry has an aim of improving the understanding of psychiatric disorders and treatments by addressing intermediate levels of understanding, between brain physiology/pharmacology and psychopathology. fMRI and behavioural studies will be presented that seek to address the hypothesis that core clinical features of different psychiatric disorders represent different disorders of neural valuation (Gradin VB et al. 2011 Brain 134(6) 1751-1764; Gradin VB et al 2013 under review). For example, anhedonia in depression reflects abnormally reduced valuation of rewards, schizophrenia involves abnormalities in the valuation/salience of stimuli, and addiction is associated with abnormalities in the valuation of drugs and non-drug related rewards. Particular neural signals and brain mechanisms are highlighted by this approach, suggesting novel approaches to understanding illness and therapeutic mechanisms.

S21
GENETIC ANALYSIS POINTS TO MICROGLIAL ACTIVATION AS A KEY EVENT IN THE PATHOGENESIS OF ALZHEIMER’S DISEASE
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Genetic analysis of autosomal dominant Alzheimer’s disease identified APP mismetabolism as the underlying event in this form of the disease with mutations in APP, PSEN1 and PSEN2 as causative and all mutations making the deposition of the Ab peptide as the underlying initiating factor. the amyloid cascade hypothesis for the disease (Hardy J, et al. Science 2002, 297:353-6). However, these forms of the disease explain a tiny proportion of the disease (perhaps 1%) and it remained an open question as to the extent to which other more common forms of the disease, shared pathogenic mechanisms. In the more common, late onset form of the disease, apoe4 had long been known to be a major risk factor, and while the mechanism of its pathogenicity still remains unclear, its role in cholesterol metabolism is well established. In the last 5 years, genome wide association studies have identified an increasing number of other loci with common variability of low effect. Clusterin, complement receptor 1, PICALM, BIN1, MS4AE and SORL1 being this first of these reported (Harold D, et al. Nat Genet. 2009, 10:1088-93). Bioinformatic analyses have mapped these genes to three broad biochemical pathways: cholesterol metabolism, endosomal vesicle recycling and the innate immune system (Jones L, et al. PLoS One. 2010, 5:e13950). Using exome sequencing, we have recently identified rare, loss of function mutations in the TREM2 gene as high risk variants for the disease (Guerreiro R, et al. N Engl J Med 2013, 368:117-127). A role of TREM2 is the maintenance of microglia in the autophagic phenotype and the inhibition of the switch in the microglial phenotype to the cytokine producing phenotype. Together with biochemical data, implicating CR1 in the activation of microglia by Ab (Crehan H, et al. Neurobiol Dis, 2013, 54:139-149), these data suggest that a key component in Alzheimer pathogenesis is the activation of microglia Ab. The data are consistent with the view that those who effectively respond to Ab deposition by phagocytosing the deposits have a more favourable outcome than those in whom the response switches to an inflammatory response.
S22

ENABLING EARLY DETECTION AND INTERVENTION IN DEMENTIA

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Dementia is a major public health problem that poses an increasing burden on the health and wealth of societies worldwide. The understanding of basic biology and early clinical expression of dementia has significantly improved in the last decade. Policy makers, regulators, leading experts, drug developers and patient advocacy groups recognize the need for timely diagnosis and intervention. Of the 800,000 people living with dementia in the UK, less than half have a diagnosis. Without this, they are denied access to support, information and potential treatments that can help them to live well with their condition. Problems with episodic memory can be the first warning signs of Alzheimer’s disease (AD) and among patients with mild cognitive impairment, tests of episodic memory are the best predictors of subsequent conversion to AD. Across a number of studies, the Paired Associates Learning (PAL) test shows a high sensitivity and specificity in differentiating mild AD from healthy older adults. For clinical trials as well as clinical practice, we have designed a dementia screening tool using PAL as the first step in an investigational process to prioritise access to more expensive / invasive investigations. This tool is based on a dataset of more than 4000 older adults collected through a number of different UK research projects. This large dataset allows a very accurate assessment of the expected level of memory performance for any individual aged 50 to 90 years. Cognition screening tools can play a vital role in the early detection of dementia in clinical trials and in healthcare practices by standardizing procedures, enabling wide-scale data collection, implementing performance based reimbursement and safety monitoring for in market disease modifying drugs and have a positive impact on the financial resources of the healthcare system (with or without disease modifying treatments). To accomplish early detection in clinic, tools that are now used in clinical trials to operationalize the new clinical criteria for prodromal AD, need to be implemented into the doctors’ office. The fact that enrolment of prodromal AD in clinical trials is still difficult indicates that new cognitive screening tools have yet to find their way into mainstream healthcare. Once new Alzheimer drugs for early intervention (eg. vaccines) become available, it is important that the appropriate diagnostic screening instruments are in clinic, otherwise drugs for early intervention won’t find the patients.

Drs Riedel & Blackwell are employees of Cambridge Cognition Plc.

S23

NEUROIMAGING AS A BIOMARKER FOR DIFFERENT FORMS OF DEMENTIA

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The role of neuroimaging has radically changed over the last decade, from that of simply ruling out other cerebral lesions to providing important information to assist differential diagnosis, enhance early diagnosis and offer the possibility of monitoring treatment response. Many imaging biomarkers have been described for Alzheimer’s disease and other types of dementia, including dementia with Lewy bodies and Fronto-temporal dementia, some of which have now been incorporated into new revisions of clinical and research diagnostic criteria. One of the more recent developments has been amyloid PET imaging and it is clear that amyloid imaging can offer additional and complementary information to that obtained by structural imaging. Amyloid PET, along with temporo-parietal hypoperfusion/ hypometabolism on SPECT/PET and hippocampal atrophy on MR, is increasingly recognised as an imaging biomarker for AD, akin to changes on dopaminergic SPECT which are a robust biomarker for D LB. This presentation will summarise the use of current and proposed imaging biomarkers for dementia, focusing on the differentiation between Alzheimer’s disease and dementia with Lewy bodies. New data on the use of MR measures of cortical thickness will be presented, suggesting that cortical thickness may be a sensitive measure for characterising grey matter loss in AD and D LB, showing promise as a diagnostic technique. The importance of such imaging changes is not only for enhancing the speed and accuracy and of clinical diagnosis of dementia subtype, but as biomarkers for subject stratification in future clinical trials, and as putative intermediate outcome measures in trials of disease modification.

S24

DISEASE MODIFYING DRUGS FOR ALZHEIMER’S DISEASE: PERSPECTIVES FROM A DRUG DEVELOPER’S POINT OF VIEW

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As the multifactorial nature of Alzheimer’s disease (AD) becomes more clear, the challenges of devising a time-limited intervention that alters its downward course come into greater focus. The contribution, timing and mechanism of insults such as amyloid toxicity, inflammatory mediators, metabolic aberrations, and brain trauma must be better understood to enable the design and successful testing of interventions that slow or stop its inexorable progress. This talk will address some of the scientific, practical and economic considerations inherent in advancing disease-modifying AD therapies including the difficulty of finding translatable model systems to establish confidence in new mechanisms, of establishing evidence for target engagement in the clinic, and of underwriting proof of concept and studies designed to meet regulatory standards for approval. Despite the considerable challenges of today, important advances in basic science, translational tools, clinical trial approaches, public-private partnerships, and regulatory standards give hope that progress against the disease will accelerate in the coming years.

Dr. Nye is an employee of Janssen and a shareholder of Johnson & Johnson.
S25

ASSESSING ANTIPSYCHOTIC DRUG EFFECTS ON SALIENCE IN ANIMAL MODELS

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Animal behavioural methodologies used to measure salience allocation in rodents are reviewed in a historical context. Despite differing methodologies and nomenclatures such procedures have in common the measurement allocation to behaviours that respond to changes in the associability of environmental stimuli. It has been suggested that antipsychotic drugs restore appropriate salience allocation to environmental stimuli via DRD2 blockade. Using a null mouse approach we investigated whether dopamine D2 receptors (DRD2) are necessary for antipsychotic drugs to modify salience allocation. Salience allocation was measured as the enhancement of low baseline LI - or the reversal of pharmacologically-disrupted latent inhibition (LI). Low baseline LI was induced by reducing pre-exposure to the tone to 40 presentations. Both haloperidol and clozapine enhanced low baseline LI in wild-type but not in DRD2-/- mice, suggesting a requirement for DRD2. D-amphetamine abolished LI similarly in both backgrounds, and remarkably, both clozapine and haloperidol reversed D-Amphetamine abolition of LI in DRD2-/-, demonstrating that antipsychotics can influence salience allocation disruption as measured in the LI paradigm in the absence of DRD2. These findings suggest that while DRD2 can be necessary for antipsychotics to enhance baseline salience allocation, there is also an additional, non-DRD2-dependent mechanism that is unmasked in the presence of D-Amphetamine. Using a combined genetic and pharmacological approach in conjunction with a specific behavioural measure of salience allocation has identified both DRD2 and non DRD2 dependent influences of antipsychotic drugs on salience allocation that would not have been detectable using any single approach alone.

S26

SALIENCE AS A BEHAVIOURAL PHENOTYPE IN GENETIC AND PHARMACOLOGICAL ANIMAL MODELS OF SCHIZOPHRENIA

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A aberrant salience (i.e. inappropriate attribution of salience to irrelevant experiences) has been related to the presence of positive psychotic symptoms in schizophrenia. Abnormal striatal dopamine activity has been documented in patients with schizophrenia, while clinical and preclinical studies have also shown that dopaminergic dysregulation disrupts the normal process of contextually driven salience. Studies employing cross-species paradigms of salience attribution confirm that this construct may represent a psychosis-relevant endophenotypic marker which may assist in the identification of novel antipsychotic drug targets. Investigations of salience processes in mice mutant for genes directly associated with risk for schizophrenia, or pathophysiological processes implicated in schizophrenia, have been described in the literature. Risk for psychosis also appears to involve gene-gene [epistatic] interactions and gene-environment interactions in phenotypic regulation. This talk will describe issues relating to investigating salience-related phenotypes in schizophrenia risk gene mutant mouse models, as well as models of gene-gene-environment interactions in schizophrenia. These data indicate how, from a neurobehavioural perspective, studying salience misattribution processes in relevant genetic and pharmacological models may constitute a useful approach for identifying novel antipsychotic targets and evaluating existing antipsychotic agents.

S27

CLINICAL STUDIES OF SALIENCE DYSSREGULATION AND IMPLICATIONS FOR NOSOLOGY OF SCHIZOPHRENIA

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Survival of an individual or species depends upon the ability to adequately respond to stimuli that are connected to obtaining food, acquiring progenies or avoiding danger. Consequently, the mechanisms which allow identification and appreciation of such stimuli are of utmost importance. Incentive motivational salience of stimuli is a major component of this process. Incentive salience is considered to be a motivational attribute given by the brain to stimuli related to a positive or negative experience. From an evolutionary perspective these mechanisms should be present. Our primitive ancestors, living in the oceans hundreds mya, should have possessed these abilities as well, in order to survive. Therefore, it can be postulated that these abilities are anchored in the most primitive parts of the human brain. In this opinion paper, the author will try to deconstruct the salience network into two sets of, partly closed, subcortical circuits, which will be named respectively the ‘extrapyramidal’ and ‘limbic’ subcortical circuits. Part of the limbic circuits has been described by Sowards and Sowards (2003, Brain Res Bull 61:25-49) and by Liotti and Pansepp (2004. Textbook of biological psychiatry. Hoboken NJ, Wiley-Liss, 33-74). The limbic sub circuits start in limbic cortical areas, run through basolateral amygdala and/or limbic basal ganglia to hypothalamus and thereafter via thalamus back to prefrontal and insular cortex. The extrapyramidal sub circuits start in other isocortical areas, run through the striatum and other basal ganglia to thalamus and thereafter to different frontal areas. The activity of these circuits is regulated through the mesencephalic dopamine system, which is in turn regulated by medial prefrontal areas. According to this model the prefrontal cortex regulates the activity of the mesencephalic dopamine system, and this system regulates the activity of the subcortical circuits which in turn regulates the activity of the prefrontal cortex. In schizophrenia, a dysfunction of the medial prefrontal cortex presumably causes insufficient inhibition of the basolateral amygdala. This results in over activity of the limbic subcortical circuit inducing feeling unsafe and insecure. Another result might be the activation of cortical areas involved in the detection of cues that might indicate threat or danger. This is reflected by an increased salience with respect to stimuli indicating negative experiences and decreased salience towards stimuli associated with appetitive opportunities. The existing evidence, however limited, for this organization of salience network and its pharmacological implications for the current construct of schizophrenia will be discussed.
In recent years, there have been two approaches to the question of abnormal salience in schizophrenia. On the one hand, Kapur’s hypothesis of excessive motivational salience emphasises the role of dopamine in the attribution of aberrant salience to information, leading to the formation of delusions or to hallucinations. The hippocampus and subcortical nuclei play key roles. On the other hand, Palaniyappan and Liddle’s concept of abnormal proximal salience emphasises abnormality of the Salience Network, a neural system that mediates the switching between brain states according to the demands of current circumstances. Insula and anterior cingulate cortex are the key nodes, though subcortical sites also play a role. The neurotransmitters that mediate signalling between the key nodes are glutamate and GABA, while dopamine plays a modulatory role. Systematic profiling of LSN2463359 and LSN2814617 alongside other previously described molecules will help determine their role in the different domains under investigation. In addition, these compounds were found to attenuate deficits in reversal learning in another rodent model of schizophrenia, the neurodevelopmental MAM E17 model. The systematic profile of LSN2463359 and LSN2814617 alongside other previously described molecules will help determine more precisely how mGlu5 potentiator pharmacology might provide therapeutic benefit.
S31

COGNITIVE TRAINING IN SCHIZOPHRENIA

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In addition to the core features, individuals with schizophrenia typically exhibit difficulties with cognitive processes such as memory. Such difficulties can be remediated through cognitive training. A recent meta-analysis has demonstrated that cognitive training improves both cognition and psychosocial function at a moderate effect size (Wykes et al., 2011 American Journal of Psychiatry, 168(5), p 472-485). However, cognitive training typically requires supervised practice on standard psychological paradigms; dropout rates and the costs of constant supervision can be high. Computer-games are known for being highly motivating and attention grabbing and much recent attention has focused on the idea that cognitive remediation therapy may be improved by using simple computer-games as a vehicle for delivering training (Sahakian, 2011 Brain waves module 1: neuroscience, society and policy, p 61-68). The current study developed a new neurogame for a cognitive training program that is fun and easy to install on portable devices such as the iPad. This study aimed to test whether training on this neurogame ‘iPad app’ improves cognition in individuals with schizophrenia. Whether such training impacts on schizophrenia symptomatology, health, mood and wellbeing was also investigated. In this proof of concept study, results reveal improvement across several cognitive processes including memory as well as improved symptomatology and overall well-being. Acknowledgement This research was funded by a grant from Janssen/J&J.

S32

MONITORING SYMPTOMS IN BIPOLAR PATIENTS: TRUECOLOURS

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True Colours is a service that has been developed to help people manage long term health conditions. It was originally developed for use by people who have bipolar disorder. It is an easy to use technology that enables health monitoring by texting or emailing answers to simple health-related questions. The answers are converted into a record that may be viewed on-line: https://truecolours.nhs.uk and/or printed out by patient or doctor. There are a range of scales and personalized patient reported outcomes available and they can be used at a range of sampling frequencies. Clinically this assists mood management in relation to events that have happened during the week, or the start of a new medication or therapy. By monitoring symptoms patients can learn how to make small changes to lifestyle that can have a big impact on wellbeing. The system has provided the primary outcome for two clinical trials, and for a ground breaking new psychological intervention for bipolar disorder. It has also provided a new method for analysing the phenotype of bipolarity and can be used to perform Experience Sampling Methodology using research participants’ own mobile phones. The evidence TrueColours has provided for long term inter-episode mood instability has changed our view of what bipolar is. Its chronicity and the role anxiety symptoms, fuelled by pervasive flashforward imagery, may be regarded in future as the primary disturbance in bipolar disorder. If so, this will change what the target for treatment should be. A de-emphasis on acute episodes and relapse prevention could liberate investigators to achieve greater innovation in pharmacological and psychological management of bipolar disorder. Acknowledgement: This publication represents independent research funded by the National Institute for Health Research (NIHR) UK under its Programme Grants for Applied Research Programme (Grant Reference Number RP-PG-0108-10087). The views expressed in this publication are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

S33

EFFECT OF INTERFERON-ALPHA TREATMENT ON CORTICAL GLUTAMATERGIC FUNCTION

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The development of depressive symptoms is a recognised complication of treatment with the cytokine, interferon-α, with up to 40% of patients developing major depression over three months of therapy. This effect has been seen as supporting inflammatory theories of the pathophysiology of major depression. Major depression has been associated with changes in glutamatergic activity and recent formulations of interferon-induced depression have implicated neurotoxic influences which could also lead to changes in glutamate function. Data will be presented from a recent study which used magnetic resonance spectroscopy (MRS) to measure both glutamate and its major metabolite, glutamine, in patients with hepatitis C who received treatment with pegylated-interferon-α and ribavirin. MRS measurements of glutamate and glutamine were taken from a voxel including pregenual anterior cingulate cortex in 12 patients before and after 4-6 weeks treatment with interferon. Interferon treatment led to an increase in cortical levels of glutamine (p = 0.02) and a significant elevation in the ratio of glutamine to glutamate (p<.01). Further, changes in glutamine level correlated significantly with ratings of depression and anxiety at the time of the second scan. These data indicate that treatment with interferon-α is associated with MRS-visible changes in glutamatergic metabolism. Functional interpretation of changes in spectroscopic measures is not always straightforward; however there is growing evidence that increased glutamine relative to glutamate is consistent with glutamatergic overactivity and thus altered resting state activity. Given the well-established role of medial prefrontal cortex including anterior cingulate in emotional processing and mood disorders such changes are well placed to influence risk of developing depression. The changes seen differ from those reported in major depression which suggests that the pathophysiology of interferon-induced depression may be distinct from that of major depression more generally, and may be more similar to the pattern of effect seen in bipolar depression. Financial Support: This study was supported by the Medical Research Council, the Academy of Medical Sciences and Wellcome Trust, and the John Fell Oxford University Press (OUP) Research Fund. Dr Taylor was a NIHR Clinical Lecturer through the Oxford University Clinical Academic Graduate School. Additional support was received from the Oxford NIHR Biomedical Research Centre.
S34

INFLAMMATION AND THE GENERATION OF NEUROTOXINS: CAN THE ACTIVATION OF THE TRYPTOPHAN-KYNURENINE PATHWAY IN DEPRESSION AND SCHIZOPHRENIA SUGGEST NOVEL TARGETS FOR PSYCHOTROPIC DRUG DEVELOPMENT?

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Introduction: Although immune reactions are necessary to defend against danger signals, the mediator molecules such as cytokines can be detrimental to the organism if the exposure is longer than necessary or in certain abnormal concentrations. The neuroprotection and neurotoxicity induced by the interaction between certain cytokines and the metabolites from tryptophan catabolism, the neuroactive kynurenes, which is partly influenced by corticosteroid action plays an important role in several neurotransmissions such as serotoninergic, dopaminergic and glutamatergic transmissions and receptor functions such as N-methyl-D-aspartate receptor or alpha7-nicotinic-acetylcholine receptor. While the molecules in normal concentrations are essential to the normal glial-neuronal interaction, any changes that induce imbalance in the network between those molecules could disturb the interaction.

Methods: Series of studies were carried out on cytokines and kynurenines changes in patients with major depression who were medication naive and who were treated with different antidepressants and schizophrenia patients who were medication naive or under medication. Some associated genes were also studied.

Results: The results indicated that in those patients especially who were medication naïve there was imbalance in kynurenines and those imbalances were associated with response to treatment and severity of some symptoms.

Conclusion: Manipulation of kynurenine pathway may be a novel target for future development of psychotropic medications.

S35

INFLAMMATORY EFFECTS ON MEDIAL TEMPORAL LOBE METABOLISM IMPAIR HUMAN SPATIAL MEMORY

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Introduction: Once considered an immune-privileged site it is now clear that the immune system plays an integral role in many fundamental neuronal processes including long-term potentiation, synaptic plasticity and neurogenesis critical to learning and memory. Immune mechanisms regulate each of these processes in health. However, during systemic infection this positive regulatory function is disrupted, resulting in acute memory impairments. When inflammation is severe, cognitive impairment may become persistent and when chronic, age-related cognitive impairment and progression of neurodegenerative diseases such as Alzheimer’s disease is accelerated.

Methods: Twenty healthy participants underwent 18FDG-PET scans before, then 4 and 8 hours after, experimental inflammatory challenge (using typhoid vaccination) or control (saline) injection. After the first two sessions, participants performed a virtual reality spatial memory task analogous to the Morris water maze where they learned then recalled the identity and spatial location of two sets of 16 objects. Recall of object identity and spatial location of both object sets was repeated after scan three to test differential effects on early encoding and later consolidation processes. A mirror-tracing procedural memory task was performed after each scan to test general effects of inflammation on psychomotor responses and motor learning.

Results: Cytokine analyses (IL-6, IL-1ra) confirmed a robust increase in inflammation following typhoid vaccination: group x time interaction (p=0.003, p=0.017). Inflammation also resulted in a selective impairment in memory for objects’ spatial location but not identity: group x encoding session interaction (F(1,1)=5.01, p=0.039 and F(1,17)=0.66, p=0.43). Importantly, inflammation did not compromise mirror-tracing performance (group x time interaction: F(1,18)=1.00, p=0.33) with performance improving across both in time (main effect of time: F(2,18)=23.58, p<0.001) confirming an absence of general effects of inflammation on psychomotor responding. PET analyses showed that inflammation was associated with a significant reduction in glucose metabolism within a discrete cluster focussed on the right parahippocampal/ perirhinal cortex. Further effects of inflammation on resting parahippocampal glucose metabolism mediated impairing actions on memory for objects spatial location. Effects of inflammation were observed within 4 hours of inflammatory challenge and remained static at 8 hours supporting an action on early encoding rather than later consolidation processes.

Conclusions: Together these data demonstrate an acute sensitivity of human medial temporal lobe structures to peripheral inflammation. They highlight a mechanism through which inflammatory modulation of MTL function may selectively compromise memory processes that are characteristically affected in age-related cognitive decline and early stages of neurodegenerative disorders, notably Alzheimer’s disease.

S36

THE GUT-BRAIN AXIS IN MAJOR PSYCHIATRIC DISORDERS: COULD THIS BE A NEW APPROACH TO MODULATING ABNORMAL BRAIN FUNCTION?

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Introduction: Recent years have witnessed the rise of the gut microbiota as a major topic of research interest in biology. Studies are revealing how variations and changes in the composition of the gut microbiota influence normal physiology and contribute to a variety of diseases. Accumulating data now indicate that the gut microbiota also communicates with the CNS — possibly through neural, endocrine and immune pathways — and thereby influences brain function and behaviour. Understanding the mechanisms underlying such effects especially during early-life may be crucial for gaining an understanding of neurodevelopmental disorders such as autism spectrum disorder and schizophrenia and stress-related psychiatric disorders including depression and anxiety.

Methods: Strategies we have used to parse the microbiome-gut-brain axis include study the effects of probiotic bacterial strains, many of which can generate neuroactive metabolites, on behaviour and stress response. In parallel, germ-free animals are important tools in investigating the impact of microbiota on brain development and we have taken advantage of this model in the context of behaviours relevant to stress and sociability.

Results: Specific Lactobacilli and Bifidobacteria strains have marked effects on anxiety and cognitive behaviours and can attenuate the stress response. These effects were coupled with alterations in GABA receptor levels in many key brain areas. Interestingly, the vagus nerve is needed for these effects to be manifested. Additionally, we show that male but not female germ-free animals have a significant elevation in the hippocampal concentration of 5-HT and its main metabolite coupled with alterations in GABA receptor levels in many key brain areas. The mechanisms underlying these effects are a mixture of both direct and indirect effects of gut microbes on the host. Alterations in the microbiome have been linked to changes in the expression of genes encoding neurotransmitter receptors and enzymes involved in neurotransmission such as serotonergic, dopaminergic and glutamatergic transmissions and receptor functions such as N-methyl-D-aspartate receptor or alpha7-nicotinic-acetylcholine receptor. While the molecules in normal concentrations are essential to the normal glial-neuronal interaction, any changes that induce imbalance in the network between those molecules could disturb the interaction.

Conclusions: The emerging concept of a microbiota–gut–brain axis suggests that modulation of the gut microbiota may be a tractable strategy for developing novel therapeutics for complex CNS disorders ranging from anxiety, depression, autism and schizophrenia. The author and his work are supported by Science Foundation Ireland (grant nos. 02/CE/B124 and 07/CE/B1368).
MA01

ANTIDEPRESSANTS, POLYUNSATURATED FATTY ACIDS AND GLUCOCORTICOID PRE-TREATMENT MODULATE INFLAMMATORY RESPONSES IN HUMAN HIPPOCAMPAL PROGENITOR CELLS

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Introduction: Inflammation has been implicated in the pathogenesis of depression. Some studies suggest that the efficacy of antidepressants and fish oil in depression may be due to their anti-inflammatory properties. We set out to investigate these properties in a relevant model of depression – inflamed human hippocampal progenitor cells. Furthermore, we aimed to explore the apparent paradox presented by the co-existence of high levels of inflammation and glucocorticoids in depressed populations (given that glucocorticoids are potently anti-inflammatory).

Method: Inflammation was induced in the human hippocampal progenitor cells by the addition of the pro-inflammatory cytokine IL-1β (10ng/mL). Each of four antidepressants – venlafaxine, sertraline, agomelatine and moclobemide – at concentrations of 100nM and 1µM and two polyunsaturated fatty acids – DHA and EPA – at concentrations of 1µM and 10µM were co-incubated with IL-1β for a period of 24 hours. The inflammatory response was measured by evaluation of IL-6 levels in the supernatant, using ELISA. Gene expression of cytokines and regulatory proteins in the cytokine pathway were measured by qPCR, and NF-κB DNA binding efficacy was measured using an NF-κB transAM kit. We also pre-treated the cells with varying concentrations of dexamethasone before IL-1β treatment to evaluate the effect on the inflammatory response.

Results: Upon co-incubation of cells with IL-1β and venlafaxine (1µM) or EPA (10µM), levels of IL-6 in the supernatant were decreased by 16% (p<0.05) and 11% (p<0.01), respectively. Conversely, sertraline (1µM) and DHA (10µM) increased the amount of IL-6 detected upon co-treatment with IL-1β by 8% (p<0.05) and 18% (p<0.01), respectively; moclobemide and agomelatine had no significant effect on IL-6 levels. The anti-inflammatory effect of venlafaxine appeared to be at least partially transcriptional: there were trends towards decrease in IL-6 gene expression (11%) and NF-κB DNA binding (7%). The anti-inflammatory effect of EPA was also matched by a decrease in NF-κB binding activity (15%, p<0.001). Paradoxically, the increase in IL-6 produced by sertraline was associated with a decrease in NF-κB binding (11%, p<0.001). Finally, pre-treatment with dexamethasone potentiated subsequent inflammatory responses, in a dose- and time-dependent manner with the greatest potentiation (38%, p<0.01) occurring at a dexamethasone dose of 100nM with a pre-treatment interval of 24 hours.

Conclusions: These results indicate that antidepressants may have varying effects on inflammation in human hippocampal stem cells – with pro- and anti-inflammatory effects demonstrated. These effects seem to be mediated by changes to the functional activity of NF-κB. Further, glucocorticoid pre-treatment appears to potentiate subsequent inflammatory response.

Funding: Studentship for MH from King’s Overseas Research Studentship, NARSAD Young Investigator Grant for PZ

MA02

INVESTIGATING THE EFFECT OF PRE-TREATMENT SLEEP ABNORMALITIES ON THE EMERGENCE OF INTERFERON-Α-INDUCED DEPRESSIVE DISORDER IN A COHORT OF HIV AND HEPATITIS C VIRUS COINFECTED PATIENTS

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Depressive disorder is a well-documented side effect of interferon-α (IFNα) treatment for chronic hepatitis C virus (HCV) infection, and a common reason for premature treatment discontinuation [Martin-Santos et al. 2008. Aliment Pharmacol Ther 27(3). 257-265]. Sleep abnormalities prior to starting IFNα treatment have been demonstrated to reasonably reliably increase the vulnerability for IFNα-induced depressive disorder in HCV-monoinfected individuals [Franzen et al. 2010. Psychiatry Res. 177(1-2). 240-245]. A significant proportion of those infected with HIV worldwide are co-infected with HCV and receive treatment, but little research has been conducted to investigate the impact of sleep on IFNα-induced depressive disorder in this group. This study aims to investigate whether baseline sleep abnormalities are predictive of IFNα-induced depressive disorder in HIV/HCV-coinfected patients.

Introduction: Inflammation has been implicated in the pathogenesis of depression. Some studies suggest that the efficacy of antidepressants and fish oil in depression may be due to their anti-inflammatory properties. We set out to investigate these properties in a relevant model of depression – inflamed human hippocampal progenitor cells. Furthermore, we aimed to explore the apparent paradox presented by the co-existence of high levels of inflammation and glucocorticoids in depressed populations (given that glucocorticoids are potently anti-inflammatory).

Method: Inflammation was induced in the human hippocampal progenitor cells by the addition of the pro-inflammatory cytokine IL-1β (10ng/mL). Each of four antidepressants – venlafaxine, sertraline, agomelatine and moclobemide – at concentrations of 100nM and 1µM and two polyunsaturated fatty acids – DHA and EPA – at concentrations of 1µM and 10µM were co-incubated with IL-1β for a period of 24 hours. The inflammatory response was measured by evaluation of IL-6 levels in the supernatant, using ELISA. Gene expression of cytokines and regulatory proteins in the cytokine pathway were measured by qPCR, and NF-κB DNA binding efficacy was measured using an NF-κB transAM kit. We also pre-treated the cells with varying concentrations of dexamethasone before IL-1β treatment to evaluate the effect on the inflammatory response.

Results: Upon co-incubation of cells with IL-1β and venlafaxine (1µM) or EPA (10µM), levels of IL-6 in the supernatant were decreased by 16% (p<0.05) and 11% (p<0.01), respectively. Conversely, sertraline (1µM) and DHA (10µM) increased the amount of IL-6 detected upon co-treatment with IL-1β by 8% (p<0.05) and 18% (p<0.01), respectively; moclobemide and agomelatine had no significant effect on IL-6 levels. The anti-inflammatory effect of venlafaxine appeared to be at least partially transcriptional: there were trends towards decrease in IL-6 gene expression (11%) and NF-κB DNA binding (7%). The anti-inflammatory effect of EPA was also matched by a decrease in NF-κB binding activity (15%, p<0.001). Paradoxically, the increase in IL-6 produced by sertraline was associated with a decrease in NF-κB binding (11%, p<0.001). Finally, pre-treatment with dexamethasone potentiated subsequent inflammatory responses, in a dose- and time-dependent manner with the greatest potentiation (38%, p<0.01) occurring at a dexamethasone dose of 100nM with a pre-treatment interval of 24 hours.

Conclusions: These results indicate that antidepressants may have varying effects on inflammation in human hippocampal stem cells – with pro- and anti-inflammatory effects demonstrated. These effects seem to be mediated by changes to the functional activity of NF-κB. Further, glucocorticoid pre-treatment appears to potentiate subsequent inflammatory response.

Funding: Studentship for MH from King’s Overseas Research Studentship, NARSAD Young Investigator Grant for PZ
**MA03**

**DEPRESSION AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH HEPATITIS C UNDERTAKING INTERFERON-ALPHA (IFN-α) TREATMENT**

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Clinical conditions, such as depression and chronic fatigue have often been associated with impairments in health-related quality of life, including lower social and physical functioning. There is increasing evidence suggesting that the activation of the immune system and the release of immune products, such as cytokines, affect behaviour and contribute to the onset of depressive symptoms. The treatment of choice for chronic viral hepatitis C, interferon-alpha (IFN-α), induces the production of other innate immune cytokines, and has been associated with the development and exacerbation of clinical conditions, such as depression. This in turn can impair the quality of life and affect treatment compliance. The aim of this study is to test whether clinical depression before starting IFN-α treatment is a possible predictor of a worse quality of life throughout the treatment.

We recruited 48 HCV patients undergoing IFN-α therapy (mean±SEM age: 43.3±1.6 years; gender: 75% males). Subjects were assessed using a prospective cohort design, at baseline and at treatment weeks 4, 8 and 12. Quality of life was assessed over the previous 4 weeks before starting IFN-α treatment, using the Medical Outcomes Study Short-Form 36 (SF-36). The SF-36 assesses 8 primary domains, such as emotional role limitation, vitality (energy versus fatigue), wellbeing and general health perception. The Inventory of Depressive Symptomatology (IDS) was administered at baseline in order to assess severity of depressive symptoms.

Patients who were depressed at baseline had lower scores in health-related outcomes at baseline and also had worse quality of life throughout the treatment, when compared with patients who were not depressed at baseline. Specifically, depressed patients had significantly lower scores on specific domains, such as emotional role limitation, vitality, wellbeing and general health perception (p=0.012, p=0.001, p<0.0001 and p=0.014, respectively), when compared with non-depressed. In particular, depressed patients had lower energy scores at baseline, treatment week 4, 8 and 12 when compared with non-depressed (40.7±16.3 vs. 68.1±19.2, 26.3±16.4 vs. 47.7±28.2, 21.0±11.5 vs. 43.5±28.6, 22.3±13.7 vs. 42.9±30.8, respectively). Scores in general health perception were also significantly different between depressed and non-depressed at treatment week 4, 8 and 12 (41.7±19.1 vs. 57.4±23.8, 38.7±21.1 vs. 54.8±22.6, 38.7±16.5 vs. 56.8±25.4, respectively). Our findings show that being depressed before starting IFN-α treatment is associated with worse quality of life throughout the treatment and suggest that depressed patients are more vulnerable to the effects of IFN-α, which itself may contribute to the worsening of such conditions.

**Research Funders:** This work was supported by the grant “Persistent Fatigue Induced by Interferon-alpha: A New Immunological Model for Chronic Fatigue Syndrome” from the Medical Research Council (UK) MR/J002739/1. Additional support has been offered by the Commission of European Communities Seventh Framework Programme (Collaborative Project Grant Agreement no. 22963, Mood Inflame).

**MA04**

**INTERFERON-ALPHA-INDUCED DEPRESSION: THE INVOLVEMENT OF THE KYNURENINE AND TRYPTOPHAN PATHWAY**

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Interferon-alpha (IFN-α) is the standard treatment for chronic hepatitis C virus infection. This treatment clears the virus, but induces major depression and other neuropsychiatric adverse effects in 30-50% of subjects. Although the biological mechanisms through which IFN-α treatment causes depression are still not clear, it has been hypothesised that the serotonergic system may be involved. Tryptophan is the primary precursor of serotonin and upon activation of inflammatory pathways is broken down into kynurenine, and other neurotoxic and neuroprotective metabolites. The aim of this study is to investigate changes in tryptophan metabolism and subsequent alterations in kynurenine pathway metabolites during IFN-α treatment and their contribution to the development of IFN-α-induced depression. 27 patients with chronic hepatitis C virus infection (mean±SEM age: 44.5±2.2 years; gender: 77.8% males) were assessed using a prospective cohort design; at baseline and at treatment weeks 8 and 24 (TW8 and TW24) of IFN-α therapy. Severity of depressive symptoms was assessed using the Inventory of Depressive Symptomatology. Plasma levels of tryptophan, 3-hydroxykynurenine, kynurenic acid and kynurenine were measured at the same time points using high performance liquid chromatography (HPLC). Data were analysed using SPSS. Depression scores were significantly higher at TW24 and TW8 when compared to baseline (mean=SEM: 24.5±3.1; 24.2±2.9; 14.2±2.5 respectively, p<0.001). Tryptophan levels (ng/ml) were significantly lower at TW24 and TW8 when compared to baseline (10.9±0.3; 11.4±0.4; 12.7±0.4 respectively, p<0.001). Kynurenine levels (ng/ml) were significantly higher TW24 and TW8 when compared to baseline (518.5±23.7; 474.1±16.7; 444.6±18.0 respectively, p<0.05). The ratio of tryptophan to kynurenine was also higher at TW24 and TW8 when compared to baseline (48.2±0.3; 42.6±0.4; 35.5±0.4 respectively, p<0.001). There was a trend for higher levels of 3-hydroxykynurenine (ng/ml) at TW24 and TW8 when compared to baseline (5.8±0.4; 6.5±0.4 respectively) however this was not significant (p=0.14). A partial correlation, controlling for baseline depression scores showed a positive correlation between depression scores and 3-hydroxykynurenine levels at TW24 (r=0.43, p<0.05). Moreover, baseline levels of kynurenic acid were negatively correlated with depression scores at both TW8 and TW24 (r=-0.36, p=0.08 and r=-0.39, p<0.05). Our data show that IFN-α significantly affects tryptophan metabolism leading to an increase in levels of potentially neurotoxic metabolites. Our findings also suggest that the reduced peripheral availability of tryptophan and the increased production of neurotoxic tryptophan metabolites contribute to the pathophysiological processes leading to IFN-α-induced depression.

This research was funded by the Medical Research Council and by the Commission of European Communities Seventh Framework Programme (Collaborative Project Grant Agreement no. 22963, Mood Inflame).
MA05
OMEGA-3 FATTY ACIDS IN THE PREVENTION OF INTERFERON-ALPHA-INDUCED DEPRESSION
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Introduction: Interferon (IFN)-α therapy for chronic hepatitis C virus (HCV) infection is frequently associated with major depressive episode (or IFN-induced depression) (Dantzer et al, 2008, Nat Rev Neurosci 9, 46-56; Su et al, 2010, Biol Psychiatry 67, 550-557; Lin et al, 2010, Biol Psychiatry 68, 140-147). The prevention with selective serotonin reuptake inhibitor (SSRI) antidepressants has been shown effective, but the routine prophylaxis with antidepressants might be argued to expose more patients (who do not develop IFN-induced depression) to an unnecessary medication exposure and adverse effects. Omega-3 (or -3) polyunsaturated fatty acids (PUFAs) deficits have been shown to be associated with risk of depression (Lin et al, 2010, Biol Psychiatry 68, 140-147; Oster et al, 2009, CNS Neurosci Ther 15, 128-133; Huang et al, 2008, J Psychiatric Res 42, 58-63; Su et al, 2008, J Clin Psychiatry 69, 644-651) and IFN-induced depression. Omega-3 PUFAs are safe and effective in the treatment and prevention of depression and psychotic disorders (Lu et al, 2010, Neuropsychopharmac 35, 2238-2248; Lin et al, 2007, J Clin Psychiatry 68, 1056-1061; Lin et al, 2012, Molecular Psychiatry 17, 1161-1163). Here we tested the effects of omega-3 PUFAs, both docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), against placebo in prevention of IFN-induced depression.

Methods: We conducted a 2-week, double-blind, placebo-controlled trial, comparing EPA (3.5 g/d), DHA (1.75 g/d) with placebo, in patients with chronic HCV before their IFN-α therapy. The structured Mini-International Neuropsychiatric Interview (MINI) was applied every other week to determine the occurrence of major depressive episode during 24 weeks of IFN-α therapy.

Results: One hundred and fifty-two subjects were randomized to DHA, EPA, or placebo groups, and were followed for 24 weeks. The incident rates of IFN-induced depression were significantly lower in EPA, but not in DHA, than in placebo pre-treatment groups (10% vs. 28% vs. 30%, respectively, p=0.037). Both EPA and DHA pre-treatment significantly delayed the onset of IFN-induced depressions compared to placebo pre-treatment (12.0 vs. 11.7 vs. 5.3 weeks, respectively, p=0.002). EPA and DHA were found well tolerated in this HCV population.

Conclusions: Omega-3 PUFAs appear to be effective in the prevention of IFN-induced depression in HCV patients received IFN-α therapy. Sources of financial sponsorship: The work was supported by the National Science Council NSC101-2628-B-039-001-MY3 (Taiwan) and Royal Society 102-2911-1-039-501 (Taiwan & UK).

MA06
INFLAME-BEAT: ELEVATED INFLAMMATION AND NEUROTOXIC DIVERSION IN THE KYNURENINE PATHWAY OF TRYPTOPHAN METABOLISM IN HEART DISEASE PATIENTS WITH DEPRESSION
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Introduction: Inflammation in medically ill patients is associated with high prevalence of depression. In coronary heart disease (CHD) patients, in addition to psychological and social morbidity, depression exacerbates adverse cardiac outcomes, increasing the risk of cardiovascular morbidity and mortality (Miller et al., 2002, The American Journal of Cardiology, 90: 1279-1283). However, the physiological mechanisms underlying the increased incidence of depression in patients with CHD are yet to be understood. Alteration of the hypothalamic-pituitary-adrenal axis is observed in a significant proportion of patients with major depression and seems to reflect an impaired ability of glucocorticoid hormones to exert their physiological effects (Pariente, 2006, J Psychopharmacol, 20: 79-84). In addition, disturbance in tryptophan metabolism pathway and the shift towards neurotoxicity potentially contributes to depression (Wicher et al., 2004, Molecular Psychiatry, 10:538-44). This project aims to understand the role of inflammation in the development of depression in patients with heart disease.

Methods: The Inflame-Beat project is a 2-year prospective cohort study. CHD patients with depression (n=29) and without (n=58) were recruited. Depression status was assessed by means of CISR (Clinical Interview Schedule revised) for diagnosis of depression, and Beck depression inventory for depressive symptoms. Plasma and salivary cortisol were measured using commercially available ELISA kits. Gene expression of glucocorticoid receptor (GR) was conducted via qPCR. GR function was measured on isolated peripheral blood mononuclear cells (PBMC) using the dexamethasone inhibition of lipopolysaccharide-stimulated IL-6 production method.

Results: Depressed CHD patients showed higher levels of CRP in serum compared with CHD non-depressed (mean 7.39 vs. 4.93 mg/L, p<0.05). Both plasma cortisol levels and salivary cortisol awakening responses were significantly lower in depressed patients. The depressed group exhibited a significant reduction in GR expression (-31%, p<0.05) accompanied by a reduced GR function (IC50: 8.12 vs 7.59 [M], p<0.01). Serum tryptophan levels were significantly lower in depressed patients (10.42 vs 12.64 µg/ml, p<0.01) who also showed an increased kynurenine/tryptophan ratio (74.43 vs 62.21, p<0.05) which in turn was associated with an increased in 3-hydroxykynurenine levels (r=0.432, p<0.01).

Conclusions: Reduced glucocorticoid responsiveness due to decreased number and sensitivity of GR may lead to insufficient glucocorticoid signalling and thus elevation of inflammation in CHD patients with depression. An increased inflammatory response in turn may lead to diversion of the kynurenine pathway towards the neurotoxic branch.

This study was supported by EU-FP7-HEALTH-F2-2008-222963 “MOODINFLEAME”; British Council-Partek Partnership; Biomedical Research Council, King’s College London; and ECNP Young Investigator Award to Livia Carvalho.

MA07
A SYSTEMATIC REVIEW OF INFLAMMATORY BIOMARKERS IN RELATION TO TREATMENT-RESISTANT AFFECTIVE DISORDER
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Since the emergence of the macrophage theory of depression (Smith, 1991, Medical Hypotheses, 35(4): 298-306), the presence of an elevated inflammatory response in both unipolar and bipolar disorders has been supported by a body of literature, and there are indications that inflammation may represent a ‘state’ rather than ‘trait’ marker in these patients (Janssen et al., 2010, Human Psychopharmacology, 25(3): 201-215). However, the nature of the relationship is still uncertain despite a range of research. In light of this, and in the search for clinically useful predictors of treatment response in affective disorder, a systematic review of the relationship between inflammation and treatment response was conducted. MEDLINE, EMBASE, PsycINFO and Google Scholar were searched to identify relevant studies, which included any investigation reporting inflammatory change in affective disordered patients alongside response or resistance to treatment. A narrative review that examined a wide variety of possible confounding variables was conducted. Meta-analysis was not carried out due to substantial methodological heterogeneity between studies. 35 studies were included in the review, measuring a total of 1621 patients. The most frequently analysed inflammatory variable was interleukin-6 (IL-6) which, in 6 out of 13 studies, showed higher IL-6 levels to be associated with non-response to treatment. However, there was still substantial inconsistency between individual studies and with other immune markers discrepancies between studies were even more pronounced. In conclusion, despite some evidence of inflammation as a predictor of poor treatment response, there are further complexities in this relationship still to be unravelled. The authors suggest that looking at disorder subtypes, and identifying specific aetiological factors such as childhood adversity, are likely to be more fruitful paths for future research to follow.
MA08

GENE EXPRESSION AS PREDICTORS OF ANTIDEPRESSANT RESPONSE USING ROC ANALYSIS IN THE GENDEP STUDY

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To improve the “personalized-medicine” approach to the treatment of depression, we need to identify biomarkers that, assessed before starting treatment, predict future response to antidepressants. We tested the leukocyte mRNA expression levels of genes belonging to glucocorticoid receptor function, inflammation and neuroplasticity, in 34 healthy controls and 74 depressed patients, as part of the GENDEP study. In a previous report (Cattaneo et al., 2013; Neuropsychopharmacology 38(3):377-85), we found that the levels of IL-1β, MIF and TNF-α at the baseline were all strongly and negatively correlated with treatment response (IL-1β, r=-0.56; MIF, r=-0.62; and TNF-α, r=-0.44; all p<0.0001). However, the contribution of the 15 genes to prediction may have not been adequately captured by simple correlation analyses. In order to better evaluate the accuracy of these predictors, we have run a receiver operating characteristic (ROC) analysis. N=23 patients (31%) did not respond to antidepressants (escitalopram or Nortryptiline), that is, did not show a reduction in MADRS score of 50% or more. Using “lack of response” as positive actual state in the ROC analysis, four genes plotted above the reference line (that is, higher gene expression predicting lack of response) with areas under the curve (AUCs) that were indicative of at least “fair” predictive value: MIF (0.9), IL-1β (0.8), TNF-α (0.8) and FKBP-5 (0.7). All the other genes had AUCs <0.7, indicating poor predictive values. Further analyses indicated that the expression values of these genes that had the best combination of sensitivity and specificity in predicting lack of response were: 1.35 for MIF, 1.56 for IL-1β, 1.55 for TNF-α, and 1.34 for FKBP-5. Our data suggest that monitoring the levels of these genes could identify depressed patients who are least likely to respond to first-line antidepressants, and this could allow doctors to consider early introduction of more assertive therapeutic approaches of combining antidepressants or adding adjuvant therapies. All the authors have no financial interests to declare. The GENDEP project was supported by a European Commission Framework 6 grant (contract reference: LSHB-CT-2003-503428). This specific project has been supported by a grant from the Commission of European Communities Seventh Framework Programme (Collaborative Project Grant Agreement no. 22963, Mood Inflame) and a Clinician Scientist Fellowship from the Medical Research Council, UK (G108/6063), to CMP; by a NARSAD young investigator award to PZ; by a grant from the Psychiatry Research Trust, UK (McGregor 97) to CMP and AC; by grants from the Italian Ministry of Health (Ricerca Corrente) and Regione Lombardia (ID:17387Sal-13) to MG; and by salary support to CMP, GB, and PZ, and a Studentship to CA, from the National Institute for Health Research Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London.

MA09

DEVELOPING AN ANIMAL MODEL TO STUDY INFLAMMATION AND STRESS IN DEPRESSION

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Multiple lines of evidence suggest that the immune system is compromised in depressed patients; however it is not known whether inflammation is a consequence or one of the risk factors of the disease (Haroon E et al, 2012 Neuropsychopharmacology 37(1) 137-62). To develop an animal model to study the role of inflammation in depression, we propose to sensitize mice with an acute exposure to lipopolysaccharide (LPS), and then expose these mice to unpredictable chronic mild stress (UCMS). To validate the transient sickness effect of a single LPS exposure, we injected adult BALB/cj mice with either 0.15mg/kg (LPS 0.15) or 0.33mg/kg LPS (LPS 0.33) or saline (Veh). Body weight, food intake and locomotor activity in the home cage were assessed at various time points post injection. In addition, mice were tested in the forced swim and open field test 24 hr and 72 hr post injection, respectively. A significant reduction in body weight was observed in mice treated with LPS 24 hr post injection (Mean±SEM, n=12: Veh=25.1±0.5 LPS 0.15=23.6±0.4, LPS 0.33=23±0.3), which recovered 48 hrs post injection (Drug X Time F[8,33]=14, p<0.001). Body weight changes were accompanied by a significant reduction in food intake at 24 hr (Mean±SEM, n=10-11: Veh=3.7±0.3, LPS 0.15= 2.1±0.4, LPS 0.33=1.3±0.3), which also recovered 48 hr following LPS injection (Drug X Time F[8,28]=6, p<0.01). Locomotor activity in the home cage was significantly reduced 2 hours post LPS injection (Mean±SEM, n=7: Veh=142±1±92 LPS 0.15=663±95, LPS 0.33=747±120) and returned to control levels 48 hr post LPS injection (Drug X Time F[8,18]=5, p<0.001). LPS did not alter behaviour in the open field test. 24 hours post LPS injection, mice spent more time immobile in the forced swim test (Mean±SEM, n=36: Veh=8±8±13.1 LPS 0.15=105±9.6 LPS 0.33=126±8.4; Drug factor F[2,33]=3, p<0.05). These data demonstrate that a single LPS exposure induces transient changes indicative of sickness behaviour, corroborating previous research using LPS to stimulate the immune system in mouse. Subsequent experiments will combine acute exposure to LPS with UCMS to test the utility of this approach to study the interaction between the inflammatory system and chronic stress.

The project is funded by Janssen Pharmaceutica NV studentship.
ABSTRACTS

MA10

EXPOSURE TO ANTENATAL DEPRESSION, NEONATAL BEHAVIOURAL DYSREGULATION AND THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS

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Aims: To examine the effect of exposure to antenatal depression on neonatal regulatory behaviour and their HPA axis, in order to improve the understanding of the mechanisms of developmental programming.

Methods: Pregnant women were recruited at 25 weeks gestation; cases had a DSM-IV diagnosis of major depressive disorder (MDD) during pregnancy and controls had no history of psychiatric disorder. Demographics and maternal mood were assessed at baseline. Offspring behaviour was assessed at 6 days post-partum with the Neonatal Behavioural Assessment Scale (NBAS), and neonate saliva cortisol was measured before and after the assessment. Offspring of case and control women were compared for regulatory behaviour during the assessment. Correlations were measured between neonatal behaviour and cortisol response.

Results: 104 neonates were assessed with the NBAS (55 control offspring, 49 case offspring). Non-parametric tests were performed for the analyses. Compared with control offspring, case offspring were less alert (Z=3.27, p=0.001), less responsive to animate (Z=3.82, p<0.001) and inanimate (Z=3.53, p<0.001) stimuli, less mature in their motor responses (Z=3.03, p=0.002), more active (Z=2.15, p=0.03) and irritable (Z=1.98, p<0.05), and less able to regulate their state (Z=2.43, p=0.015). Saliva cortisol was taken from 52 neonates (19 control offspring and 33 case offspring) just before the administration of the NBAS and immediately following. Overall, difficulties in neonatal regulatory behaviour (alertness, motor maturity, activity, irritability and state regulation) were significantly correlated with increased cortisol levels following the administration of the NBAS.

Conclusion: In support of current proposed mechanisms of foetal programming, these results show that exposure to maternal depression in utero is associated with suboptimal neonatal behaviour at 6 days. Furthermore neonatal regulatory difficulties are associated with increased HPA axis activity following the stress of being handled during the assessment.

The study was funded by Central Research Fund, University of London, Foundation for the Study of Infant Death.

MA11

THE EFFECT OF CHRONIC RESTRAINT STRESS ON ANXIETY-RELATED BEHAVIOUR IN THE ELEVATED PLUS MAZE IN JUVENILE MICE

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Introduction: Adolescent depression is a prevalent condition affecting up to 6% of 13-18 year olds (Masi et al., 2010, Expert Opin Pharmacother, 11:375-386). Antidepressant drugs clinically used to treat adult depression are associated with poor efficacy and increased suicidal behaviour when used in adolescents. There are currently few animal models of adolescent depression. Stress is consistently correlated with an increased risk of depression, both in adults and adolescents. In rodents, restraint is a widely used method of stress (Buyntskis and Mostofsky, 2009, Neurosci Biobehav R, 33:1089-1098), and chronic restraint stress has been shown to increase anxiety and depression-related behaviours in adult mice (Kim and Han, 2006, J Neurosci Res, 83:497-507). This study aimed to develop a model of adolescent depression by investigating the behavioural effects of chronic restraint stress in juvenile mice.

Methods: Individually housed male BALB/cAnNCrl mice (Charles River UK), aged 4-5 weeks (juveniles) and 9-10 weeks (adults) were randomised into stressed and non-stressed groups (n=8/group). Stressed mice underwent 7 days of restraint (2 hours per day) in a restraint device, whilst non-stressed mice were gently handled each day. Two days following the last restraint session, all mice were tested in the elevated plus maze (EPM), in a 5 minute session under lighting conditions of 20 lux in the open arms and <1 lux in the closed arms. Behaviour in the EPM was recorded by MotorMonitor software (Campden Instruments) using infra-red beam breaks. The effects of stress, compared with non-stress, were analysed using unpaired t-tests (In VivoStat software).

Results: In juvenile animals, chronic stress increased the time spent, the distance travelled, and the number of entries into the open arms (P<0.05). Similarly, in adult animals, chronic stress increased the time spent, and the distance travelled, in the open arms (P<0.05). Stress had no effect on total locomotor activity in the EPM in either adult or juvenile animals.

Conclusion: Chronic stress produced an anxiolytic-like behaviour in the EPM in both juvenile and adult mice. The increased exploration of the open arms of the EPM in stressed mice suggests that the open arms are less aversive after chronic restraint. This may reflect increasing resilience on exposure to stress. Ongoing studies measuring changes in corticosterone will confirm whether the restraint stress paradigm impacts on neuroendocrinological measures of stress.

This study was supported by a Medical Research Council Doctoral Training Grant (AMS) and an MRC In Vivo Strategic Skills Award (SJB).

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EFFECTS OF INTRAUTERINE STRESS ON ADULTHOOD AGE-RELATED DISEASE: A 25 YEAR PROSPECTIVE INVESTIGATION

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Background: Psychosocial adversity is associated with adulthood inflammation and elevated age-related disease risks (Danese et al. 2009, Arch Pediatr Adolesc Med, 163, 1135-43). In this study we test a foetal programming hypothesis by investigating the impact of very early life adversity (i.e. exposure to depression in utero) on adulthood risk factors for age-related disease.

Methods: The sample comprised a subgroup (n = 50) of participants from the South London Child Development Study. A prospective longitudinal design was employed. Data on offspring exposure to depression in utero (36 weeks gestation), exposure to childhood maltreatment (11 years) and adulthood depression (25 years) were obtained from parents and offspring through clinical interview. Furthermore, offspring underwent a physical examination at 25 years from which biological markers of age-related disease were assessed.

Results: Offspring exposed to depression in utero had significantly higher levels of high sensitivity C-reactive protein (mean difference = 2.04; p < .01) and significantly lower levels of high-density lipoprotein cholesterol (mean difference = -0.04; p < .01) compared to offspring not so exposed. Multiple regression analyses revealed these effects to be independent of the effects of concurrent adulthood depression and a history of childhood maltreatment.

Conclusions: Exposure to depression in utero appears to be an independent predictor of adulthood inflammation and age-related disease risks.

Funding: This study was supported by grants from the MRC UK, Psychiatry Research Trust and South West GP Trust.
HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS RESPONSE TO SOCIAL STRESSORS IN DEPRESSION, PTSD AND PSYCHOSIS

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Introduction: Social stressors have been recognised as an important role in the onset and relapse of different psychiatric conditions including psychosis, depression and post-traumatic stress disorder (PTSD). The hypothalamic-pituitary-adrenal (HPA) axis is the main biological system involved in the stress response and abnormalities in its activity have been seen in all these psychiatric disorders. However, since most of the studies have been so far conducted in relatively small samples, it is still unclear whether and how the HPA axis response to a social stressor differs among psychosis, depression and PTSD. Therefore, the aim of the study is to investigate the HPA axis response to a social stressor by conducting a meta-analysis of studies, which performed the Trier Social Stress Test (TSST), or comparable distressing paradigms, individuals with psychosis, depression or PTSD.

Methods: A literature search in PubMed and PsychINFO, using key words and MeSH terms such as HPA, HPA response, stress response, cortisol, social stress, social stressor, depression, psychosis, PTSD, TSST, Trier was performed. Out of 83 studies identified, only 14 included either patients with depression (6 studies), or psychosis (3 studies) or PTSD (3 studies) used a comparable social stressor and had comparable research protocol. Methodological quality of all studies was assessed according to specific quality criteria. Pooled effect size (Hedges’s g) on cortisol peak response after the stressor was compared. In order to take into account the effect of high basal cortisol level (elevated in depression, psychosis and PTSD) on cortisol peak response, we extracted data to calculate the cortisol area under the curve with respect to ground (AUCg) and to increase (AUCi). Differences were compared using Pooled effect size (Hedges’s g).

Results: Preliminary data shows that after the social stressor task, individuals with depression showed a similar response compare with controls, while individuals with either PTSD or psychosis showed a blunted response compared to controls. When comparing the overall cortisol production we found no differences between patients with depression and healthy controls in AUCg and AUCi. On the other hand people with psychosis showed a significant lower AUCg when compared to healthy control as well as a lower AUCI albeit only to a trend level.

Conclusions: People with depression have a stress response similar to healthy controls while individuals with either PTSD or psychosis have a blunted response to social stress. The last finding is in keeping with a blunted cortisol awakening response found in first episode psychosis patients. Identifying divergent profiles of HPA axis activation across different psychiatric conditions may help to understand the role of the HPA axis in the trajectory to different disorders.

USING GROWTH MIXTURE MODELLING TO ANALYSE DIURNAL CORTISOL DATA: A PILOT STUDY

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Introduction: Data in psychopharmacological studies often comes from repeated measurements over time. Growth curve modelling offers several advantages in analysing such data over traditional approaches: it can flexibly account for missing data and non-linear change, and can be used to answer a wide range of research questions relating to patterns of change over time, such as identification of unobserved sub-populations. The present study employs a growth mixture model approach to test the feasibility of using this method in a dataset of diurnal cortisol data.

Methods: Diurnal salivary cortisol data was pooled from several studies conducted in our department. Data in these studies came from patients with a diagnosis of depression or psychosis, and healthy controls. Participants were asked to collect saliva samples at 6 time points (awakening, +15 mins, +30 mins, +60 mins, midday, 8pm) during one day. Participants with more than 2 missing values in these time points were excluded from the analysis. The final sample size was N=501. Mplus7 was used for all analyses.

Results: The average diurnal cortisol curve showed a typical early peak with a decreasing course thereafter. Several models assuming different numbers of sub-classes were subsequently tested for their fit to the data. According to the Bayesian information criterion, a model assuming three classes provided the best fit to the data. Class 1 comprised 9.8% of the participants and showed higher overall level of cortisol, with a sharp awakening response. The majority of participants (82.6%) fell into class 2, with lower levels of cortisol and a somewhat smoother awakening response. Class 3 included 7.7% of participants and showed a flattened curve with low cortisol levels. Classification quality was high (entropy = 0.864).

Conclusions: Growth mixture modelling is a flexible approach to analysing longitudinal biological data and identifying development of sub-classes over time. In this study, we were able to successfully use growth mixture modelling in a heterogeneous sample of participants whose saliva cortisol levels were measured at six time points in the course of a day. The results suggest that there are separable subgroups in our data. Further studies could build on these results by identifying predictors and clinical outcomes of these classes.

Jasmin Wertz receives funding support from the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London. The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

HAIR CORTISOL ANALYSIS IN PSYCHIATRIC ILLNESSES - A REVIEW

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The role of chronic stress on health and its contribution to the development of mental illness is highly controversial. Most studies looking at chronic stress and its effects on mental health have used either inappropriate scales or biological specimens which do not accurately reflect chronicity. The use of hair is proposed as a novel specimen, where cortisol levels can be obtained and averaged over relatively long periods of time, therefore representing chronic levels of this hormone. A systematic review was carried out. Articles for this review were initially identified through searches of the PubMed, Ovid MEDLINE and PsychINFO databases. Each search cross-referenced keywords reflecting hair cortisol analysis with any psychiatric disease outcomes. To augment the yield of the database search, we also searched reference sections of review articles in the area. This review makes an attempt at synthesising all the published studies on hair cortisol concentration related to psychiatric disorders (mainly post-traumatic stress disorder, general anxiety disorder, bipolar and unipolar depression); it describes and summarises their findings in the aim of providing a clear picture of the current state of this line of research. This review uncovers a potential for certain disorders to show hypercortisolemia (major depressive disorder), or hypocortisolemia (posttraumatic stress disorder and general anxiety disorder). Hair cortisol concentration shows promise as a biomarker to differentiate between the different disorders, and may help further unravel the biological links between stress and related psychiatric conditions. Future directions in this area are described.
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THE ANTIGLUCOCORTICOID AUGMENTATION OF ANTI-DEPRESSANTS IN DEPRESSION (ADD) STUDY: METHODS, RECRUITMENT AND PATIENT CHARACTERISTICS

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Many patients with depression do not respond to first or second line antidepressants and are considered to have treatment-refractory depression (TRD). Alteration in cortisol dynamics impacts the clinical and serotonergic response to antidepressants; this, and a previous efficacy trial (Jahn et al. (2004), Archives of General Psychiatry, 61:1235-1244), supports the evaluation of the cortisol synthesis inhibitor, metyrapone in TRD. The ADD study is a randomised controlled trial of augmentation with metyrapone (500mg twice daily for 3 weeks). Recruitment (target 140) was carried out in centres in Newcastle, Manchester, Leeds, Bradford and Middlesbrough.

Patients were required to be aged 18-65, have SCID-confirmed depression, a Massachusetts General Hospital (MGH) score of antidepressant treatment of 2-10 and a Hamilton Depression Rating Scale (HDRS) score of at least 18 at screening and randomisation. The five-factor inventory (FFI) and childhood trauma questionnaire (CTQ) were completed at baseline. Primary endpoint was at five weeks (two weeks after completion of treatment) with double-blind follow-up continued for six months after randomisation. 877 potential participants responded to contact from their primary (27.0%) or secondary (36.5%) care team or to advertisement/ media reports (36.5%). Of these, 284 were screened, 173 were eligible and 165 were randomised. Patients recruited from secondary care represented 57.0% of eligible screenings. Randomised subjects’ age was 46.3±10.5 (mean±SD) years with 60% female. Screening HDRS score was 23.2±3.9, which was significantly greater than randomisation HDRS (22.3±3.4; t=4.0, p<0.001). MGH score was 4.8±1.9, 57% had comorbid anxiety disorders. Neuroticism scores were high (34.4±4.3, possible range 8-40) and positively correlated with baseline HDRS (r=25, p<0.01). Total and subscale CTQ scores (total 45.6±18.7, emotional neglect 13.7±6.15, physical neglect 8.61±3.79, emotional abuse 9.79±5.19 and sexual abuse 8.04±6.10) were elevated compared with normative community data (Scher et al. (2001), J Traumatic Stress, 14(4):843-857) (p<0.001). The variety of sources utilised in the recruitment strategy will be expected to increase the generalisability of the results. Baseline patient characteristics were in line with existing TRD literature. Neuroticism has previously been associated with poor treatment prognosis (Enns, MW, et al. (2000), J Affective Disorders, 60:33-41) and we demonstrated high neuroticism which correlated with HDRS. Raised childhood emotional neglect, found in this cohort, has been associated with neuroticism and altered glucocorticoid receptor function (Watson, S, et al. (2007), Neuropsychiatric Disease and Treatments, 3(5):647-653) so the outcome of an antiglucocorticoid augmentation strategy will be of interest in this population.

Funding: NIHR Efficacy and Mechanism Evaluation Programme.

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ALDOSTERONE INCREASES EARLIER THAN CORTICOSTERONE IN NEW ANIMAL MODELS OF DEPRESSION: IS THIS AN EARLY MARKER FOR DEPRESSION ONSET?

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Introduction: Aldosterone may be a key factor in the genesis of depression. Enhanced secretion of aldosterone occurs in depressed patients and is associated with symptom severity. However, little attention has been given to its possible role. Aldosterone is normally involved in cardiovascular function but it also has central effects. These are mediated by mineralocorticoid receptors (MRs). MR’s in brain are generally occupied by more abundant glucocorticoids. However, there are some brain areas such as the nucleus solitarius, where aldosterone is able to activate MRs in the presence of glucocorticoids. Under certain conditions and in particular under sodium depletion (during daytime) aldosterone is regulated by the renin-angiotensin system (RRA), whereas under sodium load (during sleep) aldosterone is mainly driven by ACTH. Building on this we suggest that their concentration ratio at a given time point may bring new information on aldosterone regulation in depression. Interestingly, MR antagonists have been shown to reduce depression-like behaviour in rats.

Methods: We have recently described two further animal models in male rats which demonstrate enhanced depression-like behaviour (Forced Swim Test). The first is based on sub-chronic tryptophan depletion (SCTD) and the second on chronic Mg2+ depletion. Results: Findings show that serum aldosterone rises earlier (7 days SCTD) than corticosterone (14 days SCTD) in male rats whereas in females this occurs even earlier at 4 and 7 days SCTD respectively. Mg2+ depleted rats showed enhanced depression-like behaviour and significantly increased aldosterone concentrations (p<0.05) whereas corticosterone concentrations were similar to control. Conclusions: Findings suggest that the aldosterone/corticosterone ratio is significantly reduced at 14 days in males and at 4, 7 and 14 days in female SCTD models respectively (p<0.05 in all cases). Contrarily, in the Mg2+ depletion model the ratio was significantly increased (p<0.05).

Funding: NIHR Efficacy and Mechanism Evaluation Programme.

Studies were funded by HEIF 5 at Oxford Brookes University.
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ALDOSTERONE AND BLOOD PRESSURE IN YOUNG PEOPLE AT INCREASED RISK OF DEPRESSION

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Introduction: There is accumulation of evidence showing associations between depression and cardiovascular disease (CVD). The pathophysiological mechanisms linking the two conditions are not yet well understood but may include, among others, the activation of renin-angiotensin-aldosterone system (RAAS) resulting in high circulating levels of aldosterone, a hormone involved in blood pressure (BP) regulation (Broadley et al, 2002; Heart;88(5):521-3. Emanuele et al, 2005; Arch Med Res.; 36(5):544-8). Animal models of depression suggest that elevations in aldosterone may be an early biomarker of depression (Franklin et al 2012 J Psychiatr Res.; 46(11):1394-7). In the current study we assessed central (aortic) blood pressure and evening salivary aldosterone in young people at increased risk of depression through virtue of having a depressed parent.

Methods: 83 healthy people (aged 16-20 years; mean age=18.9±1.0) with a biological parent with a history of major depression (FH), and 71 controls (mean age = 19.1±0.8) with no parental depression were recruited. The two groups were matched for age and gender. Participants provided evening saliva samples on a work day for measurement of circulating aldosterone levels measurement. To assess blood pressure, radial artery waveform was recorded by applanation tonometry of the radial pulse to generate an ascending aortic waveform and central blood pressure was derived based on a mathematical transfer function (SphygmoCor, AtCor Medical). Data was analysed with SPSSv20, t-tests and correlations were performed.

Results: There were significant group differences in aldosterone levels (t(115) = 3.72, p <0.0001; peripheral systolic BP (t(144) = 2.32, p = 0.02; and central systolic BP (t(144) 2.73, p = 0.007, that were all higher in the FH. These effects were not due to differences in current mood, trait anxiety, perceived stress, smoking behavior, BMI, physical activity and heart rate which did not differ between the groups (all p values >0.1). Aldosterone and central systolic BP were positively correlated; r=0.23, p=0.01, but there was a trend correlation between aldosterone and peripheral systolic BP; r=0.18, p=0.06. When considered separately by group, these correlations remained for the FH: r=0.25, p=0.04; but there were none in the control group; r=0.07, p=0.63.

Conclusions: This evidence shows that young people at increased risk of depression have slightly raised BP and elevations in evening salivary aldosterone. There was an association between aldosterone and central systolic BP but only in the high risk group. Therefore, aldosterone could play a role in the pathophysiology of familial depression, and may be the mechanism linking depression risk to CVD risk.

Acknowledgements: This study was funded by the Medical Research Council (MRC)

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A NOVEL ANIMAL MODEL FOR AUTISM

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Introduction: In the human clinic, prenatal exposure to the antiepileptic drug Valproate (VPA) is associated with postnatal somatic malformations and cognitive dysfunctions, which include the autism spectrum disorders. A novel behavioural and biochemical animal model for autism based on subchronic, low doses of prenatal VPA is presented. Our model differs from the original VPA model in which only a single high dose of VPA (600mg/kg) is injected at day 12.5 of pregnancy. Previously, we found an increased cell number in the neocortex using our subchronic treatment regimen, whereas the one-high dose VPA model used by other groups has been previously shown to reduce neuron numbers. Our increased cell number finding is consistent with the results of Courchesne et al reporting an abnormal excess number of neurons in the prefrontal cortex of autistic males (Courchesne E, et al. Neuron number and size in pre- frontal cortex of children with autism. JAMA. 2011;306(18):2001-2010). Here we further evaluate the subchronic VPA model behaviourally and biochemically.

Methods: Eighteen pregnant rats were exposed to daily, clinically relevant doses of VPA (20 and 100mg/kg) or saline injected as a vehicle from the 12th day of pregnancy until birth. The offspring were studied for alterations behaviour, namely play behaviour and memory in the novel object recognition (NOR). Furthermore, changes in the striatal levels of 5-HT using High Performance Liquid Chromatography (HPLC) where investigated.

Results: The VPA-pups treated with the lower dose of 20 mg VPA/kg/days expressed significantly less play behaviour compared to the vehicle-treated animals and the pups receiving 100 mg VPA/kg/day (p=0.05). In line with the behavioral data, pups from the low VPA group had significantly lower levels of 5-HT in the striatum compared with the other groups, a finding consistent with the involvement of serotonin in social play behavior (p=0.01). Furthermore the adult female rats had increased memory in the NOR test compared to controls.

Conclusions: The combination of behavioral and biochemical studies is necessary in the characterisation and development of a novel model of autism. All parameters investigated here are relevant to the human condition and reinforce the use of the offspring of subchronic VPA-treated rats as a model of human autism. A valid animal model of autism may result in a better understanding of the developmental changes occurring during pregnancy and leading to autism in the human condition. Furthermore an animal model is the first step in the testing of new pharmacological treatments of autism.

Financial Sponsorship: Aarhus University, Denmark Center of Functionally Integrative Neuroscience, Aarhus University Hospital, Denmark
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CHILDMHOOD TRAUMA IN BIPOLAR DISORDER

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Introduction: There has been little investigation of early trauma in bipolar disorder despite evidence that stress impacts on the course of this illness (Etain et al, 2008, Bipolar Disorders; 10: 867-876). We aimed to compare the rates of childhood trauma in adults with bipolar disorder to those of a healthy control group, and to investigate the impact of childhood trauma on the clinical course of bipolar disorder.

Methods: Baseline assessment data was used from a randomised placebo controlled trial of mifepristone treatment in bipolar depression (Watson et al, 2012, Biological Psychiatry; 72: 943-949). Retrospective assessment of childhood trauma was conducted using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al, 2003, Child Abuse and Neglect; 27: 169-190) in 60 outpatients with bipolar disorder being treated for a depressive episode and 55 control participants across two centres in North East England and New Zealand.

Results: Higher rates of childhood trauma were observed in patients with bipolar I and bipolar II disorder compared to controls (U = 280.5, P = 0.004; U = 203.0, P = 0.003). Logistic regression, controlling for age and gender, identified emotional neglect to be the only significant CTQ subscale associated with a diagnosis of bipolar disorder (β = 0.185, P <0.001). Childhood history of sexual abuse was not a predictor. Associations with clinical severity or course were less clear.

Conclusions: Childhood emotional neglect appears to be significantly associated with bipolar disorder. Our study confirms the findings of two previous studies (Etain et al, 2010, Journal of Trauma and Stress; 23: 376-383; Fowke et al, 2012, Clinical Psychology and Psychotherapy; 19: 450-457), that patients with a diagnosis of bipolar disorder have higher rates of childhood trauma compared to healthy controls. However, our findings differed in identifying emotional neglect, as opposed to an earlier finding of emotional abuse (Etain et al, 2010, Journal of Traumatic Stress; 23: 376-383) to be the single significant subscale associated with bipolar disorder.

Emotional neglect suggests a pervasive deficiency in the parent-child relationship (Glaser, 2002, Child Abuse and Neglect; 26: 697-714), has been linked with HPA axis dysregulation in adults (Watson et al, 2007, Neuropsychiatric Disease and Treatment; 3: 647-653) and has been previously shown to be related to depression (Spinhoven et al., 2010, Journal of Affective Disorders; 126: 103-112). Replication of this study is required, with further investigation into the neurobiological consequences of childhood trauma, particularly emotional neglect.

Funding: The study was funded by the Stanley Medical Research Institute (REF: 03T-429) and the Medical Research Council.

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QUETIAPINE’S EFFECTS ON EMOTIONAL PROCESSING AND SLEEP OBSERVE ABNORMALITIES SEEN IN BIPOLAR PHENOTYPE

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Introduction: Psychiatric illnesses, including bipolar disorder, are characterised by disrupted emotion processing and circadian rhythms. Effective treatments may exert their effects through mitigation of either of these factors. Quetiapine is an atypical antipsychotic that can stabilise mood from any index episode of bipolar disorder. We assessed emotional processing and circadian rhythms in medication-naïve bipolar phenotype individuals compared to controls (study 1) and in healthy volunteers following quetiapine vs. placebo treatment (study 2).

Methods: In study 1, we compared 32 bipolar phenotype individuals with 32 controls. In study 2, we compared 20 healthy volunteers who received 150mg quetiapine XL (titrated over 3 nights) for 7 nights with 20 matched controls who received placebo. In study 1, sleep-wake actigraphy was completed for 9-16 days prior to assessment day. In study 2, assessment of emotional processing took place on Day 8, and actigraphy was completed for 7 days pre-dose and during drug administration.

Results: In study 1, the bipolar phenotype was associated with significantly enhanced target sensitivity for surprised faces (F(1,58)=4.552, p=0.037) and a trend towards enhanced target sensitivity for positive vs. negative words during emotional recognition memory (F(1,58)=3.495, p=0.067). Bipolar phenotype individuals also showed a trend towards increased activity during the least active 5 hours of sleep (F(1,36)=3.913, p=0.056) and a trend towards reduced total sleep time (F(1,36)=3.321, p=0.077). Study 2 revealed that quetiapine treatment was associated with a trend towards reduced target sensitivity for surprised faces (F(1,36)=3.875, p=0.057), a trend towards more conservative response style for angry faces (F(1,36)=3.434, p=0.072) and a significantly more conservative response style for positive vs. negative words during emotional recognition memory (F(1,35)=4.983, p=0.032). Quetiapine treatment was also associated with significantly increased total sleep time (F(1,29)=18.528, p<0.001) and sleep efficiency (F(1,29)=5.577, p=0.025), and a trend towards improved intra-daily variability (F(1,29)=3.109, p=0.088).

Conclusions: The effects of seven-day quetiapine administration opposed many of the abnormalities recorded in individuals with the bipolar phenotype, specifically greater target sensitivity for surprised faces, enhanced processing of positive vs. negative emotional words during a memory task and reduced total sleep time. The present findings suggest a number of mechanisms through which quetiapine may stabilise mood and circadian rhythms and through which its clinical effects may be mediated. This research was funded by an MRC studentship awarded to PLR.
A LONGITUDINAL EXAMINATION OF THE EFFECT OF LITHIUM MAINTENANCE THERAPY ON GLOMERULAR FUNCTION IN PATIENTS WITH AFFECTIVE DISORDERS: A POPULATION BASED COHORT STUDY (2000-2011)

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Introduction: For over three decades there has been an ongoing debate about the effect of lithium on renal function. The quality of available data is poor and there is a need for large scale epidemiological studies that control for confounders.

Methods: The aim was to examine the effect of lithium maintenance therapy on renal function, using record linkage of population based datasets available via the University of Dundee’s Health Informatics Centre (HIC; https://medicine.dundee.ac.uk/health-informatics-centre). The design was a cohort study of patients newly commenced on lithium maintenance therapy in Tayside, Scotland, between 01.01.2000 and 31.12.2011. Patients with incidence exposure to other first line drugs (Quetiapine, Olanzapine, Semisodium Valproate; no previous lithium exposure) provided a natural comparator group. The HIC longitudinal datasets allowed exposures to be precisely calculated via records of dispensed prescriptions. Patients with a previous diagnosis of glomerular or tubulo-interstitial disease or baseline CKD stages 4/5 were excluded. The primary outcome was the estimated Glomerular Filtration Rate (eGFR) using the CKD-EPI equation. Analysis was via a random coefficients model (PROC MIXED; SAS 9.2).

Results: 1,120 patients (305 lithium exposed, 815 exposed to comparator drugs) between 18 and 65 years qualified for analysis with 13,963 eGFR values available. Mean exposure length to lithium was 55 months (SD 42, min 6, max 144). Mean decline in eGFR/year for the combined groups was 1.5 ml/min/1.73m2 (standard error [SE]4.2 ml/min/1.73m2) measured as a fixed effect, and more pronounced in subgroups with baseline CKD stage 2 or 3. There was no statistically significant difference between lithium and comparator group in time/exposure interaction. The final model identified statistically significant predictors for a reduced eGFR as age, baseline eGFR, co-morbidities, co-prescriptions and a categorical lithium toxicity marker. As an alternative exposure parameter mean lithium serum level, but not exposure length was significant.

Conclusions: The analysis suggests that there is no difference between lithium and comparator group with respect to the effect of lithium on the rate of decline in eGFR over time. Patients with impaired baseline renal function show a more pronounced decline in eGFR over time, with no difference between exposure groups. Our results therefore shed doubt on the previous concept that long-term lithium therapy is associated with nephrotoxicity in the absence of episodes of acute intoxication, and that duration of therapy and cumulative dose are the major determinants of toxicity.

Funding HIC provided datasets free of charge for a MSc dissertation. No other funding.

COMPARATIVE ANALYSIS OF TREATMENTS FOR THE PREVENTION OF MANIC AND DEPRESSIVE RELAPSE IN BIPOLAR DISORDER

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Prevention of relapse in bipolar disorder is a major clinical priority. Pharmacological treatment plays a key role in relapse prevention. Illnesses differ, with some people more prone to depression and others to manic episodes. Recent clinical guidelines suggest that choice of preventative strategy should reflect this, so people where mania predominates might receive agents more likely to prevent manic relapse. However, there has been a relative lack of consistent objective data on which to differentiate between agents to make these choices. A systematic review was performed of placebo-controlled, randomised trials on the prevention of relapse in bipolar disorder. Data were extracted for rates of both relapse rates into depression and into mania or mixed episodes. Pooled estimates of effect (Relative Risk) were calculated by meta-analysis for each active agent where data was available. Separate relative risk estimates for prevention of depression and prevention of mania/mixed episodes were obtained. A novel graphical presentation was employed to capture effectiveness of agents in preventing relapse into each pole and uncertainties around those estimates. Studies were identified comparing placebo to a range of active treatments including antipsychotics, lithium, anticonvulsants and an antidepressant, imipramine. In total across these studies, over 3000 participants had been randomised to receive active maintenance treatment. Graphical analysis indicated that several agents (lithium and antipsychotics) had similar effects in prevention of mania but differed in their propensity to alter rates of depressive relapse. A different and more diverse pattern of effect was observed for the anticonvulsants and antidepressant where data were available. This analysis confirms the observation that available maintenance treatments differ in the extent to which they protect against manic and depressive relapse in bipolar disorder. Understanding these differences may help to inform more rational choices of personalised preventative treatment. Financial sponsorship: None.

MELATONIN IN ACUTE MANIA INVESTIGATION (MIAMI-UK) – PRELIMINARY RESULTS FROM AN RCT

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Introduction: Melatonin (MLT) has been used as a hypnotic in slow release form (Circadin), licensed in the UK for > 55 years age. MLT administration can lead to circadian phase adjustment and may be anti-gonadotrophic. This is the first double-blinded RCT to investigate MLT as an add-on treatment for hypomania or mania in Italy. 5) Berkshire NHS Foundation Trust, Prospect Park Hospital, Reading. UK

Methods: Participants in this add-on trial were in- or out-patients with bipolar disorder and relapsing into hypomania or mania. Participants were recruited but were only randomised when their Young Mania Rating Scale (YMRS) score was >/=20, to extended release Circadin 2mg/day or matching placebo, taken 1-2 hours before bed for 21 days. Ratings included the YMRS, Altman Self Rating Mania Scale (ASRMS), Leeds Sleep Evaluation Questionnaire (LSEQ), QIDS-C and SR (for depression). Activity counts of the actigraph were stored in 1 minute epochs, allowing 22 days of continuous use. Recorded data were analyzed with Cambridge Neurotechnology Ltd. Actiwatch Sleep Analysis software.

Results: Sixty one bipolar patients were screened and 41 (22 female; aged 18-62; mean age 41.0) randomised. Of the 41 patients, 13 were inpatients throughout the study, 18 patients and 10 had a mixed in and outpatient stay. The primary endpoint, YMRS at 21 days, showed no difference between circadin patients and the placebo group (p=0.4470). Fewer patients had ASRMS>10 at day 21 in the Circadin group (p=0.0500). For the depression scales the proportion of patients improving with a self-report measure QIDS-SR ≤5 at 21 days was statistically significantly greater on circadin (p= 0.0462) but the clinician rated version QIDS-C was not (p=0.4301). There were no differences between Circadin and placebo in LSEQ parameters at 21 days.

Conclusions: Although these findings are preliminary, an initial perspective is that the self-report measures of mood may be more sensitive to some mood parameters than the clinician rated scales. This dissociation between measurable symptoms and signs could be an emerging difference in the patients’ perception of recovery from mood episodes while using a slow release version of a natural neuro-hormone, but will need replication in a larger sample size.

Funded by NIHR

The Melatonin In Acute Mania Investigation (MIAMI-UK) project is supported by the National Institute for Health Research (NIHR) Research for Innovation, Speculation and Creativity (RISC) Programme. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.
**MB01**

**THE EFFECTS OF CAFFEINE AND GLUCOSE DRINKS ON A SIMULATED MORNING DRIVE TO WORK AFTER RESTRICTED SLEEP**

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Introduction – sports and energy drinks are widely sold with claims to enhance performance when fatigued. Sports drinks contain sugars to provide energy, whilst energy drinks contain both sugars and caffeine. Earlier research has shown that caffeine drinks can improve simulated driving performance, but with significant effects seen only after hours of a sustained drive (Mets et al 2011 Psychopharmacology 214, 737-745). The present study investigated a 15 minute simulated drive (typical commute) after a restricted (4 hours) night sleep.

Methods – Eleven male and ten female healthy young adults (mean 23, 18-37 years) received 250ml of Lucozade (R) body fluid 16.5g carbohydrate/71Kcal; Red Bull (R) energy drink 27.5g carbohydrate/113Kcal, caffeine 80mg; and energy drink placebo amongst other ingredients, in a balanced order, using a double blind repeated measures design spread over 2 weeks. After a minimum 12 hours without alcohol or caffeine, assessments included two 15 minute simulated drives using a DASS (Stowood Scientific) divided attention steering simulator, with the first drive before and the second 30 minutes after treatment administration. Subjective mood (Bond & Lader VAS scales) was assessed pre drive, then before and after the post treatment drive. Sleep restriction was monitored with actiwatches (CamNtech).

Results – Post treatment differences from baseline were analysed using ANOVA followed by paired comparisons. Significant driving measures with ANOVA (P<0.05) provided significant paired comparisons (P<0.05) with improvements for energy drink compared to placebo for response time and steering deviation. Energy drink also reduced steering deviation from the ceiling of the road compared to sugar drinks. Significant (P<0.05) treatment contrasts for VAS mood included greater alertness, attentiveness and feeling more energetic after energy drink compared to both placebo and sports drink, but no treatment differences for coordinated, happy and relaxed mood dimensions.

Conclusions – Energy drink (caffeine + sugar) was found to be superior to energy drink (sugar) on objective driving performance including steering accuracy and response time to a peripheral stimulus, as well as increasing alert, attentive and energetic mood dimensions. These findings suggest that in a sleep restricted state the caffeine content of energy drinks may be superior in combating fatigue than sugar alone. Improved driving performance was of particular interest as earlier studies recorded improvement with caffeinated drinks after hours of driving. The shorter duration of action of sugars (e.g. Scholay and Kennedy 2004 Psychopharmacology 176, 320-330) might have been predicted to improve performance for the 15 minute drive assessed here.

No financial sponsorship was received for this study.

**MB02**

**INSOMNIA AND RISK TAKING**

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Individuals with insomnia report daytime cognitive impairment as a particularly debilitating aspect of the disorder; more so than nocturnal symptoms. Many studies have reported that low-level cognitive processes associated with sleepiness (e.g. vigilance) are either unaffected in this population or receive compensatory effort to maintain high functionality. Instead, complex tasks which engage higher level cognitive processes might be more affected and may underlie functional impairment in insomnia, e.g. problem-solving, decision making and risk taking. Despite this, there is a paucity of research looking at insomnia and decision making. We investigated associations between insomnia severity and performance on a computerised measure of contingency dependent risk taking. Ninety-four healthy young adults (78% female, mean age =20.31) completed a self-report measure of insomnia severity (Insomnia Severity Index), current sleepiness (Stanford Sleepiness Scale), negative affect and attentiveness (visual analogue scales), cognitive failures (Cognitive Failures Questionnaire) and the Risky Choice Task (Fairchild et al., 2009). On each trial, participants chose between a risky, experimental gamble (in which the expected value (EV) of gains and losses was systematically varied) and a safe, control gamble (which only involved small losses and gains, and had an EV of 0). Participants were instructed to gain as many points as possible. Insomnia severity was associated with risk taking on trials in which the experimental gamble had a low EV (< 40 and < 10). Choice of the experimental gamble on unfavourable trials (EV = -40) was further associated with self-reported inattentiveness and sleepiness (ps< .01). In contrast, moderate risk taking (when the experimental gamble had an EV of -10) was associated with negative affect. Insomnia severity was associated with self-reported negative affect (p<.01), sleepiness (p<.05), cognitive errors (p <.01) and inattentiveness (p<.05). However, the relationship between insomnia severity and risk taking remained significant when controlling for these variables. Insomnia severity was not associated with decision making on trials with favourable outcomes. Our results show that insomnia severity is uniquely related to risk taking on trials in which selecting the risky choice is maladaptive. The results are consistent with previous studies which have found that sleep deprivation is associated with reduced regard for negative consequences when faced with the possibility of high levels of reward, and that disruption to the emotional ‘valuation’ of risks and consequences of behaviour may be a feature of insomnia.

**MB03**

**SLEEP DISTURBANCE AND PAIN SEVERITY: THE INFLUENCE OF AFFECTIVE AND ATTENTIONAL STATE**

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Sleep disturbance is reported amongst two thirds of chronic pain patients. There is a complex relationship between chronic pain and sleep; pain can disrupt sleep and, conversely, poor sleep can exaggerate pain intensity. This cyclic relationship not only exacerbates drive states but also induces both somatic and non-somatic attentional problems. This study aims to evaluate the reciprocal relationship between these concomitant disorders and their subsequent impact on pain levels. A total of 242 patients were recruited from an outpatient pain clinic (Frenchay Hospital, UK). Patients were provided with a self-report questionnaire booklet containing: the Brief Pain Inventory, Pittsburgh Sleep Quality Index (PSQI), Patient Health Questionnaire and Pain Vigilance and Awareness Questionnaire. Using three components of the PSQI (daily disturbance, efficacy and perceived quality) hierarchical linear regression analyses were used to assess what factors of sleep contribute to alterations in mood, pain-related awareness and pain. Twenty one patients failed to complete the questionnaires. Patients (n = 221) were aged between 20 and 84 (mean = 51.8, S.D = 15.2), 59% female and the majority of white ethnicity (94.1%). Regression analyses found that the model with all variables included predicted the most variance in pain severity [R2=.283, F (1, 214) = 12.81, p <.001]. When looking at the contribution of the independent variables, both mood (β = .289, t = 3.60, p <.001) and pain-related awareness (β = .27, t = 4.00, p <.001) influenced pain severity. The addition of mood to the model reduced the contribution of pain-related awareness and importantly, caused sleep disturbance to no longer have an effect (β = .068, t = .890, p =.374). The influence of sleep appears to be mediated by both mood and pain-related awareness. Structural equation modelling was used to further explore this mediation. Sleep disturbance contributed to increased negative mood states and to heightened pain-related awareness, but did not directly influence pain severity. Instead, the relationship between sleep disturbance and heightened pain severity is mediated by negative mood states and maladaptive attention processes. Such processes may be critical in amplifying the effects of sleep deprivation in chronic pain and can prolong and exacerbate pain states. Understanding how these factors influence the effects of sleep disruption could be critical in facilitating treatment options for patients.
MB04
MANAGEMENT OF INSOMNIA WITHIN GENERAL PRACTICE: A QUESTIONNAIRE AND QUALITATIVE INTERVIEW STUDY
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Introduction. BAP guidelines for treatment of insomnia and other sleep disorders (Wilson et al. J Psychopharmacol 2010; 24: 1577-1600) noted although low doses of sedating tricyclic antidepressants such as amitriptyline are often used to treat insomnia in primary medical care, the evidence base to support this intervention is limited. We wished to gain an understanding of current general practitioner (GP) management strategies for insomnia and their experience of and attitude to the use of psychotropic medications for insomnia.

Methods. Postal questionnaire survey of 308 GPs working in a wide variety of practices in urban and rural settings in the south of England, followed by face-to-face qualitative interviews with a purposive sample of 21 GPs to gather rich contextual data that could not be collected in the survey.

Results. The questionnaire survey had a usable response rate of 56%. The majority (80%) of GPs reported seeing a patient with a sleep problem at least once a week. Respondents look for signs of depression and anxiety and if present treat these first. ‘Sleep hygiene’ advice is provided by the majority (88%) of GPs but is often insufficient, and many feel under pressure to prescribe. They reported only limited access to secondary care services or practitioners with expertise in CBT for sleep problems. Benzodiazepines and ‘Z drugs’ are commonly prescribed (that is, used in between 30-69% of patients with sleep problems: reported by 11.4% and 16.8% of respondents, respectively), but often reluctantly and for short periods, because of perceived problems with dependence and tolerance. Many more GPs (31.3%) commonly prescribe low dose amitriptyline to manage patients with insomnia, and perceive amitriptyline to be effective in many cases and a longer-term option for patients with ongoing sleep problems.

Conclusions. Amitriptyline is frequently prescribed to primary care patients with insomnia, despite a poor evidence base to support its use. Further research is required to assess the potential effectiveness and acceptability of low-dose amitriptyline in the management of insomnia.

Declaration of interest. Funded by Primary Care and Population Sciences, University of Southampton.

MC01
EFFECTS OF LEVOCETIRIZINE (5 MG) AND HYDROXYZINE (50 MG) ON COGNITIVE AND PSYCHOMOTOR PERFORMANCE DURING SIMULATED DIVING AT 30 AND 10 METERS
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Introduction. Information on the effects of antihistamine drugs under hyperbaric conditions is scarce, even though these drugs are widely used by divers. The purpose of this study was to investigate the effects of levocetirizine and hydroxyzine on cognitive and psychomotor performance during simulated diving.

Methods. Twenty-four healthy male divers were recruited at The Royal Netherlands Navy. In a double blind, crossover trial they received levocetirizine (5 mg), hydroxyzine (50 mg), or placebo. Six cognitive and psychomotor tests measuring reaction time and number of errors were conducted on mobile phones and included arrow reaction time, number pairs, arrow flankers, memory scanning, paired associate learning, and serial sevens. In addition, a mental effort scale and the Karolinska Sleepiness Scale (KSS) were completed. Measurements were conducted at baseline (T1, before treatment administration, on surface), during simulated diving at 4 Bar/30 meters (T2, 60 min) and 2 Bar/10 meters (T3, 80 min), after returning to surface (T4, 140 min), and after recovery (T5, 200 min, at surface). Data was analyzed with SPSS, using GLM for repeated measures.

Results. Hydroxyzine significantly impaired performance in five out of six tests (p<0.05). Increased reaction time and number of errors was most pronounced at 2 bar and after the simulated dive (T4-T5), reflecting Cmax of the drug (2h). Impairment after hydroxyzine was accompanied by significantly increased sleepiness scores (T2-T5, p<0.05). Mental effort to complete the tests was significantly increased at T2-T5. In contrast, levocetirizine did not significantly impair cognitive and psychomotor performance during simulated diving. After recovery (T5), KSS scores after levocetirizine were significantly increased relative to placebo (p=0.001), which was accompanied by a significant increase in reaction time on the memory scanning test (p=0.041) and serial sevens test (p=0.003). No significant effects were found for levocetirizine on number of errors.

Conclusions. Hydroxyzine significantly impaired cognitive and psychomotor functioning during simulated diving and thereafter. Effects of levocetirizine were inconsistent and seen only after recovery from diving. Future studies should continue to examine the effects of drugs under hyperbaric circumstances, taking into account diving-related parameters such as depth, underwater effects (cold, anxiety, etc), and time of diving.

Funding. This study was funded by The Royal Netherlands Navy, National Diving Center (Delft), and Utrecht University.

MC02
PROFILING COGNITIVE DYSFUNCTION ACROSS THERAPEUTIC AREAS USING THE CAMBRIDGE NEUropsychological TEST AUTOMATED BATTERY (CANTAB)
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Introduction: CANTAB tests have been used extensively in cognition research in a variety of central nervous system (CNS) disorders including Alzheimer’s disease (AD), mild cognitive impairment (MCI), schizophrenia, attention deficit hyperactivity disorder (ADHD), and depression. CANTAB tests measure performance in cognitive domains such as memory, executive function and attention. In addition, CANTAB tests are sensitive to detect cognitive impairments as well as effects of pharmacological and other treatments to achieve cognitive enhancement. Taking advantage of a large accumulated database across different studies over the past 10 years, the present study collated CANTAB data to demonstrate differential sensitivity relative to healthy controls in the cognitive profiles of patients with AD, schizophrenia and ADHD.

Methods: Pooled data from our clinical trials database were analysed to investigate and compare the magnitude of cognitive deficits in patients with AD, schizophrenia and ADHD relative to healthy age-matched controls. Thirteen studies were included in the analyses, with a total of 978 AD patients; 554 schizophrenia patients; 769 ADHD patients; and 250 healthy control subjects.

Results: Distinct cognitive profiles were found across patient populations, with AD patients being particularly impaired on an episodic memory test (Cohen’s d = 2.56), while patients with schizophrenia were particularly impaired on tests of executive function and sustained attention (Cohen’s d = 1.51 and 1.57 respectively). The ADHD patients mainly showed poorer performance on speed of processing and memory tasks relative to matched controls (Cohen’s d = 0.73 and 1.12 respectively).

Conclusions: This pooled data analysis shows that CANTAB is an effective tool for measuring and symptomatic profiling of cognitive dysfunction in neurodevelopmental, neuropsychiatric and neurodegenerative disorders. Importantly, the study showed that, while individual cognitive tests are sensitive tools to detect differences in a variety of cognitive domains in patients with CNS disorders relative to healthy controls, a battery of CANTAB tests is an informative tool which can be used to reveal patterns of cognitive dysfunction across key therapeutic areas. This paves the way for a dimensional approach to measuring cognitive impairments across diagnostic categories.
**MC03**

**D-CYCLOSERINE DOES NOT IMPROVE DRUG-RELATED CUE EXPOSURE: WHAT CAN WE LEARN FROM ANIMAL DATA?**

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Introduction: Drug-related cues play an important role in drug dependence and relapse, and interventions such as cue exposure therapies (CET) have been developed to reduce reactivity to them. CET is largely based on classical conditioning principles in which drug cues are presented in the absence of drug and therefore act as Pavlovian extinction trials. However, CET in the addictions has yielded weak or inconsistent results, but preclinical work with rats indicates that extinction learning may be enhanced with NMDA receptor agonists, which therefore may be useful adjuncts to CET. This has been supported by some promising results using the NMDA partial agonist D-cycloserine (DCS) in CET for anxiety and phobia. To date, a small number of studies have tested DCS on drug-related CET with mixed results. This study builds on previous research using a higher dose of DCS (250 mg) in conjunction with CET in smokers and examining the generalization of effects to other relevant behaviours. Methods: Fifty daily smokers (~10 cigarettes/day, smoke within one hour of waking) not currently trying to quit were recruited and randomly allocated to receive either DCS or placebo paired with CET. They attended four sessions approximately one week apart comprising screening/baseline (session one), drug administration and CET (sessions two and three), and cue reactivity tests (session four). Primary outcome measures were subjective craving and cardiovascular responses following a cue exposure test (session four). Secondary outcome measures were generalization tests of cognitive bias (modified Stroop), cigarette smoking (concurrence choice) and smoking behaviour (cue-related topography). Results: While there was evidence of reduced craving across CET training sessions (P<.001), no drug group differences were observed on any of the primary (Ps >.12) or secondary (Ps >.26) outcome measures. The null findings will be discussed in light of recent drug CET studies, which also found weak or null effects.

Conclusions: There is a growing body of literature suggesting that augmented CET using DCS is weaker in the field of addiction than anxiety. However, preclinical animal research appears to have made the transition more successfully than preclinical human research. This may be in part due to the relative failure of human studies to fully utilize animal data to inform research design, and the importance of cross translation will be discussed. Finally, novel avenues for research design and investigation will be offered that take account of current animal findings.

Funding: Pfizer Inc.

**MC04**

**EFFECTS OF REWARD EXPECTANCY ON ATTENTIONAL BIAS FOR REWARDING STIMULI ARE OUTCOME-SPECIFIC**

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Introduction: Attentional bias for drug-related cues is thought to be caused by the expectation of imminent substance availability, which is a consequence of repeated pairings of substance effects with environmental cues. In a recent study (Field et al., 2011, Addiction, 106, 1097-1103) we showed that anticipation of imminent alcohol availability increased attentional bias for alcohol-related cues in social drinkers. A follow up study (Jones et al., 2012, QJEP, 65, 2333-2342) revealed that reward anticipation had generalized effects: Anticipation of either chocolate or alcohol led to increased attentional bias for both alcohol and chocolate cues. However, in that study this general transfer effect may have been an artefact of the method used. We sought to replicate these findings using a modified methodology more suitable for investigating outcome-specific effects of reward expectancy. Methods: The current study used an eye tracking computer task in order to evaluate the effects of reward anticipation on attentional bias for rewarding cues in individuals (N = 35) who regularly consumed chocolate and alcohol. On a trial by trial basis, participants were informed about chances of winning (100%, 0%) either a chocolate or beer point on that trial. Points would be exchanged for beer and chocolate at the end of the study. Subsequently, a pair of chocolate-related or alcohol-related and matched-neutral pictures was displayed, and participants’ eye movements were recorded.

Results: Repeated measures ANOVA revealed a trend for a reward type x probability x picture pair x picture type interaction on eye movement dwell times (F(1, 28) = 3.86, p = .06, mp2 = .12). Within-subject t-tests showed that attentional bias for chocolate was significantly elevated on 100% vs. 0% chocolate trials (i.e. when participants expected to win chocolate). The same pattern of results was found for attentional bias for alcohol, which was greater on 100% alcohol compared to 0% alcohol trials. There were no crossover effects, in that anticipation of alcohol did not influence attentional bias for chocolate cues and vice versa.

Conclusions: In contrast to the previous study, these results indicate outcome-specific effects of reward expectancy on attentional bias for rewarding cues. Attention seems to be selectively driven towards a rewarding stimulus which is anticipated innately. Those findings contribute to a better understanding of implicit cognitive mechanisms associated with attentional bias and reward-driven behaviour.

Funded by a University of Liverpool PhD studentship.

**MC05**

**THE EFFECT OF AROUSAL ON ATTENTIONAL BIAS TO REWARDING CUES**

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Introduction: Individuals who regularly drink alcohol often show an ‘attentional bias’ to alcohol-related stimuli. The magnitude of this attentional bias is moderated by the probability of receiving a reward. However, little is known about the mechanisms that drive this effect. One possibility is that reward anticipation evokes a state of arousal which leads to hypervigilance and therefore enhances attentional bias for motivationally salient stimuli. The current study examined whether arousal would influence attentional bias to subsequently-presented rewarding stimuli. Methods: Thirty-one social drinkers (27 female) who also ate chocolate regularly were recruited for an eye-tracking study. Positive, Negative and Neutral valenced IAPS pictures were chosen from the International Affective Picture System (IAPS). On each trial of a computerised task, IAPS pictures were presented for 2s immediately before presentation of pairs of rewarding and matched neutral pictures (alcohol-neutral and chocolate-neutral picture pairs). Participants’ eye movements (gaze dwell times) were recorded with an eye-tracker. Following the task participants rated both the valence and arousal of each IAPS picture.

Results: Contrary to hypotheses, attentional bias for alcohol and chocolate cues was not elevated when those cues were preceded by highly arousing (positive or negative) IAPS pictures, relative to when preceded by neutral pictures (p > .1). However, participants rated the negative pictures as significantly more arousing than both the positive and neutral picture sets. An exploratory post-hoc analysis revealed that attentional bias for both alcohol and chocolate after negative pictures was significantly positively correlated with arousal ratings for negative pictures, even after controlling for the perceived valence of those pictures. Therefore, although there was no overall effect of arousing pictures on attentional bias, participants who rated negative pictures as extremely arousing showed elevated attentional bias for rewarding cues that were presented immediately after those pictures.

Conclusions: Attentional bias to rewarding cues is elevated after exposure to negative pictures that are rated as highly arousing, although large between-subject differences in arousal ratings masked this effect. Future studies should clarify these findings by focusing on the relationship between attentional bias and subjective arousal elicited by IAPS pictures on a picture-by-picture basis.
MC06

NEUROCOGNITIVE ENDOPHENOTYPES IN ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

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AttentionDeficit/Hyperactivity Disorder (ADHD) is a highly heritable neurodevelopmental disorder with childhood onset characterized by a complex multifactorial pattern of inheritance. Succeeding in unraveling genetic liability for such complex clinical conditions has been challenging as genetic studies have shown an inconsistent pattern of replication (Farace et al., Biol. Psychiatry, 57:1313-1323). Vulnerability markers, also called endophenotypes, are thought to lie in between the effect of the genes and the overt behavioural phenotype (Almasy and Blangero, 2001, Am J Med Genet 105(1): 42-44) and therefore should boost statistical power in molecular genetic studies aiming to identify susceptibility genes linked to the disorder (Leshner et al., 1998, Trends in Neurosci. 21(3): 102-105; Doyle et al., 2005, Biol. Psychiatry 57(11): 1324-1335. The aim of this study was to identify cognitive and neuroanatomical endophenotypes in adult ADHD.

Methods: Twenty age-matched adults diagnosed with ADHD according to DSM-IV-TR, twenty unaffected first degree relatives and twenty typically developing controls had a magnetic resonance imaging (MRI) scan on a 3T Siemens scanner, and performed two computerized cognitive tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) assessing motor inhibition (Stop Signal Task – SST) and sustained attention (Rapid Visual Information Processing - RVP). MRI data were processed using voxel-based morphometry with DARTEL algorithm implemented in SPM8; local GM and WM volume were used as dependent variables, group as fixed factor, total intracranial volume and age were used as covariates.

Results: Adults with ADHD and their unaffected first degree relatives showed a significant decrease in grey matter volume compared to controls in the right inferior frontal gyrus (r-IFG) and increased white matter volume in the posterior part of the right inferior fronto-occipital fasciculus (r-IFOF). The ADHD group also shared significant sustained attention impairments with their unaffected first degree relatives compared to controls. In contrast, response inhibition abilities were not found to be different across groups. Finally, correlation analysis showed a moderate dissociation between cognitive functions and neuroanatomy such as there was a positive significant correlation between sustained attention scores and r-IFG (r = 0.267; p = 0.039) but not with r-IFOF (r = 0.002; p > 0.985), while SST scores correlated positively with r-IFOF (r = 0.294; p = 0.023) volume but not with r-IFG volume (r = -0.103; p = 0.435).

Conclusions: Neuroanatomical abnormalities in the right inferior frontal gyrus and in the right inferior frontooccipital fasciculus are endophenotypes in adult ADHD and might constitute biological vulnerability markers for the disorder. Sustained attention is also impaired in both patients and unaffected first degree relatives, and might represent a cognitive vulnerability marker for ADHD. Finally correlation analysis showed that sustained attention abnormalities might be underpinned by grey matter abnormalities in the right inferior frontal gyrus, relating a cognitive endophenotype to a neuroanatomical endophenotype.

Sources of financial sponsorship: This work was supported by a joint Medical Research Council (MRC)/Wellcome Trust grant to the Behavioural and Clinical Neuroscience Institute. VAP was supported by a studentship from the MRC and was based in University of Cambridge, Department of Psychiatry.

MC07

META-ANALYSIS OF EMOTION RECOGNITION DEFICITS IN MAJOR DEPRESSIVE DISORDER

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Over 30 years of research has explored how depression is associated with facial emotion recognition. However, studies have investigated this relationship using various paradigms, multiple stimulus sets and several experimental tasks, thus rendering comparisons of results across studies difficult. Additionally, there has been little effort to determine the size of this effect and whether or not studies are being properly powered to detect it. We conducted a meta-analysis to synthesize the findings across relevant studies for the recognition of emotion in depressed individuals compared to controls. Studies of facial emotion recognition which included depressed and control samples were identified up to the beginning of June 2013 utilizing PubMed and Web of Science. Studies using schematic or artistically rendered faces, neuroimaging paradigms, multiple stimulus sets and several experimental tasks, thus rendering comparisons of results across studies difficult. Additionally, there has been little effort to determine the size of this effect and whether or not studies are being properly powered to detect it. We conducted a meta-analysis to synthesize the findings across relevant studies for the recognition of emotion in depressed individuals compared to controls. Studies of facial emotion recognition which included depressed and control samples were identified up to the beginning of June 2013 utilizing PubMed and Web of Science. Studies using schematic or artistically rendered faces, neuroimaging studies and studies that included drug treatments were excluded. Meta-analysis of k = 23 independent samples, within a random-effects framework, indicated impaired recognition of emotion (k = 23, d = -0.17, 95% CI -0.26 to -0.08, p < 0.001). Critically, this was observed for anger, disgust, fear, happiness and surprise (ks = 8 to 23, ds = -0.15 to -0.39, ps < 0.08), but not sadness (k = 22, d = -0.08, 95% CI -0.22 to -0.07, p = 0.29). Sensitivity analysis indicated that no single study was disproportionately contributing to this pattern of results. Power analysis based on an effect size estimate of d = -0.17 indicated that a sample size of approximately 545 cases and 545 controls would be required to detect this association with 80% power at an alpha level of 0.05. These findings suggest that the emotion recognition impairment in depression might be underpinned by grey matter abnormalities in the right inferior frontal gyrus, relating a cognitive endophenotype to a neuroanatomical endophenotype.

Sources of financial sponsorship: This work was supported by a joint Medical Research Council (MRC)/Wellcome Trust grant to the Behavioural and Clinical Neuroscience Institute. VAP was supported by a studentship from the MRC and was based in University of Cambridge, Department of Psychiatry.

MC08

HABENULA RESPONSES DURING APPETITIVE AND AVERSIVE CONDITIONING IN MAJOR DEPRESSIVE DISORDER

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The lateral habenula (LHb) has been used to respond to cues that predict aversive stimuli in non-human primates (Matsumoto & Hikosaka, 2009, Nat Neurosci, 12(1), 77-84) and has been implicated in reinforcement processing and the pathophysiology of major depressive disorder (MDD) (Roiser et al, Biol Psychiatry, 66(5),441-450), possibly via reciprocal connections with monoaminergic nuclei. We report the first high-resolution fMRI investigation of hemodynamic responses during appetitive and aversive conditioning in the LHb in MDD. Unmedicated MDD patients (n=10) and matched controls (n=10) performed a Pavlovian conditioning task where they were exposed to conditioned stimuli (CSs) that preceded reinforcing outcomes (win £1; lose £1; and painful electric shock) in a probabilistic manner. Neural responses were monitored using high-resolution T2* echo-planar imaging (1.5mm isotropic), and T1-weighted (0.77mm isotropic) images were obtained to accurately identify the habenula (Lawson, et al, 2013, NeuroImage, 64(0), 722-727). Breathing and heart-rate data were collected to correct for pulse-related artefacts. Using a temporal difference learning algorithm, trial-by-trial values for win, loss and shock predicting CSs were derived for each subject and used as parametric modulators in the fMRI analysis. We replicated our previous result that habenula responses were positive to shock-predicting CSs and negative to reward-predicting CSs in healthy volunteers (Lawson et al, 2013, submitted). We found no significant group differences in habenula responses to win and loss CSs (P>0.7), but habenula responses to the value of shock CSs were negative in MDD subjects (t(18)=1.857, p=0.080). These surprising results may reflect a difference in how depressed patients process aversive stimuli, with important implications for understanding the constructs of anhedonia and learned helplessness.

This research was funded by the Medical Research Council.
MC09

FACE EMOTION RECOGNITION IN DEPRESSION: CLARIFYING THE ROLE OF CHILDHOOD TRAUMA

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Introduction: Epidemiological studies show that a remarkably high proportion of depressed adults report having experienced childhood trauma. Altered emotional processing may mediate this relationship between childhood trauma and depressive symptomatology. For example, there is evidence that children with a history of physical abuse show preferential processing of anger over other emotions. However, how this altered emotional processing contributes to the later development of depression has not yet been clarified.

Methods: Thirty-six depressed patients and 36 healthy individuals, subdivided into those with and without a history of childhood trauma, completed a facial emotion recognition task in which they were exposed to emotions of fear, anger, happiness and sadness. The main outcomes were number of errors in recognising emotions and speed of emotional processing (response time).

Results: Healthy individuals with a history of childhood trauma made significantly more errors in recognising negative faces of fear, anger and sadness but fewer errors for positive faces of happiness than those without childhood trauma. An opposite pattern was found in the group of depressed patients. Depressed patients were significantly slower to respond to all emotions than healthy individuals.

Conclusions: Resilient individuals may display positively biased emotion recognition, which prevents them from manifesting depressive symptoms despite their early experiences of childhood trauma. In contrast, negatively biased emotion recognition may be amplified by the experiences of childhood trauma in other individuals who are predisposed to be vulnerable to depression. Thus, individual differences in emotional processing may differentially influence the pathogenesis of depression as a function of childhood trauma.

This study is supported by NIHR Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, King’s College London.

MC10

DECISION MAKING AND RISK TAKING IN YOUNG PEOPLE AT INCREASED RISK OF DEPRESSION

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Introduction: One of the core cognitive symptoms of depression is the difficulty with making decisions. Previous work examining decision making suggests that currently depressed patients are risk averse (Murphy et al (2001), Psychol Med; 31:679-693; Smoski et al (2008), J Behav Ther Exp Psychiatry; 39(4): 567-576) which has been argued to reflect a dysregulation in reinforcement systems. A related possibility is that aberrant decision making processes may themselves predispose at risk individuals to develop depression; for example an overly conservative approach to risk is likely to reduce exposure to all but the most certain rewards. In this study we tested this possibility by investigating whether young people at increased risk of depression show a risk-averse style of decision making. Methods: 69 healthy people (aged 16-20 years; mean age=18.9±1.1) with a biological parent with a history of major depression (FH), and 49 controls (mean age = 19.1±0.8) with no parental depression were recruited. The two groups were matched for age and gender and performed the computerised Cambridge Gambling Task, a probabilistic decision-making task that dissociates risk taking from impulsivity (CANTAB®). The critical outcome measure, which assessed the degree of risk taken by participants during task performance, was the average proportion of points gambled across all trials. Additional measures of decision making behavior include measures of the quality of decision making (proportion of trials in which the best gamble was chosen), deliberation time (latency) and a measure of impulsivity (delay aversion). Data was analysed with SPSSv20 and one way ANOVAs and t-tests were performed. Results: As predicted, there was a significant group difference in the measure of risk taking (F(1,110) = 6.23. p = 0.01), with the family history positive group taking fewer risks (betting fewer points) than the control group. These effects were not due to differences in current mood, trait anxiety, perceived stress, rumination, dysfunctional attitude or neuroticism which did not differ between the groups (all p values > 0.15). Similarly, the effects could not be accounted for by differences in gross task performance or impulsivity as the groups did not differ on the other measures of decision making behaviour; quality of decision making (F(1,110)=0.41, p=0.53); deliberation time (F(1,110)=2.25, p=0.14); delay aversion (F(1,110)=0.47, p=0.50).

Conclusions: While young people at increased risk of depression were generally similar to the control group in their approach to decision making, they demonstrated a significantly more conservative approach to risk, similar to that previously described for currently depressed patients (Murphy et al (2001), Psychol Med; 31:679-693). This finding is consistent with evidence of dysfunction in the neural circuitry involved in decision making and reward processing such as the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) in this high risk group (McCabe et al (2012), Biol Psychiatry, 72: 588-594). Most importantly, these findings suggest that alterations in decision making processes precede the onset of depression and may represent one route by which risk of depression is mediated.

Acknowledgements: This study was funded by the Medical Research Council (MRC)

MC11

EVIDENCE FOR SPECIFIC TASK SWITCHING DEFICITS IN VEGANISM

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Switching at will between different tasks and rules captures the essence of adaptive cognition during executive functioning. Task switching paradigms index the switch cost (SC) - the difference in reaction time (RT) between switch and repeat trials. Elevated switch costs following neurodegeneration, for example Parkinson’s disease, and brain damage (Kehagia et al., 2009; 2012) implicate corticostriatal interactions and catecholaminergic neurotransmission. Beyond disease, conscious lifestyle choices may also be associated with differences in executive function. Here, we hypothesised that veganism, which leads to lower protein intake compared to meat-eaters, may also be linked to executive functioning in groups of young healthy adults who (n=12, mean age= 22.3 yrs, mean diet duration= 28.5 months) and meat-eaters (n=15, mean age= 22.1 yrs). While pre-existing factors cannot be fully discounted, one candidate explanation for this pattern of results is the known lower serum creatine levels in non-meat eaters. Creatine is a substance which is key to energy homeostasis in the brain. Combined with the existing literature, our findings predict that creatine may also be linked to executive functioning in veganism. This study was funded by the Medical Research Council (MRC)
THE EFFECT OF KETAMINE ON FUNCTIONAL CONNECTIVITY AND ITS MODULATION BY RISPERIDONE AND LAMOTRIGINE

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Introduction: The NMDA antagonist ketamine induces glutamatergic dysfunction in humans and has been linked to transient induction of psychotomimetic symptoms. The effects of ketamine on the blood oxygen level dependent signal in the brain have been widely studied; however, its effects on whole-brain connectivity are only beginning to be studied. Here we investigate the effects of ketamine on regional coupling during resting-state and examine the modulatory effect of risperidone and lamotrigine pre-treatment on ketamine-induced connectivity patterns. We hypothesise ketamine will have a robust effect on connectivity within the brain and pre-treatment with lamotrigine and risperidone attenuating this connectivity state through modulation of glutamate levels.

Methods: Data were collected from sixteen healthy male volunteers over four sessions in a placebo-controlled cross-over experiment. These sessions comprised a control session and three sessions involving a ketamine infusion. In order to investigate the effects of glutamatergic and anti-psychotic drugs on the ketamine response, two ketamine infusion sessions included an oral pre-treatment of either lamotrigine or risperidone. Given the distributed effects of glutamate on local and long-range transmission in the brain, we applied graph-theory centrality measures to assess the degree to which ketamine alters regional connectivity. These centrality measures were used as a feature set for multivariate group comparisons using a Gaussian process classification (GPC) in order to investigate differing patterns of centrality across the whole brain.

Results: We observed that ketamine robustly and predictably altered network centrality measures throughout the brain with respect to the placebo condition. Risperidone was found to significantly alter baseline centrality in comparison to placebo. Moreover pre-treatment with risperidone robustly modulated the centrality observed for the subsequent ketamine infusion in comparison to the placebo pre-treated ketamine infusion. The classifier was unable to accurately distinguish between lamotrigine and placebo pre-treated ketamine states, but was able to significantly separate the saline condition from the ketamine state pre-treated with lamotrigine.

Conclusion: Here we demonstrate the effectiveness of using centrality measures for whole brain, multivariate group comparisons within a drug study. Our results identify discriminating patterns of centrality in subcortical and posterior cortex related to ketamine infusion compared to saline. Importantly, whilst lamotrigine which is known to modulate ketamine-induced glutamate levels, here, it did not significantly modulate ketamine-related regional connectivity; risperidone pre-treatment however significantly modulated the centrality due to ketamine administration. This suggests that the modulation of connectivity produced by ketamine may be primarily due to NMDA receptor blockade rather than increased glutamate levels.
MC14

THE EFFECT OF MDMA ADMINISTRATION ON THE PRUNING OF DECISION TREES

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Introduction: Serotonin (5-HT) has been proposed to play an important role in decision-making by reflexively ‘pruning’ away aversive options from decision trees during complex planning (Huys et al, 2012). Administration of 3,4-methylenedioxyxymethamphetamine (MDMA) acutely increases levels of 5-HT, which are then thought to be depleted for some days following its use (Curran and Travill, 1997), during which period mood has been reported to be lowered. In order to test the hypothesis that pruning is related to 5-HT we employed a decision-making task that has previously shown to index pruning 3 days after MDMA administration, and 3 days after placebo administration in a double-blind, placebo-controlled, randomized design.

Methods: In the task, participants had to navigate between 6 environmental states, each of which led to two other states; every transition was associated with a deterministic reward or punishment (win 140p, win 20p, lose 20p, or lose 70p). On each trial, participants had to devise a sequence of 3, 4 or 5 moves in order to maximize their total winnings. The task consisted of 90 trials: on 30 of which it was optimal to avoid the 70p large punishment (No Large Loss Optimal: NLLO trials); and on 60 of which it was optimal to transition through it (Large Loss Optimal: LLO). Comparison of accuracy on these two trial types to produce a ‘difference estimate’ (NLLO-LLO) provides an index of how strongly participants are influenced by the reflexive pruning process. Additionally, we calculated the proportion of trials LLO on which participants avoided the 70p large punishment, and instead took the next best option that avoided the large punishment.

Results: whilst participants showed no difference in overall accuracy or reaction times 3 days after MDMA administration compared with placebo, both indices of pruning were significantly decreased after MDMA. Furthermore, there was a trend towards a significant correlation between the change in participants’ ‘difference estimate’ and positive mood (amicableness) as defined by the Visual Analogue Mood Scale.

Conclusion: These results are consistent with the putative decrease in 5-HT 3 days after MDMA administration, which appeared to weaken participants’ ability to efficiently prune away options featuring strongly negative outcomes in a decision tree. Future research should examine the extent to which this pruning process is compromised in psychiatric disorders that may be caused by dysfunctional 5-HT transmission, such as depression.

MC15

A PROOF-OF-CONCEPT INVESTIGATION OF GENOTYPE-DEPENDENT NORADRENERGIC EFFECTS ON IMPULSIVITY

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Introduction: Growing evidence suggests a strong genetic component to impulsivity, in particular genes encoding elements of the catecholamine system, such as the noradrenergic system and the gene encoding the β-subtype of the α2-adrenergic receptor - ADRA2B. Polymorphisms in this gene (such as the Δ901 deletion variant) have been shown to enhance NA transmission and improve aspects of impulsivity, such as response inhibition (Lei et al, 2012, Europyschopharmacology, 37, 1115). It has suggested that this occurs as the Δ901 polymorphism results in a reduced functionality of the ADRA2B autoreceptor involved in presynaptic regulation of noradrenergic signalling (Small et al, 2001, J Biol Chem, 276,4917). The aims of this study are to measure the effects on impulsivity of (i) the Δ901 variant on various aspects of impulsivity (ii) reboxetine - a selective noradrenaline reuptake inhibitor (SNRI) and (iii) interactions between the Δ901 variant and reboxetine (Chamberlain et al,2007, Biol Psychiatry,62,977).

Methods: A double-blind, randomised, placebo-controlled, between-group intervention was carried out in 72 healthy white male volunteers using a 4mg dose of reboxetine. Salivary collection of DNA samples was used to enable genotyping for the Δ901 ADRA2B polymorphism. Two hours after intervention, participants were administered three tasks measuring impulsivity. These were the Stop Signal Response Paradigm, Two Choice Impulsivity Paradigm and the Iowa Gambling Task.

Results: IBM SPSS Statistics 20 was used for data analysis of results. There were no statistically significant effects of Δ901 genotype, reboxetine or genotype x reboxetine interaction on analysis of the SSRT or IGT data. However a non-significant trend genotype x reboxetine interaction, with a p value of 0.099, was found on analysis of the TCIP: Δ901 variants performed better (showed less impulsivity) when given placebo, whilst performance was impaired with reboxetine. Wt individuals performed better (less impulsive) when given reboxetine, compared to a more impulsive performance when given placebo.

Conclusions: These results are consistent with the notion that the ADRA2B Δ901 variant results in a loss of function in the pre-synaptic autoreceptor, and consequently leads to increased amounts of intra-synaptic NA than in WT. Impulsivity is associated with a hypo-activity of the catecholamine system, particularly NA. Whilst higher levels of NA can be beneficial, it is known that levels that are too high can be detrimental. If NA levels were outside of the optimum range, performance on tasks measuring impulsivity could be reduced.

Funding for this project was provided by Brighton and Sussex Medical School.
MC16

EFFECTS OF BDNF AND KIBRA SINGLE NUCLEOTIDE POLYMORPHISMS ON HUMAN MEMORY RELATED BRAIN ACTIVATION

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Introduction: Two single nucleotide polymorphisms the Brain Derived Neurotrophic Factor (BDNF) Val66Met polymorphism and the KIBRA polymorphism, have been found to modulate episodic memory and underlying neuronal circuitry. However, brain imaging studies have proved inconsistent in this respect, with some studies showing effects in one direction (decreased hippocampal activation in BDNF met carriers) and others showing the opposite pattern (increased hippocampal activation in BDNF met carriers). The study aimed to determine whether the BDNF and KIBRA polymorphisms exert an observable effect on declarative memory performance and underlying activation in the mediatal temporal lobe.

Methods: 55 healthy subjects were recruited for the study. Subjects performed an declarative memory task in the fMRI scanner involving encoding and retrieval of scenes and several neuropsychological tasks from the CANTAB battery outside the scanner. For consistency with previous studies, we adapted the imaging task from a previous study that found effects of the BDNF polymorphism on brain activation (Hariri et al., 2003, The Journal of neuroscience, 23, 6690-4). Primary fMRI analyses focused on activation during successful encoding and retrieval in MTL regions. Potential interactive effects between KIBRA and BDNF polymorphism were also assessed.

Results: In contrast to previous studies, there was no significant effect of the KIBRA polymorphism on activation during encoding in medial temporal lobe regions (p>0.05). There was no significant effect of the BDNF polymorphism on encoding related activation. Carriers of the BDNF Met allele showed increased activation in the right hippocampus during successful retrieval but this was contrast-specific and unaffected by met allele load. One effect of KIBRA polymorphism on retrieval in the right hippocampus was observed with an uncorrected for multiple comparison approach. There were no significant group differences on behavioural performance measured with the fMRI task or the CANTAB task for either genotype or their interaction.

Conclusions: Despite attempts to reproduce the methodology of previous studies as closely as possible, we found no strong evidence for a modulatory role of the KIBRA or BDNF polymorphisms on human memory performance or underlying activation in the mediatal temporal lobe, although the Met allele of the BDNF polymorphism may exert a subtle effect on the efficiency of memory retrieval. Results suggest that effects of these SNPs on memory circuitry may not be as robust as previously suspected from cross sectional studies.

MC17

COGNITIVE PROFILES OF SELECTIVE 5-HT1A AGONISTS IN RODENT MODELS OF SUSTAINED ATTENTION, IMPULSIVITY AND WORKING MEMORY

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Cognitive dysfunction is a characteristic of numerous neurological and psychiatric disorders. Pre-clinical evidence suggests stimulation of post-synaptic 5-HT1A receptors in the prefrontal cortex (PFC) will produce pro-cognitive effects. F15599 is a preferential post-synaptic 5-HT1A agonist which may have pro-cognitive effects. This project assessed the impact of F15599 (0.04 – 0.32 mg/kg) on working memory performance in rodents using the odour span task (OST), and sustained attention and impulsivity measured with the 5-choice continuous performance test (5 C-CPT). Results from the 5 C-CPT were compared to the 5-HT1A agonist F13714 (0.0025 – 0.04 mg/kg), which demonstrates preferential activation of 5-HT1A autoreceptors in the raphe nucleus, to determine if the effects of F15599 were due to selective agonism of post-synaptic 5-HT1A receptors. F15599 did not enhance OST span or reverse a ketamine (20 mg/kg)-induced deficit in this test, but impaired performance at higher doses (0.32 mg/kg). Similarly, results from the 5 C-CPT showed impairments on correct responses, omissions, correct rejections, false alarms and latency to nose poke, which were attributed to the highest dose (0.32 mg/kg) causing detrimental effects. Results with F13714 produced a similar profile action in the 5 C-CPT, with the highest dose (0.04 mg/kg) impairing attention. The results suggest that activation of post-synaptic 5-HT1A receptors may not improve basal cognitive performance in working memory and attention. However, as impairments with F15599 occurred at doses above those selective for post-synaptic 5-HT1A receptors, agonism of the latter may not have deleterious effects on basal performance in these domains. In future studies, it would be desirable to investigate the effects of F15599 in animals whose cognitive performance is impaired by stress or other pharmacological challenges for example PCP, as previously reported by Depoorteree et al. (2010) European Neuropsychopharmacology 20, 641-654. Key words: 5-HT1A agonist, cognition, F15599, odour span task, 5-choice continuous performance test, working memory, attention.
MC18
THE BEHAVIOURAL RESPONSE TO THE ALPHA2A ADRENOCEPTOR AGONIST, GUANFACINE, DIFFERS IN NEUROKININ-1 RECEPTOR KNOCKOUT (NK1R−/−) AND WILDTYPE MICE
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Mice with functional ablation of substance P-prefering neurokinin 1 receptors (NK1R−/−) display neurochemical and behavioural abnormalities resembling those seen in Attention Deficit Hyperactivity Disorder (ADHD). These include: locomotor hyperactivity in the light-dark exploration box (LDEB); and impulsivity and inattentiveness in the five Choice Serial Reaction-Time Task (5-CSRTT) (Yan et al., 2011, PLoS One, 6:3;17856). Here, we investigated whether the α2A adrenoceptor agonist, and approved ADHD treatment, guanfacine, reduces hyperactivity and improves cognitive performance. Mice were tested once-weekly in the 5-CSRTT, using a variable inter-trial interval (VITI), 30 min after treatment with guanfacine (0, 0.1, 0.3 or 1mg/kg, i.p.) or no injection. Each treatment was given to each mouse once, as a counterbalanced sequence. The lowest dose of guanfacine (0.1mg/kg) improved inattentiveness in NK1R−/− mice, but not wildtypes (P=0.004). This was a selective effect on attention because this dose did not affect the total number of trials completed, latency to correct response or latency to magazine. These results support evidence that guanfacine improves the spatial working memory (Arnsten et al., 1988, J Neurosci., 8:4287-4298). By contrast, amelioration of impulsivity or increased inattentiveness at higher doses (0.3 or 1mg/kg) were paralleled by a reduction in arousal. This was corroborated in the LDEB; guanfacine treatment reduced locomotor activity more robustly with increasing doses (F(4,40)=14.04, P<0.001). However, this effect was more marked in NK1R−/− mice, likely due to underlying disruptions to noradrenergic neurotransmission and α2A adrenoceptor function (Fisher et al., 2007, Eur J Neurosci., 4:1195-204). NK1R−/− mice also expressed more passive avoidance than wildtypes (F(1,40)=7.46, P=0.009), which was unaffected by guanfacine (F(3,32)=2.07, P<0.05), and so we next compared the behaviour of the two genotypes in the elevated plus maze (EPM) using the dose of guanfacine that was effective in the 5-CSRTT (0.1mg/kg). This was of interest because; 1) patients with ADHD often present with comorbid anxiety disorders, and 2) guanfacine reduces anxiety-like behaviour in the SH rat (which is also used in ADHD research) but not its control strains (Langen et al., 2011, Atten Defic Hyperact Disord, 3:1-12). Compared with wildtypes, NK1R−/− mice displayed a clear anxiogenic profile (F(1,6)=17.79, P=0.006), which was unaffected by guanfacine (F(1,12)=1.16, P=0.05), mimicking the findings in the LDEB. We conclude that guanfacine improves certain aspects of cognitive performance in NK1R−/− mice, at a dose that does not affect arousal or emotionality, as in ADHD patients.

This work was funded by the MRC (UK) and RenaSci Consultancy Ltd.

MC19
OPTOGENETIC STIMULATION OF GLUTAMATERGIC NEURONES IN THE RODENT PREFRONTAL CORTEX IMPROVES DISCRIMINATION PERFORMANCE IN AN OBJECT RECOGNITION TASK
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The prefrontal cortex (PFC) is known to be involved in mediating working memory for the acquisition of spatial and visual object information (Kesner, Ragozzino 2003, Behav Brain Res,146,159-165) and plays an important role in the integration of object and place information but not familiarity discriminations (Barker et al 2007, J Neurosci, 27,2948-2957). Optogenetic techniques enable the temporal control of distinct cell types in specific neural circuits, using light sensitive cation channels to induce neuronal activation. We used viral-transfected channel-rodopsin2 (ChR2) under the control of a glutamatergic specific promoter (CamKIIα) to investigate the effects of selective activation of excitatory pathways in the novel object preference (NOP) and object-in-place (OIP) tasks. We also assessed the functional activation of ChR2 expressing glutamatergic neurones using cFos immunohistochemistry. A lentivirus vector was used to deliver ChR2 bilaterally into the adult rodent mPFC (male Lister-Hooded rats, n=7), sham animals (n=6) received PBS injections. A midline cannula was implanted to provide direct access for an optrode attached to a fibre coupled laser (λ=473nm) that delivered bilateral light pulses (5ms, 50Hz, 30 sec duration). Animals underwent light stimulation during the 5 min delay between sample and test phases in NOP and OIP tasks, with light stimulation (on/off) counterbalanced in a within-subject design. In a separate cohort (n=3) cFos activation was assessed after light stimulation in unilaterally injected animals. ChR2 expression was confirmed in cortical glutamatergic neurones using immunohistochemistry. Optogenetic stimulation within the mPFC induced cFos immunoreactivity in the ChR2 expressing hemisphere compared to the sham hemisphere (570±37 vs 154 ± 37, p<0.05). In the OIP task stimulation caused a significant stim x group interaction (F(1,11)=11.74, p=0.006) with an increase in discrimination in ChR2 expressing animals under stimulation conditions (t(6)=−4.45, p=0.004). No main effect of stimulation or group was observed; discrimination remained unaffected by stimulation in sham animals. Stimulation of the mPFC during the NOP task showed no effects on discrimination performance. Our results show that optogenetic stimulation induces activation of glutamatergic neurones in the adult rodent mPFC causing enhancement of OIP discrimination performance. This suggests that selective activation of glutamatergic pathways immediately post-acquisition, strengthens the encoding of object and place information. Our findings support evidence that acquisition of OIP memory is dependent on excitatory neurotransmission during long and short retention delays (Barker, Warburton 2008, J Neurosci,28,2837-2844). We also confirmed that the mPFC does not play a role in object-familiarity discriminations.

This work was supported by funding from the Wellcome Trust.
MC20

THE KIBRA POLYMORPHISM IS ASSOCIATED WITH ABNORMAL SYNAPTIC ACTIVITY AND BEHAVIOURAL PERFORMANCE DURING ERROR PROCESSING

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Introduction: The KIBRA rs17070145 single nucleotide polymorphism (SNP) has been associated with altered cellular, synaptic and cognitive function with some evidence for higher risk for late-onset Alzheimer’s disease. KIBRA is highly expressed in cognition related structures including the hippocampus and frontal cortex. Functional Imaging studies have shown that C/C carriers have increased task related frontal cortex activity and increased synchronization in areas associated with the default mode and executive control resting state networks including the medial frontal cortex and anterior cingulate cortex (ACC). Error-related negativity (ERN) is a rapidly peaking negative deflection following erroneous behavioural responses which reflect error-processing and monitoring, with functions that are subserved by neural networks involving the frontal and ACC. While the KIBRA SNP has been shown to modulate hippocampal related neurocognitive performance, the functional effects of the KIBRA polymorphism on synaptic activity related to the ACC/frontal cortex are yet to be determined.

Rationale: The aim of the present study was to examine the effects of the KIBRA SNP on synaptic activity related to error processing using an Error Related Negativity (ERN) paradigm utilizing the Eriksen Flanker task.

Methods: Healthy subjects (free from medication and physical or psychiatric illness) were genotypeed for the KIBRA polymorphism with 59 subjects included in the study (30 C/C allele and 29 T allele carriers) in total. These subjects underwent testing with the Eriksen Flanker task whilst EEG recordings were taken from the scalp. Event-related potentials (ERPs) (i.e. ERN) and behavioural changes (i.e. post error slowing; PES) were calculated and compared amongst groups in SPSS using repeated measure ANOVA's and T-tests with the use of equivalent non-parametric tests for non-evenly distributed data.

Results: Compared to the C/C carriers, T carriers showed a larger ERN (group difference = 1.883uV; F(1,52)= 8.272; p=0.006) accompanied by reduced PES (t(52)=2.572, p=0.013), suggesting abnormal error related synaptic activity and associated behavioural adjustment.

Conclusions: The KIBRA polymorphism was associated with functional and behavioural abnormalities in error processing linked to the ACC and frontal cortex. The larger ERP amplitude and associated reduction in post-error slowing, suggests potential compensatory effects in the error-processing network in carriers of the T allele. This study was funded by GlaxoSmithKline Pharmaceuticals.

MC21

THE EFFECT OF BDNF VAL66MET POLYMORPHISM “MET LOAD” ON ERROR PROCESSING

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Introduction: The brain-derived neurotrophic factor (BDNF) plays an important role in synaptic plasticity and connectivity in the human brain. Carriers of the Met allele of the BDNF val66met polymorphism have been found to show suboptimal cognitive performance and the gene variation has also been linked to susceptibility to neurodegenerative disorders.

Rationale: The purpose of the present study was twofold. First, we aimed to examine the effect of Met load which has not been done before. Second, we intended to replicate previous findings on the synchronization of error-specific neural networks (Beste et al, 2010) among Met carriers.

Methods: 60 healthy drug-free subjects (20 Met/Val, 20 Val/Met, 20 Met/Met carriers) were recruited for the study. Groups were matched for age and gender. Subjects underwent testing with the Eriksen flanker task while measuring EEG from the scalp. Event-related potentials, time-frequency power spectrum and phase-locking factor were calculated and compared among groups. The study was double-blinded.

Results: Met carriers show a significant reduction in post-error slowing compared to the Val/Val group (p=.05). The ERP signature of error-detection, the error-related negativity, did not show significant group differences. However, significant group differences in time-frequency power and phase-locking in the delta frequency band emerged, suggesting less synchrony in error-processing neural networks in Met carriers (p<.03). Furthermore, the within-group variability of theta power were significantly predicted by the anterior cingulate cortex grey matter volume in Met carriers (p<.02).

Conclusions: Structural and functional differences in neural networks supporting error-processing and post-error behaviour are significantly affected by BDNF variants.
Introduction: Alzheimer’s disease (AD) is the commonest form of dementia affecting 3 million EU citizens [1]. One histological characteristic of AD is the proteinaceous accumulation of hyperphosphorylated tau to neurotoxic neuronal neurofibrillary tangles (NFTs) [2], resulting in fatal neurodegeneration [3]. To investigate the pathological consequences of NFTs, the murine hTau model has been engineered, expressing human tau isoforms and forming NFT-like aggregations in spatiotemporal-associated brain regions, relevant to AD [4]. However, their behavioural correlates have hardly been studied. Verification of an association between tau aggregation and behavioural abnormalities is needed to support the use of this model as one of dementia, and for the development and testing of novel therapeutic strategies for this incurable condition.

Methods: Transgenic hTau mice were compared to murine Tau knock-out mice (TauKO; hTau background) and wild-type (wt) mice, all being male. They were tested at two, four, six, nine and twelve months-of-age corresponding to increasing stages of tauopathies in hTau mice [4] in a series of behavioural tasks measuring episodic spatial working memory [spontaneous alternation (SA): Y-maze], locomotor and anxiety-related behaviour (open field; elevated plus maze), novel object recognition and location memory, as well as acquisition, memory and extinction of associative learning (contextual fear conditioning). Forebrain integrity was also repeatedly assessed in the food burrowing test. Group performances were compared with an analysis of variance followed by planned comparisons. p values indicate statistical significance.

Results: Body Mass of hTau mice was unaltered until they reached twelve months of age. Results from the open field test and elevated plus maze indicated unaffected locomotor activity and anxiety-related behaviour in hTau mice ruling out these factors as confounders for the cognitive tasks. hTau mice displaced less food than wt mice from four to nine months in the food burrowing test (F = 13.32, p < 0.001). In the contextual fear conditioning task, four- and nine-month-old hTau mice demonstrated enhanced associative learning performance (F = 3.22, p = 0.042), whereas only two- to four-month old wt mice extinguished contextual fear memory (p=0.05; one-sample t-test). Spatial memory performance was reduced in hTau mice in both the spontaneous alternation (F = 4.1, p = 0.018) and the novel object location task (F = 2.69, p = 0.008). hTau mice spent more time exploring the objects in the discrimination trial of the novel object test (F = 3.8; p = 0.024), but not during the sample phase.

Conclusions: The behavioural abnormalities of hTau mice indicate dysfunction of the frontal cortex and hippocampus relevant to AD. They appear to occur alongside early hyperphosphorylation of tau proteins and prior to impairments of forebrain synaptic plasticity [2,4]. These results extend previous findings that showed cognitive deficits at late stages only [2]; and support the potential of this model to be used in the study of tau-related cognitive consequences in relation to AD.
**MD03**

**OPTIMISING [18F]-FALLYPRIDE IMAGING FOR D2/3 RECEPTOR OCCUPANCY STUDIES IN ALZHEIMER'S DISEASE**

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Introduction: Dopamine D2/3 receptor PET tracers have been instrumental in optimising antipsychotic prescribing in young psychotic people, by establishing a ‘therapeutic window’ (60-80%) of striatal D2/3 receptor occupancy within which symptom reduction is accompanied by minimal motor side effects. This area of research has been neglected in older people, particularly those with dementia, who are highly susceptible to the adverse effects of antipsychotic medication and might derive considerable benefit from the application of such imaging techniques. In a previous study (Dunn et al, 2013, JCBFM, In Press) we successfully adapted [18F]-fallypride imaging using an interrupted scanning protocol which reduced the length of individual scanning sessions. The current study aimed to further adapt and optimise pre- and post-treatment [18F]-fallypride imaging protocols for use in D2/3 occupancy studies in Alzheimer’s Disease (AD).

Methods: Six participants with AD (3 male; 85.0+-5.6 years; MMSE 16.0+-2.4) were scanned at baseline, prior to commencing amisulpride for the treatment of behavioural or psychotic symptoms. Of these, 4 were scanned after 27.0+-6.1 days amisulpride treatment (dose range 25-50mg daily), when a therapeutic response (symptom reduction of >25%) had been achieved. Scans were carried out on a GE VCT Discovery PET-CT scanner. Each session consisted of a single bolus intravenous injection of 250MBq [18F]-fallypride. Regional [18F]-fallypride binding potential (BPND) was determined using data collected during 3 sampling times at baseline (0-30; 60-90; 210-240 minutes) and post treatment (0-20; 40-60; 110-150 minutes) (Method 1). Image data were re-analysed after reducing sampling times to 20 minutes at baseline (0-20; 40-60; 220-240 minutes) and post-treatment (0-20; 40-60; 130-150 minutes) (Method 2). Within-subject change in [18F]-fallypride BPND was used to determine D2/3 occupancy in striatal (caudate, putamen) and extrastriatal (thalamus, amygdala, inferior temporal gyrus) regions for Method 1 and 2.

Results: There was high agreement between BPND values derived using methods 1 and 2 in both baseline and post-treatment protocols (mean change <2% in all regions, apart from the inferior temporal gyrus, which showed <4.5% change). Similarly, regional D2/3 occupancy showed a mean absolute difference of <2% between methods, in all regions but the inferior temporal gyrus (5.89%).

Conclusion: The adapted protocol is highly feasible for use not only in AD, but across a range of cognitively and neurologically impaired clinical populations. We aim to utilise this protocol in future studies to clearly and robustly define the therapeutic window of antipsychotic medication in AD.

This project was funded by Guys and St Thomas’ Charity, the National Institute for Health Research (NIHR) and the Medical Research Council (MRC).

**MD04**

**SOUVENAID®, A UNIQUE NUTRIENT COMBINATION HAS BEEN SHOWN IN CLINICAL TRIALS TO IMPROVE MEMORY IN EARLY ALZHEIMER’S DISEASE**

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Introduction: Souvenaid is a Food for Special Medical Purposes that has been designed to support synapse formation and function. Thereby improving episodic memory, in patients with early Alzheimer’s disease (AD) by improving macro- and micro nutrient deficits characteristic of early AD. Synaptic membrane phospholipid synthesis depends on the circulatory supply of a number of precursors and cofactors that are often present at low levels in individuals with AD. The precursors and cofactors feed the Kennedy pathway, the process responsible for the production of membranes. The aim of Souvenaid is to boost the levels of the key precursors (omega-3 polyunsaturated fatty acids, uridine monophosphate and choline) and cofactors (phospholipids, folic acid, vitamins B6, B12, C and E, and selenium) for the Kennedy Pathway to reverse synaptic membrane phospholipid synthesis in patients with early Alzheimer’s disease (AD). Souvenaid is well tolerated and well accepted by patients with AD.

Conclusions: Souvenaid has been shown to improve episodic memory in patients with early AD, but current evidence suggests that it may not provide cognitive benefits in patients with more advanced AD. Souvenaid is well tolerated and well accepted by patients with AD.
ABSTRACTS

AUDIT OF ANTI-DEMENTIA DRUG PRESCRIBING IN AN INPATIENT SETTING

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Introduction: The number of patients diagnosed with different subtypes of dementia is increasing constantly. Recent efforts to raise awareness about dementia bring more and more people in the GP and psychiatrist’s offices and there is still a general opinion that this particular illness is under-diagnosed. Unfortunately some of these patients that we see every day will receive a devastating diagnosis – “You have dementia!”. The question that follows naturally from both patients or carers is – “What are the treatment options?”. Although unfortunately, we don’t yet have a cure for dementia, there have been remarkable progresses made towards marketing medication that can aid in the management of dementia. We believed it would be really interesting to scrutinise our practice and see exactly what are the reasons behind choosing one anti-dementia drug rather than another. Are we following NICE guidance and BNF recommendations, and if not why? Is our practice safe and patient centred and more important how can we improve it? Method: We audited the drug cards and notes of the inpatients in our two dementia wards (Holly Ward and Oak Ward) at the Redwoods Centre, Shrewsbury, Shropshire. The period we choose was November 2012 and we looked at a total of 24 inpatients diagnosed with different types of dementia. We designed our own audit tool that comprised of both NICE Guidance and BNF recommendations regarding dementia drugs and scrutinise our practice against this tool. We looked at their anti-dementia drugs and went through their notes to identify the type and severity of dementia, using their MMSE or ACE-R scores. We also looked at physical co-morbidities and possible contraindication to treatment. Looking at both single and combination therapies between different anti-dementia drugs, we tried to identify if cognitive, functional, behavioural or global improvement was noticed and documented since starting the medication. Last but not least we placed a special emphasis of carers, patients and family being involved and in agreement with the decision. Results and conclusions: Although we found that within our sample all anti-dementia drugs were used there is a big disproportion between choices. 45.8% of our patients were on Memantine, 25% on Rivastigmine, 16.6% on Donepezil and only 4.1% on Galantamine. 8.3% of patients were on combined regimes of dementia drugs. We showed 91.6% adherence to recommendations when it came to choice of medication considering type and severity of dementia and 100% adherence on reviews and demonstrating overall improvement in our patient’s functioning. In all the cases the prescriber showed good understanding and recorded appropriately the potential contraindications and if present these were kept under close monitoring by the medical team. Unfortunately we failed to meet the criteria when it comes to reflect carers and family involvement in our decision making, with only 41.6% of cases having this clearly documented. Overall although we have showed good progress towards keeping with the guidelines there is still room for improvement and reflection on our practice and this audit represents our effort to do so.

PRESCRIBING OF ANTIPSYCHOTICS IN PATIENTS WITH DEMENTIA IN INPATIENT SETTING– IS OUR PRACTICE MIRRORING THE NICE GUIDELINES?

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Introduction: During the progress of their illness many patients with dementia will experience at some point some distressing behavioural and psychological symptoms. Many patients will receive medication to try and manage these symptoms and a lot of times antipsychotics will be used as first line options. Trying to educate and inform doctors, carers and patients about the potential benefits and risks of using antipsychotics has often been emphasized. As part of this effort new NICE Guidelines have made very strict recommendations for using antipsychotic medication in dementia. It is currently a national priority in the UK to try and reduce the use of antipsychotics in dementia patients. Despite this, recent reports show that still, many regions in the UK are above the recommended guidelines when prescribing antipsychotics. We are therefore joining the effort to raise awareness and scrutinise our own practice to see whether it meets the NICE criteria and if not try to identify areas we could modify in order to ensure a safe practice. Methods: During November 2012 we have looked at all 24 inpatients in our two dementia wards (Holly Ward and Oak Ward) in the Redwoods Centre, Shrewsbury, Shropshire. We have selected those patients on antipsychotics. We designed an audit tool that comprised of the new NICE Guidelines for safe prescribing of antipsychotics in dementia and have analysed all of our selected patients against those criteria. We looked at the age, type and severity of dementia and antipsychotic prescribed for each patient. We also analysed the reasons for prescribing, length of time on the antipsychotic and how often is it reviewed. More important we looked at physical co-morbidities, especially the history of Strokes and also we put emphasis on whether the carers were made aware of risks of prescribing antipsychotics and involved in the decision making. We believe that it is particularly interesting audit as it looks at the inpatients setting, while other audits have focused more on the community setting. We believe that antipsychotic prescribing is really important because by definition the hospital settings deals with patients that have challenging behaviour and it is really important to show a good use of non-pharmacological methods as well as a responsible and safe use of antipsychotics. Results: We found that 54% of the dementia patients were on antipsychotics (13 out of 24). Although the percentage of patients on antipsychotics remains high, there is an overall decrease compared to previous audits. We found areas where our practice was in complete adherence to the NICE Guidelines and we are talking here about reasons for prescribing, regular reviews and most important considering the physical co-morbidities as well as a few other criteria. Surprisingly, only 46% of the patients were on Risperidone, which is the licensed antipsychotic. In only 13% we found that clear documentation that this decision has been discussed with the carer. Although we are doing well and progressing in some areas we believe that it is extremely important to strive towards obtaining 100% adherence to NICE Guidelines when it comes to prescribing antipsychotics in dementia and ensure a safe practice, something that can be obtained by carrying out and presenting this type of reflections into our practice.
SERVICE EVALUATION: IMPACT OF ROUTINE SPECIALIST ASSESSMENTS IN AN ELDERLY MENTALLY INFIRM (EMI) NURSING HOME

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Introduction: Lightmoor View is a 75 bed nursing home which provides facilities for elderly mentally ill in Telford, Shropshire. It caters mostly for patients with a diagnosis of dementia. Residents have access to specialist mental health services in a monthly clinic at the care home.

Objective: To prevent psychiatric crisis and admission to Shelton hospital/Redwoods Centre Methodology: Residents at Lightmoor View were referred to psychiatrician by their general practitioner. Clinics were held once a month during the period May 2011 to April 2012 (no clinic held in November 2011). During these clinics, concerns were addressed; management plans were formulated, specifying therapeutic interventions. Mental health act section 117 aftercare meeting with relevant social workers were also arranged during these clinics. Referrals to the clinic were made by the general practitioner in conjunction with the nursing home staff. No CMHT input was provided for residents; however some were seen by a memory clinic nurse.

Results: Over the year 71 appointments were made, for 41 different patients. 23 patients were seen once, 11 were seen twice, 4 were seen 3 times, 1 was seen 4 times and 2 were seen 5 times over the course of the year. 24 different female patients were seen and 17 male patients were seen over the period. Residents referred were aged between 66 and 96, and all had a formal diagnosis of dementia. However one patient had coexisting bipolar disorder, one patient had Down syndrome and four patients had coexisting Parkinson’s disease. The reasons for referral were: 63%-Behavioural 4%-117 review 27%-medication review 6%-Deterioration Of the 71 referrals for 41 different patients, there were no admissions to Shelton Psychiatric hospital. This is a further improvement on data from the period April 2008-2009, when the service was running, where two admissions to Shelton hospital. The formal annual antipsychotic review was carried out in February 2012 with 14 patients having their antipsychotics reviewed, but antipsychotic medication was also reviewed throughout the year in relation to medication reviews and in response to behavioural disturbances. Discussion: Admissions to the acute psychiatric hospital were completely avoided during the year period with monthly specialist input. The early intervention by specialist mental health services prevented multiple accommodation moves and disruptions to patient’s routine. Therefore residents had a better quality of life and were able to stay in a familiar environment. Early intervention and continuity of care also allowed problems to be dealt with then followed up in further clinics if required.

Conclusions: The provision of specialist care to nursing home residents in partnership with general practitioners, nursing home staff and social services is required to maintain the quality of care for people suffering with dementia at Lightmoor view care home. Ultimately this service could be further extended to other EMI nursing homes which would further prevent admissions to acute psychiatric facilities. This is line with the National Dementia Strategy and the Darzi review. Department of health. Living well with dementia: a national dementia strategy. February 2009. Available from: URL: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_085825

IMPACT OF REMISSION OF OBSESSIVE-COMPULSIVE DISORDER AND SYNDROME ON PROGNOSTICATION AND TREATMENT STRATEGIES

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Introduction: Traditionally, obsessive-compulsive disorder (OCD) is considered to be a chronic and unremitting disorder. For example, in a two year prospective clinical study, Eisen and colleagues (2010, J Clin Psychiatry, 71: 1033-9) identified only 6% of treatment-seeking adults with OCD to have undergone full remission. Evidence from relapse-prevention studies has suggested that the discontinuation of medication in treatment-responders substantially increases the risk of relapse. Consequently, long-term maintenance treatment with pharmacotherapy and possibly even cognitive behavioural therapy has been recommended. However, there is a remarkable lack of evidence regarding the naturalistic course of the disorder.

Method: A recently published longitudinal investigation examined remission rates in a population-based sample of subjects with OCD (n=30) and sub-diagnostic obsessive-compulsive syndrome (OCS) (n=81) over a 30 year period, from around the age of 20y to 50y (Fineberg et al., 2013, Int J Psychiatry Clin Pract, [Epub ahead of print]). Remission was strictly defined and required a symptom-free state lasting for at least 3 consecutive years, without later relapse. Results: By the age of 50y, 63.4% of subjects with OCD and 81.5% with OCS had fully remitted. The mean ages of remission were roughly 39y (95% CI, 34.83-42.94) for OCD and 35y (95% CI, 32.76-37.33) for OCS, and the onset of remission was delayed by roughly 8y in treatment-seeking individuals, suggesting a better prognosis for less severe illness. Seeking professional help, longer duration of illness, greater number of OC burdened years and the presence of comorbid anxiety disorders were associated with significantly reduced remission rates.

Conclusions: Although the prognosis for the treatment seeking sub-sample was less favourable and roughly one third of OCD cases did not remit by 50years of age, the results nevertheless suggest that the overall prognosis for obsessive-compulsive syndromes including OCD might be more positive than is commonly believed. Efforts to better identify ‘poor prognosis’ cases a priori might result in a more rational use of long-term medication in OCD. Financial sponsorship: This work was supported by the Swiss National Science Foundation (Grant number 32-50881.97)
ME02

DEVELOPING A NEW SCHEDULE FOR ASSESSING THE ONSET OF SYMPTOMS AND LATENCY TO TREATMENT IN PSYCHIATRIC DISORDERS: AN INTERNATIONAL COMPARISON

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Introduction: Psychiatric disorders often remain undiagnosed and untreated for many years, but relatively little is known about factors which influence the latency to treatment and there are no standardized tools to assess this phenomenon (Altamura et al., 2010, Int Clin Psychopharmacol. 2010;25(3):172-9). The University of Milan has developed the Psychopathological Onset and Latency to Treatment Questionnaire (POLTQ), to record influences and to establish whether POLTQ is suitable for use in collaborative studies.

Methods: The POLT-Q was administered to 256 Italian outpatients and inpatients and a consecutive sample of 50 British outpatients, with a range of psychiatric disorders. Diagnoses were recorded with reference to DSM-IV-TR criteria. Demographic and clinical data were evaluated using SPSS.20. Where available the notes of the British patients were examined, to check the previous history.

Results: POLT-Q took an average of 10 minutes to complete, in each centre. The Italian group had a mean age of onset (AO) of 30.7 years (SD 15.1): age at first treatment was two years earlier than age at first diagnosis (36 years; SD 19.4) with a mean delay of 4.5 years. Pharmacological treatments were the most common intervention. Patients with mood disorders (52%) had an AO of 33.2 years (SD 15.8) and latency to treatment was 36 months (SD 16.7). Patients with anxiety disorders group (32%) had a lower AO of 29.6 years (SD 14.7) and average latency of 50.7 months. The British group had a mean AO of 24.2 years (SD 10.9). The age at first diagnosis overlapped with the age of first pharmacological treatment, at around 28 years (SD 10.24), with a mean delay of 4 years. Most patients first underwent a pharmacological (66%) rather than a psychological treatment, mainly antidepressants (84%). Patients with mood disorders (72%) had an AO of 23.9 years, latency to treatment of 35.3 (SD 7.4) months, mean age at first treatment and diagnosis of 26 years, latency to pharmacological treatment of 43.9 months. Patients with anxiety disorders (20%) had an AO of 24.6 years (SD 6.8) and average delay to treatment of 4.2 years.

Conclusions: Despite variations in health systems, patients had broadly similar features. POLT-Q was positively judged by patients and clinicians, could be used without difficulty in busy outpatients and inpatient services, and appears suitable for further evaluation in multi-centre studies.

Disclosures: POLTQ was supported by a grant from the ECNP-NI.

ME03

A DOSE OF RUTHLESSNESS: INTERPERSONAL MORAL JUDGMENT IS HARDENED BY THE ANTI-ANXIETY DRUG LORAZEPAM

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Methods: The POLT-Q was administered to 256 Italian outpatients and inpatients and a consecutive sample of 50 British outpatients, with a range of psychiatric disorders. Diagnoses were recorded with reference to DSM-IV-TR criteria. Demographic and clinical data were evaluated using SPSS.20. Where available the notes of the British patients were examined, to check the previous history.

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ME03

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Neuroimaging indicates emotional brain systems are more strongly engaged by moral dilemmas in which innocent people are directly harmed than by dilemmas in which harm is remotely inflicted (Greene et al., 2001, Science, 293, 2105–2108). To test if this emotional engagement involves anxiety, we investigated the effects of 1 mg and 2 mg of the anti-anxiety drug lorazepam on the response choices of 40 healthy volunteers in moral-personal, moral-impersonal, and nonmoral dilemmas. Using repeated measures Analysis of Variance, we found lorazepam caused a dose-dependent increase in participants’ willingness to endorse responses that directly harm other humans in moral-personal dilemmas but did not affect response choices in moral-impersonal dilemmas or nonmoral dilemmas, revealing that lorazepam significantly increased ruthlessness in moral-personal dilemmas, F(2, 38)5.6, p. = 005. Furthermore, a clear dose-response effect of lorazepam on ruthlessness in moral-personal dilemmas was indicated by simple contrasts: placebo versus 1 mg, F(1, 39)5.9, p. = 020; placebo versus 2 mg, F(1, 39)11.8, p. = .001. Within the set of moral-personal dilemmas, lorazepam increased the willingness to harm others in dilemmas where harm was inflicted for selfish reasons (low-conflict dilemmas) as well as responses to dilemmas where others were harmed for utilitarian reasons (i.e., for the greater good, high-conflict dilemmas). There was a very large main effect on moral-personal dilemma response choices of conflict type (low and high), F(1, 39)294.3, p. = 001, as well as a strongly significant main effect of drug (placebo, lorazepam 1 mg, lorazepam 2 mg), F(2, 38)7.6, p. = 001. There was no significant interaction between conflict type and drug, F(2, 38)0.2, p. = 814, indicating that lorazepam effects on response choices did not differ significantly between low- and high-conflict moral-personal dilemmas. This suggests that anxiety exerts a general inhibitory effect on harmful acts toward other humans regardless of whether these harmful acts are selfish or utilitarian. Lorazepam is a sedative drug, but we found that lorazepam slowed decision times equally in all 3 dilemma types: its capacity to increase ruthlessness in moral-personal dilemmas was not caused by sedation.

This research was funded by a Medical Research Council grant to Adam M. Perkins.
ME04
DIFFERENTIAL IMPACT OF ANXIETY SYMPTOMS AND ANXIETY DISORDERS ON TREATMENT OUTCOME FOR PSYCHOTIC DEPRESSION IN THE STOP-PD STUDY
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There are conflicting results on the impact of anxiety on depression outcomes. The impact of anxiety has not been studied in major depression with psychotic features (“psychotic depression”). We analyzed data from the Study of Pharmacotherapy for Psychotic Depression (STOPPD) that randomized 259 younger and older participants to olanzapine plus placebo or olanzapine plus sertraline for 12 weeks. We assessed the impact of specific anxiety symptoms from the Brief Psychiatric Rating Scale (BPRS) (“tension”, “anxiety” and “somatic concerns” and a composite anxiety score) and disorders (panic disorder and GAD) on psychotic depression outcomes (improvement in depression by HAM-D-15, improvement in psychotic symptoms by BPRS psychosis subscale and probability of remaining in the trial for 12 weeks), using linear or logistic regression. Age, gender, education and benzodiazepine use (at baseline and end) were included as covariates. A significant difference between treatment groups was observed only for education (greater in olanzapine/placebo group). Anxiety symptoms at baseline and anxiety disorder diagnoses differentially impacted outcomes. On adjusted linear regression there was an association between improvement in depressive symptoms and both the composite anxiety score (regression coefficient = 0.348; 95% CI: 0.064-0.632 p=0.017) and “tension” (coefficient = 0.784; 95% CI: 0.169-1.400; p=0.013). There was an interaction between “tension” and treatment group, with better responses in those randomized to combination treatment if they had high baseline anxiety scores (coefficient = 1.309; 95% CI: 0.105-2.514; p=0.033). On adjusted logistic regression no anxiety symptom was associated with remaining in the trial, there were significant interactions between both “tension” and the composite anxiety score with treatment group. For improvement in psychotic symptoms, there was a significant association with tension in participants aged under 60 (coefficient = 0.626; 95% CI: 0.150 to 1.103; p=0.010) but not in those aged 60 and over (coefficient = -0.028; 95% CI: -0.388 to 0.332; p=0.879). Similar results were obtained for the composite anxiety score. There were no interactions between any anxiety symptom and treatment group for improvement in psychotic symptoms. In contrast, on adjusted linear regression, diagnosis of panic disorder (but not GAD) was associated with worse clinical outcome in terms of improvement in depressive symptoms, (coefficient=0.654; 95% CI: 0.192-1.116; p=0.007) but without interaction with treatment. Our results suggest that analysis of the impact of anxiety on depression outcome should differentiate specific anxiety symptoms and diagnoses.

Funding: Grants; US Public Health Service, NIMH, National Center for Research Resources. Eli Lilly and Pfizer donated olanzapine, sertraline and placebo.

ME05
EFFECT OF 7.5% CO2 INHALATION ON THE HUMAN EYE-BLINK STARTLE RESPONSE
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Inhalation of 7.5% carbon dioxide (CO2) reliably increases anxiety and autonomic arousal in healthy humans and provides a translational, experimental model of anxiety for animal and human research. CO2 inhalation in rodents indicates that the amygdala is an important chemosensor which directly detects increasing CO2 concentrations to provoke fear behaviours (Ziemann et al. 2009, Cell 139: 1012-1021). Human neuro-cognitive models also emphasise the role of the amygdala in threat appraisal. However, it is not known whether the amygdala mediates CO2-induced anxiety in humans. We examined the effect of 7.5% CO2 inhalation on a peripheral behavioural measure of amygdala activity - the human eye-blink startle reflex. 27 healthy volunteers (16 female; mean age = 20.62, SD = 2.14) were screened for physical and mental wellbeing. Participants subsequently completed a modified affective eye-blink startle task whilst inhaling 7.5% CO2 and air for 20 minutes (inhalation order counterbalanced across participants). The magnitude and latency of startle eye-blinks in response to a sudden onset 96dB burst of white noise was recorded whilst participants viewed negative and neutral pictures (order randomised). Inhalation of 7.5% CO2 (compared to air) produced significant increases in post-inhalation levels of state anxiety, negative affect and systolic blood pressure (p's < .001), and increased concurrent measures of skin conductance and heart rate taken throughout the inhalation period. CO2 challenge did not increase startle magnitude to negative or neutral images. However CO2 challenge significantly delayed the onset of the startle response across trials (p = .015). Furthermore, CO2-induced increases in state anxiety and negative affect (relative to baseline) were associated with increased heart rate following CO2 inhalation (r's > .47, p's < .05), but did not correlate with startle magnitude or latency. Our findings suggest that CO2 inhalation can reliably increase feelings of anxiety and autonomic arousal, but do not provide evidence that CO2 challenge increases amygdala activity, as measured by eye-blink startle magnitude. These findings accord with recent evidence that individuals with bilateral amygdala damage do experience fear following CO2 challenge (Feinstein et al. 2013, Nature Neuroscience 16: 270-272). Further research should examine whether slowed startle latencies result from CO2-induced changes in attention control and hypervigilance to contextual threat distractors (Garner et al. 2011 Neuropsychopharmacology 36 1557-1562).

ME06
AN INVESTIGATION OF NEUROIMMUNOLOGICAL AND COGNITIVE FACTORS IN GENERALISED ANXIETY DISORDER - AN ASSOCIATION?
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Introduction: To date, the presence of inflammatory symptoms and the crucial role of cytokines have been well documented within psychiatric disorders such as Post-Traumatic Stress Disorder, Panic Disorder, Obsessive Compulsive Disorder and Depression and it follows, therefore, that cytokine levels may play a role in Generalised Anxiety Disorder (GAD). However, research within this area is sparse. There is a high research need for better understanding of the heterogeneous role of specific cytokines in GAD, and how they affect cognitive function. Aims: The aim of this study was to investigate the potential role of peripheral inflammatory disturbances in GAD, and to examine whether there is an association between cognitive dysfunction and inflammatory status in patients with GAD. We hypothesized that anxious state and dysfunction in cognitive processing implicated in anxiety may be associated with peripheral inflammation in patients with GAD compared with healthy controls. Methods: Patients who met the ICD-10 diagnostic criteria for GAD and healthy controls were recruited. Levels of anxiety and depression were measured using self-reported measures; The State-Trait Anxiety Inventory, The Anxiety Sensitivity Index and The Hospital Anxiety Depression Scale. The Attention Network Task (ANT) was used to measure attentional control, which includes alerting, orienting and executive control. Serum levels of cytokines including IL-1, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12p70, IL-13, TNF-α and IFN-γ were measured using a multiplex immunoassay Meso Scale Discovery (MSD, Human Demonstration 10-Plex).
Results: Data presented here is a partial representation of an ongoing larger study. Data collected from 9 GAD patients, and 10 matched healthy controls were analysed. Independent samples Mann-Whitney U test indicates that there were significant differences between the GAD group and the healthy control group in terms of TNF-α and executive control. Conclusion: Consistent with the dysregulation of TNF-α production in depression, this project provides research evidence for similar immune dysregulation in GAD, as well as cognitive dysfunction, in particular impaired executive control. The study suggests that impaired attentional control may be associated with a specific inflammatory marker. Due to limited timescale for conducting the study and relatively small sample size, further work from the larger sample is needed to verify these preliminary findings.

The project is funded by the University of Southampton.
ME07
PREBIOTIC INTAKE REDUCES THE WAKING CORTISOL RESPONSE AND ALTERS EMOTIONAL BIAS IN HEALTHY VOLUNTEERS
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There is now compelling evidence for a link between enteric microbiota and brain function. The proliferation of some gut bacteria modulates cortisol secretion in mice, and has anxiolytic effects in both rodents and humans (see Cryan & Dinan, 2012, Nature Reviews Neuroscience, 13, 701-12). At present, the central effects of one or a combination of two different bacterial species (probiotics) have been examined, but it seems likely that proliferating several intrinsic gut microbiota with prebiotics (nutrients for intestinal bacteria) may afford greater benefits to the brain than a single species alone. The present study, therefore, investigated the effect of prebiotics on cortisol secretion and emotional processing in healthy volunteers. Forty-five healthy volunteers were randomized to either one of two prebiotics (fructooligosaccharides [FOS] or Bimuno-galactooligosaccharides [B-GOS]) or a placebo for 3 weeks. Awakening salivary cortisol was sampled before and after treatment. On the final day of treatment participants completed the Emotional Test Battery (ETB; Harmer et al., 2004, American Journal of Psychiatry, 161, 1256-63) a computerised task battery assessing the processing of emotionally salient information. Salivary cortisol responses did not differ significantly between groups at baseline but were significantly lower following B-GOS treatment compared with placebo (significant interaction between treatment group x day of sampling x sampling time-point in a repeated measures ANOVA [F(8,164)=1.20, p=.05]). Analysis of behavioural data revealed decreased attentional vigilance to negative versus positive information in an attentional dot-probe task after B-GOS compared to placebo treatment (group x emotion x masking condition, [F(2,41)=3.14, p=.05). The FOS treatment group did not perform differently to the placebo group in this task and there were no significant effects of prebiotic treatment on the remaining tasks of the ETB. Our study demonstrates that the manipulation of gut microbiota with B-GOS lowers cortisol secretion in healthy volunteers, which is in keeping with the effects of probiotics (Messaoudi et al., 2011, British Journal of Nutrition, 105(5), 755-64). In addition, B-GOS was shown to alter the processing of negative versus positive information as measured by attentional vigilance, which is believed to play a key role in anxiety and its modulation by anxiolytics (Browning et al., 2007, Journal of Psychopharmacology, 21(7), 684-90; Murphy et al., 2008, Psychopharmacology, 199(4), 503-15).

Funded by the BBSRC and Clasado Ltd, and an MRC Studentship (KS).

ME08
THE EFFECT OF PREFRONTAL TRANSCRANIAL DIRECT CURRENT STIMULATION ON ATTENTION NETWORK FUNCTION IN HEALTHY HUMANS
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Introduction: Neuropsychological models suggest that deficits in prefrontal attention control mechanisms are involved in the aetiology and maintenance of maladaptive ruminative thinking and dysfunctional worry in mood and anxiety disorders. Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation modality, which alters cortical tissue excitability through applying a weak direct electrical current via scalp electrodes overlying targeted cortical areas. tDCS may represent an effective treatment option for patients with mood and anxiety disorders. We examined the effect of 20 minutes of 2mA prefrontal tDCS on the efficiency of three attentional networks: alerting (maintaining an alert state), orienting (the selection of information from sensory input) and executive control (resolving cognitive conflict). Method: 22 healthy volunteers were screened for physical and mental wellbeing and randomized to receive either 2mA active tDCS (anode over left PFC, cathode over right PFC; n = 11; 6 females; mean age = 20.3 years) or sham (control) tDCS (n = 11; 8 females; mean age = 20.9 years). Active and control groups did not differ on standardized questionnaire measures of trait anxiety or attention control, nor baseline measures of state anxiety, alertness, heart-rate or blood pressure. Scalp electrodes were placed bilaterally over prefrontal sites. Participants sat still during the 20 minute double-blind stimulation period. Post-stimulation measures of mood and autonomic arousal were taken before participants completed a modified attention network test (ANT) - a cued reaction time flanker task in which participants make a speeded response to a central arrow target that is flanked by distractor stimuli and cued by either a temporal-onset (alerting) or spatial location (orienting) stimulus. Results: Executive attention control was significantly greater following active compared to sham prefrontal tDCS (p < .05). Groups did not differ in alerting and orienting network function nor in post-stimulation levels of anxiety, mood and autonomic arousal. Thus the effect of active tDCS on executive control occurred independent of current mood. Conclusions: Our initial findings suggest that twenty minutes of active tDCS over prefrontal cortex is associated with greater executive control in healthy humans. Prefrontal stimulation had a selective effect on executive attention control, and supports evidence from magnetic stimulation and brain imaging studies to implicate prefrontal cortex in attention control. Results suggest that prefrontal tDCS might usefully target deficits in executive attention control that characterise mood and anxiety disorders.
University of Southampton VC Studentship Award

ME09
COMPARABLE EFFECTS OF 7.5% CARBON DIOXIDE INHALATION AND TRAIT ANXIETY ON ATTENTION CONTROL.
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Introduction: Inhalation of 7.5% carbon dioxide (CO2) increases anxiety and autonomic arousal and provides a novel experimental model of generalized anxiety. We recently demonstrated that 7.5% CO2 challenge can impair attention control in healthy volunteers (Garner et al. 2011, Neuropsychopharmacology, 36, 1557-1562), consistent with broader deficits observed in clinical anxiety using related paradigms. Here we directly compare the effects of CO2 challenge in low trait anxious individuals against the typical (unchallenged) patterns of attention control observed in high trait anxious individuals.
Method: Sixty participants were recruited according to their scores on standardized measures of trait anxiety. Twenty participants had scores above the population average (high trait anxiety group- HTA). Forty participants with below average levels of trait anxiety were randomized to either a low trait anxiety carbon dioxide group (CO2) or low trait anxiety control group (LTA). Participants attended a single test session in which they completed an antisaccade eye-tracking task during inhalation of normal air (HTA and LTA groups) or air enriched with 7.5% CO2 (CO2 group). Heart rate and state anxiety were measured before (baseline) and following the inhalation period. Results: Baseline levels of state anxiety were significantly higher in the HTA group compared to the LTA and CO2 groups (who did not differ). CO2 inhalation subsequently significantly increased levels of state anxiety above those observed in the LTA group, but comparable with those observed in the HTA group. Performance on the eye-tracking antisaccade task (error rate) was similarly impaired in the HTA and CO2 groups compared to the LTA group (p <.01). These group differences remained after controlling for state anxiety and were also evident in those participants who did not experience elevated state anxiety.
Conclusions: 7.5% CO2 challenge induced deficits in antisaccade performance in low anxious individuals that were comparable with those observed in trait anxious individuals, but differed from an LTA control group. The effects of CO2 challenge and trait anxiety on attention control were independent of elevated state anxiety and suggest that CO2 inhalation may directly challenge neuropsychological mechanisms that characterise generalized trait anxiety rather than transient state anxiety. These findings further support the 7.5% CO2 challenge as an experimental model of generalized anxiety disorder.
MRC research grant MR/J011754/1 awarded to Garner, Baldwin & Munafo. MRC/ESRC studentship grant ES/H018514/1 for Ainsworth, awarded to Garner & Baldwin.
AUDIT OF PHYSICAL HEALTH MONITORING IN OLD AGE PSYCHIATRIC INPATIENT UNIT WELLER WING BEDFORD HOSPITAL

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Introduction: Some psychiatric illnesses and medications tend to predispose patients to elevated risk of metabolic syndrome. The metabolic syndrome is a cluster of features (hypertension, central obesity, glucose intolerance/insulin resistance, and dyslipidemia) that is predictive of both type 2 diabetes and cardiovascular disease which in turn increases the risk of strokes especially in elderly population. Clinical guidelines at the South Essex partnership Trust as well as NICE guidelines strongly emphasize that patients admitted to psychiatric inpatient units should have physical health examination along with physical health monitoring according to the local trust policy. A clinical audit was conducted to detect adherence to the local policy.

Data Collection /Method: The older people inpatient assessment unit in Weller Wing has 15 beds and serves for patients over the age of 65 with a functional or organic mental illness. The Audit 1 took place in July 2012. The following data were obtained retrospectively from case notes of patients admitted to the unit in the last 6 months during the period Jan 2012-June 2012: Waist circumference, height, BMI; BP; Routine and fasting blood tests: triglycerides, HDL cholesterol, glucose and ECG were recorded on a self-devised Performa The initial results were presented within the team as well as brief educational talk to the junior doctor and a monitoring tool was implemented. The difficulty to access to basic equipment such as a tape measure and weighing scales was addressed with the staff. Following this intervention a re-audit was conducted in February 2013 to examine any change in practice. The data was again collected retrospectively.

Results: For each audit we included 18 patients, the sample contained both male and female patients with established diagnosis and prescribed psychotropic medications. Overall performance in first audit was poor. Routine and fasting blood tests recorded measurement of 33% in the first week with exception of BP 66%, weight and height 55%. on admission. There was no recorded measurement for waist and BMI. In second audit we managed to demonstrate marked improvement of 100% in waist, height, BMI and BP. Routine and fasting blood tests achieved 83% in each test except prolactin which may be explained by being less clear recommendation in routine practice. Two patients, 11% refused bloods and ECG.

Conclusion: Simple strategies can make difference. This audit was quick, easy and cheap, revealed well below standards of health screening in audit 1. However reauditing evidently produced a measurable and significant improvement in practice. Financial Sponsorship: No funding received to conduct this audit.

SSRI TAKING AND EMOTIONAL/CLINICAL RESPONDING IN BORDERLINE PERSONALITY DISORDER

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Introduction: According to a Cochrane review, antidepressants are not widely supported for the treatment of borderline personality disorder (BPD), still many patients are taking them for long periods. We wanted to understand how different aspects of BPD are most likely affected by treatment with SSRI antidepressants, based on findings from a bigger sample in which we explored associations among BPD symptoms with path analysis.

Methods: We tested 20 BPD patients (mean age M=34.45; SE=1.96) in a research project (n=69; all females) also including a depressed (MDD) and a healthy group (mean age M=32.62; SE=1.06). Measures: SSRI: self-report; Anxiety: STAI, HDRS, MINI 6.0.0; Depression: HDRS, BDI; Disgust: Disgust Scale Revised (DSR); Self-disgust Scale (SDS); Body Experiences Questionnaire (BEQ); Feelings of Guilt Scale (FGS); Cambridge Depersonalization Scale (CDS); Personality Assessment Inventory, Borderline Subscale (PAI-BOR); IQ: Culture Fair 2A. Emotional functioning was measured with a visual task with emotional images. The preliminary analyses (n = 69) were Bayesian path models to explore general relationships (n=69). Next we focused on the BPD patients divided into 2 groups: being on SSRI (n1=9) and no-SSRI (n2=11). For firmer conclusions (unconfounded by distributional issues), we used objective Bayesian approach for testing between-group differences (MANOVA design). Finally for validation of conclusions and precise Bayesian effect size (Bayes Factor) we evaluated the hypothesis with a differences-within-equality-constraints approach.

Results: In the path analysis, BPD symptoms were most markedly related to self-disgust, feelings of guilt, and experiencing the body as unpleasant. Anxiety was a general antecedent of the disorder, leading via depression to lowered IQ. Depersonalization was a likely consequence of BPD severity. In the Bayesian MANOVA, people on SSRIs reported markedly lower levels of depersonalization symptoms than those not taking an SSRI (β=-4.43, p=0.024). SSRI taking had no association with responding in our test of emotional functioning. Anxiety, depression, scores on the BEQ, disgust, feeling of guilt and borderline symptomatology were not significantly associated with SSRI taking in our study. For the self-disgust dependent variable, tested in a separate model, SSRI had no effect. In supplementary Bayesian analyses, the hypothesis suggesting general reduction of symptoms (lower symptomatology in the treatment group) obtained less support than the model including equality constraints.

Conclusions: In our study sample (n=20), SSRIs did not influence BPD-related symptom severity or emotional responding. However, SSRI taking seems to be associated with less depersonalization.

Sponsorship: University of Cambridge Cambridgeshire and Peterborough NHS Foundation Trust Talisman Trust.
NATURE AND PREVALENCE OF PSYCHOTROPIC DRUG PRESCRIBING FOR PEOPLE WITH PERSONALITY DISORDER

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Drug treatments are widely used for a diagnosis of personality disorder (PD) despite few robust studies of efficacy and safety. Our previous audit of prescribing for 278 patents in three mental health trusts (Crawford et al 2011) found that 1. both the type of PD and the context in which treatment is delivered seem to have an impact on whether drug treatment is prescribed, 2. the majority of people with PD in contact with mental health services are prescribed long-term psychotropic medication, and 3. that people with antisocial PD are less likely to be prescribed medication despite high levels of comorbid Axis I disorders in this group. In 2012, the Prescribing Observatory for Mental Health (POMH-UK) initiated an audit-based quality-improvement programme (QIP) on prescribing for PD. The standards and treatment targets in the baseline clinical audit were largely derived from recommendations in the NICE guideline on borderline personality disorder (2009). They reflected the limited evidence available to justify the use of medication for PD alone. For example, one treatment target was that antipsychotic drugs should not be used for the medium and long-term treatment of borderline PD. Performance against the standards and targets was assessed in a national baseline audit that included over 2,500 patients in 41 mental health NHS Trusts. Some key findings were as follows: 1. Around 4 out of 5 patients were prescribed at least one drug from one of four medication groups: antipsychotics, antidepressants, mood stabilisers and sedatives; 2. Just over half of patients with PD alone (i.e. without any co-morbid mental illness) were prescribed at least one antipsychotic and the vast majority of these prescriptions were of at least a 6-month duration; 3. Benzodiazepines were prescribed in about a third of those patients with PD alone, while Z-hypnotics were prescribed in around a fifth; 4. Two-thirds of patients had a written crisis plan which was accessible in the clinical records, but less than half of these plans mentioned medication, and in just over a quarter there was no evidence that the patient had been involved in its development. These findings highlight the discrepancy between clinical practice in this area and the national guideline recommendations, derived from a limited evidence base that requires augmentation. POMH-UK will continue with this QIP, including the development of change interventions to support local Trust actions plans to address areas for improvement as indicated by their benchmarked data.

DARE TO MAKE A DIFFERENCE PROJECT EVALUATION (2011-2012) FOR PRIMARY AND SECONDARY SCHOOLS

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Introduction: It is well recognised that raising awareness and providing education regarding the needs of patients with dementia and their carers is an important element of services. This Dementia Awareness-Raising and Education (DARE) Project considers the development of such a service for schools in Telford and Wrekin, Shropshire, and West Midlands, which aims to increase awareness and promote education concerning the needs of people with dementia and their families with school children in Telford and Wrekin. The project has been funded for 12 months and has been implemented in 3 schools involving 200 primary and secondary school children. The project was developed and led by Dr Ejaz Nazir, Consultant Old Age Psychiatrist and supported by Gill Foster, senior nurse.

Method: Three primary and secondary schools took part in the project. One hundred primary and secondary school children from Blessed Robert Johnson School, sixty secondary children (all year 11 girls) from Newport High School and 40 secondary school children from Adams’ Grammar School, Newport participated in the project in three separate sessions lasting for an hour each. The students engaged in a number of activities which included: • Power point presentation on various aspects of dementia tailored to the needs of the schoolchildren from a wide range of ability and background • Demonstration of the model of brain highlighting the parts affected in dementia • Role play by students familiarising with the memory test called Mini Mental State Examination • Discussion of 2 case studies present in an easy to understand way highlighting the need for early recognition and psychosocial intervention • Quiz on dementia consisting of 10 questions to test knowledge • Handout/leaflet on dementia

The feedback questionnaires were completed anonymously by the students as well as the teacher. Results Completed questionnaires were returned from the following: Students (year11) n = 58 Teacher n = 1 The students recorded a variety of comments regarding changes in their view and how care can be improved and the emerging themes from their comments were as follows: • People with dementia deserve to be treated with dignity and respect at par with other people • People with dementia can still have a quality of life as other people • Change in perception of the role of professionals involved in helping people with dementia • Now I can understand and sympathise with people with dementia • I was not aware of what having dementia entailed before the session • I understand more about dementia and how it affects lives • I knew nothing about dementia but now I know what difficulties there are and how to identify dementia Comments of the teacher included: • Students seem to have engaged in the power point presentation and memory testing • Perhaps case studies could have been developed e.g. how would you prepare someone for a move to nursing home and what do carers need • A number of students said they had a much better understanding Comment made on Q6 – Do you feel that you have benefitted from the DARE Project? (n=58) • I was able to convey information I gathered from the session to friends and family, which shows that the project is an efficient way of raising awareness – I value the knowledge I have gained

Conclusion: The DARE Project appears to have been positively received and valued by all the 58 students of one school who have had contact with it. Feedback from the other school was awaited. Actions 1. To promote the project in other schools in Telford and Wrekin by liaising with the school PSHE agenda. 2. Extend the time allocation in schools by attempting to secure additional funding via stakeholder event.
PSYCHOTIC-LIKE EFFECTS OF KETAMINE - RELATIONSHIP TO BRAIN ACTIVITY

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Introduction: Ketamine, an uncompetitive NMDA receptor antagonist, induces effects that resemble the positive, negative and cognitive symptoms of schizophrenia. We investigated the effect of ketamine administration on brain activity as indexed by blood oxygen level dependent (BOLD) response, and its relationship to ketamine-induced subjective changes, including perceptual distortion.

Methods: Thirteen healthy participants volunteered for the study. All initially completed a self-rated assessment of their mental state using the Psychotomimetic States Inventory (PSI). They then underwent a 15 minute functional MRI acquisition with a computer-controlled ketamine infusion (target blood level = 150ng/mL; approx 0.26mg/Kg over 20s followed by a slow infusion of approx. 0.42mg/Kg/hr) commencing after 5 minutes. After the scan, participants completed a second PSI assessment, rating their experiences at the time of the strongest drug intensity.

Results: Participants reported significant increases in levels of perceptual distortion, cognitive disorganisation, delusional thinking, mania and anhedonia following ketamine administration. Ketamine led to widespread cortical and subcortical increases in BOLD response (FWE-corrected p < 0.05), and a trend towards decreased BOLD response in subgenual anterior cingulate (FWE-corrected p = 0.075). Self-rated perceptual distortions correlated with increased BOLD response in parietal and occipital cortices (FWE-corrected p < 0.05). Regional activations to best memories were increased in the right anterior temporal cortex under ketamine versus placebo and responses to worst memories were reduced bilaterally in the anterior temporal cortex (p < 0.0005 uncorrected). Positive correlations were observed between anterior temporal responses during memory recollection and emotional responses (p < 0.05, Pearson correlation). The results imply that ketamine reduces negative emotion felt on re-experiencing painful memories by reducing anterior temporal lobe responses to them, helping to explain how the drug may be useful in exposure therapy for PTSD. The intensification of emotionally positive memories may also be therapeutically exploitable e.g. in cognitive bias modification.

This research was supported by funds provided by the British public service broadcaster Channel 4©. The authors have no conflicts of interest.

THE EFFECT OF MDMA ON RECOLLECTING EMOTIONALLY POTENT AUTOBIOGRAPHICAL MEMORIES: AN FMRI STUDY WITH IMPLICATIONS FOR MDMA-ASSISTED PSYCHOTHERAPY

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4,3-methylenedioxymethamphetamine (MDMA) is a potent monoamine-releaser that has recently been found to be remarkably effective in conjunction with psychotherapy for post-traumatic stress disorder (PTSD). The neurobiological mechanisms behind MDMA’s potential therapeutic utility are poorly understood. Exposure-therapy for PTSD requires that patients revisit traumatic memories. Functional magnetic resonance imaging (fMRI) was used to investigate the effect of MDMA on recollection of painful (‘worst’) and positive (‘favourite’) personal memories. Participants performed a blocked autobiographical memory recollection paradigm after oral administration of 100mg of MDMA–HCl or ascorbic acid (placebo) in a double-blind, repeated-measures design. Verbal memory cues describing participants’ very worst (e.g. ‘remember Danny getting shot’) and best memories (e.g. ‘remember the beach’) were visually presented and activations during an eyes-closed recollection period were modelled and compared against an eyes-closed resting baseline. Participants rated their favourite memories as significantly more vivid, emotionally intense and positive after MDMA than placebo (p < 0.005, 2-tailed t-tests) and their worst memories were rated as less negative and more positive, although these were trend-level effects (p < 0.1, 2-tailed, t-tests). Regional activations to favourite memories were increased in the right anterior temporal cortex under MDMA versus placebo and responses to worst memories were reduced bilaterally in the anterior temporal cortex (p < 0.0005 uncorrected). Positive correlations were observed between anterior temporal responses during memory recollection and emotional responses (p < 0.05, Pearson correlation). The results imply that MDMA reduces negative emotion felt on re-experiencing painful memories by reducing anterior temporal lobe responses to them, helping to explain how the drug may be useful in exposure therapy for PTSD. The intensification of emotionally positive memories may also be therapeutically exploitable e.g. in cognitive bias modification.

This research was supported by funds provided by the British public service broadcaster Channel 4©. The authors have no conflicts of interest.

MODULATION OF EFFECTIVE CONNECTIVITY WITHIN THE DEFAULT MODE NETWORK BY PSilocybin - A DYNAMIC CAUSAL MODELLING FMRI STUDY IN HEALTHY VOLUNTEERS

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Psilocybin is a non-selective serotonin-2A receptor agonist and classic psychedelic drug. Psychodelics alter consciousness in a marked but idiosyncratic way, making them important tools for the scientific study of consciousness. Recent fMRI studies revealed decreased activity and connectivity within the default mode network after psilocybin. Here we utilised stochastic dynamic causal modelling (DMC), a measure of effective connectivity, to enquire how these changes had been caused at the level of modulated neuronal dynamics. Participants brain activity were scanned using fMRI under resting state condition on two separate occasions, on which either placebo or psilocybin was administered intravenously halfway through the scanning period. The timeseries of three nodes were extracted for the DCM analysis based on their known interconnectivity and sensitivity to psilocybin; these were the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC) and the medial thalamus. Four plausible models were specified in which infusion of psilocybin modulated different sets of extrinsic connections. The relative evidences for these models were compared using Bayesian model selection and one clearly winning model was identified. In this model, psilocybin modulated top-down connections (i.e. mPFC to PCC, mPFC to thalamus, and PCC to thalamus) as well within-region connections (e.g. PCC to PCC). Examining the specific nature of these effects, it was found that psilocybin had selectively reduced mPFC-PCC connectivity. This result is consistent with the dense expression of serotonin 2A receptors on top-down projecting deep-layer pyramidal neurons. They suggest that psychedelics alter consciousness by the selective removal of top-down hierarchical control to elicit a general disorganising influence on spontaneous brain activity.
The effects of satiation on brain responses to rewarding and aversive stimuli.

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Evidence suggests that physiological responses to eating affect reward-related neuronal processes that contribute to meal termination, but the effect of eating to satiety on the neuronal responses to rewarding and aversive food-related stimuli in the human brain has yet to be investigated. We used a novel functional magnetic resonance imaging task to study the neural response to both pleasant and aversive food tastes and pictures. Sixteen healthy volunteers (8 male, 8 female) were each scanned on two separate test days, before and after either eating a lunch meal to satiation or having not eaten for 4 hours. BOLD fMRI responses and subjective ratings to the sight and/or taste of chocolate (rewarding stimuli) and mouldy strawberries (aversive stimuli) were assessed. A whole-brain cluster-correction analysis showed a main effect of satiation (p < 0.05), and we report local maxima (uncorrected) where eating to satiation attenuated BOLD responses to both rewarding and aversive stimuli. Significant decreases in RSFC were observed between the midbrain and ventral striatum, midbrain and hypothalamus, and midbrain and insula. Increases were observed in the dorsomedial prefrontal cortex (dmPFC) and ventro-medial prefrontal cortex (vmPFC). The results suggest that eating to satiety attenuates reward-related brain responses to aversive stimuli in the orbitofrontal cortex, ventral striatum, hypothalamus, insula, hippocampus, and midbrain.
**MG08**

**EFFECT OF NALTREXONE ON NEURAL REWARD AND AVersive PROCESSING; IMPLICATIONS FOR COMpulsive DISORDERS**

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Introduction: Opioid antagonism reduces the consumption of palatable foods in humans but the neural substrates implicated in these effects are less well understood. The aim of the present study was to examine the effects of the opioid antagonist, naltrexone, on neural response to rewarding and aversive sight and taste stimuli.

Methods: We used functional magnetic resonance imaging (fMRI) to examine the neural responses to the sight of chocolate (positive) and mouldy strawberry (negative) stimuli in 20 healthy volunteers who received a single oral dose of naltrexone (50mg) and placebo in a double-blind, repeated measures, cross-over, design.

Results: Relative to placebo, naltrexone decreased reward activation to chocolate in the dorsal anterior cingulate cortex (p=0.004, whole brain corrected) and caudate/thalamus (p<0.008, whole brain corrected), and increased aversive-related activation to unpleasant strawberry in the amygdala (p=0.028, svc) and anterior insula (p=0.035, svc).

Conclusion: These findings suggest that modulation of key brain areas involved in reward processing, cognitive control and habit formation, including the ACC and caudate as well as brain areas involved in the processing of aversion and avoidance such as the amygdala and insula might underlie the reduction in food intake associated with naltrexone. These results support further investigation of opioid treatments in obesity and possibly compulsive disorders.

Funded by Oxford University Department of Psychiatry and GW Pharma.

**MG09**


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Introduction: Though GABA is the major inhibitory neurotransmitter in the brain, involved in a wide variety of brain functions and many neuropsychiatric disorders, techniques to measure its presence in vivo in the human brain remain elusive. One complication is the metabolic pool of GABA associated with the tricarboxylic acid cycle, raising questions regarding the source of any changes in GABA concentration measured using MRS. The synaptic GABA reuptake inhibitor tiagabine, which selectively blocks GAT1, has been used to demonstrate indirectly changes in GABA as a neurotransmitter using MEG (Muthukumaraswamy et al., 2013, NeuroImage 66 36-41) and the “GABA shift” using PET with [11C]Ro15-4513 (Myers et al., 2012, JCBFM 32 S66). A similar tiagabine challenge was therefore used to test the sensitivity of 3-difference edited 1H-MRS.

Methods: Volunteers were scanned twice on the same day (healthy male, age = mean±SD = 33±10, n = 10), each scan including a structural sequence and 3 MRS acquisitions with voxels located in the occipital cortex (3.0x3.0x3.0 cm3) and right and left “limbic” regions, defined superior to the optic chiasm (2.5x3.0x3.5 cm3). Tiagabine (oral, 15 mg) was administered 90 minutes before the second scan and subjects were required to report levels of sedation on a visual analogue scale. The frequency-domain range covering the GABA peak in MEGA-PRESS spectra from each voxel were fitted by a Gaussian peak. The ratios of the integral of these curves to the water signal were multiplied by a factor to quantify GABA concentration in institutional units (i.u.), approximately equivalent to mM.

Results: 15 mg tiagabine was shown to significantly affect “sleepiness”, subjectively measured at the end of each scan (mean±SD: 2.0±4.2 to 30.5±15.3, t = 5.90, P < 0.0001). No changes in GABA concentration estimated using MEGA-PRESS were found in the occipital voxel group between pre- and post-dose scans (t = 0.153, P = 0.441). Similarly, no changes were found in limbic voxels (left: t = 1.08, P = 0.159; right: t = 0.775, P = 0.241).

Conclusions: GAT1 blockade recompartmentalises GABA such that concentrations in the synapse are increased, but total brain GABA may not be significantly affected. Though subjective effects of 15 mg tiagabine consistent with increased GABAergic neurotransmission were observed, MEGA-PRESS did not detect GABA concentration changes post-dose. This suggests that localised synaptic GABA increases outside the cell involved in neurotransmission are insignificant compared to dynamic intracellular GABA.

This work was funded by an MRC studentship.
MG10
IMAGING THE IMIDAZOLINE2 BINDING SITE WITH THE NOVEL PET LIGAND [11C]BU99008 IN A HIGHER SPECIES: EVALUATION AND CHARACTERISATION

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The density of the Imidazoline2 binding sites (I2BS) is changed in both neurodegenerative and neuroinflammatory conditions where glia function is altered, e.g. Alzheimer’s Disease (Garcia-Sevilla et al., 1999 Ann. NY Acad. Sci., 881, 392-409). The development of a positron emission tomography (PET) ligand for these sites could prove invaluable in the understanding of such disorders. We have previously identified and evaluated a PET ligand in pig, [11C]BU99008 (Kealey, et al., 2013 J. Nucl. Med. 54, 139-44). Presented here is the in vivo evaluation and characterisation of this ligand in a higher species, rhesus monkey. PET imaging was performed in two female rhesus monkeys. Arterial blood was taken to measure plasma input functions and to determine the fraction of parent compound remaining over time. Time activity curves were generated for a number of brain regions of interest. These were fitted to 1-tissue (1T) and 2-tissue (2T) compartment models, as well as the multilinear analysis (MA1) kinetic model for comparison and selection of the optimal model. Regional volumes of distribution (VT) were then calculated using the best model. The specificity and selectivity of [11C]BU99008 was determined using blocking experiments with the I2BS ligand BU224 (0.01, 0.03, 0.1, and 0.3mg/kg) and the MAO inhibitors moclobemide (1mg/Kg, MAOA) and lazabemide (0.5mg/Kg, MAOB). [11C]BU99008 was metabolised fairly rapidly and at 30 min post radioligand injection, only about 23% of the radioactivity corresponded to the parent. Brain uptake was good resulting in a heterogeneous distribution, with reversible kinetics. Regional uptake levels were highest in the: globus pallidus (GP), caudate (CAU) and thalamus (THA); intermediate in the cingulate cortex (CIN), putamen (PUT) and frontal cortex (FNT); and lowest in the occipital cortex (OCC) and cerebellum (CER), which was consistent with the regional distribution of I2BS. The uptake was dose dependently reduced by pre-treatment with BU224, with almost complete blockade, 93%, at the highest dose. Uptake was not blocked by pre-treatment with either MAO inhibitor. The MA1 model was shown to be the method of choice for analysis of [11C]BU99008’s binding parameters. The VT values calculated ranged from 115.6 (GP) and 110.2 (CAU) to 48.5mL/cm (CER). Blocking with 0.3mg/Kg of BU224 reduced VT to ~20mL/cm in all brain regions. These data indicate that [11C]BU99008 appears to be a promising radioligand for in vivo imaging of the I2BS, and warrants further evaluation in humans.

This work was funded by a grant from the MRC in partnership with GSK.

MG11
ASSESSMENT OF ENDOGENOUS OPIOID PEPTIDE RELEASE WITH RADIOLIGAND BINDING – IN VITRO AND EX VIVO STUDIES WITH [3H]DIPRENORPHINE AND [11C]CARFENTANIL.

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Imaging endogenous opioid peptide release (EOPR) with PET would increase our understanding of the role of the opioid system in neuropsychiatric disorders. It has been proposed that [11C]carfentanil (CFN; µ-receptor agonist) is sensitive to EOPR following acute amphetamine challenge (AAC) (A. Colasanti et al.,2012.Biol Psych,72(5),371-7). This has not been assessed with [11C]diprenorphine (DPN; µ,δ,κ-receptor antagonist). As well as direct competition of radioligand by endogenous neurotransmitter, an agonist induced internalisation process has been proposed to participate in the decrease in binding observed in these studies (M. Laruelle,2000,J Cereb Blood Flow Metab,20(3),423-51). We have investigated the ability of [3H]DPN and [11C]CFN to bind in different cellular conditions, reflective of those experienced by a receptor following agonist induced internalisation, using in vitro saturation binding in rat whole brain homogenates (minus cerebellum) (0.001-10nM). EOPR by AAC or methadone injection, [3H]DPN (8.24±0.21MBq,n=5) or [11C]CFN (12.24±1.053MBq,n=4) was injected (I.V .), thirty minutes later, brain regions were dissected and time activity curves were generated for a number of brain regions of interest. These were fitted to 1-tissue (1T) and 2-tissue (2T) compartment models, as well as the multilinear analysis (MA1) kinetic model for comparison and selection of the optimal model. Regional volumes of distribution (VT) were then calculated using the best model. The MA1 model was shown to be the method of choice for analysis of [11C]BU99008’s binding parameters. The VT values calculated ranged from 115.6 (GP) and 110.2 (CAU) to 48.5mL/cm (CER). Blocking with 0.3mg/Kg of BU224 reduced VT to ~20mL/cm in all brain regions. These data indicate that [11C]BU99008 appears to be a promising radioligand for in vivo imaging of the I2BS, and warrants further evaluation in humans.

This work was supported by a BBSRC CASE PhD studentship award with GSK.
MG12

MAPPING STRESS RESPONSES USING MANGANESE-ENHANCED MAGNETIC RESONANCE IMAGING (MEMRI)

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Introduction: Stress is a risk factor for the development of psychiatric conditions such as depressive and anxiety-related disorders. The progression of these brain diseases is associated with changes in the ability to deal with stress, which is impaired with advancing disease progression. Monitoring stress responses could therefore be used as an indicator of therapeutic efficacy in preclinical drug development research. We aimed to monitor stress responses using MEMRI and the impact a corticotropin-releasing factor receptor 1 (CRF1) antagonist (known as CP-154,526) had on stress maps. The contrast agent manganese acts as a calcium agonist and has been shown to accumulate in active neurons, leading to a higher signal intensity in areas of higher neuronal activity (Faas et al. 2010. NeuroImage. 49(3), 2607-2617). CRF1 signalling plays a critical role in the response to stress and is deregulated in depressive, anxiety and neurodegenerative disorders (Scullion et al. 2013. Journal of Alzheimers Disease. 34:781-793).

Method: A total of 6 B6D2F1 mice were used in this experiment. Two mice out of the total were randomly allocated to each of the following groups: unstressed, stressed and stressed - CP-154,526 treated. All mice received an intraperitoneal injection of manganese (30mg/kg) 3 hours prior to the stress session. The stressed - CP-154,526 treated mice received an intraperitoneal injection of CP-154,526 (10mg/kg) 30 minutes prior to the stress session. The stress session was carried out through confinement and isolation of the mice. The mice's physiological state and behavioural responses were monitored (defecations, self-grooming & vertical activity) and the mice were scanned 24 hours after the stress session. The MEMRI scans of the mice were analysed according to the intensity of the hippocampus, after normalisation, using MATLAB.

Results: The normalised mean intensity of manganese in stressed - CP-154,526 treated mice (1.243) was lower than that of stressed mice (1.322) and the control mice (1.268). Due to there only being two mice per group, a relevant statistical level could not be obtained. At the time, further work was needed to improve the sequence and quality of scans before increasing the group size.

Conclusions: CP-154,526 leads to a lower accumulation of manganese in the hippocampus and may therefore limit the stress response of B6D2F1 mice following a stress session. CP-154,526 may represent a novel treatment for depressive and anxiety disorders.

Sources of financial sponsorship included the British Association of Psychopharmacology and the School of Biomedical Sciences, University of Nottingham.

TA01

ACUTE TREATMENT WITH 13-CIS-RETINOIC ACID INDUCES A DOSE-DEPENDENT NEGATIVE COGNITIVE AFFECTIVE BIAS IN RATS

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13-Cis-retinoic acid is the active ingredient of the anti-acne medication, roaccutane. It is one of a number of drugs licensed for therapeutic use which also carry a warning of drug-induced adverse psychiatric side effects. Data from patients suggests that treatment with roaccutane is associated with an increase in symptoms of depression (Bremner et al., 2012. J. Clin. Psychiatry 73: 37-50). We have recently developed a novel rodent assay to test drug-induced cognitive affective biases which may predict drug-induced antidepressant and pro-depressant effects in man. In this study, the effects of 13-Cis-retinoic acid were investigated in rats using this affective bias test.

Male Lister-Hooded rats (n=16) were trained to perform the affective bias test. The methods uses a bowl-digging task where rats acquire two independent memories for a substrate-reward association using within-subject discrimination learning sessions. For this study, one substrate-reward association was learnt following acute treatment with 13-Cis-retinoic acid and one following control treatment. The absolute reward value was kept consistent across all sessions. 24hrs after the last pairing session, animals were presented with both reward-paired substrates in a choice test and %choice for the treatment-paired substrate was recorded over 30 trials. The first study used a fully randomised Latin square design (0.0, 1.0, 3.0 mg/kg, i.p.). This was followed by a single dose study using 10mg/kg, i.p. Results were analysed using a RM ANOVA or one-sample t-test. Treatment with 13-cis-retinoic acid tended to induce a negative affective bias (1.0-3.0mg/kg, RM ANOVA F=3.18, p = 0.056) and a 10mg/kg dose induced a significant negative bias when administered using the single dose method (t15=4.1, p = 0.0009). These data suggest that treatment with 13-cis-retinoic acid induces a negative affective bias in rats reducing the relative value of the rewarding experience encountered following acute drug administration. This result is similar to our previous observations with the CB1-antagonist/inverse agonist, rimonabant and benzodiazepine inverse agonist, FG7142, as well as psychosocial stress-induced negative affective states. This work adds support to theories about cognitive neuropsychological mechanisms in depression (Roiser et al., 2012, Neuropsychopharmacol. 37: 117-136; Pringle et al., 2011, Prog. Neuropsychopharmacol. Biol. Psychiatry 35: 1586-1592) involving a direct and acute relationship between affective state and cognitive processes associated with memory for positive experiences, which may have long-term effects on behaviour.

This work was funded by a British Association for Psychopharmacology in vivo training grant.

TA02

CENTRAL AMYGDALA LESIONS BLOCK ANTIDEPRESSANT-INDUCED POSITIVE AFFECTIVE BIAS IN RATS

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Cognitive mechanisms are now thought to play a role in the development and perpetuation of mood disorders (Harmer et al., 2009, Br. J. Psychiatry, 195:102-108; Roiser et al., 2011, Neuropsychopharmacol., 37:117–136). Recent studies suggest that acute antidepressant treatment induces positive affective biases in both healthy volunteers and depressed patients, however the underlying mechanisms involved in the development of affective bias is not fully understood. Neuroimaging studies have shown that antidepressant treatments have acute effects on amygdala function in response to emotional stimuli, therefore this region may play a crucial role in the development of positive bias associated with antidepressant efficacy. To test the hypothesis that affective bias is mediated through the amygdala we used a novel affective bias test (ABT) for rats (Stuart et al., 2013, Neuropsychopharmacol., PMID:23503126) and targeted lesions of the central amygdaloid nucleus. The ABT uses a bowl-digging task where rats encounter two independent positive experiences (finding food reward in a specific digging substrate). Treatment or control is administered prior to the experience, and the absolute reward value is kept consistent across all sessions. Affective bias is quantified in a preference test where both rewarded substrates are presented together and the rats’ choices recorded over 30 randomly reinforced trials. 32 male Lister Hooded rats received bilateral excitotoxic lesions to the central amygdaloid nucleus or sham surgery (n=16). Animals subsequently underwent ABT pairing sessions where they received either venlafaxine (3mg/kg, i.p.) versus vehicle treatment to induce a positive affective bias, or the anxiogenic FG7142 (5mg/kg, i.p.) to induce a negative bias. A two-way ANOVA revealed a significant drug effect (F2,50=4.75, p<0.01) and drug×lesion interaction (F2,50=4.67, p<0.05). As with our previous studies, sham animals made significantly more choices for the venlafaxine-paired substrate, indicating a positive affective bias. This effect was significantly attenuated in lesion animals (t25=2.43, p<0.02), with the lesion group showing no overall bias. FG7142 induced a significant negative bias in sham animals but not in lesion animals, however the difference between the two groups was not statistically significant. These data show that bilateral amygdala lesions prevent the development of venlafaxine-induced positive affective bias, and suggest that the amygdala represents a key site of action for antidepressant drugs. The results with FG7142 suggest that mechanisms outside of the amygdaloid nuclei are involved in anxiogenic-induced negative bias.

SA Stuart is supported by BBSRC and Pfizer.
TA03

ELEVATED VMAT1 EXPRESSION ASSOCIATED WITH TRANSIENT POST-NATAL FLUOXETINE EXPOSURE IN WISTAR RATS CORRELATES WITH BEHAVIOURAL DESPAIR

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Introduction: Reduced serotonin transporter (5-HTT) expression is associated with abnormal affective and anxiety-like symptoms in humans and this has been suggested to be a developmental mechanism that explains the association of low-expressing 5-HTT promoter alleles with increased vulnerability to psychiatric disorders such as depression (Ansorge et al., Science 2004; 306, 879-881).

Methods: Here we investigated the effects of transient early-life exposure (postnatal days 8 to 21) to fluoxetine, a selective serotonin reuptake inhibitor (SSRI) (10 mg/kg per day, i.p.), in male Wistar rats with a view to exploring the consequences as a possible model of depression.

Results: Rats thus treated with fluoxetine showed a small but significant loss in weight gain which persisted into adulthood. Fluoxetine-treated rats showed depressive-like features in adulthood as judged by decreased escape directed behaviour and propensity to become immobile in the forced swim test (FST) but no anhedonic phenotype was observed in the sucrose preference test. No other behavioural anomalies were observed in these animals in the elevated X-maze or social approach-avoidance paradigm and this lack of effect could not be attributed to impaired sensorimotor processing as their prepulse inhibition response was normal. Microarray analysis of transcriptional changes occurring in the hippocampal dentate gyrus of adult animals exposed to fluoxetine during postnatal development revealed a total of 332 transcripts to be differentially modulated (1.5 fold-change; p<0.05), as compared to the postnatal saline control. Interrogation of these gene transcripts and their validation using real-time PCR allowed the identification of three key gene changes: Slc18a1/VMAT1 (~100% increase), Syn2/synapsin II (~20% decrease), and Ptpn2/protein tyrosine phosphatase, non-receptor type 2 (~20% decrease).

Conclusion: A Pearson analysis of VMAT1 expression with the immobility score obtained in the forced swim test revealed a significant correlation (R=0.0848, p<0.05; n=5) suggesting dysregulation of VMAT1 may play a role in behavioural despair.

This work was supported by a Strategic Research Cluster grant from Science Foundation Ireland (03/IN3/B403C, 2003; 07/IN1/B1322, 2007) and an Irish Research Council for Science, Engineering and Technology Postgraduate Grant (KH).

TA04

EFFECTS OF ROBOXETINE ON EMOTIONAL PROCESSING IN HEALTHY VOLUNTEERS MAY BE DETERMINED BY COMT VAL158MET GENOTYPE

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Introduction: The impact of genetic variation on emotional processing is increasingly being recognised. A common polymorphism in the COMT gene (val158met) has been associated with individual differences in emotional processing, with evidence suggesting superior emotional processing in val carriers (Mier et al., 2010, Molecular Psychiatry, 15, 918 - 927). It may be the case that emotional processing mediates the relationship between the COMT genotype and vulnerability to emotional disorders. Given its selectivity for catecholamine neurotransmitters, COMT gene variation may be particularly relevant for the effects of noradrenergic antidepressants such as reboxetine on emotional processing. To date, no studies have examined such genotype dependent pharmacological effects in relation to emotional processing. It was hypothesised that COMT val158met genotype would modulate this effect and we therefore set out to examine the effects of the noradrenaline reuptake inhibitor (NRI) reboxetine on emotional processing in healthy volunteers based on COMT genotype.

Methods: Seventy-five healthy Caucasian male volunteers, aged 18-40 years, were successfully genotyped in relation to the COMT val158met polymorphism. The study took the form of a double-blind, randomised, placebo-controlled, between-group intervention using a single 4mg dose of the selective noradrenergic reuptake inhibitor (SNRI) Reboxetine. Two hours post-treatment participants completed an incidental learning task, including the encoding, free recall and recognition of 72 pictures matched for valence and arousal.

Results: With placebo, the emotional enhancement of memory for negative pictures observed in COMT val carriers was absent in met homozygotes (t(30) = 2.59, p = 0.02), despite equivalent valence and arousal ratings. There was also a significant interaction between COMT genotype and intervention group [F(4, 140) = 3.3, p = 0.01], such that reboxetine improved emotional memory for both negative and positive pictures (relative to neutral), in met homozygotes, but had no effect in val carriers. These findings support the hypothesis that emotional processing is impaired in met homozygotes and selectively improved by reboxetine in this group.

Conclusion: Abnormalities in emotional processing are increasingly considered as a cognitive marker for depressive/anxiety disorders and the mechanism of action of antidepressant drugs is increasingly understood to involve the modulation of emotional processing. The influence of COMT genotype on the effects of NRI antidepressants such as Reboxetine on emotional processing may therefore impact on these and have relevance to individual responses to antidepressant treatment.

This study was funded by Brighton and Sussex Medical School.
ADVERSE EFFECTS FROM ANTIDEPRESSANT TREATMENT: FINDINGS FROM THE GENPOD STUDY

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Introduction Premature discontinuation of antidepressant drugs is a frequent clinical problem. Adverse effects are common and reported to be one of the main reasons for discontinuation of antidepressant treatment. We aimed to investigate the time profile of adverse effects induced by the selective serotonin reuptake inhibitor (SSRI) citalopram and the noradrenaline reuptake inhibitor (NARI) reboxetine over 12 weeks of treatment. Additionally, we investigated the association between adverse effects at 2 weeks and discontinuation by 6 and 12 weeks.

Methods: 601 depressed individuals were randomly allocated to either 20mg of citalopram daily or 4mg of reboxetine twice daily. A modified version of the Toronto Side Effects Scale (TSES) was used to measure 14 physical symptoms at baseline (medication free) and at 2, 6 and 12 weeks after randomisation. Random effects logistic regression models were used to investigate the adverse effect profile of the two antidepressants and investigate if physical symptoms decreased progressively over the 12 weeks. Logistic regression models were used to investigate whether specific physical symptoms at 2 weeks were associated with discontinuation from antidepressant treatment by 6 or 12 weeks. Sensitivity analyses were performed that only included individuals that adhered to treatment. All models were adjusted for severity of baseline depression, recruitment centre and if appropriate drug type and baseline physical symptom. Data were analyzed using Stata version 12.1

Results: The majority of adverse effects persisted for 12 weeks for individuals who adhered to medication. There was evidence of an association between constipation (OR 2.82, 95% CI 1.06 to 7.48, p=0.04) and nausea (OR 2.41, 95% CI 1.03 to 5.67, p=0.04) with higher odds of discontinuation from citalopram by 6 weeks, and suggestive evidence of an association between agitation (OR 1.78, 95% CI 0.96 to 3.29, p=0.07) and dizziness (OR 1.78, 95% CI 0.93 to 3.40, p=0.08) with higher odds of discontinuation from reboxetine. Drowsiness (OR 0.40, 95% CI 0.17 to 0.94, p=0.04) was associated with reduced odds of discontinuation from citalopram. Over the 12 weeks, 9 physical symptoms were more frequently reported with reboxetine treatment and 2 with citalopram. Over twice as many people stopped treatment with reboxetine (n=108) than with citalopram (n=51) after 6 weeks.

Conclusions: We report that adverse effects do not significantly reduce over a 12 week treatment period for individuals adhering to medication. Specific adverse effects occurring early in treatment may be useful to predict individuals who discontinue antidepressant treatment by 6 weeks.

Financial Disclosure The study was funded by the Medical Research Council (grant reference: G0200243).

NEXT GENERATION SEQUENCING: BEYOND GENETIC ASSOCIATION

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AZD6765 is a novel low-trapping NMDA open channel blocker currently under investigation as a potential adjunct treatment for patients with depression who have a history of inadequate response to multiple prior treatments. DNA was collected and banked from consenting individuals in a Phase II clinical study, enabling a rapid and focused genetic analysis to explore potential genetic contributions to clinical response. GABRA2 was selected for analysis guided by publications linking family alcohol dependence, ketamine response, depressive symptoms and variations in this gene. Four variations in GABRA2 - two in linkage disequilibrium (LD) (rs11503016 & rs17537359) and two outside of a defined LD block (rs3756007 & rs1372472) - were associated with change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) (29 variations were evaluated; 4 influenced baseline change at 95% confidence, and one remained statistically significant on further testing [99.7% confidence]). Next generation sequencing (NGS) was subsequently employed, providing comprehensive genomic coverage of the region (to hunt for potential causative variants). Although no causative variants were identified, significant learning was generated by this approach. In particular the effort required to explore the data generated and the absence of an ideal control group (1000 genomes data were used as a baseline) highlighted some of the challenges in this field. Genetic association studies are easy to perform but difficult to interpret without rigorous follow up. However, because an extremely careful candidate selection approach was applied prior to genotyping, the associations were considered sufficiently interesting to warrant further work. An ongoing second Phase II study will provide an opportunity to test for replication. Targeted NGS (in concert with a custom HaloPlexTM targeting kit) was performed with the original study population to explore in depth the entire genomic sequence around the associated variations. The genetic variation tested was associated with MADRS change from baseline in placebo-treated individuals as well as those treated with AZD6765, although not to the same degree; the results suggested the potential for both a “prognostic” and a “predictive” drug response effect (common to many therapy guiding tests). The integration of biomarker discovery activities into clinical programs is complex. However, the potential value to the patient in identification of the population most likely to respond to therapy should not be overlooked. Our work demonstrates both the feasibility of such work, but also the problems where sample numbers can limit opportunities for the discovery of new markers influencing disease progression as well as therapeutic response.

Funding: AstraZeneca Pharmaceuticals LP.
TA07

ANTI-ANHEDONIC EFFECTS OF KETAMINE AND ITS NEURAL CORRELATES IN DEPRESSION

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Almost 40% of depressed patients suffer from clinically significant anhedonia, the loss of enjoyment or desire towards a previously pleasurable activity. Critically, these patients have poorer treatment prognosis than their non-anhedonic counterparts. Accumulating evidence suggests that standard treatments for depression have little efficacy in treating anhedonia; there is currently no FDA approved treatment for anhedonia. The noncompetitive N-Methyl-D-aspartate receptor (NMDAR) antagonist ketamine has shown remarkable consistency in rapidly ameliorating depressive symptoms in both unipolar and bipolar depression. However, it is unknown whether ketamine also possesses any anti-anhedonic efficacy. In a randomized double-blind placebo-controlled crossover study we assessed ketamine’s anti-anhedonic effects in a sample of 33 treatment-resistant patients diagnosed with bipolar disorder. We evaluated levels of anhedonia using the Self-Hamilton Pleasure Scale (SHAPS). In a subsample of these patients (N=21) we also measured the neural response to both placebo and ketamine infusion using [18F] fluorodeoxyglucose positron emission tomography (PET). We regressed changes in anhedonia levels (ketamine-placebo)/placebo at 230 minutes post-infusion onto difference images to identify mediating effects of ketamine’s anti-anhedonic capacity. Finally, we assessed the neurobiology of anhedonia by correlating scores on the SHAPS at the time of the PET scan with glucose metabolism. Our analyses comprised both a region of interest approach, focused on the reward consumption network (ventral striatum and orbitofrontal cortex), and a whole brain investigation. Our results indicate that levels of anhedonia were significantly reduced following ketamine in comparison to placebo (main effect of drug, F(1,507)=138.515, p<.001). This reduction lasted from 40 minutes to 7 days, following one infusion. Our PET analyses indicate a role for ventral striatum in ketamine’s anti-anhedonic response (r=-.48, p=.036); individuals with the largest increase in metabolism in ventral striatum had the highest anti-anhedonic response 230 minutes post-infusion. Finally, we evidence relationships between levels of anhedonia post-ketamine and post-placebo. Notably, following ketamine, we found that heightened activity in the posterior cingulate positively correlated with levels of anhedonia (Pcorrected =.009), while decreased levels of anhedonia were found to be associated with greater amygdala and insular glucose metabolism (Pcorrected=.007), at the whole brain level. Our results add increasing weight to the potential for NMDAR antagonists in treating depression. Importantly, anhedonia has been targeted as a tractable endophenotype for the heterogeneous depression classification; elucidating the neural mechanisms behind both the endophenotype and its treatment are the critical stepping-stones for progress in psychiatry outlined in the Research Domain Criteria. Supported by/grant awarding body: This study was supported by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health, and Department of Health and Human Services.

TA08

EFFECTIVENESS AND TOLERABILITY OF TRANSCRANIAL DIRECT CURRENT STIMULATION IN MAJOR DEPRESSION: A SYSTEMATIC REVIEW

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Introduction: Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation modality, which alters cortical tissue excitability through applying a weak direct electrical current via scalp electrodes overlying targeted cortical areas. It is a novel treatment for major depression, with potential advantages over other interventions; we wished to ascertain the level of efficacy and tolerability of tDCS and to identify which patients might benefit most.

Method: A literature search of PsychINFO, Web of Science (MEDLINE, Biosis), EMBASE, Science Direct and Cochrane Central Register of Controlled Trials (CENTRAL), for the period January 1995 to January 2013; followed by scrutiny of reference lists of primary research papers, reviews, and meta-analyses, examination of customized e-alerts from NHS Evidence Alert, and discussions with experts in the field.

Results: Early studies focused on attempts at stimulating the brain-stem and used electrode-montages in which the anode was placed close to the eyebrows. Recent tDCS studies have favored a bi-frontal montage with the anode and cathode positioned over contra-lateral frontal areas. The evidence from randomized controlled trials (RCTs) for the efficacy of tDCS in major depression is inconsistent: 5 RCTs show an advantage for active tDCS over sham tDCS, but 3 RCTs do not demonstrate a significant separation between active and sham safety. Efficacy is not established in patients with previously treatment-resistant depression or patients already undergoing antidepressant treatment. Efficacy in established patients with previously treatment-resistant depression or patients already undergoing antidepressant treatment. RCTs which involved use of higher currents are more likely to have established efficacy, but the effect of the number of treatment sessions is unclear. tDCS appears to have a good safety and acceptability profile, with only mild adverse effects reported in most trials. The only ‘serious adverse event’ recorded in published tDCS RCTs was a case of suicide, considered unlikely to be directly related to tDCS. Four cases of tDCS-associated hypomanic episodes have been reported, all in patients with bipolar depression.

Conclusions: tDCS may represent an effective treatment option for patients with major depression, and is a potentially useful alternative to antidepressant medication in patients who do not wish to take or cannot tolerate antidepressant drugs. In depressed patients with a low level of treatment resistance, it has comparable acute phase efficacy to fluoxetine, possibly with an earlier onset of effect. The current body of evidence does not support the use of tDCS in treatment resistant depression.

Declaration of interests. Funding to the University of Southampton from the Medical Research Council Experimental Medicine in Mental Health programme, to explore neuropsychological mechanisms underlying the effects of tDCS.
TA09

DIAGNOSTIC STATUS PREDICTIONS USING STRUCTURAL AND FUNCTIONAL MRI IN MAJOR DEPRESSION

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Introduction: Major Depressive Disorder (MDD) is a mood disorder characterised by persistent and disabling symptoms of low mood, anhedonia, hopelessness, guilt, lack of energy, suicidal thoughts, and altered appetite and sleep. It is a clinically heterogeneous disorder and the trajectory of illness can vary greatly between patients. Responses to available treatments are inconsistent and there are no reliable established pathophysiological mechanisms or biomarkers. Multivariate pattern analysis (MVPA) and feature selection are methods to identify consistent patterns within clinical datasets, including from functional imaging. The present study sought to develop an accurate objective predictor of diagnostic status - MDD vs. healthy matched controls using structural and functional neuroimaging data in conjunction with Support Vector Machines (SVMs).

Methods: Structural T1 weighted images and event-related fMRI images from twenty adults with MDD (aged 33 - 71) and twenty-one healthy adults (aged 25 - 72) were included in this study. Structural T1 weighted images were processed using SPM8 (DARTEL). Standard leave-one-out cross-validation (LOOCV), feature selection (which adaptively selects which brain regions to include for analysis) and a Gaussian SVM were used in this analysis. fMRI data was obtained while subjects engaged with a paradigm involving win and loss events. SPM8 was used to pre-process fMRI data and the first level analysis of a random effects event related design used to calculate win and loss event contrast images. These win and loss contrast images were entered into the identical LOOCV-SVM process as the structural MR images.

Results: Individual subject predictions of diagnostic status with 85% (p< 0.001) were achieved using grey matter images. For white matter, accuracies of 71% (p<0.009) were achieved. Using the win contrast images from each subject and SVM (as described for processing T1 weighted images) a classification accuracy of 84% (p< 0.001) was achieved. Notably, the loss contrast images achieved a higher predictive accuracy of 97% (p< 0.001).

Conclusions: It is possible to use MVPA and Feature Selection to make highly accurate objective individual subject predictions of diagnostic status. The brain regions selected automatically during Feature Selection have been previously reported in conventional group-level t-test studies of MDD. fMRI loss event stimuli allowed particularly accurate prediction (97%), suggesting that the neural processing of loss events is particularly abnormal in MDD, consistent with cognitive-behavioural theories of MDD.

Additional information B. Johnston is supported by a SINAPSE-SPIRIT studentship and the University of Dundee. This study was funded through awards from a local Anonymous Trust and has been adopted by the Scottish Mental Health Research Network (SMHRN - http://www.smhrn.org.uk/trials/trials.asp?trialID=32).

TA10

INVESTIGATING DIMENSIONS OF REWARD AS TRAIT MARKERS FOR DEPRESSION

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Introduction: Reward dysfunction in the human brain has been suggested as underlying anhedonia in depression and as a possible endophenotype as it seems to predate the onset and persist into recovery. We have shown previously that those who are “at risk” of depression have decreased neural processing of reward (chocolate) which supports the idea of reward dysfunction as a neural biomarker for depression. However, how the separate neural dimensions underling “wanting” and “liking” are affected in those “at risk” has not yet been investigated.

Methods: Using SPM8 parametric modulation analysis we correlated the brains response with the subjective report of “pleasantness” “wanting” and “intensity” in 13 unmedicated recovered depressed patients with a history of major depression compared to 14 healthy age/gender matched controls and 25 young people (aged 16-21 years) with a biological parent with depression compared to 25 age/gender matched controls.

Results: We found that the pleasantness and wanting ratings of the stimuli had lower positive correlations with the fMRI BOLD signal in the anterior cingulate cortex (ACC) ([4 46 24] Z=2.8 svc p=0.04) in the recovered depressed volunteers compared to the healthy controls, but not in the family history group. We found that the wanting ratings also had lower positive correlations with the DLPFC ([46 -6 8] Z=3.14 svc p=0.017) and the ventral striatum ([4 6 -8] Z=2.2 p=0.01 uncorrected) in the recovered depressed volunteers but not the family history group. We found that the intensity ratings had lower positive correlations with the caudate ([18 18 8] Z=3.09 svc p=0.03) the subcallosal gyrus ([10 2 -14] Z=3.61 svc p=0.01 whole brain corrected) the ACC ([12 46 14] Z=3.1 svc p<0.03) the insula ([26 20 -12] Z=3.05 svc p<0.03) and the mOFC ([4 36 -6] Z=3.26 svc p<0.01) in the recovered depressed volunteers compared to the healthy controls, but higher positive correlations with the insula ([4 46 24] Z=2.68 svc p<0.04 and the ACC ([2 18 40]) Z=2.65 svc p<0.04 in the family history group.

Conclusions: These results suggest that the neural response is directly related to the subjective experience of reward during the scan and that the separate subjective dimensions such as wanting and liking might differ as state/trait markers for depression. The results from this type of study suggest the development of specific interventions for those before the onset of depression which might be different from that needed for patients who have already experienced depression.

This work was funded by the MRC Grant no: HQRORVo
INTRODUCTION: Functional movement disorders (FMD) are a group of disorders characterised by physical symptoms resembling neurologic disorders but occurring without a known organic cause. These disorders occupy a ‘grey area’ between psychiatry and neurology. This difficulty of categorization, in conjunction with an absence of pathophysiological understanding, has greatly limited diagnosis and treatment of FMD, despite its prevalence in neurology clinics. We hypothesised that some aspects of FMD symptomology could be explained by a deficit in reversal learning, where participants must learn to select a previously-undesirable cue upon reversal of its reward contingency, given that abnormal illness behaviour persists despite major adverse consequences. This could maintain false inferences driving aberrant percepts in FMD. Previous studies found reversal learning deficits in disorders including major depression (MDD), a frequent comorbidity of FMD patients, but comparison between disorders is limited by methodological differences between studies.

METHODS: We investigated reversal learning in FMD patients (n=11), unmedicated MDD patients (n=15), and healthy control participants (n=28). In a computerised task, symbols probabilistically associated with monetary gain, loss, or no change were presented as pairs in two condition types, reward (£0.20 win/no monetary change) and punishment (£0.20 loss/no monetary change).

RESULTS: Both patient groups showed reduced post-reversal performance in the reward domain, an increased number of perseverative responses, and reduced learning rates relative to controls in model-based analyses (p<0.05). No differences between the two patient groups were found.

CONCLUSIONS: We found a reduced ability to flexibly change responding following reward reversal in both patient groups. These results indicate a deficit common to both FMD and MDD in the ability to reverse reward associations. We speculate that this abnormal processing could result in a failure to unlearn previously-reinforced habitual behaviours to a cognitively-based form.

REFERENCES:
Green et al. 2012, Arch Gen Psychiatry; 69: 1014-21. The electrophysiological basis of this reduced coupling is unknown. Here, we used event-related 64-channel EEG to investigate medication-free participants with remitted MDD (n=10, no current symptoms), compared with control participants with no personal or family history of MDD. We report a preliminary analysis of 10 participants in each group. Participants were presented with shortened versions of written statements describing actions which were contrary to socio-moral values described by social concepts (e.g. “stingy”, “tactless”). In these statements, the agent was either the participant (self-agency condition, N=90, highly associated with self-blame), or another person (other-agency condition, N=90, highly associated with self-blame). Signal was averaged over the 350-500 ms post-stimulus time-window in a fronto-central cluster of 6 electrodes. There was a marginal interaction of agency by group in the theta (4-8 Hz, d=0.91) and alpha (8-14 Hz, d=0.89) bands. Marginal main effects of agency and group, but no interaction, were found in the delta band (1-4 Hz). These results indicate that N=21 in each group are needed to confirm these preliminary results. If confirmed, these self-blame-selective changes in alpha and theta power could serve as a trait biomarker of vulnerability to major depressive episodes. This work was funded by an MRC clinician scientist fellowship to RZ. JAG was funded by an EPSRC PhD studentship.

TA12

ELECTROPHYSIOLOGICAL CORRELATES OF SELF-BLAMING BIAS IN REMITTED MAJOR DEPRESSIVE DISORDER
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Individuals with major depressive disorder (MDD) exhibit overgeneralization of self-blaming feelings (e.g. guilt) relative to those related to blaming others (e.g. indignation). This ‘self-blaming bias’ remains detectable even after full remission from symptoms, and is thus a vulnerability trait marker. A previous study demonstrated that self-blaming bias is associated with temporoparietal reductions in functional coupling on fMRI (Green et al. 2012, Arch Gen Psychiatry; 69: 1014-21). The electrophysiological basis of this reduced coupling is unknown. Here, we used event-related 64-channel EEG to investigate medication-free participants with remitted MDD (n=10, no current symptoms), compared with control participants with no personal or family history of MDD. We report a preliminary analysis of 10 participants in each group. Participants were presented with shortened versions of written statements describing actions which were contrary to socio-moral values described by social concepts (e.g. “stingy”, “tactless”). In these statements, the agent was either the participant (self-agency condition, N=90, highly associated with self-blame), or another person (other-agency condition, N=90, highly associated with self-blame). Signal was averaged over the 350-500 ms post-stimulus time-window in a fronto-central cluster of 6 electrodes. There was a marginal interaction of agency by group in the theta (4-8 Hz, d=0.91) and alpha (8-14 Hz, d=0.89) bands. Marginal main effects of agency and group, but no interaction, were found in the delta band (1-4 Hz). These results indicate that N=21 in each group are needed to confirm these preliminary results. If confirmed, these self-blame-selective changes in alpha and theta power could serve as a trait biomarker of vulnerability to major depressive episodes. This work was funded by an MRC clinician scientist fellowship to RZ. JAG was funded by an EPSRC PhD studentship.

TA13

SCREENING FOR PHYSICAL HEALTH PROBLEMS IN PATIENTS WITH FUNCTIONAL MOVEMENT DISORDERS AND MAJOR DEPRESSION
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INTRODUCTION: Patients with severe mental illness are at significantly increased risk of diabetes and cardiovascular disease (CVD). National Institute for Health and Clinical Excellence (NICE) guidelines advise that this patient group should undergo regular screening for diabetes and other CVD risk factors. Previous studies show that monitoring of physical health in patients with schizophrenia is sub-optimal: little is known about the monitoring of physical health in patients with complex and severe affective disorders. The aim of our study was to ascertain the proportion of patients with affective disorders who had been screened and monitored for metabolic abnormalities in accordance with NICE guidelines.

METHODS: A retrospective case-note study of electronic and paper records of consecutively newly referred patients attending a regional specialist tertiary referral service for patients with complex, severe and treatment-resistant affective (mood and anxiety) disorders, between January 2010 and March 2013. In each patient, we searched for documented evidence of glucose testing, body weight measurement, blood pressure recording, and estimation of lipid profile and serum prolactin over the 12 months prior to attending the appointment. The frequency of contact with healthcare services was recorded to provide an estimate of the opportunities for testing.

RESULTS: The notes of 133 newly referred patients (50 men, 63 women; mean age 50.6 yrs, range 19-85 yrs) were examined. Primary diagnoses were unipolar depressive disorders 52 (46.0%), bipolar disorder 33 (29.2%), anxiety disorders and OCD 13 (11.5%), 15 patients (13.3%) had other disorders. Forty patients (35.4%) had comorbid mental disorder and 42 (37.2%) a coexisting physical illness. Documented evidence of monitoring of physical health and screening for diabetes or metabolic abnormalities was limited: 5 (4.4%) patients were weighed, 10 (8.8%) had blood pressure recorded, 18 (15.9%) were screened for diabetes, 9 (8.0%) were screened for dyslipidaemias, no patients were screened for raised prolactin. Monitoring was more frequent in patients with anxiety disorders than in those with unipolar depressive disorders or bipolar disorder. Monitoring was also more frequent in patients over 40 yrs. The mean number of appointments over a period of 12 months was 6.9 (SD 7.7) and 12 (10.6%) patients had a hospital admission: indicating that there were many opportunities for screening which were not taken.

CONCLUSIONS: This retrospective case-note survey demonstrates that physical health monitoring of patients with affective disorders is sub-optimal. Efforts should be made to facilitate the screening for and monitoring of physical health in this at-risk patient group.
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There is evidence that risk of preterm birth (PTB), low birth weight (LBW) and intrauterine growth restriction (IUGR) is significantly higher in depressed pregnant women. A recent meta-analysis by Grote et al (2010, Arch of General Psychiatry; 67(10):1012-24) showed that the pooled relative risk of PTB, LBW and IUGR was significantly higher in depressed women (RR 1.39, 1.49 and 1.45 respectively at 95% CI). Maternal depression may have an impact on the unborn foetus through uterine artery blood flow and studies have demonstrated abnormal uterine blood flow and foetal growth restriction in depressed pregnant women. To examine foetal ultrasound scans in depressed and non-depressed pregnant women and identify the translational component which results in babies born to depressed mothers having altered stress response and developmental changes. Prospective case-control study of depressed pregnant women and controls recruited from a London hospital. All women have ultrasound scans at approximately 10 weeks and 20 weeks of gestation; a subset of women have growth scans at 32 weeks. Foetal parameters of foetal heart rate (FHR), crown-rump-length (CRL) and nuchal translucency (NL) are recorded in the first trimester. Foetal measures of biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femoral length (FL) are recorded in the second trimester scans. The Structured Clinical Interview for DSM IV Axis I Disorders is used to assess present and previous history of mental disorder and use of anti-depressant medication. Information about demographics and obstetric outcome is collected from the hospital notes. Data collection is ongoing. Results are of preliminary analyses of data from 109 women, of whom 53 are controls and 56 cases, 58 (51%) are white, 56 (51%) are primigravida and 13 (12%) were taking antidepressant medication at baseline. Initial results show that CRL is significantly higher in cases (t=2.29, p<0.05) with no other significant difference in foetal parameters and measures between cases and controls, although most are lower for cases.

BPDC, HC and FL are significantly lower in women taking anti-depressant medication (t=2.22, p<0.05; t=2.45, p<0.05; t=2.37, p<0.05 respectively). Regression analyses indicate that medication status predicts lower BPD and FL even when taking into account diagnostic status. There are no significant differences according to maternal ethnicity, age, parity, or alcohol use and smoking status. Conclusions: Foetuses of women taking anti-depressant medication in the second trimester of pregnancy have a significantly lower BPD and FL compared to foetuses of women not on medication.

**TA16**

**DEPRESSION IN PREGNANCY: AVERSE OBSTETRIC AND FOETAL OUTCOMES**

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TA17
DO YOUR NEIGHBOURS MATTER? ETHNIC DENSITY IN WOMEN WITH POSTNATAL DEPRESSION AND WITH PERSONALITY DISORDER IN LONDON, UK
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Introduction: The ‘ethnic density hypothesis’ proposes that individuals living in areas with higher proportions of people of the same ethnicity exhibit better mental health outcomes. Here we investigate the role of ethnic density in postnatal depression (PND) and personality disorder (PD).

Methods: 2 171 newly delivered mothers (1164 (53.6%) ethnic minorities and 1007 (46.4%) white respondents), aged 15-48 years, were randomly recruited across London. At six weeks post-partum, participants were screened for PND, using the Patient Health Questionnaire (PHQ-9), and for PD, using the Standardised Assessment of Personality Abbreviated Scale (SAPAS). Women who scored >12 on the PHQ-9 and >4 on the SAPAS screened positive for PND and PD respectively. Using participant addresses, Lower Super Output Areas (LSOAs) were matched for each postcode. Ethnic density was extrapolated from data generated by the Office for National Statistics, based on the 2001 UK Census, for each LSOA. Ethnic density is defined as the proportion of individuals in the respective ethnic group over the total area population.

Results: 4.8% and 14.1% of the screen positive sample was found positive for PND and PD respectively. There was a significant difference between the ethnic density of women screening positive for PND (M=17.9, SD=18.8) compared to those who did not (M=27.5, SD=24.3); t(122)=3.04, p < .001, and for women screening positive for PD (M=22.5, SD=21.5) compared to those who did not (M=27.8, SD=24.5); t(446)=3.92, p<.001. Using logistic regression, there was evidence of a decreased risk of PND (odds ratio 0.98 (95% confidence interval 0.96 to 0.99); p = .001) and of PD (odds ratio 0.99 (95% confidence interval 0.985 to 0.999); p = .03) in areas of higher ethnic density, independently of partner status and ethnicity.

Conclusion: Living in areas of higher ethnic density was protective in our sample developing PND, even after adjusting for other confounding variables. For PD, we also found a protective effect of living in areas of higher ethnic density, independent of other confounding variables.

The study was funded by the Foundation for the Study of Infant Deaths, UK.

TA18
REAL-TIME FMRI NEUROFEEDBACK CAN IMPROVE AMYGDALA REGULATION DURING EMOTIONAL STIMULATION
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The amygdala is a key node in the processing of emotional information, particularly arousal, and its activity decreases with various emotion regulation strategies (Oehsner et al. 2012 Ann NY Acad Sci, 1251:E1-E24). Increased activity and hyperreactivity of the amygdala is typical in most affective disorders (e.g. Hamilton et al. 2012 Am J Psychiatr 169:693-703). Successful treatment of affective disorders is associated with reduced or normalized activity of the amygdala (Quide et al. 2012 Neurosci Biobehav R 36:626-644). However, insufficient response or even resistance to treatment is a problem in a substantial percentage of patients suffering from affective disorders. Neurofeedback using real-time functional magnetic resonance imaging (rtfMRI) could represent an additional approach to improve emotion regulation by giving direct feedback of amygdala activity and of emotion regulation. We aimed in this pilot study to develop and test the feasibility of this approach for training to regulate the amygdala. Negative emotional facial expressions were used to activate the amygdala. Six healthy participants underwent four training sessions (about weekly, in total 24 scans). In each session, the amygdala was first localized functionally contrasting negative emotional and neutral pictures. The so derived region of interest was used for calculating feedback in the following feedback runs. Amygdala activity was indicated in real-time to the participants as changing colour of blocks on both sides of the stimuli in the feedback runs (red = high activity, blue = low activity). For down-regulation of amygdala activity, participants were given typical emotion regulation strategies (e.g. reappraisal, reality check) during the regulation conditions. For reasons of comparison and contrast, we added passive viewing conditions of the faces. Data were analysed post scanning on an individual basis, extracting beta weights of the amygdala and dorsomedial prefrontal cortex using paired t-tests. The participants applied mostly cognitive and attentional strategies. All participants managed down-regulation of amygdala activity assisted with rtfMRI neurofeedback during stimulation with negative emotional faces. This down-regulation improved significantly from first to last session (p = .004, effect size d = 1.34). This effect was significant in five of six participants (no difference of the trend-line from zero slope in one participant). Dorsomedial prefrontal cortex and insular cortex were bilaterally more active during regulation. However, repeated training had no significant effect in these regions. In conclusion, this pilot study supports further development of rtfMRI neurofeedback training of amygdala down-regulation during stimulation as well as for other mechanisms in other brain regions. Further studies should replicate the finding and optimize aspects of the training ("dosage", duration, intensity, instruction,...) prior clinical application.

This study was supported by a project grant of the Swiss National Science Foundation (SNSF).

TB01
EVIDENCE FOR LITHIUM-LIKE EFFECTS OF EBSELEN ON 5-HT2A RECEPTOR FUNCTION MEDIATED VIA IMPASE INHIBITION
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Inhibition of inositol monophosphatase (IMPase) and phosphoinositide (PI) signalling is a putative mechanism underlying the mood stabilizing and impulsivity lowering effects of lithium [Birrige et al., 1989, Cell, Vol 59, 411-419]. In a recent re-purposing study of clinically used drugs we identified ebselen as a potent IMPase inhibitor [Singh et al., 2013, Nat Communications, 4:1332]. The 5-HT2A receptor activates the PI cycle and its blockade may be linked to the therapeutic effects of lithium. Hence we studied the effect of ebselen, a psychological drug on 5-HT2A and a selective IMPase inhibitor (L-690,330) on behavioural and molecular effects of the 5-HT2A receptor agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) in mice. Adult male C57BL/6 mice were treated with vehicle, ebselen (1, 5 or 10 mg/kg) or L-690,330 (0.5 or 0.8 mmol/kg) followed 1 h later by DOI (2 mg/kg). Lithium was administered either acutely (10 mmol/kg) or repeatedly (first dose 10 mmol/kg then 3 mmol/kg twice daily for 3 or 7 days) followed by DOI (2 mg/kg). Lithium was administered either acutely (10 mmol/kg) or repeatedly (first dose 10 mmol/kg then 3 mmol/kg twice daily for 3 or 7 days) followed by DOI (2 mg/kg). DOI-induced head twitch responses (HTR) and ear scratch responses (ESR) were scored 5 min after agonist injection for 15 min. DOI-induced c-fos mRNA was also measured in mice pretreated with either ebselen (10 mg/kg) or lithium (7 days). Brains were removed 1 h after DOI injection. In situ hybridization was performed on brain sections using 35S-dATP labelled oligonucleotides complimentary to c-fos mRNA. Data were analysed statistically using Student’s unpaired t-test or one way ANOVA with post hoc LSD as appropriate (n=6-8 per group). Compared to vehicle controls, ebselen dose-dependently decreased both the HTR and ESR elicited by DOI. Acute lithium also decreased the ESR while repeated lithium decreased both the ESR and HTR. L-690,330 also reduced the ESR and HTR to DOI. DOI-induced c-fos mRNA was decreased by ebselen in specific cortical regions. Repeated lithium also reduced the c-fos response to DOI. The current data show that ebselen, lithium and a selective IMPase inhibitor decreased 5-HT2A receptor function in a behavioural model. Ebselen and lithium also reduced decreased 5-HT2A receptor function in a molecular model. These findings support the hypothesis that both ebselen and lithium attenuate central 5-HT2A receptor function through IMPase inhibition. The lithium-like effects of ebselen support its clinical testing as a mood stabilizing and impulsivity lowering agent.

This work was funded by the BSRSRC and Rosettes trst (GC, TS). IA is supported by studentships from the Onassis Foundation and Greek Government.
TB02

THC ELICITS VERY HIGH-FREQUENCY GAMMA OSCILLATIONS

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Introduction: Animal and human studies have shown that ∆9-tetrahydrocannabinol (THC) has marked effects on neural oscillations within various frequency bands, but the effect of THC on gamma oscillations in humans remains unexplored. Gamma oscillations are believed to be fundamental for attention, perception, movement and thinking. Drugs such as ketamine, and disorders such as schizophrenia are associated with elevated gamma amplitude. Here we aimed to explore the effects of THC on gamma oscillations in humans - to our knowledge, the first study to do so.

Methods: Self-paced motor activity evokes a well-characterised event-related-synchronisation (ERS) at high gamma frequency (> 65 Hz) in the contralateral sensorimotor cortex. We investigated the effects of THC on this ERS in two separate samples of healthy volunteers using EEG. Both experiments used a within-subject design, and THC was delivered intravenously (iv). In the first study (n=15), THC (1.25mg) and placebo were administered in a randomised, counterbalanced order over two visits. In the second study, (n=13) the initial pre-drug EEG was compared with the EEG following THC (1.5mg) in a single visit to the lab. After artefact reduction using mathematical modelling, Fast Fourier transforms, were used to quantify the amplitude of the ERS in two frequency bands (65-85 Hz and 85-130Hz), which were compared with two tailed t-tests.

Results: In the first study THC (compared to placebo) elicited an increase in the overall 65-130 Hz ERS (p<0.05). Visual inspection of the spectrograms revealed that THC but not placebo produced oscillations in the 85-130Hz frequency-band (amplitude under THC conditions, 0.0219 ±0.0297μV; versus placebo conditions -0.0034 ±0.0232 μV, p=0.016). In the second study we investigated whether the ability of THC to elicit >85Hz oscillations was reproducible. Again THC, but not placebo, produced oscillations in the 85-130Hz frequency band (amplitude under THC conditions, 0.0305 ±0.0507; amplitude at baseline -0.0096 ±0.0341μV μV, p=0.053).

Conclusions: This is the first study to our knowledge to explore the influence of THC on gamma oscillations in humans. In a motor task known to elicit gamma oscillations over the contralateral sensorimotor cortex, THC was associated with higher frequency gamma oscillations (>85Hz), which were not observed under placebo conditions. This was observed in 2 separate samples. Further work might shed light on the neuropsychiatric significance of this effect.

This study was supported by the Medical Research Council, The Beckley Foundation and the NIHR Biomedical Research Council for Mental Health at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, King’s College London.

TB03

DOPAMINE D3 RECEPTOR BLOCKADE VIA GENETIC DELETION OR THE NOVEL ATYPICAL ANTIPSYCHOTIC S33138 INCREASES ADULT NEUROGENESIS

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The role of dopamine in adult neurogenesis continues to be an area of controversy, with few studies addressing hippocampal neurogenesis directly. In an attempt to further clarify the role of dopamine receptor subtypes in the hippocampal subgranular zone, the present study examined the role of the D3 receptor (D3R) in adult neurogenesis in this area of the brain using D3 receptor knock-out (D3R KO) mice and the novel preferential D3R antagonist S33138 as a pharmacological tool. Results from these experiments reveal that D3R KO mice have increased baseline levels of cell proliferation measured using Ki-67, changing from 1373 to 2026 BrdU positive cells per hippocampus (p = 0.0053), as well as increased level of ongoing neurogenesis measured using doublecortin (DCX), from 10505 to 18117 DCX positive cells per hippocampus (p < 0.001), but no differences in cell survival measured using BrdU. The role of D3R was further demonstrated by a 21 day treatment of wild-type mice with 0.64 mg/kg S33138 which resulted in an increase in cell proliferation from 1373 to 1701 BrdU positive cells per hippocampus (p = 0.045) upon D3R blockade. Results from both the D3R KO mice and D3 antagonist indicate an inhibitory activity of the D3R in adult neurogenesis in the hippocampus. Ultimately these findings suggest that modification of dopamine signalling in this area may affect processes related to hippocampal neurogenesis such as memory and mood.

TB04

NEUROTOXIN-INDUCED LOSS OF CHOLINERGIC FUNCTION IN THE DORSAL STRIATUM OF WILDTYPE MICE CAUSES Locomotor Hyperactivity in the Light/Dark Exploration Box

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Mice lacking functional neurokinin-1 receptors (NK1R-/-) display locomotor hyperactivity compared to their wildtype counterparts (Yan et al. 2010, J Psychopharmacology 24:27–38). NK1R are densely expressed in the dorsal striatum, a region strongly implicated in action selection and initiation, where they are located almost exclusively on aspiny cholinergic interneurons and mediate striatal cholinergic release (Gerfen CR 1991, Brain Res 556:165-170). In turn, cholinergic activity influences both medium spiny GABAergic output neurons through activation of M1 and M¬4 muscarinic receptors (Bernard V et al. 1992, J Neurosci 12:3591-3600), and dopaminergic input neurons through activation of nicotinic receptors (Threlfell et al. 2012, Neuron 75:58-64). As a consequence, cholinergic activity is thought to play a key role in the regulation of movement. Here, we have investigated whether a lesion of NK1R-expressing neurons in the dorsal striatum of wildtype mice induces locomotor hyperactivity. The neurotoxin, substance P-conjugated saporin, was infused under isoflurane anaesthesia bilaterally into the dorsal striatum (AP: +0.6mm; ML: ±1.8; DV: -4.8). The behavioural phenotype of NK1R lesioned wildtype mice was then measured three weeks later using the light/dark exploration box (LDEB). After 90 min habituation to the dark zone of the LDEB, the mice were transferred to the light zone and their free movement across both zones monitored for 30 min. Loss of NK1R-expressing neurons in the dorsal striatum induces locomotor hyperactivity expressed by NK1R-/- mice. This is consistent with a role of striatal cholinergic activity in the regulation of movement.

This work was funded by the Medical Research Council (UK).
Introduction: P-glycoprotein (P-gp) is a drug efflux pump expressed, amongst others, on the luminal surface of the cerebral endothelial cells forming the blood-brain barrier. Studies in rodents have demonstrated that antihistamines that are substrates of P-gp display no or minor central nervous system (CNS) effects as compared to antihistamines that are not P-gp substrates (e.g. Polli et al., 2003, J Pharm Sci, 92: 2082-2089), suggesting that the presence and/or magnitude of sedation caused by antihistamines may be determined by P-gp. The present study explored whether P-gp contributes in similar ways to occurrence of sedative effects of antihistamines in humans. More precisely, the role of P-gp in the occurrence of CNS sedation after administration of cetirizine, a 2nd generation antihistamine, in healthy volunteers was investigated. Blocking P-gp was expected to increase the distribution of cetirizine and to produce more CNS sedation due to enhanced histamine-receptor binding in the brain. It was hypothesized that sedation after cetirizine administration would be apparent in combination with a P-gp blocker, but not when administered alone.

Methods: A pharmaco-fMRI study was conducted according to a double-blind, randomized, placebo-controlled, cross-over design in 13 healthy volunteers. Participants received cetirizine 15mg; verapamil 120mg (a P-gp blocker); a combination of cetirizine + verapamil; and a placebo. Brain activity was assessed while conducting the attention network task (ANT) in a 3T magnetic resonance scanner. The ANT measures three independent attention domains: i.e. alerting, orienting and executive attention (Fan et al., 2007, J Neurosci, 27: 6197-206).

Results: At the behavioral level, cetirizine combined with verapamil reduced alertness in the ANT task, as indicated by longer reaction times, when compared to verapamil alone and when compared to cetirizine alone (t12=3.11, p=0.009). Moreover, the data indicate that central cetirizine affected intrinsic alertness (i.e. vigilance) more than readiness to a target / bottom-up activation of alertness. Neural effects of cetirizine on alerting were, amongst others, apparent in the right superior temporal gyrus (t47=6.35, p=0.002). A decrease in brain activation in that region coincides with the increase in RT as measured at the behavioral level, therefore supporting the conclusion from the behavioral data showing that cetirizine decreases alertness when given in combination with verapamil.

Conclusion: Alertness was sensitive to the combined treatment of cetirizine with a P-gp blocker, suggesting that P-gp blockade may exacerbate the effects of 2nd generation antihistamines. Affinity for the P-gp transporter may therefore contribute to the lower incidence of CNS side effects.

TB06
BUPRENORPHINE AUGMENTATION IN THE TREATMENT OF REFRACTORY OCD
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Introduction: OCD is often refractory to treatment. There is a need for the development of new, non-invasive treatments for severe OCD. Rationale: There is evidence that opiates can be a useful adjunctive treatment in OCD. We summarise our experience with sublingual buprenorphine augmentation of standard pharmacological management of severe OCD.

Methods: Patients were recruited from a standard psychiatric outpatient clinic and gave their consent to the treatment trial. The severity of the OCD was rated with the Y-BOCS. The buprenorphine was introduced to their existing medication regime at a low dose and the dose increased according to response. In order to gauge the reproducibility of the response the buprenorphine was withdrawn and then reintroduced once symptoms had returned.

Results: 4 out of 7 patients with treatment resistant OCD showed a 30% reduction in the Y-BOCS score following buprenorphine augmentation. 3 of the responders were co-morbid for other Axis 1 diagnoses. All of the responders had shown some improvement with SSRIs or clomipramine. Non-responders had not shown any improvement with either antidepressant or antipsychotic drugs. Typically improvement appeared within 2 days of initiating buprenorphine and waned within 1 to 2 days of its discontinuation. The dose of buprenorphine required varied between 400 µg and 600 µg a day. One responder managed on alternate day dosing. Reintroduction of buprenorphine resulted in symptom control within 2 to 3 days. The buprenorphine treatment was not associated with significant side-effects and the improvement was maintained without progressive dose escalation.

Conclusions: Buprenorphine augmentation of standard treatment for OCD can result in clinically meaningful improvement in a proportion of refractory OCD cases. Further treatment trials are indicated.

TB07
EFFECT OF LISDXAMFETAMINE IN A RAT MODEL OF BINGE-EATING DISORDER
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Binge-eating disorder (BED) is a common psychiatric condition, affecting ~2% of the UK adult population. It occurs equally in women and men and most often in older adults. It manifests as compulsive, excessive consumption of highly palatable foods and may or may not be associated with obesity. Binge eaters frequently experience intense feelings of guilt and anxiety after a binge session, but do not indulge in purging. Lisdexamfetamine dimesylate (Vyvanse®, Elvanse®), a novel prodrug that is metabolised to d amphetamine primarily by red blood cells (Pennick, 2010, Neuropsychiat Dis Treat 6:317), is approved in the UK and Ireland for ADHD (ages 6-17) and is being clinically evaluated for managing BED in USA. This study compared the acute effects of lisdexamfetamine in rats trained to binge eat chocolate with its active metabolite, d amphetamine, and sibutramine, which was moderately effective in clinical trials of BED (Wilfley et al, 2008, Am J Psychiat 165:51-58). Forty-four adult, lean, female Wistar rats were housed individually on reversed-phase lighting with free access to standard diet and water. Ground milk chocolate was offered to each rat for 2h periods at irregular intervals to establish binge eating. Lisdexamfetamine, d amphetamine and sibutramine were administered orally. Irregular, limited access to chocolate for ~4 weeks produced reproducible bingeing, but bodyweights were not different from control rats maintained on standard diet. Lisdexamfetamine (0.1-1.5 mg/kg d amphetamine base) reduced chocolate binging by up to 86.1% at the highest dose (p<0.001). The intermediate dose of 0.3 mg/kg, lisdexamfetamine reduced chocolate consumption by 40% (p<0.001) whilst having no effect on standard diet intake. Lisdexamfetamine treatment did not decrease bodyweight compared with the control group given vehicle. d Amphetamine (0.1 1.0 mg/kg d amphetamine base) decreased chocolate binging at 0.5 mg/kg (p<0.01) and 1.0 mg/kg (p<0.001), d Amphetamine did not reduce standard diet consumption, but did reduce bodyweight (p<0.01) at the highest dose. Sibutramine (0.3 5.0 mg/kg) reduced chocolate binging (p<0.011 at 1-5 mg/kg), however there were similar reductions of standard diet consumption for all doses (p<0.05-0.01). Sibutramine also produced small bodyweight decreases (p<0.05-0.001 at 1-5 mg/kg). Animals allowed irregular, limited access to chocolate developed robust, intermittent hyperphagia that mirrored BED without associated obesity. Binge eating was markedly reduced by a single treatment with lisdexamfetamine or its metabolite, d amphetamine. Unlike sibutramine, both lisdexamfetamine and d-amphetamine reduced chocolate binging without simultaneously decreasing the consumption of normal diet. These results provide support for use of lisdexamfetamine in the clinical treatment of BED.

This study was funded by Shire Pharmaceuticals, UK.
TB08

PHARMACOKINETIC AND PHARMACODYNAMIC PROFILES OF THE PRODRUG STIMULANT LISDEXAMFETAMINE DIMESYLATE IN CHILDREN AND ADOLESCENTS WITH ADHD

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Introduction: The d-amfetamine prodrug lisdexamfetamine dimesylate (LDX) is a long-acting psychostimulant licensed for once-daily treatment of attention-deficit/hyperactivity disorder (ADHD). This was an open-label clinical trial to assess the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of LDX and OROS-MPH. Methods: Study NRP104.103 was a randomised, open-label, crossover study in children aged 6–17 years in a European, phase 3, double-blind, randomized, controlled trial (SPD489-325). Of 336 patients randomized in SPD489-325, 317 were included in the full analysis set and 196 completed the study. Plasma d-amfetamine concentrations were measured after single doses of LDX 30, 50, or 70 mg in children aged 6–12 years and OROS-MPH 18, 36, or 54 mg in children aged 6–17 years with ADHD over 7 weeks, using a randomized, double-blind, placebo-controlled design. Osmotic-release oral system methylphenidate (OROS-MPH) was included as a reference treatment. At baseline and weeks 4 and 7, parents assessed ADHD symptoms and problem behaviours using the Conners’ Parent Rating Scale-Revised (CPRS-R) at approximately 10:00, 14:00 and 18:00hrs following dosing at 07:00hrs. An analysis of covariance was applied to the change in CPRS-R total score from baseline to endpoint (the last on-treatment visit with valid data). Differences in least-squares means were compared with pre-specified equivalence levels. Conclusion: Following an early morning dose of LDX, improvements in ADHD-related symptoms and behaviours in children and adolescents with ADHD are maintained throughout the day, consistent with the plasma d-amfetamine concentration-time profile in children. Supported by funding from Shire LLC.

TB09

POST HOC RESPONDER ANALYSES COMPARING THE EFFICACY OF LISDEXAMFETAMINE DIMESYLATE AND OSMOTIC-RELEASE ORAL SYSTEM METHYLPHENIDATE IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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Introduction: Methylphenidate- and amfetamine-based psychostimulants are effective treatments for attention-deficit/hyperactivity disorder (ADHD). This was an open-label clinical trial to assess the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of LDX and OROS-MPH. Methods: Study SPD489-325 was a randomized, open-label, crossover study in children and adolescents aged 6–17 years with ADHD of at least moderate severity. Of 336 patients randomized in SPD489-325, 317 were included in the full analysis set and 196 completed the study. Plasma d-amfetamine concentrations were measured after single doses of LDX 30, 50, or 70 mg in children aged 6–12 years and OROS-MPH 18, 36, or 54 mg in children aged 6–17 years with ADHD over 7 weeks, using a randomized, double-blind, placebo-controlled design. Osmotic-release oral system methylphenidate (OROS-MPH) was included as a reference treatment. At baseline and weeks 4 and 7, parents assessed ADHD symptoms and problem behaviours using the Conners’ Parent Rating Scale-Revised (CPRS-R) at approximately 10:00, 14:00 and 18:00hrs following dosing at 07:00hrs. An analysis of covariance was applied to the change in CPRS-R total score from baseline to endpoint (the last on-treatment visit with valid data). Differences in least-squares means were compared with pre-specified equivalence levels. Conclusion: Following an early morning dose of LDX, improvements in ADHD-related symptoms and behaviours in children and adolescents with ADHD are maintained throughout the day, consistent with the plasma d-amfetamine concentration-time profile in children. Supported by funding from Shire LLC.
THE NEURODEVELOPMENTAL AND BEHAVIOURAL EFFECTS OF METHAMPHETAMINE EXPOSURE DURING PREGNANCY IN RATS

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There is an increasing rate of pregnant women taking illegal drugs such as amphetamines. It is vital to enhance our understanding of the risks associated with taking these drugs during pregnancy using relevant animal models. However to date, animal studies have diverged from the clinical scenario with respect to dose, duration of dosing and route of administration. Moreover, it is important to know whether a period of methamphetamine (MA) abstinence has any effect on offspring development. The aim of this study was to determine if MA administration to rats during pregnancy will have negative consequences on the offspring and if previous exposure to MA can still have an effect on offspring development in a subsequent pregnancy. Pregnant Sprague-Dawley dams (n=4/group) received MA (10mg/kg) or vehicle (distilled water) via oral gavage from gestational day (GD) 7 – 21. Maternal body weight, food and water consumption were recorded daily until littering. Litter sizes, sex ratios and birth weights were recorded for each litter at birth and a number of endpoints measured in the neonatal period. The neurodevelopmental parameters examined were pinna unfolding, fur appearance and eye opening whilst behavioural tests included surface and air righting reflex tests, forelimb grip test, negative geotaxis, open field and elevated plus maze tests. Four months following weaning, the dams were again mated and the same parameters measured for these pups. Data was analysed using Repeated-Measures ANOVA for maternal parameters, and for the pups Two-way ANOVA or Kruskal Wallis tests were used where appropriate. MA exposure had no effect on gestational body weights, food or water consumption. However MA-exposed litters had significantly lower birth weights compared to vehicle-exposed litters and from post-natal day (PND) 2-29. Pups exposed to MA had a significant delay in pinna unfolding, fur appearance and eye opening, as well as significantly impaired righting reflex, increased time to complete negative geotaxis, smaller ano-genital distance and impaired growth seen in body length. Interestingly a similar profile of developmental deficits was observed for offspring in the subsequent pregnancy. This study confirms findings from previous investigations that have used other exposure regimens. Overall this study demonstrates that MA exposure in utero at a pharmacologically relevant dose and route of administration has an effect on neonatal outcome as well as demonstrating long term consequences, even after a period of ‘abstinence’ from MA. Funding from The College of Medicine, National University of Ireland, Galway.

THE EFFECTS OF DIFFERENT ROUTES OF ADMINISTRATION OF METHYLPHENIDATE ON ATTENTION AND IMPULSE CONTROL IN A NOVEL 5-CSRTT

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Drugs which target catecholaminergic transmission improve impulsivity and inattention in ADHD (Arnstenn, 2009; CNS Drugs 23:33-41). Previous studies using methylphenidate (MPH) in the rat 5-choice serial reaction time task (5CSRTT) have found increased impulsive responding with no effect or detrimental effects on attention (Miletin et al., 2010; J Psychopharmacol. 24:309-21). Interestingly, the effects of MPH on brain chemistry have been shown to differ depending on the administration route (Berridge et al., 2006; Biol Psychiatry 60:1111-20). This study aimed to further investigate the behavioural effects of MPH and route of administration using a novel version of 5-CSRTT. Sixteen male Lister-hooded rats were food-restricted and trained in a novel version of the 5-CSRTT. The task did not require the animals to initiate the trials and was set with two attentional cues, the switching off of the house light followed by a variable inter-trial interval (2-5 sec) before presentation of a 0.125msec stimulus in one of the five apertures. This task reduced baseline accuracy from ~90% to between 70-75%. Once trained, animals were then tested following acute intraperitoneal administration of MPH (0.0, 0.1-1.0 mg/kg, in saline) or oral administration of MPH (Study 1: 0.0, 0.3-3.0mg/kg, study 2: 0.0 or 10.0mg/kg, in strawberry milkshake). Each study was fully randomised using a Latin-square design and data were analysed using a RM-ANOVA or paired t-test as appropriate. Following intraperitoneal administration, a significant main effect of treatment was observed for premature responses (F(2,2,32)=5.456,p<0.008), with a significant increase in premature responses at 1mg/kg (p=0.008). No main effect of treatment was observed for accuracy, omissions, correct latency and collection latency. Oral administration of MPH (0.3-3mg/kg) failed to induce any significant effects on any performance measure recorded. However, treatment with 10mg/kg MPH significantly improved accuracy in this task with no significant effects on omissions or premature responses observed. In addition, correct latency (p=0.022) but not collection latency was significantly decreased at 10mg/kg MPH. These studies suggest that MPH-treatment improves attention in rats performing a more demanding version of the 5-choice serial reaction time task. These effects are dependent on the route of administration. Previous neurochemical studies suggest that oral administration of MPH results in a greater relative effect on cortical levels of dopamine, which may underlie the effects observed in this study. In contrast, intraperitoneal administration of MPH has more effect on subcortical dopamine leading to an increase in premature responding and a lack of beneficial effects on attention.

CMW is funded by a BBBSRC CASE studentship with Lilly. Funding for this research was provided by a Medical Research Council New Investigator grant (Ref: G0700980) awarded to E.S.J.R.

LOW PERFORMING RATS MODEL THE INATTENTIVE SUBTYPE OF ADULT ADHD IN THE 5-CHOICE CONTINUOUS PERFORMANCE TASK (5C-CPT)

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5-choice continuous performance task (5C-CPT) is an enhanced version of the 5-choice serial reaction time task (5-CSRTT). The 5C-CPT assesses vigilance in a way that is similar to the human CPT, in comparison to the 5-CSRTT that assesses sustained attention [Barnes et al., (2012). Neuropharmacology, 62: 1432-41] Disturbances in the 5-choice continuous performance task (5C-CPT) is an enhanced version of the 5-choice serial reaction time task. These effects are dependent on the route of administration. Previous neurotransmitter studies suggest that oral administration of MPH results in a greater relative effect on cortical levels of dopamine, which may underlie the effects observed in this study. In contrast, intraperitoneal administration of MPH has more effect on subcortical dopamine leading to an increase in premature responding and a lack of beneficial effects on attention.

The aim of this study was to investigate the effects of psychostimulant drugs on attention, impulsivity and performance in rats separated into high and low-performers in the 5C-CPT based on attentive responses. The effects of acute methylphenidate (MPH), atomoxetine (ATMX) (0.5, 1.0, 2.0 mg/kg i.p), tolcapone (5, 10, 15mg/kg i.p) and the dopamine D4 receptor agonist, A-142996 (0.1, 0.3, 1.0 umol/kg) were assessed in the 5C-CPT in adult female Lister-hooded rats (n=40). Animals were trained for 60 sessions, then divided into two groups (high and low performers) based on set criteria. Animals were challenged on test days by increasing the variable inter-trial interval from 5s to 10s. In the low performing animals, MPH (2.0 mg/kg) and ATMX (2.0 mg/kg) significantly increased % accuracy (p<0.05) and ATMX significantly reduced false alarm rate at 1.0 & 2.0 mg/kg; p<0.05). ATMX (1.0mg/kg, 2.0mg/kg) and MPH (0.5, 1.0 mg/kg) significantly increased sensitivity index (p<0.05). MPH significantly reduced correct rejections at all doses (p<0.05). Tolcapone at 10 and 15 mg/kg significantly enhanced accuracy and sensitivity index and correct rejections at 15 mg/kg (p<0.05-0.01). A-142996 (0.6, 1.0umol/kg) significantly increased % correct rejections and sensitivity index (p<0.05=0.001). A-142996 (0.6, 1.0umol/kg) significantly reduced false-alarm rate at 0.6, 1.0umol/kg (p<0.01; p<0.001) in low performers. In summary, ATMX and MPH enhanced sustained attention in the 5-CSRTT and vigilance in 5C-CPT in low performers. Compounds not currently utilised in the treatment of adult ADHD but that are of interest mechanistically tolcapone (COMT-inhibitor) and A-142996 (D4-agonist) also enhanced certain aspects of attention; mainly vigilance in low performers only. This would suggest that low performers are sensitive to the effects of both stimulant and non-stimulant drugs. These data provide validation of a rat model for the inattentive subtype of adult ADHD. The model utilises the 5C-CPT to select animals with deficits in sustained attention and vigilance, which may then be enhanced by ADHD medication.

Research fully sponsored by the University of Manchester.
**TC04**

**REACTIVATION OF MECP2 REVERSES BEHAVIOURAL ABNORMALITIES IN A FEMALE MOUSE MODEL OF RETT SYNDROME**

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Rett syndrome is a neurodevelopmental disorder that primarily affects females and is characterised by apparent normal early development up until 6-18 months of age, followed by a period of regression and the emergence of symptoms including loss of acquired skills, impairments in mobility and speech, breathing anomalies and autistic behaviour. Mutations in the X-linked MeCP2 gene are the primary cause of Rett syndrome (RTT). Silencing of the MeCP2 gene by insertion of a lox-stop cassette in male mice has been found to induce RTT like pathology and sensory-motor deficits which are reversible by deletion of the stop cassette and re-activation of endogenous MeCP2 (Robinson et al. 2012, Brain, 135(9), 2699-2710). The main aim of this study was to perform a longitudinal behavioural analysis of the female MeCP2 knock-out mice and determine whether re-activation of MeCP2 reverses behavioural impairments. Female MeCP2 stop/cremice (Stop Cre) in which the endogenous MeCP2 allele is silenced by a stop cassette and wild-type littermates (WT Cre) were used in this study. Mice performed a battery of behavioural tests including Rotarod, Open-field, Balance Beam and Grip strength in order to assess motor ability. Based on a global and gross phenotyping screen, testing was performed at three stages of disease progression: 1) pre-symptomatic; 2) symptomatic (following symptom onset) and 3) post-treatment. Immediately following symptomatic testing re-activation of MeCP2 and deletion of the stop cassette was performed using a 4 week treatment schedule of Tamoxifen or corn oil (vehicle). After completion of re-activation mice were re-tested on all behavioural tests 6 weeks post-treatment. Data were analysed using two-way ANOVA's and t-tests where appropriate with a significance level of p<0.05. Analysis revealed that symptomatic Stop Cre mice presented with significant deficits in grip strength (p<0.0001); balance beam (p<0.0001) and distance moved in open-field (p<0.0001) compared to wild type controls. Re-activation of MeCP2 significantly improved performance of the mice on all of the behavioural tests with Stop Cre mice no different to WT's (all p's>0.05). Silencing of the MeCP2 gene induced impairments in the sensory motor functions of female mice reminiscent of deficits reported for RTT patients. Re-activation of MeCP2 and deletion of the stop cassette was able to reverse these behavioural deficits in full strengthening the contention that gene reactivation would be a viable treatment option. Studies are ongoing to determine whether re-activation of MeCP2 improves other behavioural abnormalities in the female mice.

Supported by MRC.

**TC05**

**GENOTYPE-DEPENDENT NORADRENERGIC EFFECTS ON MEMORY: A PROOF-OF-CONCEPT STUDY**

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Introduction: The impact of genetic variation on cognition in healthy individuals is increasingly apparent. Recent studies have found that certain variations in noradrenergic genes, which contribute to the control of catecholamine levels in the brain, influence emotional enhancement of memory. For example, a deletion variant of the alpha-2B noradrenaline re-uptake inhibitor (ADRA2B) gene which confers higher baseline noradrenergic activity has been shown to enhance emotional memory in healthy volunteers (Gibbs et al, 2010, Eur Neuropsychopharmacol, 20(4), 272-5). Given that drugs acting on noradrenergic neurotransmission are also known to influence emotional memory systems, their effects may also be genetically mediated. The aim of this study is therefore to explore whether the effects of noradrenergic drugs on emotional memory are moderated by ADRA2B genotype.

Methods: A randomised, double-blind, placebo-controlled, between-group intervention was conducted on 148 healthy White British males aged between 18 and 40. Buccal swabs or saliva samples were taken and analysed for ADRA2B genotype. Participants were randomised to receive either a single 4mg dose of the selective noradrenaline re-uptake inhibitor (SNRI) reboxetine, or a placebo. Two hours post-administration, participants undertook an emotional memory task that involved viewing pictures which varied in emotional valence (neutral, positive and negative) followed by free recall and recognition memory testing.

Results: Analysis of emergent data showed a main effect of ADRA2B genotype on recall memory across all emotional categories, with scores consistently higher in the deletion group. There was also a significant emotion x genotype interaction (p<0.01), with the enhancing effect of the deletion variant being greater for emotional vs neutral stimuli. This effect on recall memory manifested most for positive stimuli, more for positive stimuli and most for negative stimuli. A trend-level 3-way emotion x genotype x drug interaction (p=0.08) suggested that in the reboxetine group, recall of negative stimuli was further enhanced in the deletion group. However, recall rates in the non-deletion group were relatively suppressed by reboxetine.

Conclusions: These results are consistent with prior findings on the effect of emotional valence on memory and the role of ADRA2B genotype. Treatment with a noradrenergic drug enhanced recall memory for emotionally salient stimuli in individuals carrying the deletion variant of ADRA2B. However we also demonstrated an enhancing effect of the deletion variant on overall memory performance that has not previously been reported. These results offer new insights into gene and drug effects on cognitive and emotional processing and their interactions.

**TC06**

**METHYLPHENIDATE INDUCED PSYCHOSIS: A SYSTEMATIC REVIEW OF CURRENT LITERATURE**

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Introduction: Methylphenidate is a psychostimulant widely used as first line medication in the treatment of Attention Deficit Hyperactivity Disorder (ADHD). (Taylor et al, 2004, European Child and Adolescence psychiatry, 13(1):17-30). The FDA reports that 0.1% of newly treated ADHD patients without prior mental illness developed psychosis with Methylphenidate treatment in a pooled analysis of multiple short placebo-controlled trials. Observed psychotic symptoms included hallucinations and delusions along with agitation. Risk was higher in those with prior history of psychosis or mania. This review aimed evaluated current evidence of Methylphenidate induced psychosis in ADHD patients and factors that may be associated with evolution of psychosis.

Methods: A systematic search of literature using the data bases; Medline, Embase and Psychinfo was conducted using the keywords, Methylphenidate, stimulants and psychosis. A further hand search was conducted to identify suitable literature. Only published studies from peer reviewed journals were included.

Results: Eleven publications were identified. Two were randomised control trials, two retrospective cohort studies and seven case reports. The two randomised control trials examined the safety of Methylphenidate and none of the patients developed psychosis. One five week study had 401 patients. (Medori et al, 2008, Biological Psychiatry, 63:981-989). The other study was for six weeks.( Biederman et al, 2006, Biological Psychiatry, 59: 829-835). The two cohort studies and case series reported psychosis across all ages with the youngest being six years and the oldest forty-five years. Psychosis developed at any point during the course of treatment. Commonly reported symptoms included paranoia and other delusional beliefs, auditory and visual hallucinations and bizarre behavior. These resolved shortly after cessation of medication in all reported cases. In one study, three out of nine patients who developed psychosis were later diagnosed of chronic psychotic illness and two with bipolar affective disorder. (Cherland and Fitzpatrick,1999, Canadian Journal of Psychiatry, 44: 811-813).

Conclusions: Although literature suggests that there is a small but significant risk of psychosis associated with Methylphenidate treatment in people with ADHD, pre-existing psychotic illness and overdosing were the only predisposing risk factors identified. Data is incomplete for clear associations to be made. Atropine is the preferred option for those at risk of psychotic illness and those who develop psychosis in the course of treatment. Awareness and close monitoring of individuals on Methylphenidate treatment is essential along with maintaining registers of adverse events. Sponsorship: This study did not require any financial sponsorship and therefore was not sponsored financially.
TD01
ADOPTED IN THE AUTHORS OF THE MEASURE FOR SENSATION-SEEKING IN HUMANS
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Sensation-seeking is a core personality trait that has been identified as a vulnerability factor for a variety of psychopathologies with high social cost (Roberti et al., 2004, Journal of Research in Personality, 256–279). However, motivation for intense sensory experiences is not accounted for by many ‘rational’ accounts of decision-making, and, to date, investigation of this trait in humans has been reliant solely on self-report instruments which have limited scope for determining the brain mechanisms underlying such behaviours (e.g. Zuckerman, 1994, Behavioral Expressions and Biosocial Bases of Sensation Seeking). In this study, we invented a behavioural paradigm specifically designed to detect possible influences of the opportunity for additional intense sensory stimulation (light electric shock) on performance of a simple economic decision-making task. In the first phase, participants choose between pairs of abstract images associated with particular points values. In the second phase, one stimulus of each choice pair becomes a CS+ (0.75 chance of shock), such that the subjective value (positive or negative) each participant assigns to the extra sensory stimulation may be precisely titrated via their pattern of choice. We examined behaviour on this paradigm in 45 healthy volunteers, in addition to assessing sensation-seeking trait via traditional questionnaire measurement (the SSS-V; Zuckerman, ibid). We found choice was significantly biased towards CS+ stimuli in some participants (~18% of the total sample were below p<0.05 when tested against the binomial distribution for random choice), even when this choice involved the sacrifice of opportunity for monetary gain. This finding is consistent with the intense sensory stimulation acting as a form of additional sensory reward in these individuals. Crucially, individuals who chose a greater proportion of shock-associated stimuli also exhibited a relative speeding of their responses for these stimuli, with the opposite effect observed in participants who tended to avoid these options (p=0.679, p<0.001). This suggests that the opportunity for additional sensory stimulation influenced participants’ decisions via an approach–avoidance-like mechanism. Both proportionate choice of shock-associated stimuli and reaction time measures were significantly associated with self-reported sensation-seeking scores (r=0.342, p=0.033; and r=–0.331, p=0.040, respectively). This constitutes the first direct evidence of sensation-seeking behaviour in humans being driven by an approach–avoidance-like mechanism. Our paradigm may serve as a valuable new tool for the investigation of both the personality trait of sensation-seeking and psychopathologies associated with extreme sensation-seeking.

This research was supported by the Wellcome Trust and the UK Medical Research Council.

TD03
PRAMIPEXOLE DECREASES URGES TO SMOKE AND REDRESSES AN IMBALANCE BETWEEN DRUG AND NON-DRUG REWARD
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Introduction: when addicted individuals are exposed to drug-related stimuli, dopamine release is thought to enhance the salience of these cues, biasing attention towards them and increasing craving and drug use. Attempts to modulate this process pharmacologically might provide an effective treatment for addictive disorders. However, it is not yet known if dopaminergic effects on attentional bias are accompanied by corresponding changes in drug-related urges, craving and memory, which would support the feasibility of this strategy. Furthermore, it is currently unclear whether the effects of dopaminergic manipulations are similar across all appetitive stimuli – leaving the relative salience of drug cues unchanged – or if they can specifically reduce the salience of drug cues compared to other non-drug rewards.

Methods: a double-blind placebo-controlled crossover study was used to assess the effects of the dopamine D2/D3 agonist pramipexole (0.5mg) in 16 non-treatment seeking tobacco smokers. Eye tracking was used to assess initial orienting and maintained attention towards images in a visual probe task, which were either smoking-related or neutral. Blank packages were the same as the plain packages, but with all information on the top half of the pack removed. All packages had a health warning on the lower half of the package. Half of these health warnings were familiar to the participants, while the other half were unfamiliar. The number of eye movements participants made to the top and bottom half of the packages was measured using an eye tracker.

Results: Daily smokers showed an attentional bias to the top half of the pack, regardless of pack type. Even when the top half of the pack was blank and no brand information was present, participants made more eye movements to this region as compared with the health warnings information. This effect was observed regardless of health warning familiarity.

Discussion: These data suggest that neither a preference for branding, nor familiarity with health warnings are the cause of daily smokers’ lack of attention to health warnings. Rather, daily smokers are actively avoiding health warning messages, perhaps due to reactance to the warnings. Future research should determine what top-down cognitive mechanism is driving daily smokers’ avoidance of health warnings information on cigarette packages.

This study was funded by an MRC/ESRC interdisciplinary studentship to TP Freeman.
Animal behavioural neuroscience has identified two learning processes which underlie instrumental behavior: goal directed (mediated by knowledge of and desire for the outcome of a specific response) and habitual (a stimulus eliciting a response). Recent research indicates that stress can cause a shift from goal-directed to habitual behaviour by disrupting retrieval of the outcome representation (Schwabe et al, 2009, Psychoneuroendocrinology, 35(7), 977-986). We believe that this process may underlie relapse in drug users. A between subjects design was used. Daily smokers (n = 24) were asked to remain overnight abstinent from cigarettes before attending a study session at the School of Experimental Psychology. Participants were randomly allocated to receive either 7.5% CO2 enriched air or medical air (placebo). Participants completed a series of questionnaires (smoking history, STAI, AUDIT, ASMA, BIP, IPPI, ZISSC, SCS, QSU, STAI-state, VAS) and a computer task (acquisition test) requiring them to learn a contingency between two computer keys and two separate rewards of chocolate and tobacco (e.g. D key = tobacco). After completing these tasks, participants were asked to smoke to satiety for 10 minutes prior to completing a similar computer task (extinction, transfer and reacquisition tests) which again asked them to choose between the rewards of chocolate or tobacco whilst simultaneously inhaling either air or CO2. This study is currently unfinished and so the following analyses will be used on completion. The subjective and objective differences in anxiety levels between the CO2 group and the placebo group will be explored by observing differences across questionnaire and blood pressure measurements by employing a paired samples t-test. A mixed-model ANOVA will be used to examine the impact of the stress manipulation on the choice between tobacco and chocolate in the acquisition, extinction, reacquisition and transfer computer tasks. We hypothesize that there will be a smaller reduction in tobacco choice for the CO2 group than the placebo group between acquisition and extinction. We also expect that there will be no difference in choice in the reacquisition test, illustrating the selective impairment on the ability to retrieve the outcome representation. During the transfer test we expect that stressed participants will show enhanced stimulus control of choice consistent with a predominance of habitual control. The use of stress control training in abstinent smokers will be discussed. Funding: No external funding.

**TD05**

**CANNABIDIOL REDUCES CIGARETTE CONSUMPTION IN TOBACCO SMOKERS: PRELIMINARY EVIDENCE**

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**Introduction:** The endocannabinoid system modulates both the rewarding effects of addictive substances and associative learning processes important in the pathogenesis of addiction. Pharmacological modulation of the endocannabinoid system is therefore a promising novel approach for the treatment of addiction. We examined the potential of Cannabidiol (CBD) a non-psychotomimetic phytocannabinoid thought to inhibit anandamide reuptake and hydrolysis, in the treatment of dependent tobacco smokers.

**Methods:** In a double-blind, placebo controlled design, participants (n = 24) completed baseline measures of smoking, craving and mood before receiving either a CBD or placebo inhaler to use in an ad-hoc manner whenever they felt the urge to smoke. Participants recorded their smoking behaviour daily via an SMS-based response system throughout this week. Post-treatment assessments were then carried out to assess change from baseline.

**Results:** A large reduction in number of cigarettes smoked was seen in the group receiving CBD (p = 0.002), but not in the placebo group. There was a tendency for this effect to be maintained at follow-up two weeks later (p = 0.03). Drug effects were not seen on measures of mood or craving.

**Conclusion:** This preliminary evidence provides encouraging support for the use of CBD in the treatment of tobacco addiction. Given the impressive tolerance and safety profile of CBD in humans, it may prove to be an excellent first-line smoking cessation aid. Further, larger-scale studies are encouraged to assess the potential of CBD and other endocannabinoid modulators in the treatment of tobacco addiction.

**Financial disclosure: This research was supported by a grant awarded to SKK, CJAM and HVC by the Medical Research Council, UK.**

**TD06**

**THE ACUTE AND CHRONIC EFFECTS OF CANNABINOIDS ON EMOTIONAL PROCESSING**

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Cannabis use has been associated with various cognitive impairments. In particular, heavy cannabis users show a deficit in emotional processing (Platt et al., 2010, Drug and Alcohol Dependence 112, 27–32). Cannabis primarily consists of two cannabinoids, Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which have opposing effects on the brain and behaviour. Whilst THC is anxiogenic and produces psychotic-like effects, CBD has been shown to be anxiolytic and antipsychotic (Desouza et al., 2004, Neuropsychopharmacology, 29, 1558-1572). We aimed to 1) replicate the finding that heavy cannabis users show a deficit in emotional processing and 2) investigate the acute effects of cannabinoids (THC, CBD and THC+CBD combined) on emotional processing. Emotional processing was investigated in two studies using a static face recognition paradigm. Study 1 assessed 25 heavy cannabis users and 34 non-cannabis using control participants in a between subjects design to assess the effects of chronic cannabis use on emotional processing. In a second study we employed a randomised, double blind crossover design to compare acute effects of a single dose of THC (5mg), CBD (10mg) or a combination of THC+CBD (5mg+10mg) with placebo, on emotional processing in 48 regular cannabis users. Accuracy and signal detection analyses (discrimination index and response bias) were used to investigate participant’s emotional recognition. Study one revealed a group effect on accuracy of emotional processing and discrimination, suggesting cannabis users are less accurate and less able to discriminate different emotional faces compared to non-smokers.

In current study we employed a randomised, double blind crossover design to compare acute effects of a single dose of THC (5mg), CBD (10mg) or a combination of THC+CBD (5mg+10mg) with placebo, on emotional processing in 48 regular cannabis users. Accuracy and signal detection analyses (discrimination index and response bias) were used to investigate participant’s emotional recognition. Study one revealed a group effect on accuracy of emotional processing and discrimination, suggesting cannabis users are less accurate and less able to discriminate different emotional faces compared to non-smokers.

We hypothesized that acute exposure to cannabinoids would impair emotional processing in cannabis users. Study 2 revealed a dose-related effect of cannabinoids on emotional processing. The CBD dose significantly increased accuracy and discrimination of emotional faces, suggesting that acute exposure to cannabinoids has a differential effect on emotional processing in cannabis users. Further, the THC+CBD dose significantly increased accuracy and discrimination of emotional faces, suggesting a synergistic effect of THC and CBD on emotional processing in cannabis users.

**Financial disclosure: This research was supported by the Medical Research Council and the Economic and Social Research Council.**
ABSTRACTS

TD07

RECREATIONAL DRUGS AND SEXUAL EXPERIENCES: A CROSS-SECTIONAL INTERNET SURVEY

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Introduction: Studies show that a variety of recreational drugs can acutely enhance the motivating factor to have and pleasure taken from sex (Frohmader et al., 2010, Hormones and behaviour 58(1) 149-162). However, there has been no direct comparison of the different drugs’ effects on sexual experiences. Therefore, we investigated these effects across ten aspects of sexual experience. Furthermore, we aimed to determine which recreational drugs are most commonly used during sex and if there are differences in usage between different groups of people, specifically differences between different sexual orientations.

Methods: A cross-sectional, anonymous internet survey concerning the relationship between recreational drugs and sexual experiences, as part of a larger survey exploring patterns of drug use, was conducted globally. A total of 22,290 people took part in the survey. People rated the effects of different drugs on: erection/moistness, sexual desire, time to reach orgasm, ability to have multiple orgasms, quality of orgasm, overall performance, intimacy, sensual aspects, confidence in trying new things, and associated shame. People also stated which three drugs they most commonly used during sex. Drugs assessed were alcohol, cannabis, cocaine, GHB/GBL, ketamine, MDMA, methamphetamine, mephedrone, isopropyl nitrate (poppers), and Viagra.

Results: 66.7% of respondents reported having sex on one or more of the recreational drugs, including alcohol, in the last year. 43.9% of respondents reported having sex on one or more of the recreational drugs, excluding alcohol, in the last year. Homosexual and bisexual people grouped together reported having sex on one or more drug, including and excluding alcohol, and methamphetamine specifically, more than heterosexual people (p<0.001; p<0.001; p<0.001 respectively). Alcohol was the most, cannabis the second most, and MDMA the third most commonly used drugs during sex. However, in terms of respondents’ ratings of the effects on sexual experiences, alcohol was commonly ranked low, while drugs such as methamphetamine, GHB/GBL, and Viagra were commonly ranked high.

Conclusions: Generally, most recreational drugs assessed, in acute doses, seem to enhance aspects of motivation to have, pleasure taken from, and performance during sexual experiences as measured by self-report data. Despite alcohol being the most commonly used drug during sex, it is rated poorly, while less commonly used drugs, such as GHB/GBL, are rated more highly. Methamphetamine use, which has been associated with transmission of STIs (Semple et al., 2009, Archives of sexual behaviour 38(4) 583-590), is more in common non-heterosexual people.

Financial sponsorship: Adam Winstock’s grants, Will Lawn holds a BBSRC PhD at UCL.

TD08

DISTINGUISHING TRUSTWORTHY AND UNTRUSTWORTHY FACES IN METHADONE/BUPRENORPHINE MAINTAINED OPIATE USERS

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The ability to accurately judge the trustworthiness of others is an important adaptive human behaviour. Much attention has been given to the finding that acute oxytocin administration increases trust, but interestingly it has also been reported that acute testosterone administration reduces trust. Acute and chronic opioid use leads to lower levels of testosterone. Furthermore, methadone maintenance treatment is linked to lower testosterone levels, and relatively there is high prevalence of sexual dysfunction in these patients. Low testosterone levels in opioid users on maintenance treatment may therefore impact on trust judgements, leading to excessive trust and potentially increasing social vulnerability. To explore trust in opioid users we administered a financial investment task requiring participants to invest money in trustworthy and untrustworthy faces. It was predicted that opioid users would invest more money in all faces compared to controls, and that amounts invested would correlate with maintenance dose. Faces were computer generated and physical features manipulated to alter the perceived trustworthiness of each face. Participants were instructed to invest £0-£500 in each investor, with the aim of maximising the amount of money returned to them if a profit was made. Opiate users (n=23) maintained on methadone or buprenorphine were recruited through a specialist drug service, and compared to a control group (n=21) recruited from psychological services and a participant database. Data were analysed within a 2x2 mixed-model ANOVA, with the between-subjects factor of group and within-subjects factor of facial trustworthiness. Analysis demonstrated a main effect of facial trustworthiness, with both groups showing a tendency to invest more money in trustworthy compared to untrustworthy faces (F(1,42) = 38.39; p<0.001). However, there was no main effect of group, with no difference in total amount invested between the opiate group (M= 185.7, 95% CI: 141.3, 230.2) and control group (M= 229.0, 95% CI: 190.2, 267.7; F(1,42) = 2.28; p = .138), and no interaction between facial trustworthiness and group (F(1,42) = 0.06; p = .810). Further, money invested by the opiate users did not correlate with maintenance dose. These findings therefore indicate that, contrary to predictions, opioid users on maintenance treatment were not seen to be more trusting, and in fact results indicated the opposite trend. An important limitation of the study is the considerable variation in amount invested between all participants, questioning the ability of the task to differentiate any group effect from individual heterogeneity.

TD09

INTERNAL AND TEST-RETEST RELIABILITY OF THE MODIFIED STROOP AND THE DISENGAGEMENT TASK

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Introduction: Studies show that a variety of recreational drugs can acutely enhance the motivation to have and pleasure taken from sex (Frohmader et al., 2010, Hormones and behaviour 58(1) 149-162). However, there has been no direct comparison of the different drugs’ effects on sexual experiences. Therefore, we investigated these effects across ten aspects of sexual experience. Furthermore, we aimed to determine which recreational drugs are most commonly used during sex and if there are differences in usage between different groups of people, specifically differences between different sexual orientations.

Methods: A cross-sectional, anonymous internet survey concerning the relationship between recreational drugs and sexual experiences, as part of a larger survey exploring patterns of drug use, was conducted globally. A total of 22,290 people took part in the survey. People rated the effects of different drugs on: erection/moistness, sexual desire, time to reach orgasm, ability to have multiple orgasms, quality of orgasm, overall performance, intimacy, sensual aspects, confidence in trying new things, and associated shame. People also stated which three drugs they most commonly used during sex. Drugs assessed were alcohol, cannabis, cocaine, GHB/GBL, ketamine, MDMA, methamphetamine, mephedrone, isopropyl nitrate (poppers), and Viagra.

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Conclusions: Generally, most recreational drugs assessed, in acute doses, seem to enhance aspects of motivation to have, pleasure taken from, and performance during sexual experiences as measured by self-report data. Despite alcohol being the most commonly used drug during sex, it is rated poorly, while less commonly used drugs, such as GHB/GBL, are rated more highly. Methamphetamine use, which has been associated with transmission of STIs (Semple et al., 2009, Archives of sexual behaviour 38(4) 583-590), is more in common non-heterosexual people.

Financial sponsorship: Adam Winstock’s grants, Will Lawn holds a BBSRC PhD at UCL.
TD10

RESTING STATE SYNCHRONY IN ANXIETY-RELATED CYCLES OF ABSTINENT ALCOHOL DEPENDENT PATIENTS

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Anxiety has been linked to the initiation, maintenance and relapse components of alcohol dependence. Neurobiological models of anxiety have proposed important roles for amygdala-insula and amygdala-medial prefrontal cortex interactions in the generation and regulation of anxiety states, respectively. This study tested the hypotheses that abstinent alcohol-dependent patients would show a disruption of synchrony in these circuits as measured by resting state functional MRI. Participants were pooled from two separate studies, which examined recently abstinent (n=9; mean=28 days, SD=11) and longer-term abstinent (n=20; mean=270 days, SD=268) alcohol dependent patients (DSM-IV) versus healthy controls (n=9; n=13). All participants were male, and had no current anxiety disorder, depression, or any history of dependence to other substances, except nicotine. We constrained our analysis to pairs of nodes that have previously been shown to be associated with anxiety states in healthy and patient populations. Based on these previous findings we predicted: (1) decreased positive synchrony between right amygdala and right ventromedial prefrontal cortex (vmPFC), (2) between left amygdala and left medial orbitofrontal cortex (mOFC), as well as (3) decreased negative synchrony between right amygdala and dorsomedial prefrontal cortex (dmPFC) and (4) increased positive synchrony between left basolateral amygdala and left anterior insula. Data were analysed using FSL and SPSS. Alcohol dependent patients showed significantly elevated scores on the Spielberg State Anxiety Inventory (t=3.6, p=0.005) Spielberg Trait Anxiety Inventory (t=4.8, p<0.001), and Beck's Depression Inventory (Mann Whitney U =80.5, Z =-4.5, p<0.001), compared with healthy controls, but the early and longer-term abstinent sub-samples did not differ significantly. No significant group differences in synchrony were observed between (1) right amygdala and right vmPFC and (2) left amygdala and left mOFC. We did, however, find increased negative synchrony between (3) right amygdala and dmPFC (t=2.0, p<0.05) and decreased positive synchrony between (4) left basolateral amygdala and left anterior insula (t=4.1, p<0.001), in patients relative to controls. Resting state synchrony did not show an association with state anxiety in any of the four circuits, in patients or healthy controls. Both early and longer-term abstinent alcohol dependent patients showed increased anxiety levels relative to controls and altered resting state synchrony in two circuits, which have been previously linked to state anxiety. Notably, the significant group differences in synchrony were in the opposite direction to our predictions based on the literature. This may have been due to the effects of chronic alcoholism on resting state synchrony and further exploration is ongoing.

TD11

LAPSES OF ATTENTION DURING DRIVING IN THE ALCOHOL HANGOVER STATE

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Introduction: Only few studies examined driving the morning after a drinking session, i.e. during the alcohol hangover state, when blood alcohol concentration (BAC) has returned to zero. The purpose of this study was to examine the effects of alcohol hangover on simulated highway driving performance. Methods: In N=47 healthy volunteers, driving performance was tested the morning following an evening of consuming on average 10.2 (SD=4.2) alcoholic drinks (alcohol hangover) and on a control day (no alcohol consumed). Subjects performed a standardized 100-km highway driving test in the STISIM driving simulator. In addition to the Standard Deviation of Lateral Position (SDLP, i.e. the weaving of the car), lapses of attention were examined. A lapses was defined as a continuous change of lateral position of >100 cm for at least 8 seconds. Self-reported driving quality and driving style were scored, as well as mental effort to perform the test, and sleepiness before and after driving. Hangover severity was scored with a 1-item visual analog scale ranging from 0 (absent) to 10 (extreme). ∆SDLP (hangover – control) and ∆lapses were related to the subjective outcome measures. Results: Data from 4 subjects were excluded as they reported no hangover. Another subject was excluded because he scored positively (6 out of 10) on the hangover scale on the control day. Data from N=42 subjects are presented. Driving performance was significantly impaired during alcohol hangover as expressed by an SDLP increase of +1.9 cm (p=0.007) and increased number of lapses relative to the control day (7.7 versus 5.3 lapses, p=0.019), and an increased total lapse time (182.7 versus 127.3 seconds, p=0.040). The maximum lapse deviation did not differ between hangover and control sessions (p=0.130). During alcohol hangover, subjects reported their driving quality significantly poorer, and less safe, considerate, predictable, and responsible (p<0.001). Subjects further reported being significantly more tensed while driving and more effort was needed to perform the driving test (p=0.001). ∆SDLP and ∆lapses correlated significantly with difference scores on subjective driving quality. A significant positive relationship was found between differences scores on hangover severity and ∆lapses (r=0.373, p=0.015) and total lapse time (r=0.380, p=0.013). This relationship was not seen for ∆SDLP. There was no relationship of driving impairment with the number of consumed alcoholic drinks the night before. Conclusions: Driving is significantly impaired during alcohol hangover, as expressed in an elevated SDLP and increased number of lapses. Funding: This study was funded by Utrecht University.

TD12

SEVERITY OF ALCOHOL DEPENDENCE AND CRAVING: COMPONENTS OF THE DESIRE FOR ALCOHOL QUESTIONNAIRE

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Craiving is a central component in understanding alcohol use disorders. Yet there is a lack of consensus regarding its definition. The aims of this study were: (1) to explore the components of craving, as measured by the Desires for Alcohol Questionnaire (DAQ); (2) to examine how craving may relate to the severity of alcohol problems; and (3) to explore whether participating in a study involving exposure to alcohol-related word cues may result in increased craving for alcohol. 123 patients seeking treatment for an alcohol use disorder were recruited to complete the DAQ, and the Alcohol Use Disorder Identification Test (AUDIT). Principal components analysis was conducted on the DAQ for the overall, abstinent and non-abstinent samples. Correlations were computed between the DAQ and AUDIT scores, and differences in craving between the abstinent and non-abstinent samples were investigated. Components of craving, as measured by the DAQ, included the desire to drink, the ability to control drinking, positive reinforcement and negative reinforcement. Drinkers displayed stronger cravings (Mdn=47.00, IQR=32.0 – 65.0) than those currently abstinent (Mdn=33.00, IQR=26.0 – 43.0; U=850.0, z=3.127, p=.002, r=0.30). Intensity of craving increases with severity of an AUD in current drinkers (r=.739, p=.000). Overall, there was a positive reinforcement and negative reinforcement. Drinkers displayed stronger cravings (Mdn=47.00, IQR=32.0 – 65.0) than those currently abstinent (Mdn=33.00, IQR=26.0 – 43.0; U=850.0, z=3.127, p=.002, r=0.30). Intensity of craving increases with severity of an AUD in current drinkers (r=.739, p=.000). Notably, the significant group differences in craving were in the opposite direction to our predictions based on the literature. This may have been due to the effects of chronic alcoholism on resting state synchrony and further exploration is ongoing.
COMPUTER ASSISTED SELF-INFUSION OF ETHANOL (CASE): A PREDICTION OF THE FUTURE RISK FOR ADDICTION?

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Introduction: There are several oral alcohol self-administration (ASA) studies which could not document positive findings due to high inter-individual variability of arterial blood alcohol concentrations (aBAC) caused by idiosyncratic differences in enteral absorption. CASE overcomes this limitation and enables to unambiguously interpret each subject’s individual style of ASA.

Methods: 33 healthy young adults (family history positive FHP & negative FHN) participated in 2 consecutive sessions to assess the influence of familial alcoholism on ASA. CASE accomplishes the intravenous infusion of 6% ethanol, using an individualized pharmacokinetic model to achieve identical increments of aBAC by 7.5mg% within 2.5min each time the subject requests more alcohol. If no more alcohol is requested, aBAC decreases continuously (-1mg%/min). Subjects were instructed to request alcohol in order to produce the same subjective alcohol effects obtained at a typical weekend “all-you-can-drink” party. We analysed whether or not the subjects produced stable plateaus of aBAC during ASA.

Results: In 33 out of 46 experiments, subjects achieved and maintained stable plateaus of aBAC for at least 30 minutes during the self-infusion experiment. Fischer’s exact test revealed that FHN produced stable plateaus significantly more often than did FHP (p<0.05).

Conclusions: Using CASE we were able to distinguish between two groups of experiments (plat+/plat-), even though both had the same experimental instructions. As aBAC rises and declines quickly after each request, a stable plateau can only be reached if the subject’s perception of subjective alcohol effects concurs very well with the actual aBAC in the course of ASA. Therefore we assume that FHP are less capable to perceive alcohol effects than are FHN. These findings contribute to our knowledge of the influence of familial alcoholism on the vulnerability for future alcohol dependence. Future: We plan to conduct a pharmacological fMRI study in non-treatment seeking alcoholics using an intravenous alcohol-clamp. The study aims to examine the effects of alcohol on well-established fMRI tasks (rewards, inhibition, stress), as well as, to investigate the impact of Nalmefene (µ-opioid receptor antagonist) on such alcohol-related responses.

I BIBI EROGO SUM (I HAVE DRUNK THEREFORE I AM)

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Introduction: Initial doses of alcohol reliably prime alcohol seeking behaviours, for example craving and ad-lib alcohol consumption. Experiments investigating this process have, however, almost exclusively focused on pharmacological effects by comparing alcohol seeking behaviour following an alcohol prime to a placebo condition, with minimal research exploring the anticipated effects of alcohol (investigated with a placebo-control comparison).

Method: Twenty social drinkers completed two experimental sessions in the University of Liverpool Bar Laboratory in which they were given a placebo drink (which smelled and tasted like alcohol) or a control drink (water). Alcohol craving (Desire for Alcohol Questionnaire, DAQ; Approach and Avoidance of Alcohol Questionnaire, AAAQ) and subjective intoxication were measured before and after they consumed the drink. Participants also completed a bogus beer taste test to assess ad-lib drinking at the end of each session.

Results: The placebo drink increased craving as assessed by the DAQ and AAAQ as well as subjective feelings of intoxication, particularly light-headedness. Furthermore, participants consumed more beer in the taste test in the placebo compared to the control condition. Significantly there was an association between increased craving and beer consumed in the taste test in placebo condition only.

Conclusion: This study demonstrates that the anticipated effects of alcohol can have a significant impact on subjective (craving) and behavioural (beer consumption in the taste test) measures of alcohol seeking. The current results indicate that to accurately explore the priming effect of alcohol researchers should also investigate the anticipated effects. Indeed, taking into account anticipated as well as pharmacological effects of alcohol will arguably offer a more ecologically valid assessment of the acute effects of alcohol as responses to alcohol in naturalistic settings will reflect the combined pharmacological and anticipated effects.

CAFFEINE ALTERS THE BEHAVIOURAL AND THERMOREGULATORY RESPONSES TO MEPHEDRONE WITHOUT CAUSING LONG-TERM NEUROTOXICITY

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The illicit cathinone derivative, mephedrone, is implicated in several deaths and severe adverse events in the UK and users report that it has similar psychostimulant properties to 3,4-methylenedioxymethamphetamine (MDMA). Caffeine enhances the toxic effects of MDMA and concomitant consumption of caffeine with recreational psychostimulant drugs, such as mephedrone, is common (Vanattou-Saifoudine et al, 2012, Br J Pharmacol: 167, 946). This study investigated the effects of caffeine on the behavioural, thermoregulatory and thermochemical responses to mephedrone in the rat. Adult male Lister hooded rats (212-247g, n=8 per group, CRUK) received i.p. saline vehicle (1 ml/kg), mephedrone HCl (10 mg/kg), caffeine (10 mg/kg) or caffeine+mephedrone twice weekly on consecutive days, over three weeks, to mimic weekend ‘binge-type’ usage in humans. Locomotor activity (LMA, days 1 + 21), novel object discrimination (NOD, day 2), elevated plus maze (x-maze, day 8) behaviour, rectal temperature (day 9) and prepulse inhibition of acoustic startle (PPI, day 20) were assessed. Hypothalamus and right hippocampus, striatum and frontal cortex were collected seven days after the last injection to quantify dopamine, 5-hydroxytryptamine (5-HT) and their major metabolites by high performance liquid chromatography with electrochemical detection (HPLC-ED). Mephedrone and caffeine induced hyperactivity which was sustained for the duration of testing and was enhanced by combined caffeine+mephedrone on both LMA days (p<0.001, Bonferroni following three-way repeated measures ANOVA). During NOD, vehicle treated rats successfully discriminated the novel from the familiar object (p<0.05, Bonferroni following three-way repeated measures ANOVA) but mephedrone, caffeine and their combination impaired discrimination. Caffeine+mephedrone increased percentage time spent in the more aversive open arms of the x-maze and the number of head dips, compared to mephedrone alone (p<0.05, Bonferroni following two-way ANOVA). Mephedrone alone decreased rectal temperature until 80 min post-injection. This effect was converted to a sustained elevation in temperature by combined caffeine+mephedrone which had not returned to baseline levels at 120 min post-injection (p<0.01, Bonferroni following three-way repeated measures ANOVA). There was no significant effect of any treatment on PPI. Mephedrone alone and caffeine+mephedrone did not alter levels of dopamine, 5-HT or their major metabolites, seven days after the last of six injections, in any brain region examined. While concomitant caffeine+mephedrone did not cause long-term neurotoxicity, the data presented here demonstrate that caffeine alters the behavioural and temperature response to mephedrone which may account for some of the adverse effects experienced by users.

This study was funded by the University of Nottingham, School of Biomedical Sciences.
TD16

MEPHEDRONE, CANNABIS AND ALCOHOL: THE NEW RISKS TO MENTAL HEALTH
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Mephedrone (4-methylmethcathinone) is a relatively new recreational drug on the illicit market. Although it was a focus of media attention in 2010, there is comparatively little research pertaining to its use and neuropsychobiological effects (for an overview, see Schifano et al., 2011, Psychopharmacology, 214(3), 593-602). This study compared mephedrone, cannabis and alcohol users for aspects of mental health and depressive symptoms. A total of 115 (46 male, 48 female) participants (M = 25.46 years, SD = 6.64) were sourced from social networking websites and drug related forums and were separated into three subgroups (alcohol, cannabis and mephedrone) based on their reported drug use. Participants completed a three part online questionnaire: the first section investigated lifestyle and drug usage, the second utilised the Center of Epidemiological Studies Depression Scale (CES-D), and the final section covered reasons for using mephedrone and other illicit drugs. The dependent variables of depression scores and perceived benefits and risks were analysed using one-way between subjects ANOVAs. Though no significant difference in depression scores was observed between the mephedrone and alcohol groups, a significant difference was observed between the cannabis and mephedrone groups (p<.038). Mephedrone demonstrated a higher potential for causing depressive symptoms than cannabis and alcohol, but not alcohol alone. In addition to this, it was found that perceived benefits of mephedrone included increased feelings of happiness whilst using the drug. The findings support the hypothesis that mephedrone users suffer similar neurochemical recovery problems associated with other stimulant drugs (viz: cocaine, amphetamine, Ecstasy/MDMA). This study has contributed an understanding of mephedrone, and those who use it, from a mental health perspective. The findings may be useful in relation to the development of substance misuse advice and harm reduction campaigns. There are no sources of financial sponsorship of the study to declare.

TD17

STRUCTURAL DIFFERENCES IN THE BRAIN ASSOCIATED WITH HEAVY KETAMINE USE
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Introduction: Ketamine is a dissociative drug with growing popularity as a recreational drug, but there has been little research into the effects of heavy, long term use. Recently, a novel human study found reduced grey matter in the dorsolateral prefrontal cortex of heavy ketamine users (Liao et al., 2011, Biol Psychiatry, 69, 42-48). This same region has been implicated by a primate study (Sun et al., 2012, Addiction Biology, Epub ahead of print), and together these findings suggest an association between chronic ketamine exposure and prefrontal neurotoxicity. However, ketamine has also been shown to have the converse effect of stimulating neurogenesis in the rat hippocampus (Keilhoff et al., 2004, Biol Psychiatry, 56, 317-322), a possible mechanism for the drug’s antidepressant properties. The aim of this study was to further investigate grey matter volume differences in the brains of heavy ketamine users in order to better understand the implications of long term administration of the drug. Method: T1 weighted structural MRI images were acquired using a 3.0 Tesla Phillips Integra scanner from a group of 27 heavy ketamine users and 18 polydrug matched controls. The study focused on two regions of interest - the prefrontal cortex and hippocampus, for which explicit masks were created using WFU Pickatlas 2.5. Images were pre-processed using the technique of voxel based morphometry (VBM), and then analysed using SPM 8 software. Statistical analysis comprised a two-sample t-test, which controlled for total intracranial volume and corrected for familywise error. Results: No significant differences in grey matter volumes were found between the ketamine user group and the control group in the regions of interest, although there was a suggestion of greater hippocampal volumes in the ketamine group. Ketamine users showed elevated dissociative and schizotypal symptoms, and were impaired in working memory tasks. Conclusion: This study found limited evidence of structural differences in the brain associated with heavy ketamine use and did not replicate findings of the one previous study. Further research is required to determine whether there are irreversible structural changes arising from long term heavy use of this drug, as this would have implications for the growing population of users. Funded by the Medical Research Council (UK).

TD18

ESTABLISHING PAVLOVIAN TO INSTRUMENTAL TRANSFER WITH ORALLY DELIVERED NICOTINE AND FENTANYL IN RATS: ROUTE TO DEVELOPING MORE EFFECTIVE DRUG CESSATION MEDICATIONS
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Introduction: The lack of clinically effective long-term pharmacological invention for drug addictions has led to the investigation of non-pharmacological environmental cues in relapse subsequent to prolonged periods of abstinence. Method: The ability of nicotine- and fentanyl-associated cues to induce drug-seeking behaviours was investigated in rats via the Pavlovian to instrumental transfer paradigm. In the Pavlovian stage, rats were trained to associate an auditory conditioned stimulus (CS+; 120s) with oral consumption of nicotine (4µg/100ml in olive oil) or fentanyl (25µg/ml in distilled water) and another distinctive auditory stimulus (CS-; 120s) with no drug outcome. Subsequently rats were instrumentally trained to lever press on an ‘active’ lever for the same drug reward and an ‘inactive’ lever for no drug reward. The Pavlovian to instrumental transfer test assessed the ability of the Pavlovian drug-associated cues to invigorate instrumental drug-seeking behaviour over the non-drug-associated cues under extinction. Results: Despite both groups showing reliable acquisition in both the Pavlovian and instrumental stages for both nicotine and fentanyl, significant effects of transfer during extinction were evident with fentanyl-associated cues (CS+) relative to the non-associated cues (CS-). Fentanyl-associated cues invigorated responding on both the active and inactive levers, suggestive of a general transfer effect (n=12). Nicotine-associated cues elicited no effect during similar tests for transfer (n=24). Conclusion: These experiments support previous research for the role of non-pharmacological drug-associated cues in eliciting relapse behaviour, thus providing further evidence to target drug-associated cues for therapeutic intervention in drug addictions. The parameters for Pavlovian to instrumental transfer with nicotine require further work to identify optimal conditions.
REF19

Profiles of Lisdexamfetamine, Methylphenidate and Modafinil as Positive Reinforcers in Rats Trained to Self Administer Cocaine

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Lisdexamfetamine (LDX; Vyvanse®, Elvanse®) is a prodrug that is metabolised in red blood cells to produce the stimulant, d amphetamine (d AMF) (Pennick 2010, Neuropsychiat Dis Treat 6:317). Methylphenidate (MPH) and modafinil (MDF) are also stimulants. LDX and MPH are Controlled Drugs, but in the UK, MDF is not. All have been shown to be effective ADHD medications. Studies in drug experienced human volunteers suggest that the unusual pharmacokinetics of LDX may reduce aspects of its liability for abuse (Jasinski & Krishnan 2009a,b, J Psychopharmacol 23:410 and 419). The reinforcing effects of LDX, MPH and MDF were compared in groups of 7-10 male, Sprague-Dawley rats trained to self administer low dose cocaine (0.32 mg/kg/injection i.v.) on a FR 2 schedule of reinforcement. One hr test sessions were initiated by a non contingent injection of cocaine or the test compounds (maximum 20 injections/session). Saline (i.v.) was the control non reinforcer. All drug doses were expressed as mg/kg of base. Cocaine served as a positive reinforcer in all groups of rats (means ranged between 16.1-19.6 injections/session), whereas the control saline (i.v.) did not (means between 1.6-5.1 injections/session). Methylphenidate (0.03, 0.1 or 0.3 mg/kg/injection i.v.) served as a positive reinforcer at the 2 higher doses (mean±s.e.m.=12.5±0.5; [p<0.001 versus saline]; 16.9±2.3 [p<0.001 versus saline] injections/session, respectively). LDX (0.1, 0.3 or 1.0 mg/kg/injection i.v.) did not maintain self administration at levels significantly above saline (mean±s.e.m.=2.5±0.6; 4.6±1.6; 3.1±1.0 injections/session, respectively) and neither did MDF (0.166, 0.498 or 1.66 mg/kg/injection i.v.; mean±s.e.m.=5.0±0.6; 5.0±0.4; 5.7±1.1 injections/session, respectively). Methylphenidate maintained robust self administration in cocaine maintained rats; a result that is consistent with the common pharmacological mechanism of these two drugs (Heal, 2008, UK Patent GB 2447 949). Consistent with the findings of Deroche Gamonet et al (2002 ref), we observed that modafinil did not serve as a positive reinforcer in rats. Lisdexamfetamine also did not serve as a reinforcer in rats, probably because of its unusual pharmacokinetics (Pennick, 2011) and its delayed and gradual enhancing effect on dopaminergic neurotransmission (Rowley et al, 2012, Neuropharmacology 63, 1064). In the same vein, Kollins et al (1998) reported that the stimulant and reinforcing effects of sustained release (SR) methylphenidate in humans were attenuated and transient in comparison to those of the immediate release formulation of this stimulant, leading the authors to conclude that the SR formulation posed a reduced risk for recreational abuse. In summary, the results reveal important differences between the reinforcing profiles of these stimulants.

This study was funded by Shire Pharmaceuticals, U.K.

TE01

AN AUDIT OF ANTIPSYCHOTIC PRESCRIPTION PRACTICE IN A PSYCHIATRIC SERVICE

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Introduction: Since their introduction in the 1950s, antipsychotics have played an important role in the treatment of mental illness. A number of harmful and undesired (adverse) effects have been observed, including lowered life expectancy, extrapyramidal effects on motor control , trembling, muscle weakness , weight gain, enlarged breasts (gynecomastia) in men and milk discharge in men and women , lowered white blood cell count , diabetes, sexual dysfunction. Some of these effects have been shown to be dose related or related to rate of dose change etc. As a result, various guidelines have been formulated as to the use of antipsychotic to improve their safety profile. Objectives /Aims: The aim of this audit is to ascertain the antipsychotic prescription practice and determine its compliance or lack thereof with the guidelines, and make recommendations.

Methods: • A sample of patients currently on antipsychotics was taken . • Separate samples were taken from in-patients(12 patients) and out-patients(day hospital, 11 patients). • Case notes were assessed to determine if their antipsychotic prescription were in line with the guidelines regarding, indication, starting dose, monitor and recording efficacy, maximum dose and use of antipsychotics as prn sedatives. High dose antipsychotic use and polypharmacy.

Results: • In about 10% of day hospital patients and about 20% of in-patients indication for antipsychotics was not recorded. • In about 40% of day hospital patients indication for antipsychotic was not recorded and recorded, however it was in 100% of in-patients. • About 65% of day hospital patients and over 90% of in-patients, were not commenced on lowest possible dose. • Reason for polypharmacy was given in 100% of day hospital patients( in which polypharmacy was used) and 30% of in-patient • Antipsychotic wasn’t used as PRN sedative in any day hospital patient but used in 75% of in-patients • Recognised rating scales weren’t used to assess response to antipsychotics in any of the patients sampled. • Doses above maximum dose weren’t used in day hospital patients. In the in-patients, the reasons for using maximum doses wasn’t recorded in any of the patients sampled.

Conclusions: Following the audit, we made some recommendations. They are as follows; -Have copies of the guidelines as reminders on the ward -Insert copies of the guidelines in the induction programme for NCHDs -Regular re-audit to ensure compliance We believe if the above recommendations are implemented this would improve practice.
PREVALENCE OF HIGH-DOSE AND COMBINED ANTIPSYCHOTIC PRESCRIBING IN MENTAL HEALTH SERVICES ACROSS TIME AND CLINICAL SETTINGS

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In 2006, the Prescribing Observatory for Mental Health (POMH-UK) initiated an audit-based quality improvement programme (QIP) addressing antipsychotic prescribing practice. A baseline audit on acute, adult psychiatric wards allowed for benchmarking of such practice across individual mental health NHS Trusts, against two clinical standards derived from published clinical guidelines: 1. A standard dose of a single antipsychotic should be used; and 2. Combinations of antipsychotics should only be used when switching from one drug to another, or for augmentation of clozapine where the illness has not responded sufficiently to clozapine monotherapy. Further audits were carried out at up to 18-month intervals, and change interventions (such as a high-dose ‘ready reckoner’ for patients receiving combined antipsychotics) were made available to support local Trust strategies and actions plans to address areas where performance fell short of the standards. In addition, in 2007 a similar QIP was started in forensic services. The findings of the repeated audits up to 2010 showed a steady but modest reduction in the prescription of high-dose and combined antipsychotic prescribing (particularly including PRN antipsychotics) on acute inpatient wards since 2006 and in forensic services since 2007. The most recent POMH-UK audit in this QIP (9,537 patients in 48 mental health NHS Trusts) was conducted in 2012. As well as inpatients on acute adult/PICU wards, this QIP was widened to include rehabilitation/complex needs and forensic services. Of the 5,079 inpatients on acute adult or PICU wards, 28% were prescribed high dose antipsychotics, while the respective figures for 1,105 patients in rehabilitation/complex needs services and 3,333 patients under the care of forensic services were 24% and 26%. The vast majority of high-dose prescriptions (86%) were for combined antipsychotics, and approximately two-thirds of these combinations included a PRN antipsychotic. Our earlier data had suggested that a patient prescribed combined antipsychotics was more than 20 times more likely to be prescribed a high dose than one prescribed a single antipsychotic. In the 2012 POMH-UK sample, the most common reason for prescribing combined antipsychotics in adult acute, PICU and high secure settings was the management of acute behavioural disturbance, while in rehabilitation/complex needs and low and medium secure services it was clozapine augmentation with a second antipsychotic drug. In the total sample, combined antipsychotics were prescribed because of a poor response to antipsychotic monotherapy in 16%, despite the lack of any convincing evidence for benefit for such a strategy in treatment-resistant psychotic illness.

EVALUATING THE USE OF INTRAMUSCULAR CLONAZEPAM IN RAPID TRANQUILISATION

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Introduction: Effectively controlling agitated or aggressive behaviour in acutely unwell patients is a challenge for all mental health professionals. On in-patient mental health units this challenge may be confounded by a reluctance to accept oral medication and a fluctuating mental state. Enforcing medication by the intramuscular route is an occasional but necessary practice to ensure safety for the individual, other service users and staff. The choice of medication to use in this process (know as rapid tranquillisation) is usually either an antipsychotic or the benzodiazepine lorazepam. Unfortunately intramuscular lorazepam has recently been subject to supply problems so many trusts have sought to use alternative intramuscular (IM) benzodiazepine preparations. Based on occasional reports in the literature (Chouinard G et al (1993) Can J Psychiatry; 38 (suppl 4) S114-S121, Benazzi F (1991) Can J Psychiatry; 36: 697) our trust chose to use IM clonazepam as the alternative benzodiazepine and to guide practice and contribute to the literature we evaluated the outcome of its use.

Methods/Design: The medicines management committee developed an evaluation questionnaire for nurses administering IM clonazepam. The questionnaire was designed to be filled out within 24 hours of use and collected information on efficacy, duration of onset, doses used, current medication and adverse effects. All units and wards involved in rapid tranquillisation across the trust were included in the data collection and the medicines management team coordinated the role out and collected responses. Results: Over 14 months, 34 separate episodes of IM clonazepam use were reported covering 28 patients. 64% of patients were female with a mean age of 40 (range 14-85 years). In 65% of episodes another agent (most commonly IM haloperidol) was used concurrently with IM clonazepam. The most frequent dose of IM clonazepam used was 1mg (range 0.5-2mg). An effect was seen on average after 80 minutes (range 10-180 minutes) and this lasted on average 9.5 hours (range 2-20 hours). In 79% of episodes no adverse effects were reported but in the remainder 21%, 2 episodes of respiratory depression were noted.

Discussion and Conclusion: Intramuscular clonazepam proved a useful and well tolerated alternative to IM lorazepam in rapid tranquillisation on mental health in-patient wards. In comparison to IM lorazepam it took longer to work and had a longer duration of action which was expected based on its pharmacokinetic parameters. Similar to other IM benzodiazepines use should be followed by close physical health monitoring especially focusing on sedation levels and respiratory rate.

No financial sponsorship
ABSTRACTS

TE04

ANTIPSYCHOTICS PRESCRIBING TRENDS AND PATTERNS AMONG CHILDREN AND ADOLESCENTS WITH SEVERE MENTAL ILLNESS IN TAIWAN - A LONGITUDINAL POPULATION-BASED STUDY

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Introduction: With the widespread of second-generation antipsychotic (SGAs) uses worldwide, the prescribing patterns and uses of antipsychotics among children and adolescents were of great interest. However, most studies were from western countries between 1996 and 2006 (Olfson et al, 2006, Arch Gen Psychiatry 63(6): 679-85). To the author’s knowledge, studies exploring factors associated with SGA prescribing in children and adolescents were limited (Aparasu et al, 2007, Curr Med Res Opin 23(1): 49-56). This was the first study to assess the APs prescribing trend for the past decade and to identify factors associated with SGAs prescribing among children/adolescents with severe mental illness in Taiwan. The study was designed to assess trends and patterns in antipsychotics (APs) prescribing and to identify factors associated with second-generation antipsychotic (SGAs) prescribing among children and adolescents in Taiwan using national claimed-data.

Method: The Psychiatric Inpatients Medical Claims Data of 1996-2009 from the National Health Institute Research Database (NHIRD) of Taiwan was used. The annual prescribing rate in outpatient visits with first- (FGAs) and second-generation antipsychotics (SGAs) prescribing was examined between 2000 and 2009. Factors associated with SGAs prescribing were also investigated with GEE (generalized estimating equations) regression.

Results: A total of 42,514 visits in which antipsychotics were prescribed between 2000 and 2009. The annual APs prescribing rate was fairly stable (5.3%) in children/adolescents with severely mental illness. However, visits with SGAs prescribing increased by nearly 5 folds (p=0.00001), while those with FGAs use decreased by 58% (p=0.0001). It is noteworthy that poly-pharmacy became more prevalent from 0.7% to 8.4% (p=0.0001) in 2000 and 2009, respectively. Year of prescribing, hospital types, physician types were positively associated with SGA prescribing. It is noteworthy that diagnoses of psychotic disorders, pervasive developmental disorders/mental retardation, and other mental disorders each significantly increased the likelihood of SGAs prescribing. Service setting, urbanisation level, presence of comorbid mental disorders had no significant association with SGAs prescribing.

Conclusion: The APs prescribing among children/adolescents with severely mental illness in Taiwan revealed that SGAs have been used with increasing frequency and replacing FGAs, which is consistent with previous studies worldwide. Moreover, poly-pharmacy has been more prevalent in this population. Factors positively associated with SGAs prescribing included year of prescribing, physician type, hospital type, and diagnoses. This study urged the importance in understanding the needs, safety and effectiveness when treating children and adolescents receiving SGAs.

Acknowledgements This work was supported by the funding from National Science Council of Taiwan (NSC 98-2628-B-039 -020 -MY3).

TE05

CLOZAPINE AUGMENTATION IN A LOW SECURE FORENSIC SERVICE

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Introduction: Clozapine has been shown to be an effective treatment for resistant psychosis, although a significant proportion of patients have a sub-optimal response. The aim of this study was to investigate the effectiveness of clozapine augmentation strategies utilised in an adult, male, low secure forensic service.

Methods: Patients receiving clozapine were identified from pharmacy records. Medication histories were collated by case-note review and from pharmacy records during January and February 2013.

Results: A total of 37 patients were treated with clozapine, of whom 22 (59%) were receiving or had previously received at least one augmentation medication. In total 37 augmentation strategies were used, 11 of which had been discontinued at data collection. Reasons for augmentation were positive symptoms 15 patients (27 treatments), negative symptoms 4 patients (4 treatments), and clozapine side effects 6 patients (6 treatments). Medications used for positive symptoms (discontinuers at data collection with reason shown in parentheses) were: amisulpride n=10 (3-no benefit), lamotrigine n=6 (1-no benefit; 1-side effects; 1-patient choice), haloperidol n=2 (1-no benefit; 1-patient choice), aripiprazole n=3 (2-no benefit), lithium n=2 (0) and fish oils n=2 (0). Time to first augmentation for positive symptoms was >12 months in 9/15 patients.

Discussion: Eighteen of the 37 patients receiving clozapine required augmentation for positive or negative symptoms, suggesting a high level of treatment refractory illness amongst this group. The majority of patients received clozapine for at least 12 months prior to first augmentation. This may reflect the view that the effectiveness of clozapine increases with continued treatment during the first year. Augmentation for positive symptoms, showed some effectiveness as measured by treatment continuation. However, prescribers may have continued treatments which had only minimal benefits due to an absence of alternative options. The mean clozapine dose did not change significantly following augmentation in this group, which may have indicated reluctance amongst prescribers to reduce doses due to risk of relapse or that augmentation was only partially effective.

Sources of funding: None
PRACTITIONER ATTITUDES TO CLOZAPINE INITIATION

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Clozapine is the only antipsychotic that is effective in treatment-resistant schizophrenia. The UK National Institute for Clinical Excellence (NICE) guideline for schizophrenia recommends the use of clozapine for this indication. Despite clear recommendations, our group has shown previously that patients experience lengthy delays in prescribing (Howes, O. et al., 2012, BJ Psych, 2016;6(48):5). This study aimed to clarify barriers to prescribing clozapine as perceived by clinicians working directly with patients with schizophrenia and to generate potential solutions. A questionnaire was made available to all staff at South London and the Maudsley NHS Trust, electronically and in paper form over 12 months. In total, 144 responses were received. Self-perceived familiarity with UK NICE schizophrenia guidelines was high, with 81% (n = 113 of 140 respondents) stating that they were ‘fairly’ (45%, n = 63) or ‘very’ (36%, n = 50) familiar with the guidance. When asked to rate relative effectiveness of clozapine in treating schizophrenia on a scale of 1 to 10 (1 indicating ‘much less effective’, 10 ‘much more effective’ than other antipsychotics), the mode of the scores given was 8 (range 1 to 10, median = 8). Most (71%, n = 96 of 135 respondents) felt that patients were ‘somewhat more satisfied’ with clozapine treatment, compared with patients treated with other atypical antipsychotics. Practitioners were asked how frequently they thought a range of patient factors were responsible for delays in initiation of clozapine, once treatment was indicated. The factor most often identified as ‘very frequently’ a problem was patient refusal of, or reticence about, required blood monitoring for clozapine. When asked to consider what factors practitioners thought delayed them from initiating clozapine, significant medical factors or compliance issues were most often reported as being a ‘very frequent’ problem. A narrow majority of responders (58%) thought additional clinical and/or administrative resources would facilitate the initiation of clozapine in their workplace – specifically, dedicated staff or day hospital placements to start and stabilise clozapine in an outpatient setting. This study found most practitioners who are directly involved in patient care consider themselves familiar with guidelines for prescribing of clozapine, and believe clozapine is an effective drug choice for patients with treatment-resistant schizophrenia. The main obstacles to earlier prescribing are patient-focused – refusal of blood test monitoring or concerns about tolerability. Clinician fears about compliance or medical complications were also important. Outpatient services specifically tasked with initiating clozapine may increase earlier prescribing of clozapine.

This study received no financial sponsorship.

EFFECTS OF ANTIPSYCHOTICS ON BONE MINERAL DENSITY AND PROLACTIN LEVELS IN PATIENTS WITH SCHIZOPHRENIA: A 12 MONTHS PROSPECTIVE STUDY

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Objective: To compare effects of conventional and atypical antipsychotics on bone mineral density and serum prolactin levels in patients with schizophrenia in China. Methods: 163 first-episode inpatients with schizophrenia were recruited, to whom one of three conventional antipsychotics (perphenazine, sulpiride, chlorpromazine) or one of three atypical antipsychotics (clozapine, quetiapine, aripiprazole) was prescribed for 12 months. Bone mineral density (BMD), serum prolactin level (PRL), estrogen (E2), bone alkaline phosphates (BALP), and crosslaps (CTX) were tested before and after treatment. Same measures were conducted in 90 matched healthy controls during the same period.

Results: The post-treatment BMD value in the patients group was significantly lower than that in healthy controls (t=-3.832~5.530, p<0.01), and the incidence of osteoporosis after antipsychotic treatment was 11.4~21.7%, which was significantly higher than that in healthy controls (2.2~4.2%). There was no significant difference between groups before treatment (p>0.05). The BMD value of the conventional antipsychotic treatment group was significantly lower than that of the atypical antipsychotic group (t=2.22~3.66, p<0.05). The post-treatment PRL level of the conventional group (37.35±50.25 t=-2.131, p<0.05) was significantly higher than that of pre-treatment (25.56±9.01, t=-2.263, p<0.05), however there was no significant difference before and after treatment in the atypical group (29.79±16.03 vs 29.81±17.42, t=2.735, p>0.05). Conditioned relevance analysis revealed a negative correlation between the PRL level and the BMD value after treatment in the conventional group (r=-0.567~0.984, p<0.05), whereas no correlation was revealed in the atypical group (r=0.315~0.426, p>0.05). Conclusion: The increase of PRL might be an important risk factor leading to high prevalence of osteoporosis in patients with schizophrenia who are on long term use of conventional antipsychotics.

The project is funded by Shandong medicine and health technology development programs and the Health Department of Shandong Province (Grant reference number: 2007HZ08).

IS THE QUALITY OF REPORTING FOR ANTIPSYCHOTIC PHASE II/III TRIALS GOOD ENOUGH?

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Background: The findings of the CATIE study called former pre-licensing trials into question. This systematic review aimed to examine the quality of reporting of phase II and III trials for new antipsychotics in the aftermath of the CATIE study.

Method: Electronic searches were conducted in EMBASE, MEDLINE and Cochrane databases as well as clinicaltrials.gov for antipsychotic trials (published January 2006- February 2012). Phase II and III randomised controlled trials for iloperidone, asenapine, paliperidone, olanzapine, lurasidone, pomaglatumet methionil and bitopertin were selected for schizophrenia and schizoaffective disorder. The reporting of the methodology was evaluated in accordance with CONSORT guidelines.

Results: Thirty-one articles regarding 32 studies were included. There was insufficient reporting of design in 18 studies and the hypotheses were not given in 26 studies. Sample size calculations were insufficiently reported in 18 studies and non-inferiority margins were also often reported inadequately. Detail regarding comparators, particularly placebos, was not sufficient in 20 studies. Randomisation methods were insufficiently reported in 18 studies as was blinding in 27 studies. The reporting of participant flow was also sub-optimal and was sometimes only found in a supplementary section. Primary outcome data was poorly reported in 6 studies.

Conclusions: The quality of reporting of phase II and III clinical trials of new antipsychotics is consistently poor. Authors are failing to adequately report design and methodological processes, potentially impeding the progress of future research on antipsychotic efficacy. Policy-makers and clinicians need high quality reporting before decisions regarding licensing and prescribing of newly developed antipsychotics are made.

Source of funding: own account.
AbstrActs

TE09

PALIPERIDONE PALMITATE FOR RECURRENT OCULOGYRIC CRISIS IN A PATIENT WITH SCHIZOPHRENIA

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Oculogyric crisis (OGC) is a bilateral condition in which eyes and lids are tonically elevated and neck is hyperextended, usually without visual complaints. The dystonic reaction is an infrequent distressing side effect of neuroleptic therapy, which usually occurs immediately after the administration of high potency antipsychotics. Studies have shown that more than 35% of patients with schizophrenia have medication compliance problems within the first 4-6 weeks of treatment and only 25% are compliant within 2 years (Nasrallah, Acta Psychiatrctica Scandinavica 115, no. 4 (April 2007): 260–7). Long acting antipsychotics may help improve compliance, but are often linked with parkinsonian side effects, including acute dystonia (Kane et al., European Neuropsychopharmacology 8, no. 1 (February 1998): 55–66). We report a case of a service user who was prescribed depot antipsychotics due to poor compliance, but recurrently developed OGC with different depot antipsychotics. However, he was able to achieve good control of symptoms, without reoccurrence of OGC with depot Paliperidone. A 28 years old male, newly diagnosed with Paranoid Schizophrenia, showed a partial improvement on PANNS score with Aripiprazole but subsequently relapsed due to poor compliance. He was commenced on Risperidol Consta, but developed severe akathesia. Subsequently, he was tried on Fluoxetine Decanoate, Moderate and Pipotiazine Palmitate depot, all of which led on to him developing OGC. Thereafter, he was commenced on Paliperidone Palmitate and the dose was gradually increased to 100 mg monthly. He achieved good control of his psychotic symptoms, without recurrence of OGC. In-vitro models with human cloned D2 receptors in tissue cultures, have shown that Paliperidone has a faster off-rate for dissociation from D2 receptors (60 sec) compared to Risperidone (27 Min) (Philip Seeman, The American Journal of Psychiatry 162, no. 10 (October 1, 2005): 1984–5). Faster dissociation from D2 receptor allows antipsychotic effect without motor side effects and prolactin elevation (Kapur and Seeman, The American Journal of Psychiatry 158, no. 3 (March 2001): 360–9). Whilst there is scope for further study of the issue, it may well be that Paliperidone depot is less likely to cause dystonic reactions and is useful in patients with poor compliance and who have propensity to develop dystonic reactions. (Informed written consent has been taken from the patient for the publication.)
Conflict of Interest: none

TE10

MTHFR 677C/T GENOTYPE IS ASSOCIATED WITH ANTIPSYCHOTIC DRUG-INDUCED WEIGHT GAIN IN PATIENTS WITH SCHIZOPHRENIA

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Antipsychotic drug-induced weight gain is a prominent side-effect of schizophrenia treatment. Genetic variants of the MTHFR gene involved in homocysteine metabolism may be important predictors of antipsychotic drug-induced metabolic side effects (Kuzman and Muller, 2012, Pharmacogenomenics, 13(8):843-846). We tested whether this genetic factor may be related to antipsychotic drug-induced weight gain in schizophreia patients. Weight gain in two cohorts of first-episode, initially drug-naive patients with schizophrenia were studied; one of Chinese Han (n=182) receiving antipsychotic treatment for 10 weeks and one of Spanish Caucasians (n=72) treated for 3 months. Blood DNA was genotyped for MTHFR 677C/T and 1298A/C by TaqMan SNP Genotyping Assays. Regression analysis showed that baseline BMI and age were significant correlates of increase in BMI in the Chinese and Spanish sample respectively, and were included as covariates. We found that Chinese patients with the 677 CC genotype (n=54) had a significantly greater increase in body mass index (BMI) at 10 weeks (1.57±0.17 kg/cm2) compared to 677 TT or TC MTHFR genotype (n=122; 1.04 ± 0.11 kg/cm2 P = 0.012). The change in BMI after 3 months treatment in Spanish patients was similarly higher with the 677 CC genotype (2.86±0.36 kg/cm2) than the T-allele carriers (2.02±0.23 kg/cm2; P = 0.017). The MTHFR 1298 A/C genotype had no significant association with change in BMI in both study groups. In previous studies, the T-allele of the -759C/T HTR2C receptor gene polymorphism has been reported to protect against weight gain in both cohorts studied here (Reynolds et al., 2002, Lancet, 359,2086-87; Templeman et al., 2005, Pharmacogenet Genomics, 15(4), 195-200). The 677C/T and 1298A/C polymorphisms of MTHFR gene showed no interaction with the -759C/T HTR2C polymorphism. The present results suggest that the MTHFR 677 C/T polymorphism has a significant influence additional to the -759C/T HTR2C polymorphism on antipsychotic drug-induced weight gain. These two polymorphisms, in addition to several other possible genetic factors, might be valuable as pharmacogenetic markers of this important and limiting side effect.

This work is supported by a Thai government scholarship.

TE11

DNA METHYLATION OF THE 5-HT1A RECEPTOR GENE PROMOTER IS ASSOCIATED WITH NEGATIVE SYNDROME RESPONSE TO ANTIPSYCHOTIC DRUG TREATMENT

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Introduction: Association of the -1019C/G (rs6295) polymorphism of the 5-HT1A receptor gene (HTR1A) with negative symptom response to antipsychotic treatment in first episode psychosis (Reynolds et al (2006) Am J Psychiat 163, 1826-1829) has been replicated in several populations. Epigenetic mechanisms such as DNA methylation are demonstrated to affect response to antidepressants and may well be important in antipsychotic response. Moreover, increased methylation of the HTR1A promoter has been found in bipolar disorder and schizophrenia compared to controls (Carrard et al (2011) J Affect Disord 132, 450–453).

Methods: To investigate whether HTR1A promoter methylation might also influence response to antipsychotic treatment, we determined cytosine methylation in the sequence around the -1019C/G polymorphism in a sample of Chinese subjects with a first psychotic episode. After extraction, genomic DNA from blood collected at treatment initiation was bisulfite-modified and the percentage methylation at each of four sites plus the polymorphism site was determined by pyrosequencing. The -1019C/G polymorphism was also genotyped. Treatment response after 10 weeks was measured by PANSS items divided into five symptom factors (Mass et al (2000) Schiz Bull 26, 167-177) as well as by the remission criteria.

Results: A significant association of genotype was observed with remission (P=0.048; n=158), but not with PANSS measures; the CC genotype was associated with greater remission. Methylation at one CpG site was significantly (p=0.006; n=80) correlated with total PANSS change after 10 weeks treatment and with change in (p=0.001) and baseline score of (p=0.021) the negative syndrome cluster, but no other syndrome score. A trend towards a significant effect was observed in the change in depression score (p=0.065).

Conclusions: These results indicate how the extent of methylation at a specific site in the promoter sequence of the HTRA1 gene can influence antipsychotic treatment response in a first-episode Chinese population. We failed to replicate in this sample the specific effect of genotype on negative and depressive symptom response, but observed a strong effect of HTR1A promoter methylation on the treatment response of negative symptoms. These preliminary findings suggest promoter methylation may contribute to determining treatment outcome, and further emphasise the role of the 5-HT1A receptor in response to antipsychotic treatment. Funding No specific financial support was received for this study.
Long acting injectable (LAI) antipsychotic medication has demonstrable effect on relapse prevention in schizophrenia (Leucht et al. 2011 Schizophr Res 127: 83-92; Tiihonen et al. 2011 Am J Psychiatry 168: 603-9). Paliperidone palmitate injection was approved for use in the UK in 2011 for the maintenance treatment of schizophrenia, and has potential pharmacokinetic and tolerability benefits over existing LAIs. We conducted a naturalistic retrospective descriptive cohort study of patients receiving paliperidone LAI in Sussex between July 2011 and June 2012 and assessed 6 month outcome, to explore its clinical utility and factors influencing discontinuation. 142 patients initiated paliperidone palmitate LAI, with a mean age of 40 years (range 19-72) and 64% were male. Schizophrenia was the most common diagnosis (63%) and 64% were outpatients when initiated. The reasons of switch to paliperidone LAI were poor adherence to existing medication (57%) and switching from a less convenient/well tolerated depot (43%; 34% from risperidone LAI). Most patients (92%) were defined as treatment resistant, having already received 2 or more adequate trials of antipsychotic medication. The mean maintenance dose was 92.2 mg, with 75mg being most frequently prescribed. 79% of patients had continued paliperidone LAI at 6 months follow up. The reasons for discontinuation were: patient refused medication (n=19), poor clinical response (n=10) and one died from reasons unrelated to treatment. No association was observed between discontinuation by 6 months and diagnosis, gender, inpatient status at initiation, use of mental health act at initiation, previous clozapine use, switch from oral or depot antipsychotic, treatment resistance or reason for switch (for chi squared, all p values >0.15). Evidence of positive clinical response was recorded within 6 months in 80% of patients and clearly sustained over 6 months in 59%. Our findings from this Sussex cohort show a lower 6 month discontinuation rate than recent findings with paliperidone LAI and a notably lower rate than reported for risperidone LAI (Taylor et al. abstracts 2012, 2006). No significant predictors of discontinuation were found. The clinical utility of paliperidone LAI is supported.

This study was supported by an unrestricted financial grant by Janssen-Cilag Ltd.

### TE13

**SEVERE COGNITIVE IMPAIRMENT WITHIN A MULTIPLY AFFECTED SOUTH ASIAN FAMILY WITH A HIGH RISK OF SCHIZOPHRENIA**

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One of the core symptoms of schizophrenia is severe cognitive dysfunction which current interventions are ineffective in treating. Cognitive impairments have a large impact on functioning and remain during positive-symptom remission. There has been limited focus on whether specific cognitive impairments are experienced by different ethnic populations. Research to date by our team has identified that South Asian patients experience similar cognitive dysfunction to Caucasian populations. It is well known that schizophrenia has a strong genetic component. Cognitive impairments are seen in unaffected siblings of schizophrenia patients. Patients with a family history of psychosis have a higher level of cognitive dysfunction than those without a family history. This genetic component may differ between ethnic groups and families and its study could enhance our understanding of this debilitating illness. The aim of this work is to investigate the cognitive deficits of members of a multiply affected South Asian family compared to a control group of chronic schizophrenia patients. Members of a family with chronic schizophrenia underwent cognitive testing using the Cambridge Neuropsychological Test Automated Battery. These were the pattern recognition memory task (PRM; visual memory), spatial recognition memory task (SRM; spatial memory), intra/extra dimensional set shifting task (IED; executive function) and stockings of Cambridge task (SOC; working memory and spatial planning). Their performance on these assessments was compared to a control group of chronic schizophrenia patients using independent groups t-tests. The family members made significantly fewer correct responses (Mean=9.33, SD=1.53) than the control group (Mean=13.52, SD=2.5) on the SRM task (t(18)=2.77, p<0.05) and fewer correct responses (Mean=12.00, SD=1.73) than the control group (Mean=17.47, SD=4.60) on the PRM task which just failed to reach statistical significance (t(18)=1.20, p=0.06). SOG and IED were not completed by enough subjects for statistical analysis. These results are consistent with previous research which suggests that people with a family history of schizophrenia are at increased risk of cognitive impairment. Further testing will determine the cognitive dysfunction experienced by other family members, both affected and unaffected. The aim of our future research is to determine whether a targeted cognitive remediation program implemented early could delay the onset of psychosis, improve functioning and reduce the severity of other symptoms in these family members.

### TE14

**ALTERED HIPPOCAMPAL AND STRIATAL FUNCTION DURING SALIENCE PROCESSING IN PEOPLE AT ULTRA HIGH RISK FOR PSYCHOSIS**

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**AbstrActs**

Introduction: The assignment of salience to novel stimuli is normally associated with activation in a hippocampal - striatal - midbrain circuit (Bunzeck and Dizdle, Neuron 51, 369-379). Contemporary models propose that psychotic symptoms arise from the inappropriate attribution of salience to stimuli (Kapur, 2003, Am J Psychiatry 160, 13-23), and that this is associated with altered function in this network (Grace et al., 2007, Trends Neurosci. 30, 220-227). We used functional MRI to test if subjects at Ultra High Risk (UHR) for psychosis demonstrate altered activation in the hippocampus, striatum and midbrain when processing stimuli that were salient due to their novelty.

Methods: Twenty-one individuals who met PACE UHR criteria and 12 healthy volunteers participated in the study. Subjects viewed emotionally neutral outdoor scenes comprising a standard picture (presented on 73% of trials), a neutral oddball (the same picture presented on 9% of trials), a novel oddball (a unique picture presented on 9% of trials) and a target oddball (the same picture presented on 9% of trials for which subjects were instructed to respond with a button press). Stimuli were presented in random order in an event-related design. Functional MRI data were collected using a 3T scanner and analysed using SPM8.

Results: The groups did not differ in terms of accuracy or reaction time for detection of the target oddball stimulus. Irrespective of task condition, UHR subjects showed less activation than controls in the right parahippocampus (p=0.01). There was a significant interaction between group and task in the head of the right caudate nucleus. In this region, UHR subjects showed greater activation to novel oddball stimuli but less activation to neutral oddball stimuli than controls (p=0.05). In controls, the right midbrain and striatum were functionally connected during novelty trials, but this connectivity was absent in UHR subjects.

Conclusions: These results indicate that increased vulnerability to psychosis is associated with altered hippocampal and striatal function during the processing of novelty salience. These data are consistent with contemporary human and animal models that propose that altered salience processing is fundamental to the development of psychosis, and that this involves dysfunction in a hippocampal - striatal - midbrain network.

This study is funded by the Wellcome Trust under grant code 091667/Z/10/Z.
COMPROMISED MYELIN INTEGRITY AND PERIPHERAL INFLAMMATORY MARKERS IN FIRST EPISODE PSYCHOSIS.

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Introduction: Evidence on the involvement of the inflammatory system in the pathogenesis of psychosis is one of the most important recent developments in translational mental health, and offers a unique opportunity to identify new therapeutic targets. Increased peripheral inflammatory markers and microglial activation have been reported in patients with psychosis. Inflammatory cytokines produced by activated microglia can affect oligodendrocytes. This is important as myelin alterations may underlie the dysconnectivity thought to crucial in schizophrenia. Quantitative visualization of myelination in vivo is now possible with a novel neuroimaging technique termed mcDESPOT, which allows direct myelin quantification (estimated as myelin water fraction, MWF). The aim of this study was to investigate the relationship between MWF and peripheral inflammatory and neuroplasticity markers in first episodes psychosis patients and healthy controls.

Methods: Ten first episode psychosis patients and 12 healthy controls matched for age and gender were included in the study. Blood levels of High Sensitivity C-Reactive Protein (hsCRP), interleukin (IL)-1β, IL-6, IL-10, Brain-Derived Neurotrophic Factor (BDNF) and mcDESPOT sequences were acquired. Myelin content and peripheral biomarkers were compared between the two groups and the relationship between myelin content and inflammatory markers was investigated.

Results: Patients showed evidence of an increased inflammatory status as demonstrated by mean levels of hsCRP, which were almost three times higher than those of controls (2.0±2.4 vs. 0.7±0.4 in controls, p=0.09). Interestingly, patients also showed significantly lower MWF throughout the brain than controls (p<0.03, corrected), a completely novel finding. Moreover, lower MWF was significantly associated with higher levels of hsCRP and other peripheral markers of inflammation, IL-1β and IL-6. In contrast, lower MWF was associated with lower levels of the peripheral marker of neuroplasticity, BDNF.

Conclusions: This work represents the first evidence of in vivo visualization of myelin content in first episode psychosis patients. Moreover these findings provide the first, albeit preliminary, evidence that peripheral markers of inflammation are correlated with dysmyelination at a central level.

Acknowledgements: The research was in part financially supported by the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London.

EFFECT OF INFLAMMATION ON MENTAL AND PHYSICAL CLINICAL OUTCOMES IN FIRST EPISODE-PsyCHOSIS

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Increased inflammation has been seen in both patients with chronic schizophrenia and first episode psychosis. It has been implicated in the development of psychosis, as well as the development of metabolic abnormalities. More recently, increased inflammation has been shown to predict components of the metabolic syndrome in patients with non-affective psychoses. This study aims to further investigate the association between inflammatory biomarkers and both mental and physical health outcomes, specifically in patients with first-episode psychosis. 47 patients with a first-episode were recruited (mean±SEM age: 29.4±1.3 years; gender: 61.7% males; ethnicity: 29.8% White British). Inflammation was assessed using a clinically relevant measure of high-sensitivity C-reactive protein (hsCRP) at baseline and three-month follow up. A lipid profile (total, HDL and LDL cholesterol; triglycerides) was also obtained at these time points. Mental health outcome was determined by treatment response. This was defined by remission of symptoms at three-month follow-up, using criteria established by the Remission in Schizophrenia Working Group based on scores on the Positive and Negative Syndrome Scale (PANSS). There were 14 non-responders (age: 26.8±2.1 years; gender: 78.6% males; ethnicity: 35.7% White British) and 33 responders (age: 30.5±1.6 years; gender: 54.5% males; ethnicity: 27.3% White British). Across all patients, there were significantly positive correlations between baseline hsCRP and baseline triglyceride levels (r= .316, p<.03), and baseline hsCRP and triglycerides levels at follow-up (r=.311, p<.03). Since previous research has shown an effect of gender and ethnicity on hsCRP levels, these were controlled for in the analysis. Non-responders showed significantly higher hsCRP levels than responders at baseline (3.9±1.6 vs. 1.3±0.4 mg/dl, p=0.04). However, there was no significant difference in hsCRP levels between groups at three-month follow up (3.1±1.3 vs. 2.6±1.0, p=0.7). Our results suggest that treatment response at three-month follow up is associated with increased inflammation at baseline. This raises the possibility of the use of baseline hsCRP as a predictor of clinical outcome, and therefore its use as a tool to identify those patients who are at greater risk of poorer clinical outcomes. The results also support previous findings, which suggest that baseline hsCRP may predict higher triglyceride levels in patients with psychosis.

Acknowledgements: This research has been supported by the NIHR BRC for Mental Health at the SLaM NHS Foundation Trust and Institute of Psychiatry, KCL, and from an ECNP Young Scientist Award, and a Starter Grant for Clinical Lecturers from the Academy of Medical Sciences to V Mondelli.
TE17

RELATIONSHIP BETWEEN THALAMIC GLUTAMATE LEVELS AND CLINICAL OUTCOME IN INDIVIDUALS AT ULTRA HIGH RISK FOR PSYCHOSIS

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Introduction: Abnormalities in central glutamatergic neurotransmission play a key role in the pathophysiology of schizophrenia. Recent research indicates that glutamatergic abnormalities may pre-date the onset of psychosis and contribute to psychosis risk. We investigated whether brain glutamate levels in individuals at ultra high risk of psychosis (UHR) at presentation to clinical services were predictive of subsequent clinical outcome.

Methods: The sample consisted of 81 UHR individuals and 59 age- and gender- matched healthy control participants. UHR status was determined using Comprehensive Assessment for at Risk Mental States (CAARMS) criteria. The study had NHS ethical approval and all participants provided written informed consent. Glutamate levels in the left thalamus were estimated using proton magnetic resonance spectroscopy at 3 Tesla (PRESS: Point-RESolved Spectroscopy; TE=30ms; TR=3000ms; 96 averages). Symptom severity and overall functioning were assessed using the CAARMS and Global Assessment of Functioning (GAF) scales respectively. Group differences in glutamate levels were determined using independent samples t-test. Relationships between symptom severity and thalamic glutamate levels were determined using Pearson’s correlation.

Results: Thalamic glutamate levels were significantly lower in the UHR than control group (t(127) = 2.15; p = 0.034). There were no significant relationships between glutamate levels and symptom severity at intake (P=0.05). Clinical follow-up measures were available in 47 of the UHR group. 32 showed an improvement in symptoms from baseline, whereas symptoms became more severe in 15 participants with 8 people making transition to frank psychosis. Thalamic glutamate levels at baseline were related to the severity of abnormal thought content (r = -0.408 p =0.004), perceptual abnormalities (r = -0.319 p=0.029) and overall functioning at follow-up (r=0.28 p=0.05), such that lower thalamic glutamate levels were associated with more marked symptoms and poorer functioning. UHR participants in whom CAARMS positive symptoms (sum of severity score on CAARMS abnormal thought content, perceptual abnormalities and disordered speech items) worsened during the study period had lower glutamate levels at baseline than UHR participants in whom symptoms improved (T45= 3.024; P = 0.004).

Conclusions: These results suggest that poorer clinical outcome in individuals at high risk of psychosis may be predicted by lower levels of glutamate in the thalamus. This is consistent with the idea that glutamatergic abnormalities predate the onset of psychosis and may provide a biomarker for psychosis risk.

This study was supported by the Medical Research Council and the NIHR Biomedical Research Council for Mental Health at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, King’s College London.

TE18

CAN WE USE CORTISOL LEVELS TO PREDICT CLINICAL OUTCOME IN PATIENTS WITH FIRST-EPISODE PSYCHOSIS?

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Introduction: Antipsychotic treatment has been shown to partially influence HPA axis activity in these patients, reducing diurnal cortisol levels, but not affecting the blunted cortisol awakening response in the same patients. The aim of this study was to investigate if baseline cortisol levels or changes in cortisol levels over the first three months of treatment could predict clinical outcome in patients with first-episode psychosis.

Methods: We collected salivary cortisol in 50 first-episode psychosis patients at baseline and after 3 months at multiple time points during the day (awakening, 15, 30 and 60 minutes after awakening, at noon and at 8pm). Data have been analyzed so far only in a proportion of patients (n=23). Patients were divided in Non-Responders and Responders according to the Remission criteria of the Schizophrenia Working Group Consensus, measuring a reduction in symptoms severity using the Positive and Negative Syndrome Scale over the first three months of treatment. Twelve patients were classified as Non-Responders and 11 as Responders. Diurnal cortisol levels and the cortisol awakening response are presented as Area Under the Curves. An independent T-test was conducted to test differences between Non-Responders and Responders in baseline cortisol levels and a paired T-test was used to test differences between baseline and follow-up cortisol levels in the two separate groups.

Results: Patients who were Non-Responders had significantly lower cortisol awakening response at baseline when compared with patients who were Responders (mean±SEM: 555.6±70.6 vs 725.3±117.0 nmol/l min, p=0.043). Cortisol awakening response tended to further decrease at 3-months follow-up in the Non-Responders group (p=0.095), while it did not change in the Responders group (p=0.6). We did not find significant difference in diurnal cortisol levels at baseline or at follow-up between Responders and Non-Responders.

Conclusions: Blunted cortisol awakening response at baseline and a further decrease in the cortisol awakening response over the first 3 months is linked to a poorer clinical outcome at 3 months follow-up in patients with first-episode psychosis. Acknowledgments: This research has been supported by the NIHR BRC for Mental Health at the SLaM NHS Foundation Trust and Institute of Psychiatry, KCL, and from an ECNP Young Scientist Award, and a Starter Grant for Clinical Lecturers from the Academy of Medical Sciences to V Mondelli.
Altered Neurochemical Profile in the Rat Prefrontal Cortex Following Maternal Immune Activation: A Longitudinal In Vivo 1H Magnetic Resonance Spectroscopy Study

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Proton magnetic resonance spectroscopy (1H MRS) has identified abnormalities in neurometabolites, including glutamate, N-acetyl-aspartate (NAA) and glutathione (GSH) in the prefrontal cortex (PFC) of schizophrenia (SCZ) patients, suggesting their involvement in SCZ pathophysiology in the adult brain. Human 1H MRS studies have failed however to capture the neurodevelopmental trajectory of SCZ-related neurometabolite abnormalities in vivo, due to a lack of validated diagnostic biomarkers for disease risk. This is important since maldevelopment of the central nervous system (CNS) is implicated in SCZ pathogenesis. Epidemiological and pre-clinical evidence indicates that maternal immune activation (MIA) during pregnancy may interfere with normal fetal brain development and thereby predispose the developing organism to the emergence of postnatal neuropathology and psychopathology in adulthood (Brown et al., 2004. Arch Gen Psychiat. 61, 774-780). The mechanisms underlying these effects however remain unknown. We therefore investigated the neurodevelopmental trajectory of PFC neurometabolites following viral MIA in rats in a longitudinal 1H MRS study. Pregnant dams were exposed to the viral mimetic polyriboinosinic-polyriboycytidilic acid (PolyIC, 4 mg/kg i.v., n=8 litters) or saline (n=3 litters) on gestation day 15 and in vivo 1H MRS data acquired from a single voxel in the rat PFC at postnatal days (P) 50, 100 and 180. MRS data were fitted and analysed using LC Model software. Behavioural assessments (amphetamine, ketamine locomotion), (1 mg/kg s.c.) were conducted in adult (P175) animals. Statistics were performed using two-way repeated measures ANOVA with post-hoc Bonferroni’s correction using SPSS 20.0 software. There were no significant effects of Poly I/C on maternal body weight, litter size, or offspring body weight compared to saline-injected controls. No specific assessments of maternal behaviour towards pups following Poly I/C or saline challenge were undertaken in this study. Offspring from PolyIC exposed dams demonstrated significantly reduced levels of the inhibitory amino acid taurine (Tau; p<0.01) and the anti-oxidant glutathione (GSH; p<0.01) in adulthood (P180) when compared to offspring from saline injected dams. No statistically significant changes were observed for any other neurometabolite at any age, although trends towards elevated glutamate and NAA were observed in adolescence (P50), which normalised with increasing age in Poly I/C offspring. Significantly increased locomotor response to amphetamine and ketamine challenges were seen in Poly I/C offspring (p<0.05) in adulthood, but not saline-injected offspring. These data provide in vivo evidence for specific neurometabolite abnormalities in the PFC following MIA, using methods translatable to humans (1H MRS). Our data suggest that viral-induced MIA induces specific adult onset decreases in taurine and GSH, consistent with data from SCZ patients. In contrast, although we found no significant changes in either NAA or glutamate, there were trends for alterations in these metabolites in adolescence. These data support the possibility that infection-mediated interference with early fetal brain development may predispose the developing organism to the emergence of specific neurochemical imbalances in adulthood, which may be involved in the precipitation of adult behavioural and pharmacological abnormalities after prenatal immune challenge.

Funding from the Medical Research Council (Grant ID: G0701748 [85253] and G1002198) whom we thank for their generous financial assistance supported this study. The authors also thank the British Heart Foundation for supporting the 7T MRI scanner at the King’s College London Preclinical imaging unit (KCLPIU).

Assessment of Working Memory and Social Behaviours in Mice with Genetic Modification of the Schizophrenia-Risk Gene Map2K7

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Introduction: Schizophrenia is a severely debilitating psychiatric disorder which affects approximately 1% of the world population. While the aetiology of schizophrenia remains elusive, there is a strong genetic component. Current research suggests that 100s of common variants each contribute a small increase in risk of developing the disease whereas rarer highly penetrant variants contributing a higher risk MAP2K7 (mitogen-activated protein kinase kinase 7) has recently been identified by our group as a candidate susceptibility gene for schizophrenia (Winchester et al 2012; Human Mol Genetics, 21:4910-4921). In the present study, the influence of dysfunction in MAP2K7 and its relation to cognitive processes known to be impaired in schizophrenia was assessed in mice heterozygous for the deletion of Map2k7.

Method: Working memory was assessed in Map2k7 heterozygous mice and WT (n=9 and n=11) mice in a radial arm maze task (Marighetto et al, 2008; Psychopharmacol, 22:511-521), homologous to the human n-back task. In addition, social behaviour was assessed using a sociability and preference for social novelty paradigm (Moy et al 2004; Genes Brain Behav, 3: 287-302)(n=7, n=8).

Results: Map2k7 heterozygous mice displayed significant working memory deficits in the radial arm maze task compared to WT littermate controls(P<0.05); a significant impairment in the n=1 and n=3, ‘n-back’ levels (P<0.05) was evident. However, Map2k7 heterozygous mice displayed a similar social behaviour profile to WT controls. Statistical analysis: All results shown are mean +/- sem where n = number of mice used, unless otherwise stated. For the social behaviour task, one way or repeated measure ANOVA were employed to determine significance of differences between genotypes. For the memory task, one way ANOVA were employed to determine significance between genotypes under the appropriate paradigms. Student T tests were employed to determine significance between genotypes for each n-back level. In all cases a P value of <0.05 was taken to be indicative of statistical significance.

Conclusion: Taken in convergence with previous studies, these results provide supporting evidence to imply reduced Map2k7 signalling may underlie some of the neurochemical and cognitive impairments seen in schizophrenia.
Introduction: Much evidence indicates the involvement of glutamate in the pathophysiology of schizophrenia (Kloet et al., 2005. Nature Rev Neurosci, 6, 463-475). It has been reported that glutamatergic neurotransmission is decreased in the prefrontal cortex and hippocampal formation in schizophrenics and in rats reared in isolation from weaning, an experimental model of this disorder (Fone & Porkess, 2008 Neurosci Biobehav Rev, 32, 1087-1102; Weiss et al., 2004. Behavioural Brain Research. 152. 279-295). This study aimed at evaluating the changes in the expression of glutamate transporters (EAAC1 and GLT1) and the glutamate uptake in the prefrontal cortex (PFC) and hippocampus of rats reared in isolation from weaning.

Methods: Two groups of Wistar rats (n=7-12/each) were used. In both groups the pups remained with their mothers (6 pups per mother) until weaning (21 days - 40g) when they were allocated randomly to one of two conditions: grouped (housed 3/cage, handled 3 times/week) or isolated (housed individually, handled once/week for cleaning purpose) for 10-13 weeks. For immunohistochemistry the animals were anaesthetized, perfused and their brains sectioned (40-um) in the PFC and hippocampus. The number of immunopositive cells (IC) was quantified bilaterally in 3 sections/rat. For glutamate uptake the animals were sacrificed by cervical dislocation, their brains quickly removed, homogenized in sucrose (0.32 M) prior to incubation with 3H-Glutamate. 3H-Glu was measured using a liquid scintillation counter. In both studies the average for grouped and isolated were compared by Student t-test (p<0.05).

Results: Isolation rearing induced a significant increase on the expression of EAAC1 in the PFC (38%, p=0.017), hilus of dentate gyrus (81%, p<0.01) and CA3 (144%, p<0.05) while no difference was found in CA1. The number of GLT1-IC did not change in the PFC (p>0.05) of isolated rats when compared to grouped rats. However, immunofluorescent labeling for GLT1 was seen associated to glial and neuronal cells in this area. Isolation rearing induced a significant increase in glutamate uptake in hippocampus (35 %, p<0.001). However, no change was found in PFC (p<0.05).

Conclusions: These results contribute additional evidence to identify how developmental factors may contribute to the reduction in the glutamatergic metabolic response reported in schizophrenia. They also suggest considering the glutamate transporters as a future therapeutic target for the treatment of schizophrenia.

Support: FAPESP, Capes, FPA.

TE22

DISC1 MUTATION INDUCED ALTERATIONS IN CEREBRAL METABOLISM AND IN THE RESPONSE TO ACUTE KETAMINE TREATMENT: A COMPARISON OF THREE DIFFERENT DISC1 MUTATIONS

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Introduction: Disrupted-in-Schizophrenia-1 (DISC1) is strongly implicated in psychiatric disease, as is NMDA receptor hypofunction. How DISC1 dysfunction impacts upon constitutive brain functioning or NMDA receptor functioning is yet to be determined. Here we characterise the impact of Disc1 gene mutation on brain functioning and on the cerebral metabolic response to the schizomimetic NMDA receptor antagonist ketamine in three lines of Disc1 mutant mice; one a Disc1 truncation (Disc1Tr hemizygous mice, Shen et al., 2008. J. Neurosci. 28: 10893) and two ENU-induced missense mutations (Disc1 100P/100P and 31L/31L mutant mice, Clapcote et al., 2007. Neuron 54: 387) in the gene.

Methods: Cerebral metabolism was determined in Disc1 mutant mice (Disc1Tr hemizygous n = 20, Disc1 100P/100P n = 18, Disc1 31L/31L n = 18) and their wild-type littermates (C57BL/6J/RscHsd, n = 20, n = 19 and n = 20, respectively) in 58 brain regions by 2-deoxyglucose autoradiography (Dawson et al., 2013. Schizopr. Bull. 39: 366). Animals were treated acutely with either 30mg/kg ketamine (i.p.) or vehicle (saline, 2mls/kg). Data were analysed using 2-way ANOVA with genotype (Wt, Disc1Tr hemizygous mice, Shen et al., 2008. J. Neurosci. 28: 10893) and two ENU-induced missense mutations (Disc1 100P/100P and 31L/31L mutant mice, Clapcote et al., 2007. Neuron 54: 387) in the gene.

Results: The Disc1 mutation present in Disc1Tr hemizygous mice had the most pronounced effect on constitutive cerebral metabolism, inducing a significant hypofrontality (prefrontal cortex hypometabolism), along with hypometabolism in the reticular thalamus and habenula. The Disc1 mutation present in both of the ENU mutant lines failed to induce significant hypofrontality. Rather, the mutation present in Disc1 100P/100P mutant mice induced widespread thalamic hypometabolism, whereas that present in Disc1 31L/31L mutant mice was more limited, inducing only cingulate cortex hypometabolism. In all three mutant lines there was evidence that the cerebral metabolic response to ketamine was significantly attenuated. Again, this effect was most pronounced in Disc1Tr hemizygous mice, which included an attenuation of ketamine induced hyperfrontality. Ketamine-induced hyperfrontality was not attenuated in either of the ENU Disc1 mutants.

Conclusion: Overall, these data suggest that Disc1 mutation modifies cerebral functioning in neural systems strongly implicated in psychiatric disorder. Moreover, the data suggest that the specific molecular nature of the mutation present in the Disc1 gene has a pronounced impact on the emergent properties of altered brain functioning at a systems level. Furthermore, we have shown that Disc1 mutation modifies the cerebral metabolic response to ketamine, supporting NMDA receptor hypoaeviation/hypofunction in these animals.

Financial support: This work was supported by an award (NS-GU-170) from the Translational Medicine Research Collaboration

TE23

EVALUATION OF SUB-CHRONIC KETAMINE TREATMENT IN A RODENT MODEL OF THE IOWA GAMBLING TASK

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It has been shown that nicotine has the potential to alleviate the cognitive deficits observed within schizophrenics. This study was aimed to assess the role impulsivity plays within schizophrenic patients to contribute towards the high levels of smoking seen within the schizophrenic population. Sub-chronic ketamine treatment within rats has been shown to act as a model for the cognitive deficits seen in patients with schizophrenia. Using a rodent version of the Iowa Gambling task (rIGT) (Zeeb FD, Robbins TW, Winstanley CA. (2009) Serotonergic and dopaminergic modulation of gambling behaviour as assessed using a novel rat gambling task. Neuropsychopharmacology 34:2329–43), impulsivity levels between controls and ketamine treated rats were analysed and the ability for nicotine to restore any changes seen was assessed. Twenty-four male hooded Lister rats were trained to choose one of two levers in the rIGT. Rats were then undertook the classic rIGT which involved presenting four choices each with differing probabilities for rewarding or punishing outcomes for a series of 30 minute sessions. Choice selection was measured throughout the testing period. Rats were then treated with varying doses of nicotine (0.05, 0.1, 0.2, 0.4 mg/kg) as well as vehicle and choice selection was measured to see if any changes could be restored. Rats that had a history of ketamine exposure chose the optimal selection more than the control saline-treated group (p<0.001) and chose the least optimal selection less (p<0.001). No difference was evident between the two middle choice selections (p<0.05). No restoration effects were observed when the rats were treated acutely with nicotine. The results from this study suggests that sub-chronic ketamine exposure decreases impulsivity which facilitates optimal choice selection. This suggests that impulsivity may not play a major role in the high level of smoking observed within the schizophrenic population. Furthermore, nicotine was not found to modify impulsive behaviour in this rodent version of the IGT.


Sources of financial support came from both the BAP and Newcastle University.
TE25
PRELIMINARY FINDINGS OF A NOVEL ELECTROPHYSIOLOGICAL ASSAY FOR NMDA RECEPTOR AUTOANTIBODIES IN PSYCHOSIS
Adams T (1), Watson S (1), Wilson S (2), Carroll B (2), Melody J (2), Garg H (2), MacMillan I (2), Brydon T (2), Hall S (3), Cunningham M (1), (1) Newcastle Univ; (2) Northumberland, Tyne and Wear NHS Foundation Trust; (3) The Univ of York

Anti-N-methyl D-aspartate receptor (NMDAR) encephalitis is a recently identified autoimmune disorder, in which neuropsychiatric symptoms are a common early feature. These symptoms take the form of acute psychosis (Dalmau et al., 2008, Lancet Neurol, 7(12), 1091-8), reduced cognitive performance (e.g. short term memory loss; Sansing et al., 2007, NCPNeur, 3(5),291-6 ), movement disorders(Dalmau et al., 2008) and catatonic symptomatology(Dalmau et al., 2008). Zandi and colleagues(2011, J Neurol, 2011, 258, 686-8) reported that three of 46 first episode psychosis patients had serum positive for anti-NMDAR antibodies. However, another study (n=7), didn’t observe anti-NMDAR antibodies in schizophrenic patients (Rhoads et al., 2011, Schizophrenia Research, 129, 213-4) Currently, anti-NMDA antibodies are identified using a cell-based assay(Vincent et al., 2011, Lancet Neurol, 10, 759-72). However, our preliminary work suggests that an electrophysiological assay is a viable alternative. We aim to further investigate the prevalence of anti-NMDA antibody positive patients in two groups: subjects recently accepted into EIP teams (n=100) and inpatients with catatonia (n=20), using the established cell-based assay and an in vitro electrophysiological assay. The cell-based assay targets the NMDAR subunit NR1, whereas our novel measure aims to look at the functional outcome of cortical gamma frequency oscillations. This electrophysiological activity is disrupted in psychosis and correlates with positive and negative symptoms in schizophrenia. In addition previous work by our group has demonstrated the exquisite sensitivity of cortical gamma oscillations to NMDA receptor antagonism (Middleton et al., 2008, Proc Nat Acad Sci USA, 105, 18572-7) To date, twenty-one subjects have been recruited. Ten have been analysed using the electrophysiological gamma oscillation assay. In four of these samples, the gamma oscillations appeared reduced in amplitude following the addition of serum and this effect was reversed following washout. The discrepant results of the two assays suggests that the electrophysiological assay may be more sensitive to either pathology (for instance, detecting abnormalities outwith the NR1 subunit) or to confounding variables; psychotropic medication or illicit drugs for instance may affect gamma frequency or amplitude. Further work to quantify the impact of potential confounds and full clinical evaluation of the positive cases is required.

This study is funded by the Jennifer Cole Charitable Trust and Northumberland, Tyne and Wear NHS Foundation Trust.
**PD1**

**IMPAIRED LEARNING AND ATTENTION IN THE BTBR MOUSE MODEL OF AUTISM**  
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Autism spectrum disorders (ASD) are characterized by differences in social behavior and communication, restricted interests and repetitive and stereotyped patterns of behavior. The BTBR T+ tf/J (BTBR) mouse is an inbred mouse strain which spontaneously shows rodent analogs of these core symptom domains, and has been used as a mouse model of autism. Despite its wide utilization, little is known about the wider cognitive phenotype of this mouse, or the mechanism of its pathology. The aim of this work was to investigate learning and attention, cognitive abilities which can be affected in autism. We characterized attentional performance using the 5-choice serial reaction time task (5CSRTT), implemented in a touchscreen apparatus. The 5CSRTT is a translational analog of the human continuous performance task, and measures accuracy, vigilance, impulsive behavior, motivation, and compulsive-like behavior. Using in vivo microdialysis, we also examined basal neurotransmitter release in the medial prefrontal cortex (mPFC), an area important for aspects of attentional control. Our experiments showed that while BTBR mice display repetitive grooming in their home cage or in a novel cage, they do not exhibit this behavior in the 5CSRTT, so it would not preclude assessment of cognitive performance. BTBR mice exhibit poor initial learning performance, decreased motivation, and a susceptibility to increased impulsivity when challenged with a long inter-trial interval condition (a long delay between initiation of the trial and stimulus presentation), as compared to C57Bl/6J mice. They also show decreased accuracy when required to detect stimuli of very short duration. BTBR mice also show decreased extracellular levels of acetylcholine, and increased levels of kynurenic acid in mPFC. These results indicate that the regulation of these two neurotransmitter systems may be abnormal in the BTBR mouse, and that BTBR mice may be of use in model learning, attentional and motivational deficits, in addition to the core symptoms of autism.

**PD2**

**TRANSLATIONAL ASPECTS IN SHANK MUTANT MICE**  
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Introduction: The molecular pathology underlying diverse neurodevelopmental disorders such as intellectual disability, autism or schizophrenia strongly supports imbalances of synaptic connections among causative mechanisms. In this context, genetic disruptions of the human SHANK gene family have been found in a variety of affected individuals. These genes (SHANK1, 2 and 3) encode large proteins organizing the postsynaptic density (PSD) of excitatory synapses thus essentially contributing to synaptogenesis and synaptic plasticity (Grabrucker et al., 2009, Trends Cell Biol, 21, 594-603)  
Methods: We have successfully generated Shank2 and Shank3 mutant mice and hitherto evaluated basic mutant neurobiology, neurophysiology and behavior (Schmeisser et al., 2012, Nature, 486, 256-260).  
Results: In both models, we rather found molecular than morphological alterations. Interestingly, each model shows a distinct and brain region-specific phenotype with respect to synaptic glutamate receptor expression and neurophysiology (e.g. NMDAR up-regulation in Shank2, AMPAR down-regulation in Shank3 mutants). Furthermore, both Shank mutants exhibit individual characteristic features of autistic-like behavior such as social interaction deficits, deficits in vocal communication and repetitive behaviors.  
Conclusions: Based on our data and especially on the different impact of Shank loss among brain regions, we are now dissecting individual circuits in our models and are searching for appropriate molecular targets that are to be used in future translational studies.  
The author(s) are supported by the Deutsche-Forschungs-Gemeinschaft (DFG), the Baustein program of Ulm University for young scientists, the Bundesministerium für Bildung und Forschung (BMBF), the Agence Nationale de la Recherche (ANR), the Fondation Orange, the Fondation FondaMentale and the EU-AIMS Innovations in Medicine Initiative (MI).

**PD3**

**MULTIMODAL NEUROIMAGING IN THE SEARCH FOR AUTISM TREATMENT TARGETS**  
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Autism spectrum disorders (ASDs) are a family of neurodevelopmental disorders affecting around 1% of the population. ASDs are responsible for a considerable burden of morbidity and financial cost to society, yet there are currently no targeted, disease-specific pharmacological treatments for the condition. To date, medical management of ASDs has been symptomatic. However, recent findings regarding the basic pathophysiology of the condition have opened the door towards novel therapeutics. In particular, emerging evidence has implicated dysfunctional GABA and/or excessive glutamate neurotransmission in ASD, sometimes referred to as the excitatory:inhibitory balance (E/I). Drugs in early clinical trials for ASD targeting E/I include arbaclofen and mGluR5 modulators. In this talk I will outline the advantages and disadvantages of these two neurotransmitter systems may be abnormal in the BTBR mouse, and that BTBR mice may be of use in model learning, attentional and motivational deficits, in addition to the core symptoms of autism.
PD4
DISRUPTION OF A PROTOCADHERIN GENE IDENTIFIED BY QTL MAPPING OF SOCIAL MEMORY IN MICE, OFFERS A MODEL TO STUDY PERVERSIVE DEFECTS IN BEHAVIOR AND CORTICAL DEVELOPMENT
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Introduction: In search of genetic mechanism underlying social cognition, we performed a quantitative genetic screen of social memory in mice. Methods& Results: A quantitative trait locus (QTL) was mapped for long-term social recognition memory in the C57BL/6JChr#A3/Naj chromosome substitution panel to a QTL harboring a protocadherin gene previously associated with autism and schizophrenia in humans. We generated mice deficient for this Protocadherin gene that showed a consistent impairment in long-term social and object recognition memory, which was not influenced by social avoidance or exploratory behaviors. We also found that this social memory deficit was accompanied by pre-adult increased locomotion and impaired rotarod performance. We sought to link these behavioral deficits to the assumed role of the Protocadherin gene in cortical lamination and found that its deficiency disrupts the integrity of the somatosensory cortex with displacement of layer specific neurons, reduced apical dendrite length and increased spine density.

Conclusions: Together, we present the first quantitative genetic screen on social memory in mice leading to the identification of a Protocadherin gene as a genetic factor important for behavioral development. The results of our functional and morphological characterization suggest a role for this gene in formation of specific neural circuits and indicate that a loss of integrity of the somatosensory cortex may contribute to the observed pervasive behavioral deficits.

PW1
USING PROTOTYPICAL FACES IN STUDY OF EMOTION RECOGNITION
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Deficits and biases in the recognition and attribution of emotion in facial expressions is a ubiquitous feature of many psychopathologies. The reliable assessment of these is therefore vital, in particular given growing evidence that pharmacological treatments directly modify these deficits and biases. However, tasks designed to assess emotion recognition often rely on stimulus sets developed several decades ago, and which comprise a small number of individuals, each with their own idiosyncratic facial characteristics. We have developed a number of novel stimulus sets for use in emotion recognition research. One key feature of the stimulus sets we have developed lies in the construction of the stimuli themselves. We employ composite faces generated from a larger number of individual photographic subjects. This established technique isolates the prototypical characteristics of emotional expressions, while removing the idiosyncratic variation in expression that is found between individuals. Another key feature is how these stimuli are then used to generate morph sequences. Many tasks typically employ sequences that run from a neutral exemplar to an emotional exemplar (e.g., neutral to happy). Instead, we have generated continua that start from an average or prototypical emotional face, constructed by compositing exemplars of each of the six basic emotion (i.e., anger, happiness, sadness, fear, surprise and disgust). This face appears genuinely emotionally ambiguous, rather than neutral. We believe this approach offers several key advantages. First, recent evidence suggests that visual representations of emotion are better described as being coded with reference to a prototype of this sort, as opposed to a neutral face (Skinner, A. L. & Benton, C. P. 2010. Psychological Science, 21, 1248-1253). Second, a neutral faces is not actually without emotional content, and some subgroups of participants (e.g., those with high levels of anxiety) default to interpreting neutral faces as threatening (Yoon, L. & Zinbarg, R. 2008. Journal of Abnormal Psychology, 117, 680-685). Third, prototypical stimuli that are genuinely emotionally ambiguous may be particular sensitive to interpretation biases characteristic of a range of psychopathologies.

PW2
D-CYCLOSERINE DOES NOT IMPROVE DRUG-RELATED CUE EXPOSURE: WHAT CAN WE LEARN FROM ANIMAL DATA?
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Hogarth L(1), Adams S(2), Howell E(2), Munafo M(2). (1)Psychology, Univ of New South Wales, Sydney, Australia; (2)Experimental Psychology, Univ of Bristol, 12a Priory Rd, Bristol, UK

Introduction: Drug-related cues play an important role in drug dependence and relapse, and interventions such as cue exposure therapies (CET) have been developed to reduce reactivity to them. CET is largely based on classical conditioning principles in which drug cues are presented in the absence of drug and therefore act as Pavlovian extinction trials. However, CET in the addictions has yielded weak or inconsistent results, but preclinical work with rats indicates that extinction learning may be enhanced with NMDA receptor agonists, which therefore may be useful adjuncts to CET. This has been supported by some promising results using the NMDA partial agonist D-cycloserine (DCS) in CET for anxiety and phobia. To date, a small number of studies have tested DCS on drug-related CET with mixed results. This study builds on with NMDA receptor agonists, which therefore may be useful adjuncts to CET. This has been supported by some promising results using the NMDA partial agonist

_results: While there was evidence of reduced craving across CET training sessions (P<.001), no drug group differences were observed on any of the primary (Ps >.12) or secondary (Ps >.26) outcome measures. The null findings will be discussed in light of recent drug CET studies, which also found weak or null effects.

Conclusions: There is a growing body of literature suggesting that augmented CET using DCS is weaker in the field of addiction than anxiety. However, preclinical animal research appears to have made the transition more successfully than preclinical human research. This may be in part due to the relative failing of human studies to fully utilize animal data to inform research design, and the importance of cross translation will be discussed. Finally, novel avenues for research design and investigation will be offered that take account of current animal findings.

Funding: Pfizer Inc.
PW3

INDIVIDUAL DIFFERENCES IN PSYCHOPHARMACOLOGY: WHERE DO THEY COME FROM AND WHY SHOULD WE CARE?

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When assessing the impact of a drug on brain or behaviour, some variation across individuals is inevitable. But how much of this is due to random processes – experimental error – and how much is systematic and potentially important? In this talk I will argue that a surprising amount of variation falls into the latter category. The first example is from a study of chronic ecstasy users, in whom we anticipated identifying profound cognitive and mood abnormalities. At first glance the results seemed disappointing – we were unable to identify robust effects. However, when stratifying the groups according to a variant in the serotonin transporter gene, we found that ecstasy users carrying a risk variant for depression were more likely to report low mood. Interestingly, we also identified an unexpected influence of this genetic variant on decision making in non-ecstasy users, a finding that has subsequently been replicated several times. The second example comes from a follow-up study, in which we used acute tryptophan depletion to manipulate serotonin experimentally. Here, the effect of tryptophan depletion on motivational responding was dependent on the same genetic variant, with greatest change in individuals in whom the depletion procedure was most effective. By contrast, in the non-risk variant group, more effective depletion was associated with improved motivation. These two studies assessed the impact of a genetic polymorphism on response to serotonin perturbation, but a more sensitive approach may be to examine the level of transcription and translation, which ultimately determines function, and might be influenced not only by several genetic polymorphisms, but also by the environment. In the third example, the expression of dopamine D3 receptors, measured in peripheral blood, influenced the change in working memory performance following administration of the D2/D3 agonist pramiptexole. In the final example, we used positron emission tomography to demonstrate that a large proportion of individual variability in the response of the amygdala to fearful faces is explained by serotonin 1A receptor binding in the raphe nuclei. These studies suggest that a large amount individual variation in psychopharmacology can be explained, and potentially is of great scientific importance. The challenge is to harness this understanding to improve mental health treatment outcomes, which may be impractical if genetic effects are small. However, neuroimaging studies are starting to provide robust markers of response to treatment, which could pave the way for a more mechanistically informed approach to diagnosis and treatment in psychiatry.

PW4

OMEGA-3 FATTY ACIDS IN DEPRESSION: THE BIOLOGICAL, THERAPEUTIC AND PREVENTIVE IMPLICATIONS

Su K-P, Director of the Mind-Body Interface Laboratory (MBI-Lab) Professor of Psychiatry, Neural and Cognitive Sciences, China Medical University, Taiwan, cobolsu@gmail.com

Clinical features, biological markers, and treatment outcomes for depression are extremely heterogeneous. The use of the current diagnostic schemas undoubtedly contributes to difficulties in finding any single biological or genetic marker for major depressive disorder (MDD) (Su KP. BioMedicine 2012). For example, the unsatisfaction of monoamine-based antidepressant therapy and the high occurrence of somatic symptoms and physical illness in patients with MDD imply that the serotonin hypothesis is insufficient to approach the aetiology of depression (Su KP. NeuroSignals 2009). Omega-3 polysaturated fatty acids (omega-3 PUFAs or n-3 PUFAs) are recently enlightening a promising path to discover the unsolved of depression. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), 2 major bioactive components of omega-3 PUFAs, are both natural anti-inflammatory and anti-depressant agents. Patients with MDD show lower levels of omega-3 PUFAs in blood tissues (Lin PY, Huang SY & Su KP. Biol Psychiatry 2010). In addition, omega-3 PUFAs are reported to be effective in MDD treatment (Lin PY & Su KP. J Clin Psychiatry 2007; Lin et al. Molecular Psychiatry 2012) and proven to be safe and effective in treatment for pregnant women with MDD (Su KP et al. J Clin Psychiatry 2008). Furthermore, pre-clinical studies also support the beneficial effects of omega-3 PUFA in cellular (Lu DY et al. Neuropsychopharm 2010) and animal models (Huang SY et al. J Psychiatric Res 2008). Increasing evidence suggests that inflammation responses play an important role in pathophysiology of several major psychiatric disorders, including MDD (Su KP et al. Biol Psychiatry 2010; Lu DY et al. Int J Neuropsychopharm 2013). Furthermore, the anti-inflammatory pathway has become a hot topic in looking for new antidepressant therapies (Lu DY et al. Neuropsychopharm 2010; Lu DY et al. Int J Neuropsychopharm 2013). Anti-inflammatory omega-3 PUFAs prove beneficial in depression and several inflammation-related physical diseases, which imply a “mind-body interface” connection (Su KP. NeuroSignals 2009). Omega-3 PUFAs may particularly benefit children, pregnant women, and/or patients with comorbid cardiovascular or metabolic disorder, who face greater risks of adverse effects from antidepressants, antipsychotics, and mood stabilizers. Cost of omega-3 PUFAs is relatively modest as compared to many psychiatric treatments and other over-the-counter natural products. Given the potential benefits and safety, omega-3 PUFAs deserve greater attention and wider application.
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