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2015 PSYCHOPHARMACOLOGY AWARDS - ABSTRACTS (PW1–PW4)
S01

IS MEPHEDRONE MORE HARMFUL THAN ECSTASY? A PRECLINICAL COMPARISON

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Although mephedrone has been implicated in a number of deaths and became illegal in Europe and the USA between 2010 and 2012, it remains available and popular for illicit use (Elliott and Evans, 2014 Forensic Sci Int 243:55-60). It has been marketed as a stimulant, euphoriant and aphrodisiac. Mephedrone is a structural analogue of the synthetic cathinone MDA, which is illegal in most countries. Despite concerns, it has been legal in the UK since 2010. It is available as a powder, pill, liquid or spray, and is often used in combination with other substances (e.g., alcohol, caffeine). Mephedrone is metabolised in the liver, primarily to 3-methylephedrine and 4-methylephedrine, which have similar pharmacological actions.

In this study, we investigated mephedrone-induced changes in behaviour, body temperature and neurochemistry in the rat and compared them to those observed following MDMA administration, by assessing changes in body temperature and locomotor activity following acute, chronic intermittent or rapid repeat administration of mephedrone, and following co-administration of caffeine. Additionally, in vivo monoamine efflux and post-mortem tissue monoamine levels in the brain were measured. Studies were designed in accordance with ARRIVE guidelines. Similar to MDMA, we found that acute administration of mephedrone induced hypothermia (p<0.001, repeated measures ANOVA) and hyperactivity (p<0.001, repeated measures ANOVA), as well as striatal dopamine efflux (p<0.001, repeated measures ANOVA) in individually housed rats at ambient room temperature. This mephedrone-induced hypothermia was affected by α1-adrenoceptor, D1 dopamine and 5-HT1A receptor antagonism, and unaffected by group housing, while the observed hyperactivity was attenuated by 5-HT1A and 5-HT1B receptor antagonism (Alves Mondini et al., this meeting). Importantly, caffeine co-administration produced a biphasic temperature response (where an initial hypothermia was converted to hyperthermia, p<0.001), while prolonging the hyperactive profile (p<0.05) and reducing anxiety-related behaviours (p<0.05) in the elevated plus maze. Unlike MDMA, rapid repeated mephedrone administration (3x10mg/kg at 2h intervals) had no cumulative effect on hypothermia, hyperactivity or striatal dopamine efflux. In conclusion, at the doses administered in the current studies, mephedrone did not cause neurotoxicity or hyperthermia in the rat; therefore the preclinical adverse effects of mephedrone appear to be less harmful than those of MDMA.

However, adverse cardiovascular effects in the rat have been observed by others (Green et al., 2014 Br J Pharmacol 171:2251-2268) and caution is required in attempting to translate the relevance of these findings to human users. Funding: University of Nottingham.

S02

LEGAL HIGHS: A RAT’S PERSPECTIVE

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Recent years have seen the rapid emergence of new psychoactive substances (NPS) with consumers perceiving the use of “legal highs” as safe alternatives to recreational drugs such as ecstasy (3,4-methylenedioxyamphetamine or MDMA). The precise pharmacological actions of NPS are not fully understood because many have not been studied at the pre-clinical level. For those that have been investigated, we know the neurochemistry of NPS can differ somewhat to that of MDMA. There is a diversity of compounds being sold as NPS including piperazines, synthetic cathinones, tryptamines and various phenylethylamine analogues. The technique of brain microdialysis in conscious freely moving rats allows us to compare neurochemical effects of NPS with those of MDMA. One of the first NPS to be studied was 1-benzylpiperazine (BZP) as it has been widely used to substitute for MDMA. We now have evidence from our own studies that like MDMA, BZP (10mg/kg, i.p.) elevates extracellular levels of serotonin, dopamine and noradrenaline in rat frontal cortex. Because BZP is a common contaminant of ecstasy pills; we have also investigated the co-administration of BZP and MDMA on extracellular monoamine levels in rat frontal cortex. MDMA alone (1mg/kg, i.p.) elevated extracellular levels of serotonin and to some extent extracellular levels of dopamine and noradrenaline. BZP alone (3mg/kg, i.p.) did not elevate extracellular serotonin relative to vehicle-treated animals. When BZP (3mg/kg, i.p.) was co-administered with MDMA (1mg/kg, i.p.) there was a further elevation of extracellular levels of these monoamines suggesting synergism for the two drugs. Another legal high known as “Benzo fury” (6-(2-aminopropyl)benzofuran or 6-APB) has to date been reported as one of the most successful substitutes for MDMA and was until recently widely available over the internet. Our brain microdialysis studies in rats have compared the neurochemical effects of 6-APB with those of MDMA. Both 6-APB (1mg/kg) and MDMA (3mg/kg) potently...
NEURAL CORRELATES OF THE LSD STATE

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Introduction: Lysergic acid diethylamide (LSD) is one of the most potent psychoactive drugs known. It profoundly alters consciousness in doses as low as 20µg and thus is a powerful tool for studying its neurobiology. LSD has a history of use as an adjunct to psychotherapy and modern studies are beginning to revisit its therapeutic potential. The effects of LSD on human brain function have never been studied before using modern functional neuroimaging. Methods: Fifteen healthy volunteers participated in a within-subjects, balanced order, placebo controlled fMRI study (4 females, mean age = 30 ± 8). Participants underwent 14 minutes of eyes-closed RS BOLD scanning 100 minutes after intravenous infusion of 75µg LSD and separately, saline (placebo). Scans were separately by at least 14 days. 1) Spatial ICA was applied to a separate RS fMRI dataset in order to yield a set of functionally familiar RS networks (RSNs). Thirteen canonical RSNs were identified that were then used in a subsequent dual regression analysis performed on the RS data acquired in the present study. 2) Seed based FC was performed using a bilateral hippocampal/parahippocampal cortex (PHC) mask. It was predicted that decreased within-RSN RSFC and decreased RSFC between the PHC and default mode network (DMN) would be observed under LSD and that these effects would correlate with the drug's subjective effects. All statistical maps were generated using whole-brain cluster-correction (Z = 2.3, p < 0.05). Results: Significant decreases in within-network FC under LSD was observed in 7 of the 13 RSNs, these effects would correlate with the drug's subjective effects. All statistical maps were generated using whole-brain cluster-correction (Z = 2.3, p < 0.05). Results: Significant decreases in within-network FC under LSD was observed in 7 of the 13 RSNs, namely the DMN, three visual networks, a retrosplenial cortex network, right frontoparietal network and a sensorimotor
network. Decreased DMN RSFC correlated positively with ratings of ego-disintegration ($R^2 = 0.28$, $p = 0.04$). Significant decreases in RSFC were observed between the PHC and the PCC. The magnitude of these decreases correlated with the intensity of LSD’s subjective effects ($R^2 = 0.51$, $p = 0.003$) and ratings of ego-disintegration ($R^2 = 0.31$, $p = 0.01$). Conclusion: Consistent with prior hypotheses, the present results implicate decreased DMN RSFC and DMN-PHC RSFC in the altered state of consciousness produced by LSD. Moreover, they suggest that these effects are related to ‘ego-disintegration’. The DMN is a high-level brain network that appears to be involved in the regulation of consciousness. Functional brain imaging work with LSD may help to advance our understanding of the neural correlates of the self or ego and the neurobiology of consciousness more generally.

**S05**

**IMAGING NEUROTRANSMITTER SYSTEMS IN BIPOLAR DISORDER**

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Bipolar disorder is an important mental health disorder which is a significant cause of socioeconomic adversity, cognitive impairment and suicide. Despite its importance, relatively little is known about the involvement of neurotransmitter systems in bipolar disorder, particularly when compared to related conditions such as schizophrenia. In this presentation I will provide an overview of findings from human neurochemical imaging studies of bipolar disorder and draw on parallel findings in disorders which are often co-morbid such as addictions and anxiety disorders. The main focus of the presentation will be on the dopamine neurotransmitter system including studies on presynaptic dopamine function, dopamine release and dopamine transporter function in bipolar disorder. I will compare and contrast findings from these studies to those in schizophrenia and discuss the implications of these for the treatment of bipolar disorder. I will also review GABA imaging in addiction and anxiety disorders and discuss the impacts of these studies for understanding the role of the GABA system in bipolar disorder. Finally, I will highlight the critical next steps needed in neurochemical imaging in bipolar disorder and discuss the challenges in imaging this patient group.

**S06**

**SUBSTANCE USE CO-MORBIDITY IN BIPOLAR DISORDER: IS DOPAMINE A FINAL COMMON PATHWAY?**

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Comorbid alcohol and drug disorders negatively impact on the course and treatment outcome of bipolar disorder (BPD). Alcohol is the most common drug used and up to 45% of those with BPD also have an alcohol use disorder. In particular mania is associated with alcohol use disorder, as are earlier onset of BPD, greater impulsivity, violence, suicidality and labile mood. There is evidence that patients with BPD are more sensitive to the effects of substances and therefore use lower quantities than may be seen in individuals with substance use disorder alone. Rather than conceptualizing one disorder as primary or secondary to the other, there is evidence of shared common vulnerabilities such as stress early life events. Many patients with BPD report using substances, such as alcohol, to reduce anxiety. Due to their comorbid substance misuse diagnosis of BPD may be delayed which incurs further complications. Despite the fact that comorbid substance misuse is the norm in BPD, there is limited information and guidance about treatment approaches or how the two disorders may alter treatment of each other though response to mood stabilisers is reduced. With regard to substance use and misuse, the role of dopamine is commonly thought of in terms of the mesolimbic system and its role in reward and motivation. However the involvement of dopamine in mediating the effects of substances varies with non-dopaminergic systems present for some drugs eg alcohol and opioids. Dopamine also plays a key role in other processes involved in substance use disorders and BPD such as impulsivity and stress. The efficacy of antipsychotics as dopamine supports dopamine dysregulation in BPD. However other effective pharmacotherapies eg ‘anticonvulsants’ do not directly target dopaminergic systems, but rather modulate GABA, glutamate and ion channels. Similarly in treating addiction, medication directly targeting the dopamine system generally show limited efficacy and none are in routine clinical use. By contrast medication targeting the opioid and GABA systems are effective and are more widely used and others including ‘anticonvulsants’ used to treat BPD are being investigated in addiction. The dopaminergic mesolimbic system is modulated by other neurotransmitter systems such as opioid, GABA, glutamate but less is known about dopamine modulating their activity. Characterizing the relationships between these neurotransmitter systems, their role in processes involved in addiction and BPD such as reward, impulsivity and stress will inform our understanding of such comorbidity and development of future treatments.
**S07**

**TARGETING THE HPA AXIS IN THE TREATMENT OF BIPOLAR: A FOCUS ON NEUROPSYCHOLOGICAL FUNCTIONING**

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In this presentation I will consider the nature of HPA axis dysregulation in bipolar disorder with emphasis on mineralocorticoid and glucocorticoid receptor function. I will consider the insight afforded by measurement of neuropsychological performance and I will present the current evidence of the efficacy of HPA axis agents on mood and neuropsychological performance. Finally I will look at future relevant therapeutic directions.

**S08**

**TAILORING PRESCRIBING CHOICES TO PREVENT DEPRESSIVE AND MANIC RELAPSE**

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This is a time of rapid advances in our understanding of bipolar disorder. The available evidence base of clinical data from high quality randomised controlled trials has expanded even in the last few years both for novel agents, and also well-established agents such as lithium, particularly thanks to their use as active comparators. It has been recognised for some time that treatments to prevent relapse differ in their relative efficacy against depressive and manic relapse. BAP guidelines have highlighted the importance of considering this in making individual treatment choices. The last few years have seen new multiple treatments meta-analyses that clarify the nature and extent of these differences and hold the promise of a more rational basis for decision-making about individualised treatment choices.

**S09**

**FROM GENES TO BRAINS AND BACK AGAIN. TRANSLATIONAL APPROACHES TO LINKING GENES TO HUMAN BEHAVIOUR IN DRUG ADDICTION**

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Drug addiction is a psychiatric disorder with a high inheritance rate, but still insufficient treatment options in the clinic. Understanding the functional genetic base is assumed to significantly improve the prevention of addiction and the design of individual treatment strategies in patients. For this purpose, identification of actual risk genes and mutations is required as much as an understanding of how a genetic risk translates to altered brain function and behaviour. Translational approaches start with, either the search for associations of genetic variants with particular consumption- and/or addiction phenotypes and the subsequent attempt to translate the findings to functional approaches in animal models with targeted alterations of specific genes. This approach has recently demonstrated a role of the gene coding for the ras-specific guanine-nucleotide releasing factor 2 (Rasgrf2) which is mediated by changing signalling patterns in monoaminergic neurons and mesolimbic brain activation during reward processing. Reversed approaches which frequently take up information on a specific gene function from other research lines characterize the role of a gene in drug addiction associated behaviours and brain function in much reduced animal models and then allow for a much focused translation into human populations. By this way, a specific role of the gene coding for alpha-Ca2+/calmodulin-dependent kinase II (αCaMKII) was shown in rodents and later translated into human addicts. αCaMKII is crucial for learning and memory, but can via its influence on emotional behaviour, brain morphology, and dopaminergic and serotonergic system’s activity control the establishment of drug rewarding effects and the initiation of consumption. For this specific role a human analogue function could be shown. Although translational approaches still need to increase their resolution for single addiction-related behaviours and drugs, growing insights may eventually allow for a translation into individualized prevention and treatment in the clinic.

**S10**

**MOVING FROM RISK GENES TO TREATMENTS FOR PSYCHIATRIC DISORDERS: PRACTICALITIES, PITFALLS AND PROMISE**

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Recent genome-wide association studies have identified risk factors that are robustly associated with psychiatric disorders. However, moving from the knowledge that ‘Variant X is associated with Disorder Y’, to an understanding of the underlying causative mechanisms, and, ultimately, to novel, rational treatments, is a mammoth task. This situation is further complicated by the fact that the majority of risk variants identified to date are non-coding, and many are located in (or near) genes whose function in the brain is obscure. Tackling this problem is arguably the greatest research challenge that our field has faced thus far. This presentation will explore potential strategies to address this challenge. It will provide ideas for how
we might investigate the impact of identified risk variants on the function of the whole brain and, ultimately, how we might understand their clinical impact and develop rational treatments. I will argue that a collaborative and truly multidisciplinary approach is essential to understand these links. As well as drawing from findings from the wider field, I will illustrate this argument using examples from my own research. First, I will show how translating, and back-translating, between animal models and studies in human volunteers, can provide understanding of the mechanisms by which genes of interest can be linked with whole brain function, as well as generating novel hypotheses. I will then outline how human neuroimaging can provide clues to the neurobiological effects of genes whose function is unknown in the brain. Finally, I will consider some of the pitfalls that may occur when attempting to translate genetic associations into therapeutic approaches. EMT is funded by a Royal Society University Research Fellowship

S11
MECHANISMS OF SYSTEMIC INFLAMMATION-INDUCED CHANGES IN COGNITIVE FUNCTION: AT THE INTERFACE OF DELIRIUM AND DEMENTIA

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Introduction. Systemic inflammation can induce cognitive dysfunction with relevance to a wide range of brain disorders in which inflammatory activation is a feature, including depression, dementia, delirium and psychosis. However, systemic inflammation may have different effects on cognitive function depending on the prior inflammatory or degenerative status of the brain. Methods/Results. In this talk I will demonstrate how bacterial endotoxin (LPS; 100µg/kg) robustly impairs contextual fear conditioning (CFC) in naive C57BL6 mice but has no effect on working memory tasks. However, various prior pathological signatories leave mice selectively vulnerable to LPS-induced working memory deficits including basal forebrain acetylcholinergic degeneration, hippocampal and thalamic synaptic loss in the ME7 model of prion disease and amyloidosis in the APP/PS1 model of Alzheimer's disease. Systemic administration of IL-1 receptor antagonist was partially protective against LPS-induced T-maze deficits but did not block impairments in CFC. LPS still produced working memory deficits in IL-1RI-/− mice, but both IL-1β and TNF-α mimicked LPS-induced deficits and dexamethasone, which blocks production of both cytokines, protected against the deficits. ME7-associated degeneration also left the brain susceptible to produce exaggerated IL-1β responses to either LPS or IL-1β and systemic LPS also increased apoptosis in the brain, which was partly IL-1RI-/− dependent and direct application of IL-1β to in vitro hippocampal sections induced non-synaptic depolarisation, leading to irreversible loss of membrane potential in CA1 neurons from diseased animals. Conclusions. Collectively the data show that systemic inflammation induces multiple dissociable mechanisms of cognitive dysfunction and that acute changes in cognitive function are dissociable from the neuronal injury that likely leads to long-term cognitive impairment. Human correlates of these data and implications for delirium and dementia will be discussed. Funding: This work was supported by the Wellcome Trust

S12
ANIMAL MODELS OF PSYCHIATRIC DISEASE: A FOCUS ON ANXIETY

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Introduction. Serotonin is thought to be critical for regulating emotion and the serotonin transporter (SERT or 5-HTT) plays a key role in controlling serotonergic neurotransmission. Gene association studies detect an influence of natural variation in the 5-HTT gene on multiple aspects of individuality in brain function, ranging from personality traits through to susceptibility to psychiatric disorders such as anxiety and depression. The neural substrates of these associations are unknown. Human neuroimaging studies suggest modulation of the amygdala by 5-HTT variation, but this hypothesis is controversial and unresolved, and difficult to investigate further in humans. Methods: Here I will talk about genetic mouse models, in which the 5-HTT is either knocked-out (5-HTTKO mice) or over-expressed (5-HTTOE mice), that we have used to investigate the behavioural and neurobiological consequences of manipulating 5-HTT expression. In these mice we recorded hemodynamic responses (using a novel in vivo tissue oxygen amperometric approach, analogous to BOLD-fMRI) and local field potentials from the amygdala during aversive learning tasks. Results: Compared to wild-type mice, 5-HTTKO mice exhibit superior learning in a task where they have to discriminate between two auditory cues, only one of which is paired with an aversive outcome (footshock). In contrast, 5-HTTOE mice show impaired learning, especially for ambiguous aversive cues that only sometimes predict shock. Moreover, amygdala hemodynamic responses and theta-
frequency neuronal oscillations are augmented in 5-HTTKO and diminished in 5-HTTOE mice. I will also present recent data investigating the cellular mechanisms through which serotonin influences amygdala processing. Conclusions: Our data support the contention that variation in 5-HTT expression affects emotional behaviour and amygdala function and highlights the translational potential of tissue oxygen amperometry to investigate brain function in behaving rodents in a manner analogous to human BOLD fMRI. This work was supported by the Wellcome Trust (Grant No. 087736).

S13
GLUTAMATERGIC THERAPIES FOR SCHIZOPHRENIA: A NEURODEVELOPMENTAL PERSPECTIVE
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Glutamate synaptic dysfunction has emerged as a central feature of the neuropathology of schizophrenia, consistent with the emerging association of genes coding for glutamate synaptic proteins in the heritable risk for this disorder and the long-established similarities between the acute and chronic effects of NMDA glutamate receptor antagonists and the signs and symptoms of schizophrenia. This presentation will build on recent neuroimaging studies from our group and others that describe similarities in the effects of NMDA glutamate receptor antagonists and network dysfunction in patients. It will present a developmental hypothesis suggesting that glutamate synaptic abnormalities are compensated for early in life by synaptic proliferation and network disinhibition resulting from failure of GABA neurons to normally develop. It will suggest that this allostatic GABAergic adaptations undermines cognitive function and triggers synaptic downregulation, which augments the impact of the normal process of synaptic elimination during adolescence. It will then suggest that these developmental phases in schizophrenia may have implications glutamatergic pharmacotherapies targeting the facilitation of NMDA receptor function or restoring the cortical balance between excitation and inhibition.

S14
PREDICTIVE VALIDITY OF ANIMAL MODELS FOR SCHIZOPHRENIA: CHALLENGES AND OPPORTUNITIES
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Drug discovery for schizophrenia relies upon validation in preclinical models. Previously, many of these models have by necessity been rather blunt instruments since our understanding of the aetiology and neurobiology of schizophrenia has been limited. Furthermore, the end point behavioural assessments made in these models have often had questionable validity to human symptom domains. Arguably this combination of factors has hindered the development of much needed new therapies for the cognitive deficits and negative symptoms of schizophrenia that are inadequately treated by current drugs. Glutamatergic dysfunction focussed upon NMDA receptor signalling is widely recognised as having a substantial role in the pathophysiology of schizophrenia. This has led to phencyclidine and ketamine based rodent models being extensively used in drug discovery. Repeated NMDA receptor antagonist models appear to have the most construct validity since they show imaging, neurochemical and cognitive flexibility deficits that parallel those in schizophrenia. However, the results of recent clinical trials with glutamatergic compounds that target metabotropic glutamate receptor 2/3 subtype and glycine transporter 1 have been disappointing. In part this may be due to an over reliance on preclinical tests of limited translational capacity but also patient selection. With increasing knowledge of the genetic basis of schizophrenia, there exists the opportunity to understand the neurobiology of gene products in relation to their impact upon neurotransmitter systems, brain networks and pathophysiology. Importantly many schizophrenia risk genes show involvement in glutamate synapse function, suggesting convergence of these genetic risk factors upon known pathophysiology. Genetic mouse models therefore offer potential for drug discovery. Recent advances in functional brain imaging analytical techniques and cognitive tests that translate between humans and rodents have provided optimism not only for a deeper understanding of schizophrenia but also for drug discovery. We have demonstrated that modafinil, a pro-cognitive agent restored sub chronic PCP-induced set shifting deficits and improved functional connectivity, suggesting that this approach offers utility for drug discovery (Dawson et al 2012, Schizophr. Bull 38:457-474). Furthermore, subchronic PCP –induced alterations in hippocampal-prefrontal connectivity and thalamo-cortical connectivity overlaps with imaging signatures in some genetic mouse models, again suggesting convergence (Dawson et al 2015, J. Psychopharm. 29, 169-177). In conclusion, functional brain connectivity phenotypes coupled with translational tasks recruiting cognitive neural circuitry offer a way forward to discover new treatments for schizophrenia, including glutamatergic strategies. Such construct -led approaches could ultimately led to improved predictive validity and reduce the current high attrition rate in drug discovery.
S15
GLUTAMATE IMAGING IN SCHIZOPHRENIA – A STEP TOWARDS STRATIFIED MEDICINE?
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There has been considerable interest in a possible role for glutamate in the aetiopathology of schizophrenia. The development of human brain imaging techniques has allowed the direct study of this hypothesis in living humans. Studies of patients with at risk mental state and first episode psychosis have generally found increased brain glutamine levels in the medial prefrontal cortex (suggested to represent increased glutamatergic neurotransmission). In contrast, in patients with chronic schizophrenia, reduced levels of glutamine and glutamate have been reported. These reductions may represent loss of neuronal density or synaptic connectivity as they closely resemble reductions in N-acetyl aspartate (a marker of neuronal integrity), and in grey matter volume that are found in patients with chronic schizophrenia. There has recently been interest in the possibility that measures of brain glutamate might be used to stratify subtypes of patients with schizophrenia – with more evident glutamatergic abnormalities being associated with particular symptom clusters or with resistance to antipsychotic treatment. In this presentation, I will summarise the results from completed and ongoing studies of brain glutamate in good and poor responders to antipsychotic drugs, and will consider whether brain imaging might be useful as a tool in the future to identify patients who would benefit from non-dopaminergic antipsychotic drugs.

S16
THE KYNURENINE PATHWAY, GLUTAMATE RECEPTORS, STRESS AND SCHIZOPHRENIA
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The kynurenine pathway is the most important route for the metabolism of tryptophan, accounting for the oxidation of around 95% of non-protein tryptophan. After being regarded solely as the synthetic route for nicotinamide and thus the essential enzyme co-factor NAD, it was discovered that the pathway includes a selective agonist at NMDA receptors (quinolinic acid; Stone and Perkins, 1981, Europ. J. Pharmacol. 72, 411-412) as well as an antagonist (kynurenic acid; Perkins and Stone, 1982, Brain Res. 247, 184-187). The latter compound blocks all ionotropic glutamate receptors [2] but is most potent blocking the glycine co-agonist site of the NMDA receptor. If reduced glutamate receptor sensitivity is critical to the emergence of schizophrenia and related disorders, abnormal activity along the kynurenine pathway could be involved. This concept is supported by reports that kynurenic acid concentrations are elevated in the brains and CSF of patients with schizophrenia. SNPs have been detected in the KMO gene which would explain this increase. Experimentally, interfering with the pathway by pharmacological inhibition, transgenic deletion or kynurenine loading produces functional and behavioural changes in animals consistent with aspects of schizophrenia in humans. Manipulating the pathway in pregnant rats leads to similar changes in the offspring in the early postnatal period and adulthood, presumably because of interference with the important roles for NMDAR in early neuronal formation, axon guidance, contact formation and synaptogenesis. There are other reasons to believe the pathway is important in schizophrenia, including its activation by corticosteroids associated with stress, which activate tryptophan-2,3-dioxygenase in the liver. The ratio of kynurenic acid to quinolinic acid or other glutamate receptor agonists also determines the extent of brain damage or protection against a variety of insults, including damage induced by cerebral inflammation. The kynurenine pathway therefore provides a means of accounting for many aspects of the development of schizophrenia. This work was supported by the BBSRC, Epsom Medical Research and the Haddon Family Trust.

S17
CURRENT AND FUTURE INSOMNIA MEDICATIONS: TOWARDS PERSONALIZED THERAPY
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Insomnia medications with high pharmacologic specificity are becoming increasingly available. Such agents pave the way for a new paradigm for insomnia therapy where specific interventions are selected to target a specific type of sleep difficulty for each patient. This personalized approach promises an improved risk/benefit ratio over pharmacologically non-specific agents which have global effects and impact many areas of the brain other than those needed to address a patient’s particular sleep problem. Personalizing therapy in this way requires identifying key subtypes of insomnia patients who will optimally benefit from each of the targeted therapies. Although this is only possible to a limited degree, ongoing research and newly emerging medications make this approach increasingly possible. In this talk we review the existing and emerging insomnia treatments in this forward-looking context, discussing the available evidence base for personalizing therapy.
REM BEHAVIOUR DISORDER – WHAT’S GOING ON AND HOW DO WE TREAT IT?
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REM Sleep Behaviour Disorder (RBD) is a relatively recently discovered parasomnia. Normal REM sleep is characterised by atonia and paralysis of the skeletal muscles. This is a protective mechanism that prevents us from acting out our dreams. In RBD this mechanism fails, the muscles retain their tone, and the patient enacts their dream in the bed. These events are frequently violent in nature and can lead to significant injury to the patient or their bed partner. RBD can be precipitated by other sleep disorders, a number of psychiatric medications and is a common symptom in Parkinson’s Disease and Lewy Body Dementia. Indeed, it can be the first symptom of these illnesses and can precede them by many years. However, the precise pathophysiology and neuroanatomical basis of RBD is still debated. The treatment of RBD involves behavioural interventions, managing exacerbating factors, and pharmacological treatments such as melatonin and clonazepam.

NO ABSTRACT PROVIDED FOR THIS PRESENTATION

EFFECTS OF MODERN PSYCHOTROPIC DRUGS ON SLEEP
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Sleep and waking processes are controlled and influenced by a wide range of neurotransmitters and brain receptors and therefore any drug which affects those neurotransmitters or receptors will potentially change sleep. Prescribed drugs which are given to promote sleep or to increase daytime wakefulness will alter sleep in specific ways according to their target and mode of action. Drugs for depression are ingested by a large proportion of the population, and so their sleep effects need to be taken into account. Agents used in psychosis, bipolar disorder and ADHD often change both subjective sleep and objective measures of sleep structure. Non-prescribed substances such as alcohol, caffeine and illicit drugs can also alter the sleep-wake pattern and it is important to be aware of these effects. This talk will give an overview of the main effects on sleep and sleepiness of commonly encountered modern psychotropic drugs.

NICOTINE LEVELS AND SELECTED CARCINOGENS AND TOXICANTS IN E-CIGARETTE LIQUID AND VAPOUR
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Introduction: Electronic cigarettes, also known as e-cigarettes, are devices designed to imitate regular cigarettes and deliver nicotine via inhalation without combusting tobacco. Because e-cigarettes do not burn tobacco, they do not produce the numerous chemicals found in conventional tobacco smoke, and hence they have been proposed as potential products for tobacco harm reduction. They are purported to be a safer alternative to regular cigarettes. E-cigarettes differ primarily in appearance, the nature and concentration of the nicotine solution, the capacity of the cartridge or reservoir (so-called “tank”) containing the solution, the nature of the heating element, and the size and type of battery. Methods: This presentation will review results of analytical testing of e-cigarettes to detect their chemical components and to investigate the presence of nicotine and toxicants that can potentially occur as impurities of ingredients or as a consequence of their degradation. Results: Nicotine solutions used in e-cigarettes vary with respect to concentrations of the drug and toxicants, and the quality control in e-cigarette manufacturing is questionable (Goniewicz et al., 2013, Nicotine Tobacco Res, 15:158–66). There are relatively few research reports regarding nicotine delivery from e-cigarettes; most of the research is based upon first generation devices. Initially, these products were shown to deliver relatively low doses of nicotine compared to tobacco cigarettes, but current devices, which use concentrated nicotine solutions, may deliver nicotine to blood at levels comparable to those derived from tobacco cigarettes (Farsalinos et al., 2014, Sci Rep, 4:4133). Propylene glycol and glycerin are the primary solvents for the nicotine. Various additives and flavorings are commonly added to the solution, including fruit and candy flavors. Although a number of toxicants have been identified in e-cigarette vapour, the levels of these toxicants are orders of magnitude lower than those found in cigarette smoke, but higher than those found in Nicotine Replacement Therapy (NRT) products (Goniewicz et al., 2014, Tob Control, 23:133–9). Conclusions: Although it cannot be said that currently marketed e-cigarettes are safe, e-cigarette vapour is likely to be much less toxic than cigarette smoke. They likely pose less direct hazard to the individual smoker than tobacco cigarettes and might help smokers quit smoking.
or reduce harm by smoking fewer tobacco cigarettes. The use of e-cigarettes as a harm reduction strategy among cigarette smokers who are unable to quit, warrants further study.

S22
COMPARING THE ADDICTIVENESS OF TOBACCO CIGARETTES VS. ELECTRONIC CIGARETTES
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Introduction: Electronic cigarettes (e-cigarettes) are a classic tobacco harm reduction tool, designed to deliver nicotine in the absence of the harmful combustible products associated with tobacco smoking. Switching completely to e-cigarettes offers considerable health benefits for the tobacco smoker although concerns have been expressed over their addictive potential. Whether it is optimal or even acceptable for users to transfer their nicotine addiction to a new form which might act as a deterrent for complete nicotine abstention is a frequently voiced concern. Methods: This talk will review the current evidence on the addictive potential of e-cigarettes compared with tobacco cigarettes and discuss methodological and conceptual difficulties associated with measuring addiction, and issues surrounding high addictive potential. Addiction ‘measurement’ can take many forms including pharmacokinetic and pharmacodynamic analysis, subjective reports and behavioural testing. Rapid delivery to the brain, use soon after waking, strong craving to use, going to great lengths to obtain the drug and difficulties quitting are all associated with addiction. Studies exploring these phenomena in relation to smoking and e-cigarette use (vaping) will be described and evaluated. Results: Notwithstanding the difficulties in measuring addiction, the current (limited) evidence suggests that e-cigarettes are less addictive than tobacco cigarettes. Conclusions: Evolving battery and atomiser technology continues to produce increasingly sophisticated devices allowing more rapid nicotine delivery thus addictive potential is likely to increase. Potential advantages of this are superior craving suppression and higher smoking cessation rates; potential disadvantages are more people using nicotine. Funds to UEL from Skycig and Totally Wicked to support the research conducted by Lynne Dawkins are gratefully acknowledged.

S23
ELECTRONIC CIGARETTES FOR SMOKING CESSATION AND HARM REDUCTION
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The growth in popularity of electronic cigarettes has led to considerable interest in their potential use to support smoking cessation attempts, or to promote harm reduction. The rationale is that electronic cigarettes provide nicotine, potentially relatively rapidly and at doses close to those achieved by cigarette smoking, but without the vast majority of the harmful constituents of tobacco smoke. This talk will describe evidence from recent survey studies (e.g., the Smoking Toolkit Study) which provide data on the numbers of smokers using electronic cigarettes to support a smoking cessation attempt, and evidence for the efficacy of electronic cigarettes for smoking cessation from randomized controlled trials, including a recent Cochrane Collaboration systematic review and meta-analysis. Evidence that electronic cigarettes might be a viable harm reduction method among smokers unwilling to quit will also be discussed. Electronic cigarettes represent an exciting public health opportunity if they can be show to be effective in promoting smoking cessation and/or reducing harm. This evidence will be discussed in the context of concerns that have been raised relating to gaps in the current evidence base, and the potential for unintended harms and consequences, such as dual use of cigarettes and electronic cigarettes. Funding: The author is a member of the UK Centre for Tobacco Control Studies, a UKCRC Public Health Research: Centre of Excellence. Funding from British Heart Foundation, Cancer Research UK, Economic and Social Research Council, Medical Research Council, and the National Institute for Health Research, under the auspices of the UK Clinical Research Collaboration, is gratefully acknowledged.

S24
ACCEPTABILITY, PATTERNS OF USE AND SAFETY OF ELECTRONIC CIGARETTE IN PEOPLE WITH MENTAL ILLNESS
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The life expectancy of people suffering from serious mental illness is up to 25 years shorter than the general population. Disproportionately high smoking rates are a major contributor to this health inequality but traditional smoking cessation interventions have generally lack effectiveness. An electronic nicotine delivery system (e-cigarettes) was evaluated as a potential method of harm reduction/smoking cessation. Firstly, a sample of 137 service users and staff from South London and Maudsley...
Foundation Trust were interviewed to assess their awareness, use and perceptions of e-cigarettes. As expected, a high proportion of service users reported daily smoking (61%) and a history of cessation attempts. Most responders were aware of e-cigarettes (93%). Sixty percent of current smokers had tried e-cigarettes with 20% using e-cigarettes in the previous 30 days. On average, participants moderately agreed that e-cigarettes were less harmful substitutes for cigarettes that would be suitable for use in mental healthcare settings. We are currently conducting a pilot clinical trial in 50 smokers with schizophrenia or bipolar disorder who are not intending to quit smoking in the near future to undergo a 6-week period in which they are provided with free e-cigarettes and we observe their e-cigarette and tobacco cigarette use, a 4-week period in which they do not receive free e-cigs and we monitor which products participants choose in the marketplace, and a 24-week follow-up visit at which smoking behaviour is assessed. In weekly study visits, we evaluate e-cigarette and tobacco cigarette use, side effects, psychiatric symptoms, respiratory symptoms, as well as e-cigarette acceptability, reinforcement, and perceived benefits and risks. Preliminary data of this pilot study will be presented. Project funded by the Maudsley Charity.

THE COST AND IMPACT OF COMPULSIVITY

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Representing the tendency to perform repetitive, unwanted, inflexible or damaging acts, ‘compulsivity’ is increasingly recognized as a contributory factor in the loss of personal control over a broad range of human behaviours prone to excess e.g. eating, gambling and checking. Associated with widespread adverse health and social consequences, compulsivity underpins a variety of chronic, costly, and functionally disabling diseases. These include addictive disorders such as substance addiction and gambling disorder, eating disorders, and obsessive compulsive disorder (OCD). These distressing lifespan disorders typically have an early age of onset, run a prolonged course, affect all population groups, regardless of gender and culture, and are associated with reduced quality of life, the development of marked psychiatric and somatic co-morbidity including high rates of depression and suicidality, as well as substantial impairment of social and occupational functioning. The global burden of disease associated with mental and addictive disorders represents a striking and growing challenge for health systems. Anxiety disorder (including OCD), addiction and mood disorder rank in the top five most costly brain disorders in the UK, recently estimated as costing (in £ million), respectively, £11,687, £11,719 and £19,238 per annum. Approximately half these costs are the indirect cost of untreated illness on the UK economy and only approximately 25% was linked to direct healthcare. Yet development of new therapies for mental disorder is slowing due to lack of clinical validation. Diagnostic systems, such as ICD-10, DSM-5, define disorders according to symptoms and syndromes, rather than neurobiological substrates. Biological heterogeneity within the diagnostic groups hampers the identification of underpinning mechanisms and remediative strategies. The EU Roadmap for Mental Health Research in Europe (ROAMER) and U.S. National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiatives call for the development, for research purposes, of new ways of classifying psychopathology based on dimensions of observable behaviour with established biological validity, irrespective of diagnosis. Trans-diagnostic approaches that cross conventional diagnostic boundaries may be of particular value for the identification of the pathophysiological mechanisms underpinning the development of human compulsivity, as a new neuropsychiatric domain, to support innovation in developing evidence-based treatments for compulsive disorders. A better understanding of the costs of compulsivity is required to transform the research agenda in this direction. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

MODELLING COMPULSIVITY, FROM ANIMALS TO HUMAN ENDOPHENOTYPES

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According to dual-system theories, behavioural repetition can lead to a shift from goal-directed action towards inflexible stimulus-response habits. In recent years, there has been growing interest in the possibility that this dual-system shift paves the way for the development of compulsive behaviours that persist despite the agent’s awareness of their negative consequences, as for example in drug abuse, obsessive-compulsive disorder, and obesity. Direct investigation of the causal
Introduction: Compulsivity is a multi-faceted term in psychiatry, referring to symptoms or behaviours that are repetitive, difficult to suppress, and undertaken in a stereotyped or habitual manner. Disorders of compulsivity are common and functionally impairing, but are often overlooked by clinicians. Examples include obsessive-compulsive disorder (OCD - the "archetype"), gambling disorder, and other less well-studied but fascinating examples such as hair-pulling disorder (trichotillomania), skin-picking disorder, kleptomania (compulsive stealing), compulsive sexual behaviour, and pyromania (compulsive fire-setting). Methods: Review of evidence-based treatments for the above compulsive disorders in adults, with an emphasis on data from double-blind placebo-controlled pharmacological trials. To include consideration of underlying brain mechanisms and neurochemical modulation of cognition. Results: Evidence to date indicates that selective serotonin reuptake inhibitors (SSRIs) are an effective first-line treatment for OCD, with some evidence to support their use in pathological skin picking and compulsive sexual behaviour. Opioid antagonists (e.g. naltrexone) show promise in gambling disorder, kleptomania, and (to a lesser degree) trichotillomania. Glutamatergic agents, especially N-acetyl cysteine (NAC), show promise
for gambling disorder and trichotillomania. The atypical neuroleptic olanzapine appears ineffective for gambling disorder, but promising for trichotillomania. Conclusions: Despite their prevalence, few compulsive disorders (with the exception of OCD) have received much scrutiny in terms of high-quality treatment trials. While initial treatment options for compulsive disorders exist, the evidence base is small. Some disorders show high placebo response, which is problematic for differentiating active treatments. Studies require replication in larger sample sizes, with longer follow-up. Funding: This research was supported by a Starter Grant for Clinical Lecturers from the Academy of Medical Sciences (AMS, UK) to Dr Chamberlain.

**S29**

**GENETIC ASSOCIATION OF SCHIZOPHRENIA AND RELATED DISORDERS WITH SYNAPTIC PROTEINS**

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Recent genomic studies have begun to reveal the highly polygenic nature of the disorder, with hundreds and possibly thousands of distinct loci involved at the population level. Despite this complexity, a number of studies have used systems biology approaches successfully to identify enrichment of genetic variants in functionally related sets of genes in schizophrenia cases. These findings are remarkable in that they converge upon a highly plausible set of biological processes and have now been replicated in several different datasets using independent approaches. Results from GWAS, CNV and sequencing studies point to convergence onto a functionally related set of proteins involved in synaptic plasticity, learning and memory. Among the gene-sets that can be tied to these processes are genes encoding members of N-methyl-D-aspartate receptor (NMDAR) and neuronal activity-regulated cytoskeleton-associated (ARC) protein complexes, targets of FMRP, and voltage-gated calcium channels (Hall et al Biological Psychiatry, 77, 52-59). More recently, work from our group (Pocklington et al, Neuron, in press), using a sample of 11,355 cases, and 16,416 controls, has shown for the first time that case CNVs are enriched for genes involved in GABAergic neurotransmission. Non-genetic studies have previously implicated GABAergic deficits in schizophrenia. Our findings now show that disrupted GABAergic signalling is of direct causal relevance rather than a secondary effect or due to confounding. Additionally, we independently replicated and greatly extended previous findings of CNV enrichment among the NMDAR and ARC gene sets involved in glutamatergic signalling. Given the strong functional links between the major inhibitory GABAergic and excitatory glutamatergic systems, our findings converge on a broad, coherent set of processes, providing firm foundations for studies aimed at dissecting disease mechanisms. Finally, there is emerging evidence that some of the same synaptic genes and mutations might also be implicated in other neurodevelopmental disorders such as Autism and Intellectual disability. This, along with other genetic and non-genetic findings, points to the possibility of shared mechanisms across neurodevelopmental disorders and the need for new approaches to patient stratification for research (Owen, Neuron, 84, 564-571). This work was supported by grants from the MRC, Wellcome Trust, NIMH, EU, and NISCHR.

**S30**

**POSTSYNAPTIC COMPLEXES AND MENTAL ILLNESS**

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The postsynaptic proteome of brain synapses is disrupted by mutations causing over 130 brain diseases. Postsynaptic proteins are organized into multiprotein complexes and studies of PSD95 complexes shows polygenic disorders including schizophrenia, autism and intellectual disability converge on these complexes. Studies of individual mutations in mice shows disruption of postsynaptic proteins cause electrophysiological and behavioural changes. Because these experiments have been reported as single gene studies and not performed in a standardized manner, it is impossible to compare results and determine quantitative differences between mutations. We have analysed over 50 lines of mice carrying mutations in postsynaptic proteins in a standardized behavioural test battery that assesses the innate and learned behavioural repertoire. In addition, synaptic physiology was examined using standardized procedures. This study represents the largest genetic study of the vertebrate synapses and reveals new principles underlying the organisation of behavior and its relevance to brain disease.

**S31**

**ARC AND RELATED PROTEINS – REGULATION OF SYNAPTIC PLASTICITY AND RISK FOR PSYCHIATRIC DISORDERS**

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The capacity for informational storage and behavioral adaptation in vertebrate species is inextricably tied to synaptic plasticity, the ability of the connection between neurons to change in strength in response to use or disuse. Traditionally viewed solely as a cellular mechanism for memory storage, experience-dependent synaptic plasticity is now recognized as a core mechanism in a broad range of cognitive functions from motivation and mood, to anxiety and pain control. In
response to specific patterns of synaptic activity (behavioral experience), excitatory synapses are persistently strengthened or weakened in processes known as long-term potentiation (LTP) and long-term depression (LTD), respectively. Recently, the protein Arc has been identified as an indispensable component for LTP, LTD, and long-term memory in mammals. Arc is induced as an immediate early gene in response to synaptic activation. Within minutes the mRNA can be delivered to synaptic sites on dendrites for local translation and function. All steps from mRNA synthesis and transport, to Arc protein synthesis and degradation are subject to tight spatial and temporal control. Hence, Arc constitutes a fine-tuned system for information storage and adaptive mechanisms of cognition. The remarkable function of Arc protein in opposing forms of plasticity may reflect its ability to engage multiple distinct effector proteins and protein interaction networks. This talk will review regulatory mechanism that dictate Arc synthesis and function in synaptic plasticity. A recent analysis of LTP in the dentate gyrus of intact rats shows that brain-derived neurotrophic factor (BDNF) drives the persistent increase in Arc. This occurs in two temporal stages mediated by biochemically distinct mechanisms of translation (Panja D et al. (2014). Two-stage translational control of dentate gyrus LTP consolidation is mediated by sustained BDNF-TrkB signaling to MNK. Cell Reports. 9, 1430–1445). To understand how Arc protein works at molecular level, we have carried out the first analysis of the biophysical and structural properties of human recombinant Arc. We find that Arc is a flexible, modular protein capable of reversible self-association (Myrum,C., (2015) Arc is a flexible modular protein capable of reversible self-oligomerization. Biochem J. doi 10.1042/BJ20141446). These properties support the notion of Arc as a flexible hub protein capable of interacting with functionally diverse partners. Finally, we discuss these data, and other recent findings, in the context of human genetic studies implicating Arc complex proteins and regulatory mechanism in schizophrenia.

S32

NOVEL PHARMACOLOGICAL APPROACHES TO TARGETING THE SYNAPSE

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There is little doubt about the importance of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subtype of ionotropic glutamate receptors in synaptic plasticity. Accordingly, AMPA receptors have for a long time been an attractive target for drugs that modulate synaptic function. Although direct activation of AMPA receptors by agonists causes seizures, positive allosteric modulators (PAMs) offer the potential to enhance AMPA receptor function in a use-dependent manner. AMPAkinines are the prototypic AMPA receptor PAMs but their progression in clinical trials has been disappointing for a variety of reasons, often unrelated to the mechanism per se. Despite their improved safety profile relative to agonists, AMPA receptor PAMs can, nevertheless, be proconvulsant such that the separation between doses that produce procognitive and proconvulsant (or even convulsant) effects – the therapeutic index – remains an important issue in the development of AMPA receptor PAMs. This presentation will review the current development status of AMPA receptor PAMs in the context of cognition enhancers for the treatment of schizophrenia.

A01

REVEALING THE ROLE OF OXIDATIVE STRESS IN THE PATHOPHYSIOLOGY OF DEPRESSION USING HUMAN HIPPOCAMPAL PROGENITOR CELLS

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Introduction: Recent findings suggest that oxidative stress (OS) has an important role in the pathophysiology of depression (N. Bakunina et al., 2015, Immunology, 144, 365–373). OS is a consequence of the biological imbalance between oxidants (Reactive Oxygen Species) and antioxidants, leading to the alteration of biomolecules and the loss of control of the intracellular redox-related signaling pathways (J. Friedman, 2011, oxidative Stress in Applied Basic Research and Clinical Practice, 19–27). The presence of excess ROS in the brain could contribute to lower neuroplasticity and reduced neurogenesis, both of which have been linked to lower mood (S. Moylan et al., 2013, Molecular psychiatry, 18, 595–606). The aim of this study was to understand the effects of oxidative stress on human hippocampal progenitor cells capable of neurogenesis as a model to study «depression in a dish». Methods: We induced OS in human hippocampal progenitor cells by treatment with tert-butylhydroperoxide (T-BHP) in different concentrations. Cell viability was assessed by the MTS assay. Level of malondialdehyde (MDA), an OS biomarker, was measured in cells supernatant using the TBARS assay. Activation of NF-κB and Nrf2 transcription factors were followed by immunostaining and TransAM kit respectively. After differentiation cells were labeled with DCX and MAP2 – markers of young and mature neurons. All images were analysed with CellInsight, a platform for automated, quantitative cell imaging. At least three biological replicates were performed for each experiment.
Results: At 100 µM, 200 µM and 500 µM, T-BHP caused a reduction of cell viability for 23%, 54%, and 74% respectively, compared with vehicle, with a concomitant increase in levels of MDA. At 50 µM and 100 µM of T-BHP, Nf-κB positive cells increased by 16% and 17% respectively, while Nrf2 dose-dependently translocated to the nucleus. At 1 µM, 10 µM and 25 µM, T-BHP increased MAP2 and DCX positive cells by 34%, 33% and 24% for MAP2 and 38% and 30% for at 1 µM and 10 µM for DCX. Conclusions: Our results show that cell damage and cell death of human hippocampal progenitor cells caused by T-BHP occur in a dose-dependent manner. We found activation of transcription factors Nf-κB and Nrf2 in response to OS stimuli. Our results also indicate higher levels of neurogenesis in cells treated with low doses of T-BHP. Thus, we conclude that ROS serve as secondary messengers and facilitate various signaling pathways regulating fundamental neurobiological processes known to be affected in depression. The research is funded by the NIHR Biomedical Research Center for Mental Health and the Medical Research Council UK.

Ao2
KETAMINE RAPIDLY RESCUES THE DETERIMENTAL EFFECTS OF IL-1β ON SYNAPTIC PLASTICITY AND INFLAMMATORY CYTOKINES IN HUMAN NEURONS
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Background: Ketamine's fast-acting antidepressant effects have opened a gateway for a better understanding of the neuropathophysiology of depression. However, the molecular mechanisms underlying this effect in humans remain unclear. Animal studies suggest potentiation of synaptogenesis and dendritic outgrowth as underlying causes for ketamine's antidepressant effects. Preliminary clinical data shows that baseline serum levels of IL-1β and IL-6 are higher in patients who responded to ketamine. The aim of this study was to evaluate the effects that ketamine had in synaptic plasticity and immunomodulation in human neurons after an immune challenge with IL-1β. Methods: Human induced pluripotent stem cell-derived forebrain neurons, incubated for 60 days in vitro were treated with IL-1β (10 ng/ml) for the last 7 days with ketamine added during the last 24h at two doses (1µM and 10µM), before fixation. Dendritic outgrowth and number of synapses were evaluated through immunocytochemistry staining using MAP2, synapsin-1 and homer1. Individual puncta for both synaptic terminals, newly formed synapses (observed through co-localization of the two synaptic markers) and dendritic outgrowth were measured using ImageJ. Cytokines and extracellular glutamate were quantified in the cells' supernatant. Results: IL-1β significantly reduced the linear density of presynaptic and postsynaptic proteins and the number of synapses compared to vehicle (p < 0.0001). Ketamine rapidly rescued this detrimental effect in the number of presynaptic (F = 2.372, p < 0.05) and postsynaptic proteins (F = 5.253, p < 0.0001) and the number of synapses (F = 7.8, p < 0.0001). Dendritic outgrowth was significantly inhibited by IL-1β (p < 0.0001) and rescued by ketamine (F = 17.3, p < 0.0001). Ketamine rapidly decreased the levels of IL-4 (F = 13.3, p < 0.0001), IL-6 (F = 37.8, p < 0.0001) and IL-8 (F = 183, p < 0.0001), compared to the upregulation induced by IL-1β (IL-4, p < 0.0001; IL-6, p < 0.0001; IL-8, p < 0.0001). Extracellular glutamate was rapidly reduced by ketamine compared to vehicle (F = 3.7, p < 0.05). Conclusions: Ketamine rapidly rescued the detrimental effects on synaptic plasticity and inflammatory cytokines caused by exposure of human neurons to an immune challenge, while reducing extracellular glutamate. These effects could potentially shed light on the underlying neuropathophysiology of depression and help with the development of future faster and more effective pharmacological therapies.

Ao3
ACUTE ADMINISTRATION OF KETAMINE, BUT NOT CONVENTIONAL ANTIDEPRESSANTS, CAUSES A POSITIVE BIAS ON A REWARD-BASED RODENT JUDGEMENT BIAS TASK
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Negative affective biases occur in patients with depression (Gotlib & Joormann, 2010, Annu Rev Clin Psychol, 6:285-312). Despite subjective changes in mood only being reported weeks after onset of antidepressant treatment, an acute dose of an antidepressant can increase positive versus negative biases in patients with depression (Harmer et al., 2009, Am J Psychiatry, 166:1178-1184) and healthy controls (Harmer et al., 2003, Neuropsychopharmacology, 28:148-152). In contrast, ketamine (an N-methyl-D-aspartate receptor antagonist) has been shown to be a rapid-acting antidepressant, with patients...
NEUROGENESIS

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Various techniques are used to analyze the functional outcomes of changes in adult neurogenesis but are often labour intensive, requiring specific genetic mouse lines. Whether or not decreases in neurogenesis cause depression is still a fierce question of debate. Several examples in the literature using these techniques show that decreases in neurogenesis alone is sufficient to induce depression while other studies show contradictory findings and indicate that a decrease in neurogenesis alone does not induce depression (Petrik D, Lagace DC, Eisch AJ. (2011) Neuropharmacology. Sep 19;62(1):21–34). Crucial experimental factors may however differ between studies, particularly, the temporal dynamics involved in the experimental procedures which may be important in determining outcome (Snyder JS, Ferrante SC, Cameron H. (2012). PLoS One. Jan;7(1):e48757). These include duration of depletion, age at which the depletion is done, and the delay between depletion and behavioural or biochemical assessment. To deplete neurogenesis we used a simple technique using an easily applied treatment of the anti-mitotic drug temozolomide (TMZ) (25 mg/kg in cycles of 4 daily doses and 3 days rest) to treat 6 week old male C57Bl6 mice (n=10). In our study we used a prolonged treatment of TMZ to reflect ideas about temporal dynamics. Animals were then allowed to recover for a period of 6 weeks from any potential adverse side effects from the TMZ treatment after which a battery of behavioural assays were performed. Results from these assays demonstrated that the neurogenesis depleted group had a significant increase (184%) in the latency to feed in the novelty suppressed feeding test (p=0.005). Despite a 20% increase in average immobility in the forced swim test in the neurogenesis-depleted group, the variation resulted in a lack of significance. Results from the open-field test showed no differences in locomotion, nor any differences in the amount of time spent in the centre. These behavioural assays indicate that mice that have been subjected to prolonged treatment with TMZ display several characteristics reminiscent of a depressive-like phenotype including hyponeophagia and reduced sucrose preference. This study was funded by Wellcome Trust Doctoral Training Programme in Neural Dynamics.
**A05**

**MR BLOCKADE REVERSES DEPRESSION-LIKE BEHAVIOUR IN SSRI-RESISTANT ANIMAL MODEL OF DEPRESSION**

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**Background:** Sub-chronic tryptophan (TRP) depletion induces depression-like behaviour (as measured by the Forced Swim Test, FST) and increases both corticosterone and aldosterone in a female rat SSRI treatment-resistant model of depression (Franklin M et al. Aldosterone signals the onset of depressive behaviour in female rat model of depression along with SSRI-resistance (in preparation)). The mineralocorticoid receptor (MR) antagonist, epleronone reduces anxiety-like behaviour and corticosterone (Hlavacova N et al. Eplerenone, a selective mineralocorticoid receptor blocker, exerts anxiolytic effects accompanied by changes in stress hormone release. J Psychopharmacology 2010;24:779–786). Methods: Adult female Sprague Dawley (SD) rats (200-220g weight) had free access to water and food with a standard lighting schedule. Animals were fed a control diet (0.2% TRP) or a low TRP containing diet (0.04% TRP) for 14 days. Rats were randomised to groups (n=8) a control or b) low TRP diets (implanted with subcutaneous time-release, matrix-driven delivery pellets [Innovative Research of America, Sarasota, FL, USA] containing the MR antagonist, spironolactone (1.2 mg/rat/day) or placebo respectively. All groups underwent the FST on day 14 and were sacrificed on day 15 when blood and brain tissue samples were collected. Various biochemical analyses were performed. Statistical analysis was by ANOVA and Tukey post hoc. Results: Low TRP diet groups demonstrated significant reductions of TRP versus control. Two-way ANOVA revealed significant main diet effect (F1,35=4.43, p<0.05) and significant diet x treatment interaction (F1,35=6.08, p<0.05) on immobility time in FST (control-placebo = 9,172±8.89, control-SPIRO = 22,514±7.4, low TRP-placebo = 30,55±5.81 and low TRP-SPIRO = 20,82±4.44 % of time). TRP-depleted rats treated with placebo but not with spironolactone spent significantly longer time immobile (p<0.05) compared to controls. TRP depletion resulted in significantly reduced time of swimming (F1,35=4.93, p<0.05). TRP depletion increased corticosterone (p<0.02) and aldosterone (p<0.02) versus control. Spironolactone significantly reduced corticosterone (p=0.05) but not aldosterone. Conclusion: Treatment of TRP depleted female rats with spironolactone reduces immobility in the FST whereas the SSRI, paroxetine does not. Our previous studies have shown that TRP depletion in female rats decreases neuroprotective kynurenic acid probably via induction of indoleamine 2,3-deoxygenase (IDO) by corticosterone and/or pro-inflammatory cytokines which are increased. We suggest that reductions of corticosterone/pro-inflammatory cytokines by spironolactone may lower IDO activity and in turn increase neuroprotection at downstream NMDA receptors, the mediators of glutamate neurotransmission and thereby decrease immobility in the FST. Acknowledgements: The study was supported by HEIF 5 funds at Oxford Brookes University.

**A06**

**ISOLATION REARING FROM WEANING TO INVESTIGATE DEPRESSIVE-LIKE BEHAVIOUR IN THE RAT**

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**Post weaning social isolation (SI) of rat pups produces irreversible developmental changes akin to core symptoms of depression; including anxiety, cognitive deficits and hippocampal dysfunction making this is a useful model to examine the pathophysiological basis of depression. This study examined whether SI-induced changes in rat behaviour are accompanied by altered hippocampal neurogenesis and plasma corticosterone. Methods: 24 male Lister hooded rats were grouped (GH, with 3 littermates) or housed alone (SI) from weaning (post-natal day 21). Four weeks later rats received BrdU (150 mg/kg i.p.) and a subcutaneous temperature transponder before consecutive measurement of open field exploration, locomotor activity/novel object discrimination (NOD), elevated plus maze (EPM), conditioned emotional associative learning (CER) and restraint stress at one week intervals. Immediately after the last test, plasma was collected for corticosterone analysis and the brain hemisected, fixed and processed for BrdU/NeuN immunohistochemistry in the hippocampal dentate gyrus (DG). Results: Compared to GH controls, SI rats showed hyperlocomotion in the open field (P<0.001 Student’s t-test, for distance (6363 ± 195, 7256 ± 94 cm respectively) and P<0.01 for velocity (7.08 ± 0.22, 8.06 ± 0.11cm/s)) and locomotor (P<0.01, 1524 ± 50,51, 1788 ± 63,53, total beam breaks) tests. Although both groups spent significantly more time (F1,42 = 640.5, P<0.001, Sidak’s test following ANOVA) in the peripheral than central zone in the open field SI rats travelled further (4763 ± 148 cm) (P<0.01) than GH (4115 ± 201 cm) in the less aversive periphery. Both GH and SI rats spent significantly more time in the less aversive closed arms of the EPM (F1,44 = 46.50) and showed no difference in object exploration in the NOD paradigm.
(F(1, 21) = 0.9891). When re-introduced into the chamber 24h (P<0.05 (169±20, 99±11 seconds respectively)) and 48h (P<0.05 (100±19, 37±21 seconds) post-foot shock conditioning in the CER, SI rats froze for significantly less time. SI rats also froze significantly less than GH when exposed to the conditioning tone at +48h consistent with impaired associative learning and memory (173±20, 87±14 P<0.01). Basal home cage plasma corticosterone levels were equivalent in SI and GH rats (69.0±3.5 and 70.4±4.9ng/ml, respectively) and restraint significantly elevated (P<0.05) levels in both groups. SI rats had significantly (P<0.05) fewer BrdU/NeuN positive cells in the DG than GH controls. Conclusions: SI rats were hyperactive in a novel arena consistent with neophobia and had impaired associative learning in the CER task which was accompanied by reduced hippocampal neurogenesis compared to GH littermates. Future studies will attempt to reverse the changes in depressive-like phenotype by treatment with an antidepressant. FD is funded by a Marie Curie Initial Training Network grant (rBIRTH).

A07

CHRONIC RESTRAINT STRESS INCREASES DEPRESSION-RELATED BEHAVIOUR IN THE SUCROSE PREFERENCE TEST IN JUVENILE AND ADULT MICE

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Depression is a prevalent condition in adolescents, affecting up to 6% of 13-18 year olds (Masi et al., 2010, Expert Opin Pharmacother, 11:375-386). As there are currently few animal models of adolescent depression, we are developing and validating a mouse model. This study aimed to investigate the behavioural effects of repeated restraint stress in the sucrose preference test (SPT) in adult and juvenile mice. Male BALB/cAnNCrl mice (Charles River), aged 4-5 weeks (juveniles) or 9-10 weeks (adults), were randomised into stressed and control groups (n=6-8/group). Stressed mice underwent either 3, 7 or 14 days of restraint (2 hours/day). Blood samples were taken from the tail vein before and after stress (Sadler and Bailey, 2013, Lab Anim, 4:316-319). Corticosterone levels in plasma were determined using an ELISA. Following restraint, all mice were tested in the SPT (12h test overnight, 5% w/v sucrose), and preference for sucrose as a percentage of total consumption was determined. SPT data were analysed using a 2-way ANOVA, and corticosterone data were analysed using a repeated measures mixed model analysis (InVivoStat software). In both adult and juvenile mice, 3 and 7 days chronic restraint stress significantly increased corticosterone above baseline (P<0.01), confirming that restraint is stressful. Following 14 days restraint, habituation of the corticosterone response was evident in adult mice, as corticosterone was no longer significantly elevated above baseline (P<0.05). Habituation was not seen in juvenile mice who showed elevated corticosterone after 14 days restraint (P<0.01). In the SPT, juvenile mice showed no significant difference in sucrose preference between stressed and control groups after 3 or 7 days restraint. Similarly, adult mice showed no significant change in sucrose preference following 3 days restraint. Conversely, 14 days restraint resulted in a reduction in sucrose preference in juvenile mice (P<0.01), and a trend towards a reduction in preference in adult mice (P=0.06), suggesting increased anhedonia and a depressive-like response. The depressive response seen here in the SPT following 14 days restraint stress contrasts with our previous data showing a paradoxical antidepressant and anxiolytic effect of chronic restraint stress in the forced swim test and elevated plus maze (Sadler and Bailey, 2013, P20Online, 11(3):Abstract 046P, Sadler and Bailey, J. Psychopharmacol, 2013, 27:A17). These data suggest that the less stressful SPT may be a more effective measure of depressive-related behaviour following restraint stress. This study was supported by an MRC Doctoral Training Grant and an MRC In Vivo Strategic Skills Award.

A08

THE EFFECT OF HOUSING CONDITIONS ON LIPOPOLYSACCHARIDE-INDUCED DEPRESSIVE-LIKE BEHAVIOUR IN MICE

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Inflammation is thought to play a key role in the pathology of depression. Administration of lipopolysaccharide (LPS) is often used to assess the role of inflammation in depressive-like behaviours, such as the forced swim test (FST) (O’Connor et al. 2009. Mol. Psychiatry. 14(5), 511-522). We have previously shown that acute LPS failed to induce a depressive-like behaviour in the FST (Wickens et al. 2014. J. Psychopharmacol. 28(8), A107). Baseline depressive-like behaviour is influenced by environmental factors, including lighting and housing conditions (Bogdanova et al. 2013. Physiol. Behav. 118, 227-239). Here, we investigated the influence of the light cycle and group/individual housing on LPS-induced depressive-like behaviour in mice. Adult male C57BL/6J mice (10-14 weeks, Charles River) were randomly assigned to LPS or control groups (n=9-15/group). Mice were housed individually or in groups of 3-4 under a normal (lights on: 06:00) or reverse (lights on:
A09 DEVELOPING AN ANIMAL MODEL OF CHRONIC INFLAMMATION RELEVANT FOR DEPRESSION RESEARCH

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There is growing evidence for the role of the immune system in depression neurobiology (Han and Yu 2014, Neurosci bull 30(3): 515–23). To study the role of inflammation in depression, and in the mechanisms of antidepressant action, a valid animal model is required. The aim of this study was to investigate the effect of repeated peripheral lipopolysaccharide (LPS) injections in adult mice to validate the potential of chronic LPS as a model of a chronic state of immune system activation seen in depressed patients, without inducing tolerance towards LPS in mice. Male 8 weeks old Balb/c mice were administered LPS (from E.Coli serotype 0127:B8, Sigma UK) or saline once weekly for 6 weeks via intraperitoneal injections. Treatment groups included 0.1mg/kg (administered 0.1 mg/kg once a week), 0.33 mg/kg (administered 0.33 mg/kg on week 1, with subsequent gradual weekly increments of the dose up to 0.83 mg/kg on week 6), 0.83 mg/kg (administered 0.83 mg/kg of LPS on week 1 and received saline for the subsequent 5 weeks) and SAL group (administered saline 100µL once weekly), N=8 for each group. Sickness behaviour response following LPS injections was assessed by body weight and food intake. Body weight measurements showed that 24hr after the first LPS injections, animals presented with weight loss, with the degree of weight loss increasing with increasing doses of administered LPS (dose factor F(3,150)=24.66 p<0.001). Similarly food intake of mice during the 24hr period following injections was reduced in a dose-dependent manner (dose factor F(3,65)=24.6 p<0.001). On subsequent weeks, gradually increasing doses of LPS (0.33mg/kg group) exerted a similar effect on food intake and weight loss. On week 6, the 0.33mg/kg group received a dose of 0.83mg/kg of LPS, and the effect on weight loss and food intake was indistinguishable from the effect this dose had on naïve animals in week 1. These data suggest that weekly injections of gradually increasing doses of LPS do not induce LPS tolerance in adult mice. Analysis of immune and neuroimmune parameters, such as the peripheral cytokine response to LPS and the level of microglial activation in the brain will further reveal the physiological outcome of repeated LPS administration. These preliminary data suggest that weekly injections of LPS with gradual dose increments might be a suitable model to maintain a chronic inflammatory state in animals without the development of tolerance towards LPS. This research has been funded by Janssen Pharmaceuticals

A10 VALIDATION OF THE AFFECTIVE BIAS TEST IN SPRAGUE DAWLEY RATS

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Cognitive processes are known to be biased by emotions resulting in cognitive affective biases (CAB). Negative affective biases, associated with memory, interpretation and decision-making have been observed in depressed patients (Roiser et al., 2012, Neuropsychopharmacol., 37:117–136). A cognitive theory of depression suggests that negative emotional processing...
is a key factor in developing depressive disorder and its persistence (Disner et al., 2011, Nat Rev Neurosci., 12:467-77). In the present study, we have investigated affective biases associated with learning and memory in rats using the affective bias test (Stuart et al., 2013, Neuropsychopharmacol., 38:1625-35). Male Sprague Dawley rats (Charles River, N=12) were trained in the affective bias test. This bowl digging task involves repeated pairing of a rewarding outcome (obtaining a food reward) with a neutral stimulus (specific digging medium) under control conditions (neutral stimulus A) or following an affective manipulation/treatment (neutral stimulus B). The absolute reward value is kept consistent across all pairing sessions and affective bias quantified using a preference test where both previously rewarded substrates (A and B) are presented together over 30 randomly reinforced trials with no affect manipulation being imposed. The neutral stimuli are changed between each experiment. Animals were tested using a negative affective state manipulation (10 min restraint stress and social isolation versus control housing), a positive affective state manipulation (social enrichment versus control housing) and acute antidepressant treatment (venlafaxine, 0.0, 3.0, 10.0mg/kg, oral vs vehicle treatment). Results were analysed using a Repeated Measures ANOVA or post-hoc, one-sample t tests against the theoretical mean of 0% choice bias. Restraint stress and social isolation (t11=6.159, p<0.0001) and social play (t11=2.367, p=0.0374) induced negative and positive bias respectively. Venlafaxine (RM ANOVA F2,11=4.305, p=0.0264) treatment before pairing sessions induced a dose-dependent positive bias towards the drug-paired substrate. These findings are consistent with previous data using the same manipulations in Lister-hooded rats (Stuart et al., 2013, Neuropsychopharmacol., 38:1625-35). They confirm that non-pharmacological manipulations of affective state and acute antidepressant treatment induces affective bias in rats. These add to the cognitive neuropsychological model in depression and antidepressant drug action (Harmer et al., 2009, Br J Psychiatry. 195:102-8; Roiser et al., 2012, Neuropsychopharmacol., 37:117–136) and support our hypothesis that similar affective biases can be quantified in non-human species. Funding for this research was supported by a University of Bristol Studentship awarded to JKP. Additional funding was provided by an MRC project grant awarded to ESJR.

A11

INVESTIGATING THE EFFECTS OF ACUTE AND CHRONIC TREATMENT WITH CORTICOSTERONE ON AFFECTIVE BIASES IN RATS

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Stress is strongly implicated in the development of depression. Since cognitive mechanisms are hypothesised to underlie the development and perpetuation of depressive states, stress-induced negative affective biases may be an important contributory factor. We have previously shown that acute psychosocial stress induces negative affective biases in rats (Stuart et al, 2013, Neuropsychopharmacology, 38:1625-1635). In this study we aimed to investigate the effects of acute treatment with corticosterone (CORT) on affective biases using the same affective bias test (ABT). We also wanted to investigate whether animals in a putative negative affective state, following chronic corticosterone administration, would show increased vulnerability to a manipulation inducing a negative affective bias. 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. Male Lister Hooded rats (300-350g, n=16) underwent ABT pairing sessions following treatment with CORT (0.0-30mg/kg, i.p.) versus vehicle. In a separate cohort (n=8/group) were treated with either CORT (10mg/kg/day, s.c.) or vehicle for 2 weeks and throughout the ABT testing. Animals subsequently underwent ABT pairing sessions where they received the anxiogenic FG7142 (5mg/kg, i.p.) versus vehicle. Effects of CORT treatment on processing of absolute reward value were also tested using a 2 pellet vs. 1 pellet discrimination study, and hedonic effects were assessed in a sucrose preference test. There was a significant main effect of acute CORT treatment (RM ANOVA: F2,47=5.5, p=0.009), inducing a negative affective bias at both 10 and 30mg/kg. In the chronic study, both CORT- and vehicle-treated groups demonstrated a significant FG7142-induced negative bias, but there was no significant group difference. Whilst CORT-treated animals retained a positive bias for an increase in absolute reward value, this bias was significantly reduced compared to the vehicle-treated group (unpaired t-test: t14=2.3, p=0.037). Furthermore, CORT-treated animals showed a significant decrease in sucrose preference (unpaired t-test: t14=2.2, p=0.043 vs. vehicle). These findings reveal that acute treatment with corticosterone induces negative affective biases in the ABT. Chronic corticosterone treatment did not increase the animals’ sensitivity to a subsequent negative affective state manipulation but did affect their ability to learn different values of reward. SAS was funded by the BBSRC.
A12
ANXIETY-LIKE BEHAVIOUR AND ALTERED STRESS RESPONSE AS A CONSEQUENCE OF PROLONGED SOCIAL ISOLATION AND CHRONIC INJECTION

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Background: Stressors, in the form of chronic injection and/or social isolation, can alter hypothalamic-pituitary-adrenal (HPA) axis activity, immune system functioning, and induce anxiety-like behaviour in rodents. Here, we examined whether varying degrees of stress altered animal behaviour and physiology. Specifically, we tested for the effects of escalating stress in the form of (a) social isolation, (b) chronic injection, and (c) the combination of social isolation and chronic injection, on animal behaviour and HPA axis functioning. Methods: Three groups of seven week old male BALB/cAnCrl mice were housed for eight weeks under one of the following conditions: (a) pair-housed (Group 1), (b) singly housed for 48h repeatedly (Group 2) or (c) permanently singly housed (socially isolated) (Group 3). All animals housed under these conditions also received daily intraperitoneal injections of saline for eight weeks. In addition, there were two groups of injection naïve animals: a group of permanently singly housed (socially isolated) animals (Group 4), and a group of pair-housed controls (Group 5).

Anxiety-and depressive-like behaviour was assessed after 4-8 weeks of social isolation and chronic injection. Whole blood was also collected 24h before, and 30 minutes after, the Forced Swim Test (FST), and plasma corticosterone was measured to assess stress reactivity for each experimental group. Results: Permanently isolated, injection-naïve animals (Group 4) had significantly increased anxiety-like behaviour in the Open Field Test (OFT) (M= 126.9 v. 94.784, N = 10, F [2,26] = 4.005, p = .023), and the NSF (M= 161.1 v. 88.8, N = 10, F [2,26] = 4.663, p = .008), another parameter of anxiety-like behaviour, and had significantly elevated plasma corticosterone levels (M= 147,930 v. 94,784, N = 9-10 N = 10, F [2,54] = 6.795; p < .001) compared with socially housed, injection-naïve controls (Group 5). Interestingly, while chronically injected animals in permanent social isolation (Group 3) were found to exhibit significantly higher levels of anxiety in both the OFT (M= 126.9 v. 28.9, N = 9-10, t (17) = 2.311, p = .034), spending significantly less time in the centre of the arena compared with socially housed, naïve controls (Group 5). Similarly, chronically injected, socially housed animals (Group 1) also had significantly higher levels of anxiety in the OFT (M= 126.9 v. 46.1, N = 10, F [2,26] = 4.725, p = .007), but also had significantly increased latency to feed times in the Novelty Suppressed Feeding Test, (NSF) (M= 161.1 v. 88.8, N = 10, F [2,26] = 4.768, p = .006), another parameter of anxiety-like behaviour, and had significantly elevated plasma corticosterone levels (M= 147,930 v. 94,784, N = 9-10 N = 10, F [2,54] = 6.795; p < .001) compared with socially housed, injection-naïve controls (Group 5). Moreover, while animals periodically isolated and injected (Group 2) had no change in anxiety-like behaviour, they did have a significantly lowered stress response (M= 64,111 v. 147,930 N = 10, t (13.71) = 7.415, p < .001), all when compared with chronically injected, socially housed animals (Group 1). Conclusion: Our data show how both chronic injection and social isolation independently induced significant anxiety-like behaviour in adult male BALB/cAnCrl mice. However, the effect of injection stress on anxiety-like behaviour was not heightened by socially isolating animals. Moreover, our data show how social isolation and/or chronic injection differentially altered HPA axis functioning in our adult mice. Funding: This work was supported by Janssen Pharmaceuticals and the NIHR Mental Health Biomedical Research Centre.

A13
LONG-TERM ESTROGEN REDUCTION INDUCED DEPRESSION-LIKE BEHAVIOR AND MEMORY IMPAIRMENT IS REVERSED BY ANTIDEPRESSANT IN OVARIECTOMIZED RATS

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Introduction: Long-term reduction of estrogen is associated with cognitive deficits, depression, and weight gain, in menopausal women (Weber et al, 2014, J Steroid Biochem Mol Biol, 142: 90-8) as well as in ovariectomized (OVX) rats (Kiss et al, 2012, Behav Brain Res, 227(1):100-108). However, despite the numerous interactions between estrogen and antidepressants, few systematic studies of antidepressants have been conducted in OVX rodents, or have addressed the cognitive and affective dysfunction typical of menopause. Thus, we compared the effects of antidepressants with different mechanisms (vortioxetine, fluoxetine, duloxetine, and vilazodone) in a rat model of OVX-induced memory impairment and
depression-like behavior. Vortioxetine is a 5-HT1D, 5-HT3 and 5-HT7 receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist, and inhibitor of the serotonin transporter (SERT). Fluoxetine is a selective serotonin reuptake inhibitor (SSRI), duloxetine is a serotonin norepinephrine reuptake inhibitor (SNRI), vilazodone is a serotonin reuptake inhibitor and 5-HT1A receptor partial agonist. Methods: Adult female Sprague-Dawley rats underwent ovariectomy and received at least 4 weeks of treatment via food p.o. (15 to 32 rats per group): control, vortioxetine, fluoxetine, duloxetine, or vilazodone. All drug doses target clinically relevant SERT occupancy levels. Animals were tested in the novel object placement test (for visuospatial memory, OP), novel object recognition test (for recognition memory, NOR), and forced swim test (for depression-like behavior, FST). Age-matched gonadally intact female rats were included as controls. Drug exposure was confirmed with ex vivo SERT occupancy analysis. ANOVA followed by post-hoc protected test was used for data analysis and p<0.05 was considered significant. Results: OVX rats had deficits in OP test (object exploration: familiar=13.2±1.6s, novel=12.6±2.0s), increased immobility in FST (%immobility: intact=50.1±2.8, OVX=63.2±2.2), and normal performance in NOR test (object exploration: familiar=12.2±2.4s, novel=22.5±2.8s). Vortioxetine treatment reversed OP deficit in OVX rats (object exploration: familiar=7.7±1.1s, novel=11.7±1.2s), reduced FST immobility (%immobility: 50.8±2.2), without affecting NOR performance (object exploration: familiar=7.3±2.0s, novel=16.2±3.8s). Fluoxetine treated OVX rats had deficits not only in OP (object exploration: familiar=8.2±1.7s, novel=8.6±2.1s) but also in NOR test (object exploration: familiar=9.7±1.9s, novel=10.1±2.5s), and had same levels of immobility in FST (%immobility: 62.9±4.1). Other antidepressants did not change performance of OVX rats. Conclusions: Ovariectomy in rats induced depression-like behavior and visuospatial memory deficits, consistent with co-morbidity of depression and cognitive deficits observed during menopause in patients. Antidepressants with different mechanisms of action were differentially effective in OVX rats: only vortioxetine both reversed memory deficits and reduced depression-like behavior. This work is supported by H. Lundbeck A/S and the Takeda Pharmaceutical Company, Ltd.

A14

ALTERED BEHAVIOURAL RESPONSES TO SELECTIVE SEROTONERGIC AGONISTS IN THE OLFACTORY BULBECTOMIZED (OB) RAT MODEL OF DEPRESSION

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The OB rat model is a well validated model of depression which is associated with changes in the central serotonergic (5-HT) system, including the 5-HT1A and 5-HT2A receptors. However, the functional consequences of such changes has not yet been examined. Thus, the aim of this study was to assess the functionality of these two receptors using the selective 5-HT1A agonist 8-hydroxy-2-(di-n-propylamino)-tetraline (8-OH-DPAT) and the selective 5-HT2A receptor agonist 2,5-dimethoxy-4-iodo-amphetamine (DOI) in this model. Male Sprague-Dawley rats (8 weeks of age) were singly housed for a week prior to surgery and throughout the study. Rats underwent either olfactory bulbectomy or sham surgery and a 4-week period elapsed before the behavioural drug challenge took place. The baseline homecage locomotor activity was monitored for 2 h, after which they received an acute subcutaneous injection of either 8-OH-DPAT (0.1, 0.25 or 0.5 mg/kg) or DOI (0.3, 1 or 3 mg/kg; n=5 per group), and monitored for a further 2 h. In the 1 h period following dosing, a number of behaviours were scored at a later date using EthoVision® videotracking software including rearing, wet dog shakes (WDS) and hind limb abduction (HLA). Data were analysed using a Two-way ANOVA or Kruskal Wallace, followed by Student-Newman-Keuls or Mann-Whitney post-hoc tests where appropriate; p<0.05 was considered significant. An increase in home cage locomotor activity was observed following DOI injection in the sham groups which was significantly enhanced in the 3mg/kg OB group (p<0.05 vs respective sham group). An increase in the 2 higher dose sham groups was observed with 8-OH-DPAT whilst the response at all doses of 8-OH-DPAT for the OB groups was significantly increased (p<0.05 vs respective sham groups). Moreover, both serotonergic agonists produced a concomitant reduction in rearing behavior, which was unaffected by olfactory bulbectomy. With DOI, all doses produced a similar degree of WDS in sham animals which was attenuated (but not significantly so) in the OB groups. With 8-OH-DPAT, there was a clear dose dependent increase in HLA in sham groups which was attenuated by olfactory bulbectomy, significantly so in the 0.25 mg/kg group. These results suggest that olfactory bulbectomy is associated with enhanced locomotor responses to both 5-HT1A and 5-HT2A receptor agonists, with a concomitant blunting of the unique behaviours associated with activation of these receptor subtypes. ZMcA is in receipt of an NUI Galway Hardiman postgraduate fellowship.
A15

A NOVEL OPIOID RECEPTOR LIGAND BU10119, AN ALTERNATIVE TO COMBINATION BUPRENORPHINE/NALTREXONE, PRODUCES ANTIDEPRESSANT-LIKE EFFECTS IN MICE

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Introduction: Kappa-opioid receptor (KOR) antagonists have a potential as novel antidepressants. However, they have a long lasting duration of action which potentially limits their use (Carroll and Carlezon 2013. J Med Chem 56: 2178-2195). Previously, we reported that combination buprenorphine/naltrexone (1mg/kg) produced a functional short-acting kappa-antagonist that was non-sedating, non-rewarding and produced antidepressant-like effects in mice (Almatroudi et al. 2013 Journal of Psychopharmacology 28 (8) A101). We have developed a novel compound that combines the properties of buprenorphine/naltrexone combination into a single compound (Cueva et al. 2015. J Med Chem, In Press), thereby simplifying dosing and treatment regimens and avoiding abuse potential. Here, we present preliminary data demonstrating that BU10119 is a functional KOR antagonist with antidepressant-like effects in the forced swim test (FST) and novelty-induced hypophagia task (NIH). Methods: Adult male CD-1 mice (8-10 weeks, University of Bath) were randomised into control or drug treated groups (n=10 per group). On test days, mice were injected intraperitoneally (10 ml/kg) with saline, buprenorphine/naltrexone combination (1 mg/kg), fluoxetine (20 mg/kg) or BU10119 (1mg/kg) one hour prior to testing behaviour. For NIH, mice were individually housed and trained for 3 days to consume condensed milk. The latency to drink and consumption were recorded in the home cage (day 4) and in the novel cage (day 5). In the FST, a 6 min swim test session was recorded and behaviour scored manually. Data were analysed using a two-way repeated measures mixed model analysis or single measures one-way ANOVA (InVivoStat 2.3). Results: In the NIH test, there was a significant effect of drug treatment on the latency to drink in the novel cage (F(4, 45) =9.15, P<0.001) but not consumption (F(4, 45) =1.25, P=0.3). Fluoxetine, buprenorphine/naltrexone and BU10119 all significantly reduced the latency to drink in the novel cage compared with controls (P<0.01). In the FST, there was a significant effect of drug-treatment on swimming and immobility behaviours (swimming: F(3, 36) =6.58, P<0.001; immobility: F(3, 36) =7.02, P<0.01). Post-hoc testing revealed that fluoxetine, buprenorphine/naltrexone combination and BU10119 significantly reduced the time spent immobile, compared to controls (P<0.01). Conclusion: In vitro pharmacology shows that BU10119 is a KOR antagonist with little efficacy at the mu-opioid receptor. Here we have shown that BU10119 has antidepressant-like activity in the FST and NIH. These effects are equipotent with the combination buprenorphine/naltrexone and consistent with its KOR antagonist activity. We are currently investigating its anxiolytic potential. This research is funded by the Government of Saudi Arabia through a PhD scholarship (AA), the Royal Society (SJB) and NIDA DA07315 (SMH).

A16

INTEGRATION OF PRECLINICAL TESTS TO ASSESS ACUTE ANXIOLYTIC AND CHRONIC ANTIDEPRESSANT EFFECTS OF DESIPRAMINE IN RATS

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The rat forced swim test (FST) is the most widely used preclinical approach for evaluating antidepressant efficacy. Although antidepressant effects are seen following short-term treatment, this does not reflect the clinical situation where chronic administration is required to produce therapeutic effects. Furthermore, despite the high co-morbidity of depression and anxiety clinically, potential antidepressants are not always assessed for their anxiolytic properties. Thus, the aim of this study was to integrate preclinical tests of anxiety (elevated plus maze (EPM) and open field (OF)) and depression (FST), in a single study design that would assess both acute anxiolytic, and chronic antidepressant effects, using the standard antidepressant desipramine (DMI). Male Sprague-Dawley rats (7 weeks old) received injections of either distilled water (control), or 2.5, 5 or 10 mg/kg DMI (n=7-8 per group). Thirty minutes after the first injection, the acute anxiolytic effects of DMI were assessed in the EPM, followed immediately by the OF. Treatment was continued for a further 13 days, at which point the antidepressant effects in the FST were examined. The FST involves two exposures to water-filled cylinders (23-25˚C): a 15 min preswim, followed 24 h later by a 5 min test swim. Rats received their 13th dose 15 min after the preswim, and their 14th dose 1 h prior to the test swim. Home cage locomotor activity was measured in the hour preceding the test swim. Tests were scored manually or using videotracking (Ethovision®). Data were analysed using One-Way ANOVA, followed where appropriate by post hoc Student-Newman Keuls; p<0.05 was deemed statistically significant. DMI had no acute anxiolytic effects in the EPM at any dose, and had no significant effect on distance moved (cm) in the OF. In the FST, chronic treatment with DMI significantly decreased immobility time and concomitantly increased climbing time in a dose dependent manner (p<0.05 vs.
control); DMI had no significant effect on swimming behaviour. Home cage locomotor activity was not altered in the hour preceding the second FST exposure, except for a significant reduction in this parameter with DMI at 2.5 mg/kg. This study demonstrated that both anxiolytic and antidepressant behavioural parameters can be successfully integrated into a single experimental design using the widely-used standard antidepressant desipramine. Further investigation of this study design should be carried out by assessing the effects of other well-validated anxiolytic and antidepressant drugs, with the ultimate intention to use this approach for assessing novel compounds for preclinical anxiolytic and/or antidepressant activity. This project was funded by a postgraduate fellowship from the Discipline of Pharmacology and Therapeutics, School of Medicine, NUI, Galway.

A17

BUPRENORPHINE, ALONE AND IN COMBINATION WITH THE NOVEL OPIOID RECEPTOR MODULATOR SAMIDORPHAN, DISPLAYS ANTIDEPRESSANT-LIKE EFFECTS IN TWO RAT MODELS

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The limitations of treating depression with monoaminergic-based antidepressants are well-documented, with a therapeutic delay and up to 30-40% of patients failing to achieve remission. Targeting the opioid system represents a novel therapeutic avenue but requires balanced modulation of opioid receptors to harness antidepressant effects while mitigating unwanted effects. Recently, the combination of buprenorphine (BUP), a partial mu-opioid agonist, with samidorphan (SAMI), a novel opioid-receptor modulator with potent mu-opioid antagonistic properties, was found to be superior to placebo for reducing depressive symptoms in patients (Ehrich et al, 2015, Neuropsychopharmacology, 1, 1-8). However, non-clinical data for this approach are lacking. Thus, we assessed the antidepressant-like activity of these compounds in the Wistar-Kyoto (WKY) rat model of treatment-resistant depression using the forced-swim test (FST) and in the olfactory bulbectomised (OB) rat model that responds to chronically-administered antidepressants. Adult male WKY rats (n=8/group, 200-250g) were tested in the FST, and received vehicle (saline, s.c.), SAMI (0.3 mg/kg), BUP (0.1 mg/kg) and a combination of BUP+SAMI at 24, 5 and 1 h prior to a 5 min second swim. In a separate study, adult male Sprague Dawley rats (n=7-9/group, 180-220g) underwent sham or bulbectomy surgery and after a 2 week recovery received 14 daily injections of vehicle, BUP, SAMI and BUP+SAMI (doses as above) and exposed to the open field test for 5 min, 24h after the last drug administration. Behaviour was recorded and analysed with the aid of EthoVision XT software. Data were analysed using ANOVA followed by SNK post-hoc where P<0.05. In WKY rats exposed to the FST test, BUP alone reduced immobility and increased swimming behaviour (P<0.05 vs. saline), an effect augmented by SAMI (P<0.05 vs. BUP alone). Locomotor activity of sham animals in the open field was not altered by drug treatment. In comparison, OB-induced hyperactivity was significantly attenuated by BUP alone and in combination with SAMI (P<0.05 vs. saline-treated OB group). In summary, subchronic BUP administration elicits an antidepressant-like effect in the WKY rat, an effect enhanced by the presence of SAMI. Moreover, chronic BUP administration elicits an antidepressant-like effect in the OB model of depression, an effect maintained with the addition of SAMI. These data support clinical evidence that opioid modulation represents a novel antidepressant strategy. Supported by an Industry-Academia collaboration: funding and SAMI provided by Alkermes. Studies conducted under ethical approval by NUI Galway’s Ethics Committee and under licence from the HPRA under EU legislation.

A18

POSITIVE ALLOSTERIC MODULATORS AT ACETYLCHOLINE RECEPTORS ENHANCE THE RESPONSIVENESS TO CITALOPRAM IN THE MOUSE FORCED SWIM TEST

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Nicotine improves depressive symptoms in humans and shows antidepressant-like effects in rodents. Monoamine release is facilitated by nAChR agonism, and behavioural effects of monoamine-based antidepressants are enhanced by nicotine as well as by selective agonism of α4β2 or α7 nAChRs. Positive allosteric modulators (PAMs) at nAChRs are pursued as an alternative to nAChR agonist, which have been associated with dependence and addiction. Here we compare the ability of NS9283, an α4β2 nAChR PAM, and PNU120596, an α7 nAChR PAM, to induce antidepressant-like effects or enhance the antidepressant-like effect of citalopram in the mouse forced swim test (mFST). Locomotor activity testing was included to
assess if drug effects in the mFST was confounded by non-specific locomotor-depressant or –stimulant effects. Female NMRI mice (25-35g) were tested for 6 minutes in the mFST (24±0.5°C), and the effect of drug treatment on total swim distance was compared to the baseline swim distance measured 24h prior to treatment. The following doses and dose combinations were tested: NS9283 (0.3-10mg/kg; n=8-10), PNU120596 (1-10mg/kg; n=7-8), NS9283 (3-10 mg/kg)+citalopram (10-30mg/kg)(n=7-8), and PNU120596 (1-3mg/kg)+citalopram (10-30mg/kg)(n=10-12). Data were analysed with analysis of covariance (ANCOVA) and Planned Comparisons on the predicted means. When given alone, citalopram increased swim distance at 30 (p<0.05) but not 10mg/kg, and NS9283 and PNU120596 did not significantly affect swim distance in the mFST. However, the combination of NS9283 and citalopram revealed antidepressant effects; mice treated with 10mg/kg citalopram+3mg/kg NS9283 or 30mg/kg citalopram+3mg/kg NS9283 swam significantly longer than animals treated with 3mg/kg NS9283 alone (p<0.001) or 10 or 30mg/kg citalopram alone (p<0.05). PNU120596 also enhanced the effect of citalopram; in mice treated with 1mg/kg PNU120596, swimming distance was increased by both 10 (p<0.05) and 30 (p<0.05) mg/kg citalopram. Similarly, in mice treated with 3mg/kg PNU120596, swimming distance was significantly increased by both 10 (p<0.05) and 30 (p<0.001) mg/kg citalopram. Citalopram increased locomotor activity, but this effect was not altered by NS9283 or PNU120596. Previously, the behavioral effect of citalopram has been enhanced by nicotine or selective agonists at α4β2 or α7 nAChRs. The current results show that similar enhancements are produced by α4β2 or α7 nAChR PAMs. In pursuit of novel ways to improve antidepressant treatment, nAChR PAMs may represent a mechanism with similar benefits but lower risk of addictive properties than nAChR agonists. All procedures were in accordance with European Communities Council Directive of 24 November 1986 (86/609/EEC) and the Danish Animal Experimentation Act. Authors declared no conflict of interest. Funding: Department of Drug Design and Pharmacology (ILF), Københavns Universitet, Universitetsparken 2, 2100 København Ø.

A19

KETAMINE AND NOT FLUOXETINE DEMONSTRATES ANTIDEPRESSANT EFFICACY IN THE WISTAR KYOTO RAT ACCOMPANIED BY DISTINCT EFFECTS ON MICROTUBULAR PROTEINS: IDENTIFICATION OF A NOVEL PLASMA BIOMARKER

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One third of depressed patients are unresponsive to antidepressant drugs, constituting a population known as treatment resistant depression (TRD). Ketamine is the only drug showing clinical efficacy in TRD patients. Decreased neuronal microtubule dynamics has been associated with the pathogenesis and treatment of depression and might represent a potential biomarker in TRD. The endogenous ‘depressed’ Wistar Kyoto (WKY) rat, unresponsive to selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, was used as a model of TRD to aid validation of microtubular proteins as plasma biomarkers. Male WKY rats (6-8 weeks; 200g; n=8 per group) were administered either fluoxetine (10 mg/kg, i.p.), ketamine (5 mg/kg, i.p.) or saline (1 ml/kg, i.p.). Immobility, defined as depressive-like behaviour, was tested in the forced swimming test (FST) 30 minutes and 7 days post-administration compared with Sprague-Dawley (SD) rats (6-8 weeks; 250g; n=8) administered saline (1 ml/kg, i.p.). Plasma was isolated 24 hours and 8 days post-administration and expression of acetylated alpha-tubulin (Acet-Tub; marker of stable microtubules) was measured as marker of microtubule dynamics by infrared Western Blotting. Data were analysed using a one-way ANOVA followed by Fisher’s LSD test. WKY rats showed significant increased immobility in FST compared with SD at 30 min (WKY+saline: 142±16 vs. SD+saline: 80±7 p<0.01) and 7 days (WKY: 152±7 vs. SD: 64±7, p<0.0001). Ketamine produced a rapid (30 minute; WKY+ketamine: 96±7 vs. WKY+Saline: 142±16, p<0.05) and long-lasting efficacy (7 day; WKY+ketamine: 61±9 vs. WKY+Saline: 152±7, p<0.001) whereas fluoxetine elicited no effects. Plasma Acet-Tub was increased two times significantly higher in WKY compared to SD rats at each time point, 24 hours (p<0.01) and 8 day (p<0.001). Fluoxetine significantly augmented Acet-Tub overexpression (p<0.05) of 25% compared to WKY+saline at 24 hour post administration, while ketamine produced no effect. Neither drug significantly altered Acet-Tub expression 8 day post-administration. WKY rats represent a model of TRD responding to acute ketamine and not fluoxetine in the FST. WKY rats overexpressed plasma Acet-Tub similar to what has been observed in the hippocampus (Cottin et al., 2012, Journal of Psychopharmacology Supplement 26 (8): A16), consistent with decreased neuronal microtubule dynamics. Acute fluoxetine increased the overexpression of plasma Acet-Tub in WKY rats, while ketamine had no effects. Importantly, acute fluoxetine has been shown to increase Acet-Tub in Lister hooded rat hippocampus (Bianchi et al., 2009, Synapse 63:359-364). Plasma microtubular proteins may represent a potential TRD biomarker of disease progression and treatment responsiveness. Supported by internal Transpharmation Ireland funding.
**A20**

3BETA-METHOXY-PREGNENOLONE EXERTS ANTIDEPRESSANT EFFICACY IN ‘DEPRESSED’ WISTAR-KYOTO RATS AND IN AGED WISTAR RATS

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The steroid-derivative 3beta-Methoxy-pregnenolone (MePreg) is a neuronal microtubule modulator showing antidepressant efficacy in animals. More efficacious and safer antidepressant drugs are respectively required for the treatment of two subpopulations of depressed patients, namely treatment resistant depression (TRD) and depression in the aged population. The endogenous ‘depressed’ Wistar-Kyoto (WKY) rat, unresponsive to selective-serotonin reuptake inhibitors (SSRIs), was used as a model of TRD to test MePreg efficacy in comparison to ketamine, which is clinically effective in TRD patients. Additionally, aged Wistar (WIS) rats were used to investigate MePreg efficacy in comparison to fluoxetine, a first line SSRI used in aged patients. Male WKY rats (6-8 wk, 200g, n=8 per group) received MePreg (10 mg/kg; s.c.), ketamine (5 mg/kg; i.p.) or corresponding vehicle solutions (sesame oil; 0.25ml/rat s.c. and 0.9% saline 1ml/kg; i.p.). Depressive-like behaviour (i.e. immobility) was tested in the forced swimming test (FST, 5 min session) 30 min post drug administration and compared to ‘healthy’ Sprague-Dawley (SD) rats administered with vehicle solutions as above. Young (3-4 mth, 200g, n=9-10 per group) and aged (24-25 mth, 640g, n=9-10 per group) male WIS rats were exposed to the pre-swim FST (15 min session) and then received MePreg (10 mg/kg; s.c.), fluoxetine (10 mg/kg; i.p.) or corresponding vehicle solutions (sesame oil; 0.25ml/rat s.c. and 0.9% saline 1ml/kg; i.p.) 24, 5 and 1 hr prior to FST (5 min session). Immobility (s) in WKY vehicle rats was significantly increased in comparison to SD vehicle rats (WKY: 95.7±9.7 vs. SD: 66.4±8.2, p<0.05). MePreg (73.4±9.2) and ketamine (74.5±10.7) both exhibited a tendency towards a rapid (30 min) antidepressant efficacy, although this did not reach statistical significance when compared to WKY vehicle rats. Immobility in aged WIS vehicle rats was significantly increased in comparison to young WIS vehicle rats (young WIS: 133±8.4 vs. aged WIS: 182±14.1, p<0.01). MePreg (106.7±8.5 and 151.6±8.8, p<0.05) and fluoxetine (100.9±8.6 and 128.3±8.1, p<0.05) both exhibited antidepressant efficacy in comparison to corresponding vehicle treated control animals (p<0.05) in both the young and aged rodent populations, respectively. MePreg and ketamine show similar and rapid antidepressant efficacy in WKY rats. Additionally, MePreg displays rapid antidepressant efficacy in both young and aged WIS, to a level comparable with fluoxetine. MePreg may represent a tool compound for the development of novel antidepressant drugs for the treatment of both TRD and depression in the aged population. Supported by internal Transpharmation Ireland funding.

**A21**

REGIONAL SPECIFIC MODULATION OF NEURONAL ACTIVATION ASSOCIATED WITH THE ANTIDEPRESSANT-LIKE PROPERTIES OF TARGETING THE NMDAR/PSD-95/NOS PATHWAY IN THE WISTAR-KYOTO RAT

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The N-Methyl-D-Aspartate Receptor (NMDAR)/nNOS pathway is a promising target in the development of novel antidepressant compounds. Inhibitors of neuronal Nitric Oxide Synthase (nNOS) display antidepressant and anxiolytic-like properties in several pre-clinical behavioural tests. Recently, small molecule inhibitors, which are selective for the PSD-95/nNOS interface within glutamatergic neurons, have been shown to produce antidepressant-like properties in mice. The Forced Swim Test (FST) is a stressor that has been shown to induce robust neuronal activation in several brain regions associated with stress coping and depressive behaviour (immobility time), which is thought to reflect a state of behavioural despair. The Wistar-Kyoto (WKY) rat is an inbred strain that displays an endogenous depressive-like phenotype in several behavioural tests. Subsequently, it is a suitable model to screen novel compounds for antidepressant efficacy. Here, the effects of the selective nNOS inhibitor, 1-(2-Trifluoro-methyl-phenyl) imidazole (TRIM), and the small molecule inhibitor of the PSD-95/nNOS interface, 4-(3,5-Dichloro-2-hydroxy-benzylamino)-2-hydroxybenzoic acid (ZL006), were assessed for changes in regional c-FOS immunoreactivity upon exposure of WKY rats to the FST. Male WKY rats (N= 6 to 8 per group) were exposed to a 15-minute pre-swim session on day 1 to acquire learned helplessness. Animals received either vehicle (i.p), TRIM (50 mg/kg; i.p) or ZL006 (10 mg/kg, i.p) 24, 5 and 1 hr prior to the 5-minute FST test session on day 2. Both TRIM and ZL006 reduced immobility time in the FST (p<0.01). Brain regions analyzed included the prelimbic cortex (PLx), lateral septum (LS), nucleus accumbens (NAc), paraventricular hypothalamic nucleus (PVN), hippocampus (dorsal and ventral regions), dorsolateral periaqueductal grey (dLPAG) and the dorsal raphe nucleus (DRN). The main observations
were as follows: exposure to the FST increased c-FOS immunoreactivity in several brain regions assessed including the LS, NAc, dorsal dentate gyrus, ventral CA1, dlPAG and the DRN when compared to non-FST exposed controls (p<0.01). FST-induced c-FOS immunoreactivity was further increased in the LS, PVN and dlPAG following treatment with TRIM or ZL006 when compared with vehicle-treated FST controls (p<0.01). By contrast, FST-induced c-FOS immunoreactivity in the hippocampus was attenuated following treatment with TRIM or ZL006 when compared with vehicle-treated FST controls (p<0.01). Additionally, treatment with ZL006 decreased the number of reduced Nicotinamide adenine dinucleotide phosphate (NADPH) positive cells in the PVN of WKY rats (p<0.001), indicative of suppression in the activity of nNOS in this brain region. In conclusion, a pattern of enhanced and reduced FST-related c-FOS immunoreactivity suggestive of a NO-regulated network where inhibition of NMDAR associated nNOS leads to activation of the septum and hypothalamus, with a concomitant inhibition of the hippocampus. Financial sponsorship obtained from Trinity College Dublin

A22

ACTIVATION OF 5-HT7 RECEPTORS (5-HT7-R) LOCATED IN THE MEDIAN RAPHE NUCLEUS (MnRN) PROMOTES ADAPTATION TO STRESS OF RATS SUBMITTED TO THE FORCED SWIMMING TEST (FST)

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5-HT7 is the most recent 5-HT-R identified, and it is expressed throughout the central nervous system, including the hippocampus and the median raphe nucleus (MnRN). It is suggested that the antagonism of 5-HT7-R has antidepressant effects when administered peripherally or directly into the hippocampus. However, little is known about the role of 5-HT7-R in the MnRN (Amanda, et al., 2012. Molecular neurobiology, v. 43, n. 3, p. 228–53; Paulo, et al., 2013. Journal of Psychopharmacology, 27(12), 1134–1140). Aim: to investigate the role of MnRN 5-HT7-R in rats submitted to the forced swimming test (FST). 119 male wistar rats (n=6-12 animals/group, 250-300g) were kept in pairs, under controlled T (23±1C), lighting (light/dark cycle 12h conditions; lights on at 6:30am); and ad libitum. Rats underwent stereotaxic surgery for implantation of a guide cannula (14mm) directed to the MnRN; One week later the protocols were performed. I) Protocol: rats received two intracerebral injections (i.c.i) of Saline (0.2µl), LP44 (0.03, 0.1 or 0.3 nmol/0.2µl; a 5HT7-R agonist) and/or SB 258741 (0.1, 0.3 or 1.0 nmol/0.2µl, an 5HT7-R antagonist) combined as: Saline+Saline, SB258741+Saline or Saline+LP44. Five minutes later they were tested in the Elevated Plus Maze (EPM). The number of entries and time spent into the enclosed (EEA) and open arms (%OEA and %TOA) were analysed using ONEWAY ANOVA followed by Dunnett. II) Protocol: rats received an i.c.i as described, but at the dose that did not change the exploration of the EPM. Additionally, a group received two i.c.i of SB258741+LP44. Five minutes after the injections, the animals were pre-exposed to a swim session (15 minutes) being tested (5 min) 24 hours later (transparent acrylic cylindrical tank with 35 cm diameter and 65 cm high, with water at 25±1 °C and 30 cm depth). The frequency (FC) and duration of climbing (TC), latency to display the first episode of immobility (LAT) and total time spent immobile (TI) were registered. Control group received the same i.c.i treatments, but was not pre-exposed to the swim session, and was tested 24h later. After, rats were anaesthetized and transcardially perfused with saline followed by 10% formalin solution, for brain removal and further histological analysis of injection sites. First protocol: none of the treatments or doses changed the basal exploratory activity (EEA: F6,51=0,82; p>0,05); (%OEA: F6,51=0,22; p>0,05); (%TOA: F6,51=0,94; p>0,05) when compared to the control group (Saline+Saline). Second protocol: no difference between groups in the FC (F3,38=0,3185; p>0,05). There was a decrease in TC in rats treated with SB258741+Saline (63,8±18,6; F3,38=3,078, p<0,05), when compared to control (126,7±12,2), and a significant reduction in LAT (F3,38=13,79, p<0,01) when animals received SB258741+Saline (29,9±2,3) or SB258741+LP44 (42,2±9,3) when compare to saline-treated rats (85,8±8,8). Nonetheless, rats treated with SB258741+LP44 showed increased TI (165,9±16,6) when compared to control (118,1±9,9), whilst Saline+LP44 reduced TI (71,3±10,8). Animals not submitted to a stress condition did not show any change (LAT: F3,27=0,6636; p>0,05); (TI: F3,27=2,760; p>0,05). Conclusion: Activation of 5-HT7-R in the MnRN promotes adaptation to stress. Ethical Approval: The Ethics Committee on the Use of Experimental Animals (CEUA) Campus of Ribeirão Preto, USP (2014.1.231.53.9; 2012.1.1425.53.0) approved the experimental protocols. Funding: Fundação de Amparo à Pesquisa do Estado de São Paulo, FAPESP, Brasil; Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)
**A23**

**THE IMPACT OF CHILDHOOD EMOTIONAL NEGLECT ON HIPPOCAMPAL FUNCTION IN ADULTS**

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Introduction: Adversity during critical developmental periods engenders an increased risk of psychiatric disorders through an as yet unidentified mechanism. We hypothesise that epigenetically mediated alteration in HPA axis function and subsequent changes in hippocampal function may mediate this vulnerability. Methods: A convenience sample of 9,983 Newcastle University students were sent an electronic questionnaire which contained the 5 emotional neglect (EN) subscale questions from the childhood trauma questionnaire, the 4 Office of National Statistics wellbeing questions and asked for postcode at age 15. 1,040 questionnaires were successfully completed. A stratified sub-sample of 32 was taken from the three clusters revealed by cluster analysis of the summed EN score. The sub-sample has been examined with clinical measures—specifically the Structured Clinical Interview for DSM-IV (SCID), the Beck Depressive Inventory (BDI) and the State-Trait Anxiety Inventory (STAI); with neuropsychological tests of hippocampal function, specifically episodic memory, future thinking and imagination. Further neuropsychological tests of emotional processing, executive function, working memory and processing speed (the attentional blink, verbal category fluency, digit spans forwards and backwards and the digit symbol substitution test) were administered. In addition, blood and saliva samples have been taken for determination of glucocorticoid receptor (GR) methylation, the cortisol waking response and for ex-vivo determination of GR function. Preliminary Results: Total wellbeing score (summed across all measured fields of well-being) was negatively correlated with both emotional neglect (r = -0.33, p = 0.01); and with childhood socio-economic deprivation (derived from postcode at age 15; r= -0.10, P= 0.01 ). Further data from the full and sub-sample will be displayed at conference. Conclusion: We have demonstrated a relationship between reported childhood adversity and deprivation with adult wellbeing and will explore the mechanistic impact of HPA axis and hippocampal function. Ethical Approval: The study was approved by the Ethics Committee of the Faculty of Medical Sciences, Newcastle University. Funding: The study is funded by the Faculty of Medical Sciences, Newcastle University.

**A24**

**THE EFFECT OF MOOD ON SOCIAL REWARD**

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Introduction: Depression features social withdrawal and lack of pleasure and motivation for social experiences (Ribot, T. (1897). The Psychology of Emotions. London, UK: W Scott). However, how social reward processing might be a specific risk factor for depression has yet to be elucidated. The aim of the current study was to examine if low mood (Beck’s Depression Inventory, BDI; Revised physical and social anhedonia scales, RPhA, RSAS) was related to responses on a novel social reward task (Sentence Completion Task, SCT). The second aim was to examine if a prosocial video might modulate responses on the SCT. The third aim was to examine if the prosocial video would modulate actual helping behaviour. Methods: Using a mixed-factorial design, we examined 50 participants’ (high-scorers; BDI ≥20, n =17 and low-scorers; BDI ≤10, n =33) responses on a SCT (e.g. anxious, eager to socialise, withdrawn) before and after a positive mood induction (prosocial video). We also examined the effects of mood and anhedonia on helping behaviour by dropping papers beside the volunteers and videoing their reactions (e.g. no. of papers retrieved, latency to help). Finally, we measured how helping behaviour was affected by the prosocial video across both groups. Results: Relative to low-scorers, high-scorers responded significantly less positively and more negatively on the SCT, with a main effect of group (p <.05). A significant interaction revealed that low-scorers showed large differences in their sadness (p <.001) and anxiety scores (p <.001) after the video, whereas high-scorers showed no significant effects of the prosocial video. We also found that high-scorers were significantly less likely to help the researcher (p <.001). Positive correlations were also found for BDI and anhedonia measures with latency to help (p <.001). Conclusions: These findings suggest that people who score highly on a BDI questionnaire are much less likely to respond positively to social rewards and are less likely to be affected by a prosocial video. The high scorers are also less likely to engage in helping behaviour. These results are interesting as they show that even non-depressed individuals who score highly on a BDI and anhedonia measures, process socially rewarding
information differently. Understanding how deficits in social reward processing might be a trait marker for depression is important in helping detect early signs of risk for depression and could aid prevention strategies. Approved by the University of Reading’s Research Ethics Committee. 2014-112-CM. Funded by University of Reading.

A25

REINFORCEMENT LEARNING, MONETARY DECISION-MAKING AND ANHEDONIA IN MEDICATION-FREE PATIENTS WITH DEPRESSION

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Introduction: Aberrant decision-making is frequently found in patients currently experiencing a major depressive episode. Cognitive theories of depression suggest that reward processing deficits may underlie both core depressive symptoms such as anhedonia, the loss of pleasure or interest in enjoyable stimuli, and transitions from euthymic to depressive periods (Eshel and Roiser, 2009, Biological Psychiatry, 2009, 68, 118-124). Previous research has largely focussed on an individual task or component of reward processing in depression, typically in medicated individuals. To date, this research has provided valuable data but has not yielded a holistic picture and the precise nature of reward processing in depression remains undetermined. Methods: Thirty healthy volunteers and 22 medication-free patients with depression (18 with unipolar and four with bipolar disorder; 19 patients were treatment resistant) completed four reward processing tasks in a randomized order. Specifically, participants completed four unique cognitive tasks which tapped reward processing components, including: monetary motivation, reinforcement learning, reward planning, loss avoidance and risk and loss aversion. They also completed the Snaith–Hamilton Pleasure Scale (SHAPS) and Temporal Experience of Pleasure Scale (TEPS) scales in conjunction with general depression scales. Group differences on relevant task components and their interactions were explored. Where applicable, computational models of choice behaviour were fitted to the data. Results: As anticipated, patients exhibited higher levels of anticipatory (SHAPS, t(55) = 14.91, P < .001; TEPS, t(55) = -6.96, P < .001) and consummatory (t(55) = -11.31, P < .001) anhedonia than healthy volunteers. Within depressed patients, levels of anticipatory were higher than consummatory anhedonia (t(23) = 5.09, P < .001). In comparison to healthy volunteers, depressed patients exhibited decreased risk aversion (t(46) = -2.24, P = 0.03), lower learning rates to less reliable stimuli irrespective of valence and poorer memory of frequent loss causing stimuli (t(47) = -2.20, P = 0.04), relative to frequent winners. However, the deficit seen in risk aversion was not found in our computational models. No significant group differences in loss aversion, loss avoidance, monetary planning or motivation were detected. Conclusions: Our results indicate that broad spectrum deficits in value-based decision-making are not found in medication free depressed patients. Nevertheless, a deficit in the representation of loss related stimuli was found; this deficit may underlie aberrant decision-making seen in depression. Further analyses are necessary to better understand the role of reward processing in depression. Funding for this work was supported by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH; grant number 04-M-0222), by a National Alliance for Research on Schizophrenia and Depression Award to CAZ, and by a Wellcome Trust-NIH PhD studentship (WT095465) to NL.

A26

THE EFFECTS OF 7-DAYS TREATMENT WITH BUPROPION ON THE NEURAL RESPONSE TO REWARD AND AVERSION IN HEALTHY VOLUNTEERS

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Antidepressants are thought to have their effects by modulating the processing of emotional information. We have previously shown that 7 days treatment with citalopram in healthy volunteers attenuated the neural response to aversive and rewarding stimuli (McCabe et al., 2010, Biol. Psychiatry, 67(5), 439-445). This study examined the early effects of bupropion (a dopamine-noradrenaline reuptake inhibitor) on the neural response to reward and aversion. We hypothesised that bupropion would reduce the neural processing of negative information and increase the processing of positive. Using a within-subjects, crossover design, seventeen healthy volunteers (mean 24 years, 9 females) received 7 days of bupropion (150 mg/day) and 7 days of placebo treatment, separated by a two-week washout phase. On the final day of each medication phase, volunteers’ underwent a fMRI scan. Pleasant (chocolate) and unpleasant (mouldy drink) cues were presented, indicating the opportunity to either work to win a chocolate taste or to avoid an unpleasant taste. Contrast analysis examined drug
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vs. placebo activity during the cues and the tastes. Relative to placebo, bupropion increased activity for both tastes in the medial orbitofrontal cortex (OFC, p=0.005, pleasant, p=0.014*, unpleasant) and for both cues in the lateral OFC (p=0.001, pleasant, p=0.045, unpleasant) and caudate (p=0.007, pleasant, p=0.01, unpleasant). Bupropion also increased activity in the subgenual cingulate (p=0.02) for the chocolate cue. This region along with the midbrain (p=0.036) was also enhanced for the chocolate taste, whilst activity in the caudate was reduced (p<0.001*). For the unpleasant cue, bupropion increased activity in the putamen (p=0.023), and vmPFC (p=0.003), whereas it reduced activity in the insula (p=0.04) and thalamus (p=0.02).

For the unpleasant taste, bupropion heightened activity in the amygdala (p=0.014*), insula (p=0.03) thalamus (p<0.001,*) and ventral striatum (p=0.014*). P values small volume correction or * whole brain corrected FWE p<0.05. Overall, our results suggest that bupropion might enhance saliency processing of motivationally-relevant stimuli in order to increase the motive to obtain rewards and to avoid punishers. Our results help explain how bupropion might act as an antidepressant. Bupropion might help people who lack the drive to go after rewards and thus experience anhedonia, but also and importantly it might also be beneficial for people who lack the drive to avoid and escape aversion, as evidenced in learned helplessness. Thus, if bupropion mechanistically promotes reward-seeking and punisher-avoidant behaviours, this might encourage more positive and less negative interactions with the environment, which over time would improve low mood. Ethical approval was obtained from the University of Reading Ethics committee. University of Reading Funding for Dr C McCabe.

A27

EARLY EFFECTS OF FLUOXETINE ON EMOTIONAL NEURAL PROCESSING IN DEPRESSED ADOLESCENTS

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Introduction: Depression in adolescence is a major health problem, associated with poor psychological function and key risk factors both for later illness and suicidal behaviours. The antidepressant fluoxetine is commonly used in this population and it is shown to have a favourable benefit-to-risk profile. However, controversy still exists about the use of antidepressants in young people and there is little research focusing on underlying mechanisms of wanted and unwanted actions in this group. The aim of this study was therefore to investigate the effects of a single dose of fluoxetine on emotional processing, as measured using fMRI. Methods: Twenty-three adolescents (13-17 years-old) with Major Depressive Disorder and 11 matched healthy controls were recruited to this study. After being prescribed antidepressant treatment by their treating psychiatrist, patients were randomised to receive their first dose of fluoxetine (10mg) or placebo in this study. 6-hours post administration, participants completed a gender fMRI task including angry, happy and fearful faces. Results: Two main findings emerged. First, when compared to healthy adolescents, depressed patients on placebo showed a trend for increased activation in the amygdala towards angry facial expressions (p=0.055), and a trend for decreased activation towards fear (p=0.062). Second, this pattern was opposite to that seen in the fluoxetine vs. placebo groups. Indeed, participants in the fluoxetine group showed decreased activation in the amygdala in response to angry faces (p=0.011), as well as increasing amygdala activity in response to fear (p=0.067). Whole-brain responses in occipital, temporal and frontal regions known to be involved in emotional processing revealed similar patterns of activation. Finally, the increase in amygdala activity in response to fear in the fluoxetine group was also associated with lower symptoms of anxiety during the first 10 days of treatment (r=-0.678, p=0.045). These neural changes were seen in the absence of overall effects of fluoxetine vs. placebo on mood or anxiety symptoms, therefore representing a direct effect of the drug. Conclusions: To the best of our knowledge, this is the first study that investigated the early mechanisms of fluoxetine in young people. These findings suggest that similarly to what is seen in adults, antidepressants act early to influence emotional processing in adolescents, an effect that is not mediated by subjective changes in mood or anxiety. The effect on anger processing in consistent with a previous study conducted in our lab with young people aged between 18 to 21 years old (Capitao et al, in press; Acute fluoxetine modulates emotional processing in young adult volunteers. Psychological Medicine), and may therefore represent a key mechanism relevant to the treatment of depression in youth, which is often characterised by co-existing symptoms of low mood and irritability. Funding support for this study was provided by the Medical Research Council, UK.
ACUTE EFFECTS OF TIANEPTINE ON EMOTIONAL PROCESSING IN HEALTHY VOLUNTEERS

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Introduction: Manipulation of the monoaminergic system has for many years dominated research and therapeutics in depression. There has been increasing appreciation however that the underlying pathophysiology is more complex than is encapsulated by the Monoamine Hypothesis alone, and as such attention has turned to novel mechanisms of action and agents. Tianeptine is an agent with putative antidepressant efficacy that challenges the traditional monoaminergic hypothesis of antidepressant action; it was initially classified as a Selective Serotonin Reuptake Enhancer (SSRE), though its exact mode of action remains controversial. One recent theory proposed as a final common pathway for the effects of different antidepressant agents suggests that clinically-effective antidepressant drugs cause early, non-conscious positive changes in the bias of processing emotional information (Pringle et al, 2011. Prog Neuropsychopharmacol Biol Psychiatry 35: 1586-1592). Changes in such biases have been shown following acute administration of a range of monoaminergic antidepressants. Here the acute effects of a single dose of tianeptine on emotional processing in healthy volunteers are explored. Methods: This was a double-blind, placebo-controlled parallel group study of 40 healthy volunteers (20 male; mean age 22; SD 2.5; range 18–30 years). Participants were randomised to either receive a single dose of tianeptine (12.5 mg) or placebo, and 60 minutes after dose administration completed an established battery of tasks measuring emotional processing, including facial expression recognition, emotional memory and attentional vigilance. Results: Tianeptine-treated subjects were less accurate in their identification of facial expressions, though this was not valence specific. The tianeptine group also showed reduced positive affective memory in a self-referential word memory task and reduced attentional vigilance to positive stimuli. There were no effects on emotional categorization. The groups were well matched and the above effects were seen in the absence of any effect of drug administration on a range of measures of subjective state. Conclusions: The current data indicate that a single dose of tianeptine does not produce the expected acute positive effects on emotional...
processing seen with other clinically effective antidepressants, despite tianeptine’s purported antidepressant efficacy. This is an intriguing finding in the context of the lack of consensus regarding tianeptine’s mechanism of action; however, the negative bias found may be consistent with the reported ability of acute tianeptine to increase the re-uptake of serotonin.

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THE EFFECTS OF ECSTASY ON EMOTIONAL PROCESSING AND SELF-AFFILIATION: A NATURALISTIC STUDY
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Introduction: 3,4-Methylenedioxymethamphetamine (MDMA) has been reported to have prosocial and empathogenic interpersonal effects (Schmid et al., 2014, Journal of Psychopharmacology, 28, 847-856), and is being investigated in clinical trials as a possible adjunct to psychotherapy in post-traumatic stress disorder (http://clinicaltrials.gov/show/NCT02102802). In this study, the effects of recreational MDMA (Ecstasy) on self-related processing and interpersonally relevant emotional processing was investigated. Methods: Recreational drug users (n=25) were tested in a naturalistic experiment on two separate days. On one of the days they ingested Ecstasy (Ecstasy session) and on the other they did not (Control session). A sample of was collected for chemical analysis to determine composition. On both days, the Self-Compassion and Criticism scale was used at three time points (T1, T2 and T3) to measure self-critical and self-compassionate responses in scenarios of perceived failure. Behavioural tasks assessed facial expression recognition and valence/arousal of facial stimuli. Trait measures were used in order to investigate the moderating effects of attachment style and dispositional self-criticism and self-compassion. Results: A repeated measures ANOVA for the subjective measures confirmed previous findings of the modulating effect of ecstasy on self-related emotional processing. (Kamboj et al., in press). During the Ecstasy session, participants scored significantly higher on self-compassion compared to the Control session (p = .002, partial eta squared = .27). In addition, participants scored significantly lower on the sub-scale measuring self-critical responses during the Ecstasy session compared to the Control session (p = .004, partial eta squared = .20). For the ratings of arousal in the behavioural task, there was an interaction between Day and Emotion, such that participants reported experiencing higher levels of arousal in response to the critical faces in the Ecstasy session than the Control session (p = .030, partial eta squared = .14). Results are still pending analysis for the mass spectrometry and the second behavioural task. Conclusions: This study shows that the modulatory effects of Ecstasy on self-compassionate and self-critical responses in instances of perceived failure found in the previous study are robust, while also controlling for the effects of other drugs and (pending results) the purity of the Ecstasy. In addition, it was found that self-reported physiological arousal in response to critical facial expressions was higher on the Ecstasy day. This study was completed within the remit of the MSc Cognitive Neuroscience research project module, funded internally at University College London (UCL) and approved by the UCL Graduate Research Committee.

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‘ANTIDEPRESSANT’ TDCS MONTAGE SLOWS EMOTIONAL FACE IDENTIFICATION
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Electrical stimulation of the dorsolateral prefrontal cortex (DLPFC) using transcranial direct current stimulation (tDCS) is purported to enhance cognition and relieve symptoms of depression (Nitsche et al., 2007, Experimental Neurology, 219,14-19). Despite these claims, relatively little is understood about the mechanisms driving the putative cognitive and emotional effects of tDCS of the DLPFC. Here we conducted a double-blind within-groups study in 30 healthy subjects (mean age: 28) to compare the effects of active anodal stimulation of the DLPFC with sham (placebo) stimulation. We mimicked the electrode montage and stimulation parameters typically used in trials of tDCS for depression and other psychiatric disorders. We found that 20 minutes of anodal tDCS of the DLPFC significantly slowed reaction times more than sham (placebo) stimulation during an emotional face identification task. A repeated-measures ANOVA comparing reaction times (for correct responses) for six different emotions for real or sham stimulation revealed significantly slower responses under tDCS F(1,29) = 20.702, p<0.001 and slower responses to negative versus positive emotions F(5,145) = 5.249, p<0.001. No interaction between emotion and tDCS was found, nor was any main effect of tDCS on accuracy. After collapsing across all negative emotions, planned contrasts revealed that active tDCS produced significantly longer reaction times for negative emotions compared to sham, t(29) = -4.090, p<0.001. The effect of tDCS on reaction times in emotional face identification builds on previous
research implicating the DLPFC in emotion perception. However, the directionality of this effect—that anodal tDCS of the DLPFC slows emotion perception—is unexpected, as is its lack of interaction with emotional valence. Potentially, the effect of tDCS on reaction times is a result of increased deliberation in emotion identification, which would suggest a novel cognitive mechanism for the putative antidepressant effects of anodal tDCS of the DLPFC. This research was funded by the Brain Research Trust (CLN).

A32

EARLY CHANGES IN NEURAL RESPONSE TO SUBLIMINAL EMOTIONAL STIMULI PREDICT CLINICAL RESPONSE TO SSRI TREATMENT IN DEPRESSION

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Introduction: Antidepressant treatment has been shown to modulate behavioural and neural markers of negative affective bias in depressed patients as early as a few days after the start of such treatment. It has been of interest whether such early changes occur when emotional information is presented at the subliminal level, i.e. while its recipients are unaware of the emotional input. These early changes in the processing of subliminal emotional information at the neural level may be the key mechanism of later clinical improvement and may act as a predictor of response over a longer period of time. Methods: 32 unmedicated patients meeting DSMIV criteria for major depression were prescribed the SSRI escitalopram (10mg) over 6 weeks. The neural response to sad and happy emotional facial expressions presented below the level of awareness and then masked with neutral facial expressions was assessed both before and after 7 days of treatment. FMRI data was acquired at a 3T scanner. Early changes in the neural response to sad vs happy facial cues were compared between those patients classified as responders vs non-responders by week 6. Results: Twenty (62.5%) patients responded to escitalopram by the end of treatment (week 6). This group had a greater reduction in neural response to sad vs happy facial expressions after 7 days of escitalopram compared to non-responders across a network of regions including the right amygdala, the right hippocampus and the right parahippocampus (P<0.05, FWE corrected whole brain analysis). Responders and non-responders did not differ in terms of depression scores after 7 days. The two groups did not differ in terms of age, gender, duration of the current episode or baseline depression scores. Conclusions: These results support the hypothesis that early changes in the neural processing of emotional information with SSRI treatment are important for later clinical improvement, even when this information is received at the subliminal level. Such early changes on the neural level may be followed by learning new, more positive associations in the context of reduced negative biases, in the absence of the objective and subjective change in mood, creating the background to such a change later in treatment. As such, early correction of subliminal negative bias may be a key mechanism of antidepressant drug action and may provide an early neural biomarker of clinical response to antidepressant treatment in depression. The study was funded by Medical Research Council.

A33

NEURAL RESPONSES TO REWARD AND AVERSION IN YOUNG PEOPLE AT INCREASED RISK OF DEPRESSION

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We have shown in previous studies that those “at risk” of depression (recovered depressed and young people with a family history of depression (FH+)) (McCabe et al., 2009, Psychopharmacology, 205, 667-677; McCabe et al., 2012, Biological Psychiatry, 72, 588-594) have neural deficits in the processing of rewarding and aversive information. However how these differences might map onto current mood in young people has yet to be elucidated. Therefore our aim was to examine the neural response to reward and aversion in young people with high scores on the Mood and Feeling Questionnaire (MFQ). We recruited young people N=16 (Female=12) scoring high on the MFQ > 27, and young people N=17 (Female=11) scoring low on the MFQ < 15, both groups were matched on age (13-18 yrs.). Using functional magnetic resonance imaging we developed a task whereby, participants were presented with a picture of chocolate or mould. Next, they were asked to rate how much they wanted to receive the taste associated with the picture. Participants then completed an effort phase in which they had to work to win a chocolate taste or work to avoid receiving an unpleasant mouldy taste. The subjects were then asked to rate the pleasantness and intensity of each taste. As expected, we did not find any significant group differences in ratings of wanting, pleasantness, intensity for the stimuli or button presses and response times during the effort phase. We found that high MFQ scorers had reduced insula, pregenual cingulate and lateral orbitofrontal cortex responses (p<.05 svc) to chocolate...
pictures, and decreased ventral medial prefrontal cortex and putamen responses (p<.05 svc) to the chocolate taste. For the aversive/unpleasant taste we found increased insula responses in the high MFQ group. We also found decreased precuneus and anterior cingulate responses to the unpleasant picture as well as decreased anterior cingulate, hippocampus, caudate and frontal medial cortex to unpleasant tastes in the high MFQ group (p<.05 svc). Our findings show that young people who score high on the MFQ have compromised neural responses to positive and negative cues in areas that have been shown to underpin motivated behaviour. Further we found enhanced processing of unpleasant taste in the insula in the high MFQ group. These results are similar to our previous results in FH+, providing further evidence that neural responses to reward and aversion might indicate a mechanism by which those “at risk” of depression could have difficulty using positive and negative information to guide adaptive behaviour. Funded by Medical Research Council PhD studentship. This study was approved by the University of Reading Research Ethics Committee.

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MAJOR DEPRESSION AND BIPOLAR DISORDER ARE ASSOCIATED WITH COMMON AND DISTINCT PATTERNS OF GREY MATTER VOLUME REDUCTION

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Introduction: Major depression (MDD) and bipolar disorder (BD) are serious conditions with largely overlapping symptomatology. Neuroimaging studies have shown both conditions to be associated with reduced grey matter volume, suggesting the presence of structural brain changes. Findings are however often heterogeneous and it is unclear whether the two conditions show common or distinct patterns of structural changes. Here we report the largest meta-analysis to date of voxel-based morphometry (VBM) studies in MDD and BD, in order to identify commonalities and differences between disorders. Importantly, we were able to include a number of original statistical maps, which greatly improved the sensitivity of the analysis compared to using reported peak coordinates alone. Methods: A literature search was conducted up to January 2015 for studies that compared whole brain grey matter volume in patients with MDD and BD vs. healthy individuals. Results were analysed using Anisotropic Effect Size Signed Differential Mapping. Original statistical maps were preferred to increase the sensitivity of the analysis, but reported peak coordinates were used if maps were not available. We used meta-analytic comparisons of effect sizes and conjunction analyses to identify regions showing common and distinct grey matter changes in the two conditions. Results: Forty-one studies which compared MDD vs. healthy individuals and 32 studies which compared BD vs. healthy controls were included in this meta-analysis, with original included for 14 of these studies. Medial pre-frontal volumetric reduction, specifically in the bilateral medial superior frontal gyri, ventromedial prefrontal cortex, and anterior cingulate cortex, was common to both conditions, as was volumetric reduction in the bilateral insular cortex. When groups were contrasted, grey matter volume reduction was found in the left hippocampus and right inferior temporal gyrus which was significantly greater in MDD than in BD. Conclusions: Both MDD and BD are associated with substantial grey matter volume decreases in the medial prefrontal cortex and insula, regions heavily involved in affective processing. Findings suggest that common morphometric alterations in key neurobiological circuits may underlie the dysfunctional mood states that characterise both conditions. Robust differences between MDD and BD were identified in the left hippocampus and right inferior temporal gyrus, where reductions were more substantial in MDD than BD. This may reflect differences in the affective or cognitive profiles of the two conditions, although it is difficult to rule out potential confounding effects of mood state or medication use in the included studies. Acknowledgements TW, DA, AJC & AHY receive funding 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. JR is supported by Instituto de Salud Carlos III (Miguel Servet Research contract, CPT4/00041, and project grant PI14/00292). We wish to thank the authors who provided statistical maps for this meta-analysis.
LURASIDONE FOR OLDER ADULTS WITH BIPOLAR DEPRESSION: ANALYSIS OF TWO DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES

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Introduction: To date, no placebo-controlled trial has been reported that evaluates the efficacy of pharmacologic treatments for bipolar disorder in older adults. The aim of the current secondary analysis was to evaluate the efficacy of lurasidone in patients aged 55 years and older with bipolar depression. Methods: Patients meeting DSM-IV-TR criteria for bipolar I depression with a Montgomery-Åsberg Depression Rating Scale (MADRS) score ≥22 were randomized to 6 weeks of double-blind treatment with lurasidone 20-60 mg/day or 80-120 mg/day (combined in the current analysis), or placebo in a monotherapy study; or lurasidone 20-120 mg/day or placebo in an adjunctive therapy study with either lithium or valproate. The primary endpoint was LS mean change at Week 6 in MADRS total score. Secondary endpoints included the Clinical Global Impression scale for use in bipolar illness (CGI-BP-S), the Quick Inventory of Depressive Symptomatology-self report (QIDS-SR16), the Hamilton Anxiety Rating Scale (HAM-A), and the Sheehan Disability Scale (SDS). Response was defined as ≥50 percent reduction in MADRS score; remission was defined as a MADRS ≤12 (both at last observation carried forward [LOCF] endpoint). Results: The proportion of older adults was 83/485 (17.1%) in the monotherapy study, and 53/340 (15.6%) in the adjunctive therapy study. In the monotherapy study, greater LS mean change at week 6 was observed for lurasidone vs placebo in the MADRS (-14.8 vs -7.1; P=0.003), the CGI-BP-S (-1.7 vs -0.8; P=0.012), the QIDS-SR16 (-6.1 vs -3.3; P=0.035), the HAM-A (-6.0 vs -2.6; P=0.069), and the SDS (-8.9 vs -6.5; P=0.315). Treatment with lurasidone was associated with significantly higher Week 6 responder rates (46.4% vs 14.8%; P=0.008) and remitter rates (37.5% vs 14.8%; P=0.036). At Week 6 in the adjunctive therapy study, mean change was numerically greater for lurasidone vs placebo on the MADRS (-13.9 vs -11.1; ns), and the CGI-BP-S score (-1.4 vs -0.9; ns) and responder rates were also numerically greater for lurasidone vs placebo (46.2% vs 37.0%; ns). A significant efficacy advantage was not observed for lurasidone compared with placebo on any of the secondary efficacy measures. Discontinuation rates due to adverse events in the lurasidone groups were comparable to placebo in both studies. Conclusions: Lurasidone monotherapy has significantly greater efficacy than placebo in the treatment of older adults with bipolar depression; efficacy was numerically, but non-significantly, greater on adjunctive therapy with lurasidone. Lurasidone was well-tolerated in the short-term treatment of older adults with bipolar depression. Clinicaltrials.gov identifier: NCT00868699, NCT00868452. Sponsored by Sunovion Pharmaceuticals Inc.

LURASIDONE FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER WITH MIXED FEATURES: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED 6 WEEK TRIAL

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Introduction: DSM-5 introduced a new diagnostic classification of unipolar major depressive disorder (MDD) that permitted use of a mixed features specifier in patients presenting with ≥50 percent reduction in MADRS score; remission was defined as a MADRS ≤12 (both at last observation carried forward [LOCF] endpoint). Results: The proportion of older adults was 83/485 (17.1%) in the monotherapy study, and 53/340 (15.6%) in the adjunctive therapy study. In the monotherapy study, greater LS mean change at week 6 was observed for lurasidone vs placebo in the MADRS (-14.8 vs -7.1; P=0.003), the CGI-BP-S (-1.7 vs -0.8; P=0.012), the QIDS-SR16 (-6.1 vs -3.3; P=0.035), the HAM-A (-6.0 vs -2.6; P=0.069), and the SDS (-8.9 vs -6.5; P=0.315). Treatment with lurasidone was associated with significantly higher Week 6 responder rates (46.4% vs 14.8%; P=0.008) and remitter rates (37.5% vs 14.8%; P=0.036). At Week 6 in the adjunctive therapy study, mean change was numerically greater for lurasidone vs placebo on the MADRS (-13.9 vs -11.1; ns), and the CGI-BP-S score (-1.4 vs -0.9; ns) and responder rates were also numerically greater for lurasidone vs placebo (46.2% vs 37.0%; ns). A significant efficacy advantage was not observed for lurasidone compared with placebo on any of the secondary efficacy measures. Discontinuation rates due to adverse events in the lurasidone groups were comparable to placebo in both studies. Conclusions: Lurasidone monotherapy has significantly greater efficacy than placebo in the treatment of older adults with bipolar depression; efficacy was numerically, but non-significantly, greater on adjunctive therapy with lurasidone. Lurasidone was well-tolerated in the short-term treatment of older adults with bipolar depression. Clinicaltrials.gov identifier: NCT00868699, NCT00868452. Sponsored by Sunovion Pharmaceuticals Inc.
ABSTRACTS

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vs -13.0; P<0.0001; effect size, 0.80), the CGI-S score (-1.83 vs -1.18; P<0.0001; effect size, 0.60), the YMRS score (-7.0 vs -4.9; P<0.0001; effect size, 0.61), and the HAM-A total score (-9.9 vs -5.4; P<0.0001; effect size, 0.78). The incidence of adverse events resulting in discontinuation was 2.8% and 5.0%, respectively, on lurasidone and placebo. Nausea was the only adverse event that occurred with an incidence ≥5% on lurasidone and greater than placebo (6.4% vs 2.0%). Treatment-emergent rates of mania and suicidal ideation were lower on lurasidone compared with placebo (2.8% vs. 5.0%; and 5.5% vs. 7.0%, respectively).

Conclusions: Lurasidone was well-tolerated and demonstrated significant efficacy in the treatment of unipolar MDD presenting with mixed features. Trial registration: ClinicalTrials.gov Identifier: NCT01423240 This study was sponsored by Sunovion Pharmaceuticals, Inc.

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ADVERSE CHILDHOOD LIFE EVENTS AND POSTNATAL MOOD EPISODES AMONG WOMEN WITH BIPOLAR DISORDER

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Background: The early postpartum has been established as a period of increased vulnerability for psychiatric mood illness. Women with bipolar disorder (BD) in particular are at elevated risk of postnatal depression (PND) and of postpartum psychosis (PP). Though adverse childhood life events (ACLEs) have been implicated in the aetiology of PND, this has rarely been studied in relation to PP. Furthermore, despite being at high risk of relapse following childbirth, little research has assessed the relationship between ACLEs and postnatal mood episodes (PNEs) exclusively in women with BD. Therefore, our aim was to explore associations between ACLEs and occurrence of both PND and PP in a large sample of women with BD.

Methods: Participants were 665 parous women with BD who had been recruited into the Bipolar Disorder Research Network study. Diagnoses and lifetime psychopathology were obtained via a semi-structured interview (SCAN). Postnatal psychiatric history and experience of 7 ACLEs were also assessed. Where available, all information obtained at interview was confirmed from psychiatric case notes. Women were classified into three groups according to postnatal psychiatric history: 1) those who had experienced no postnatal mood episode (no PNE, n=224), 2) women with a history of PND (n=223) and 3) women who had experienced PP (n=208). A Pearson's chi-square test was used to compare the prevalence of each type of ACLE between women in the no PNE group and those with a history of PND or PP.

Results: Women with PND were significantly more likely to have experienced emotional, sexual or physical abuse in childhood compared with women who had no history of a PNE (p<0.05). In particular, childhood sexual abuse was reported significantly more in the PND than the no PNE group (P<0.05). In contrast, there were no significant differences in the frequency of reporting of any ACLEs between women who had no PNE and those with PP. Conclusions: Our findings indicate that childhood abuse, sexual abuse in particular, is associated with PND among women with BD. In contrast, we found no evidence for an association between any ACLE and PP, suggesting that biological factors are likely to play a more important role in the aetiology of psychosis in the early postpartum.

Funding: This research is funded by the Wellcome Trust and Stanley Medical Research Institute. The study was given a favourable ethical opinion for conduct in the NHS (or other) by the West Midlands Multi-Centre Research Ethics Committee (MREC/97/7/01).

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GROWTH FACTORS ARE ASSOCIATED WITH TREATMENT-RESPONSE AND BIPOLARITY IN AFFECTIVE DISORDERS

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Introduction: Previous research has implicated neurogenesis dysregulation in depression and bipolar disorder (Fournier & Duman, 2012, Behavioural Brain Research, 227, 440-449; Hashimoto, 2010, Psychiatry & Clinical Neurosciences, 64, 341-357). However, the specific nature of this relationship, including how these relate to clinically important factors such as treatment response and bipolarity, is not yet understood. Elucidating the intricacies of these associations has implications for improving diagnostic accuracy and optimising treatment strategies. We aimed to obtain a preliminary understanding of whether treatment differentially affects growth factors in subgroups of depressed individuals. Method: Neurogenic
biomarkers were measured in 25 unipolar and 12 bipolar depressed patients on admission and discharge from an inpatient treatment program. Both groups were highly treatment-resistant at baseline, and 41% of the sample responded to treatment. Vascular endothelial growth factor (VEGF), soluble FMS-like tyrosine 1 (sFlt-1; soluble VEGF receptor-1) and brain-derived neurotrophic factor (BDNF) were measured in circulating serum before and after a course of naturalistic, individualised treatment (both pharmacological and psychological). Results: Unipolar patients consistently had higher levels of BDNF than bipolar patients, though the difference was only statistically significant at baseline; demonstrated with nominal P-values; p=0.013. Treatment lowered levels of BDNF only in treatment responders, with non-responders showing a slight increase in BDNF levels (p=0.033). VEGF was higher in bipolar than unipolar patients, but non-significantly at both time-points, and did not change after treatment. However, the soluble VEGF receptor 1 biomarker (sFlt-1), which disrupts VEGF signalling, showed overall decreases during admission (p=0.018), and this was confined to bipolar patients only (p=0.005). The sFlt-1 reduction was also greater in those not responding to treatment (p=0.043), while bipolarity and treatment-response were not associated. Conclusions: Our results demonstrate different patterns of BDNF and sFlt-1 level change between treatment responders and non-responders, and indicate that sFlt-1 reduction may be important in neurogenic mechanisms of bipolar treatment by facilitating VEGF action. This link between sFlt-1 and VEGF may explain current and previous null findings of VEGF change alongside treatment. The small sample is a limiting factor in detecting significant associations between growth factors, treatment response and bipolarity but these findings highlight the need for further investigation into the role of sFlt-1 in depression (especially alongside VEGF), and for bipolarity to be assessed in neurobiological depression research. We are grateful for support from the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King’s College London. This abstract presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

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PHASE SHIFT IN BIPOLAR DISORDER: AN INTEGRAL BUT LONG OVERLOOKED VARIABLE?

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Introduction: Bipolar disorder (BD) is characterised by variations in mood, including depression, mania, mixed mood or ongoing instability with a burden of significant societal and individual harm. It has been suggested that BD may be associated with disturbed circadian rhythms which potentially harbour links with its clinical phenomenology. Physiological phenomena, such as hormonal levels, are guided by well-timed rhythms which ensure stable homeostasis. In addition, biological rhythms are intricately interwoven and synchronise mutually. For instance, body temperature and sleep co-vary in their rhythm, in that temperature is reduced during darkness, which contributes inter alia to sleep. BD has been associated with internal desynchronisation, where circadian rhythms become uncoupled, leading to disturbed sleep or hormonal secretion patterns which might have pathophysiological significance. For instance in BD extended wakefulness can be antidepressant or manico-genic, while excess sleep can be associated with deteriorating depression, suggesting that changes in sleep patterns are more than an epiphenomenon. There is further evidence to suggest that, while overall circadian rhythms do not seem to have a changed frequency, their timing may be shifted. Our aim here is therefore to review the relevant literature, considering whether phase shift is an integral feature of BD, with both relevance to causality and implicated as a possible unifying feature in treatment and stability. Methods: We comprehensively reviewed the existing literature using the main medical databases (Embase, Pubmed/Medline, PsycINFO). Only human studies with patients suffering from BD I or II, seasonal affective disorder or unipolar affective disorder either with a current episode or in remission were included. For each included study, we systematically collected data regarding the publication (author names, journal, year of publication, country of origin), study design and methodology, patient and comparison group characteristics, study outcomes and the main results. Results: Thirty-eight studies comprising 998 individuals were included in this review. The results indicate that phase advances in circadian rhythms may be more common than delays and that a complex condition such as BD is unlikely to be classifiable by a uniform abnormality. Conclusions: Phase shift disruptions possibly constitute a core clinical feature of BD with relevance to deterioration. In addition, they may provide a useful focus in the multi-level management of BD, potentially unifying medication and non-pharmacological interventions. However, this review also highlights the lack of results from high-quality randomized controlled trials, which might more clearly indicate the value of chronobiologically relevant treatments in phenotype pre-specified patient samples. Funding for HH was through an Erasmus Grant.
SYMPTOMATIC AND FUNCTIONAL RECOVERY IN BIPOLAR DEPRESSION: POST-HOC ANALYSIS OF A 6-WEEK, PLACEBO-CONTROLLED LURASIDONE TRIAL FOLLOWED BY A 6-MONTH CONTINUATION STUDY

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Introduction: Full symptom resolution and functional recovery is the ultimate treatment goal for patients with bipolar depression. The objective of this post-hoc analysis was to evaluate symptomatic and functional remission and recovery in patients with bipolar depression treated with lurasidone. Methods: Outpatients meeting DSM-IV-TR criteria for bipolar I depression, were randomized to 6 weeks of once-daily, double-blind treatment with lurasidone 20-60 mg (LUR20-60), lurasidone 80-120 mg (LUR80-120) or placebo (PBO), followed by a 6-month, open-label continuation study. Recovery was defined as meeting criteria for both symptomatic remission (Montgomery-Asberg Depression Rating Scale total score ≤ 12) and functional remission (all Sheehan Disability Scale domain scores ≤ 3) sustained for at least 3 months in the 6-month continuation study. Results: At end of the 6-week, randomized, acute phase, a significantly higher proportion of lurasidone-treated subjects met criteria for recovery cross-sectionally (both symptomatic remission and functional remission) (33.3%, 91/273) compared to the placebo group (21.0%, 30/143, p<0.05, NNT=9). In the 6-month continuation study, the proportion of lurasidone-treated subjects achieving sustained recovery was 61% (85/140) and 45% (31/69), for subjects who continued lurasidone treatment (LUR-LUR) and who switched from placebo to lurasidone (PBO-LUR), respectively. The proportion of subjects attaining sustained symptomatic remission was 73.2% (112/153) for LUR-LUR subjects and 66.6% (50/75) for PBO-LUR subjects in the 6-month continuation study. The proportion of lurasidone treated subjects maintaining sustained functional remission was 64.6% (95/147) for LUR-LUR subjects and 56.7% (42/74) for PBO-LUR subjects in the 6-month continuation study. There was also a significant increase in the rate of symptomatic and functional remission from week 6 to week 32 (month 6 of the continuation study) (p<0.001, independent of the treatment groups (p=0.798, treatment-by-time interaction). Multivariate logistic modeling revealed that statistically significant predictors of sustained recovery included: lower baseline global clinical severity (CGI-BP Overall), non-white race, and taking lurasidone (rather than placebo) during the acute phase. Conclusions: These findings, derived from a 6-week acute and 6-month continuation study period, suggest patients treated with lurasidone achieved substantial rates of recovery from bipolar depression (both symptomatic and functional remission sustained for at least 3 months) in patients treated for up to 6 months in an open-label, continuation study after an initial acute treatment phase. This study is supported by Sunovion Pharmaceuticals Inc.

ONSET AND DELAY TO DIAGNOSIS OF BIPOLAR DISORDER IN THE UK: A REVIEW

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Introduction: Bipolar disorder is a lifelong and disabling condition. Evidence suggests that there is often a significant delay between onset of symptoms and presentation to healthcare services or initiation of appropriate treatment (Saunders, K; Goodwin, G.M. 2010. Advances in psychiatric treatment Vol. 16 318–328) We sought to determine the age of onset and delay to diagnosis of bipolar disorder I in patient populations recruited from the United Kingdom. Methods: A systematic review was performed to identify studies from MEDLINE, internet search and personal reference collections. Information was sought on age at onset and delay from onset to diagnosis or appropriate treatment Results: In total, we identified six suitable studies, all of a retrospective design, concerning age of onset of bipolar disorder in the United Kingdom. These studies suggest that onset is most commonly in an individual’s mid to late twenties. ((1) Raymont et al. 2003. European Psychiatry 18 13–17; (2) Hamshere et al. 2009. Journal of Affective Disorders 116 23–29; (3) Hill et al. 1996. The Sainsbury Centre for Mental Health; (4) Lloyd et al. 2005. British Journal of Psychiatry 186 126-131; (5) Kennedy et al. 2005. Am J Psychiatry 162 257–262; (6) Bipolar UK & RCPsych. 2012. Executive Summary). Data on delay to diagnosis in the UK is very limited. We identified only two appropriate studies, which reported delays of seven and thirteen years respectively. (Rogers et al. 2012. Psychiatry Danubina Vol. 24, Suppl. 1, pp 86–90; Bipolar UK & RCPsych. 2012. Executive Summary) Conclusions: Available UK data suggests a mean onset of bipolar disorder in mid to late twenties, and a substantial delay before diagnosis. However, there are significant limitations to the data available. All were retrospective studies, and were thus reliant on patients’ accurate recall of affective symptoms. Future studies should investigate where diagnostic delay occurs to inform efforts to improve early treatment of bipolar disorder. There were no sources of financial sponsorship.
EXECUTIVE FUNCTION IMPAIRMENTS IN REMITTED DEPRESSION

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Introduction: Cognitive dysfunction associated with depression represents an important dimension of the disorder. A meta-analysis (Rock PL et al. 'Cognitive impairment in depression: a systematic review and meta-analysis.' Psychological medicine 44.10 (2014): 2029-2040) revealed that persistent cognitive impairments after recovery were comparable to the impairments during episodes. Patients with remitted depression had impairments in multiple cognitive domains, including executive function. Persistent difficulties in executive functions could lead to problems in work and social life (McIntyre RS et al. 'Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions’ Depression and anxiety 30.6 (2013): 515-527). Therapeutic interventions addressing executive dysfunction in remitted depressed patients are warranted. Methods: We are currently conducting a double-blind placebo controlled study to investigate the effectiveness of modafinil on cognitive functions in people with remitted depression (UK CRN ID 17355). First session of the study involves baseline cognitive testing with clinical versions of CANTAB tests. Here we present data from the baseline cognitive function assessment from the study sample recruited to date. Participants completed tasks tapping into working memory, executive function (planning), episodic memory and sustained attention. Testing performance of the participants was compared with age matched normative data. Data was available from 21 participants (14 female, 7 male, mean age=48.04±9.40). Results: Analysis revealed that remitted patients were significantly impaired at the difficult 5 move stage of the planning and problem solving task, CANTAB Stockings of Cambridge [p=0.02 (t=2.25, df=23)], 95% CI -1.38 to -0.09. In this limited sample size (n=21), performance on the tests of episodic memory, attention and working memory tasks was not significantly different from the normative data. Conclusion: Preliminary data from our ongoing study showed that even in this relatively small sample, executive function impairments were evident in patients with remitted depression. Previously, modafinil was shown to improve executive functions. The prospective results from our study will allow us to determine whether modafinil can mitigate the executive function impairments in remitted depressed patients. Acknowledgements: This research work was completed at the Behavioural and Clinical Neuroscience Institute which is supported by a joint award from the Medical Research Council and Wellcome Trust (G00001354). This data is from
an ongoing study entitled “Effects of Modafinil on Cognitive Functions and Emotional Processing in Patients with Remitted Depression” which received ethical approval from Cambridge East REC (Reference:14/EE/0178). Muazaffer Kaser is supported by Cambridge-IDB International Scholarship for his PhD and he is supported by his affiliated institution, Bahcesehir University in Istanbul, Turkey.

**A44**

**AN EXPLORATORY STUDY TO INVESTIGATE THE EFFECT OF MINOCYCLINE ON DEPRESSIVE SYMPTOM RELAPSE AFTER RESPONSE TO KETAMINE IN PATIENTS WITH THERAPY RESISTANT MAJOR DEPRESSIVE DISORDER (TRD)**

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Introduction: The repeated intravenous (IV) administration of sub-anesthetic doses of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine induces antidepressant effects in up to 70% of patients with Treatment Resistant Depression (TRD). However, such effects are transient and chronic repeated administration of ketamine is impractical. Potential strategies to prolong ketamine-induced antidepressant effects include alternative glutamatergic modulators, which show similar downstream effects as ketamine but are devoid of acute psychotomimetic effects. Minocycline has antibiotic and anti-inflammatory properties and may modulate glutamatergic neurotransmission. Therefore, we investigated if minocycline could prevent relapse after successful response to IV ketamine in TRD. Methods: Patients with treatment resistant major depressive disorder (MDD) according to DSM-IV (IDS-C30 score ≥ 34) were included in a blinded, randomized, placebo-controlled, exploratory study. The Montgomery-Åsberg Depression Rating Scale (MADRS) was administered at baseline and throughout the treatment phases. Ketamine 0.5mg/kg IV was administered six times during a 12-day open-label (OL) treatment period, concomitantly with oral (PO) minocycline 200mg/day. Subjects with MADRS total score reductions of ≥ 50% compared to baseline during day 7 to 12 or ≥ 40% on day 12 were considered responders to ketamine. Responders were subsequently randomized to continuation of minocycline 200mg/day, or switched to placebo up to day 54 or until relapse in a blinded treatment period. Relapse was defined as a MADRS total score increase to ≥ 30 at any of the scheduled assessments during treatment. Non/partial-responders to ketamine could participate in an OL minocycline arm of the same duration. Results: Twenty-nine patients (55% female, mean age 51 [range 23 – 74] years old, mean MADRS [SD] = 33 [5.00]) received ketamine and minocycline during the OL phase. On Day 12, the mean MADRS decreased cf baseline (-15.6 [10.62]; n=26). Fourteen (54%) patients met response criteria (mean MADRS on Day 12 = 8.9 [5.5]) and were randomized to either placebo (n=7) or minocycline (n=7). Five of 15 patients who failed to meet response criteria continued OL treatment with minocycline. On day 54, three patients randomized to placebo and one to minocycline had relapsed. No clinical benefit was observed upon OL treatment with minocycline in ketamine non/partial-responders. Both treatments were well tolerated: during OL ketamine treatment dissociative symptoms (41.4%) and headache (37.9%) were the most common adverse events; minocycline treatment caused gastrointestinal symptoms in 20% of all patients. Conclusions: In this proof-of-concept study, 50% of patients with TRD responded to repeated intravenous administration of ketamine combined with orally administered minocycline during two weeks. Fewer responders who were randomized to minocycline met relapse criteria compared to those responders randomized to placebo during the subsequent 6 weeks. These preliminary results provide some support for further evaluation of central anti-inflammatory/glutamatergic modulation in mood disorders as strategies to prolong ketamine’s antidepressant effects. Janssen Research & Development, LLC acted as sponsor for this research.

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**ASSESSMENT OF PATIENT COMPLIANCE USING PHARMACOKINETIC DATA IN CLINICAL TRIALS IN DEPRESSED PATIENTS TREATED WITH VORTOXetine**

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Introduction: Within clinical research, compliance is defined as “adherence to trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements” (CDISC glossary, www.cdisc.org). Noncompliance is a major source of variance in drug response (Harter JG, Peck CC. 1991, Ann. N. Y. Acad. Sci. 618, 563–571). Direct measurement of the plasma concentrations of the drug is one way to measure compliance. Vortioxetine is a novel antidepressant with multi-modal activity. During the clinical development of vortioxetine, plasma concentrations were measured in both healthy subjects and depressed patients and the population pharmacokinetics were assessed in which the oral clearance (CL/F; defined as dose divided by the area under plasma concentration-time curve) was determined. Methods: The distributions of oral clearances of vortioxetine in 887 healthy subjects (26 clinical pharmacology single- and multiple-
A40 ABSTRACTS

A PRECISION MEDICINE APPROACH TO ANTIDEPRESSANT TREATMENT IN DEPRESSION

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Background: Antidepressants have a slow clinical onset of action, taking 4 to 6 weeks before changes in mood become apparent. Currently, no tests exist to guide clinicians as to whether their patient is responding or not. This often results in delays of many months before patients return to good mental health. The General Practice Emotional Test Battery (GP-ETB) is a set of computer-based tasks which measures antidepressant induced change in the processing of emotional information. Such changes are apparent after brief periods of treatment and before improvement in subjective mood. In the current study we assessed whether the GP-ETB could be used to predict, after 7-9 days of treatment, whether depressed patients’ mood would eventually improve after 6 weeks of antidepressant treatment. Methods: From 10 GP surgeries around the UK we recruited 74 patients who were prescribed citalopram to treat their depression. Patients completed the GP-ETB and QIDS-SR before starting treatment and then again 7-9 days later. Response to treatment was assessed using the QIDS-SR which was completed again at week 6. Using the GP-ETB and QIDS-SR scores from the baseline and 7-9 day assessment a machine learning algorithm was derived to predict whether a patient would respond or not to treatment (treatment response was defined as >50% reduction in QIDS-SR score between baseline and week 6). Feature selection and algorithm validation was performed using a leave one out validation procedure. Results: 58 patients completed the full 6 weeks of the study. Of these 22 (37%) responded to treatment. The predictive algorithm, based on baseline and day 7-9 data, was able to predict with 76% accuracy a patient's response status after 6 weeks of treatment. The predictive value was better for patients who did not respond (negative predictive value 78%) than for patients who did respond (positive predictive value 72%). Discussion: These results demonstrate that in a GP setting changes in emotional processing can provide a sensitive early measure of the antidepressant efficacy of citalopram for individual patients. Thus, the GP-ETB system shows considerable promise as a tool to improve the treatment of depression by reducing the time taken for the majority of patients to return to good mental health. Funding: This study was funded with a grant from the SBRI to P1vital Ltd

A47 THE ENDOCANNABINOID SYSTEM IN INTERFERON-ALPHA INDUCED DEPRESSION AND FOLLOWING HISTORY OF CHILDHOOD TRAUMA

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The endocannabinoid (eCB) system exhibits neuromodulatory properties. Its reduced activity has been implicated in depression, however most evidence comes from preclinical models (Zajkowska et al., 2014). Evidence suggests that exposure...
to early stress alters eCB activity, however no studies have looked at the role of childhood trauma (CT) on eCB functioning in adulthood (Agrawal et al., 2012). In this study we investigated involvement of peripheral endocannabinoids (eCBs), anandamide (AEA) and 2-arachidonoylglycerol (2-AG), in the mechanisms underlying depression development upon interferon-alpha treatment for hepatitis C (HCV) viral infection. We then looked at differences in eCB activity between patients with and without history of CT. We measured peripheral serum eCBs at baseline and treatment week (TW) 4 in 74 HCV patients, using High Performance Liquid Chromatography with Tandem Mass Spectrometry. Patients were stratified according to whether they had developed depression or not during treatment, assessed by M.I.N.I. International Neuropsychiatric Interview (Sheehan et al., 1998). To determine history of CT we used the Childhood Experience of Care and Abuse questionnaire (Bifulco et al., 2005). Our results show no significant differences in AEA (t=−.747, p=.495) or 2-AG (U=566, z=−.783, p=.436) levels between depressed and non-depressed patients at baseline. There was a significant increase in 2-AG levels from baseline to TW4 in both depressed (z=3.863, p<.001) and non-depressed (z=3.231, p<.001) patients, while no significant change in AEA levels from baseline to TW4 in both groups (depressed: t=−.711, p=.48; non-depressed: t=−1.318, p=.20). When looking at the effect of CT in the overall sample, we found a trend towards significantly lower 2-AG levels at TW4 in patients with history of CT compared with patients without it (U=429, z=−1.920, p=.055). There were no significant differences in AEA levels at TW4, or 2-AG and AEA levels at baseline, between patients with and without history of CT. When looking at the effect of CT in depressed and non-depressed patients, we found that non-depressed patients with history of CT had significantly lower AEA levels at TW4 when compared with non-depressed patients without CT (t=−2.262, p=.03). There were no other significant differences in eCB levels at either baseline or TW4, between patients with or without history of CT, in neither depressed nor non-depressed group. Our findings suggest no difference in the eCB system between depressed and non-depressed patients before and during treatment. However, depressed and non-depressed patients show different patterns in eCB activity depending on whether they have experienced CT. Furthermore, individuals with history of CT may have reduced eCB activity, a key feature in depression. This work was supported by the Medical Research Council (UK) MR/J002739/1, the European Communities Seventh Framework Programme (Collaborative Project Grant Agreement no. 22963, Mood Inflame) and the NIHR Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London.
responsiveness due to decreased expression and sensitivity of GR may lead to insufficient glucocorticoid signalling and thus elevation of inflammation in these patients. These findings may provide a better understanding of the role of inflammation in the pathogenesis of depression in CHD and an ample support of the observations in regards to inflammation as a remarkable link between these two devastating disorders. This study was supported by the NIHR BRC, BHF, EU-FP7, ECNP and NARSAD Young Investigator Awards.

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NEUROINFLAMMATION IN DEPRESSION: THE M1/M2 MICROGLIA PARADIGM

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Introduction: The presence of neuroinflammation in major depressive disorder (MDD) has been suggested by several previous studies. Recently, positron emission tomography (PET) has been employed to investigate in vivo the presence of neuroinflammation (activation of microglia) by using translocator protein (TSPO) ligands. TSPO is a five transmembrane domain protein localised mainly in the outer mitochondrial membrane and TSPO density is elevated in activated microglia. However, it is currently still unclear whether increased TSPO expression is correlated to a pro-inflammatory (M1) or protective (M2) phenotype of microglia, therefore its role as a hallmark of neuroinflammation requires further investigation. What we actually know is that M1 phenotype releases pro-inflammatory cytokines: tumor necrosis factor α (TNFα), interleukin-1 β (IL1β), interleukin-6 (IL-6), nitric oxide (NO), reactive oxygen species (ROS), while M2 phenotype releases four major anti-inflammatory cytokines to antagonize the pro-inflammatory responses: interleukin -4 (IL-4), interleukin-13 (IL13), interleukin-10 (IL-10) and transforming growth factor-β (TGF-β). In depression the M1/M2 paradigm has still not been clarified. In this study, we systematically reviewed the evidence on microglia activation in depression with the aim of clarifying the balance between M1 and M2 phenotype in this condition. Methods: We systematically searched the following databases: Medline, Embase, Scopus, PsyChInfo and Pubmed. We used the following key words: depress*, MDD, depression, microglia, microglia activation, m1 and m2. From a total number of 1374 articles, 38 articles met our inclusion criteria and were considered for our systematic review. Results: We found five from seven of the post-mortem studies reviewed suggest activation of microglia (ramified and ameboid microglia) in depressed patients. We found only two in vivo PET studies looking at microglial activation using TSPO ligands in patients with depression. While the first study comparing mildly depressed and controls subjects did not find significant elevated TSPO, the second and more recent study focusing on moderate-severe MDD subjects showed increased microglial activation in patients when compared with controls. Preclinical models of depression (such chronic stress models) appear associated with increased levels of pro-inflammatory cytokines, which have been previously linked with the expression of M1 phenotype. Conclusions: The evidence from preclinical models of depression suggests increased expression of M1 phenotype in this condition; however, no study has yet investigated increased TSPO expression in relation to microglia phenotype in humans. Future studies should explore the possible association between peripheral pro-inflammatory cytokine profile and current evidence of neuroinflammation in patients with depression. Financial Sponsorship: nothing to declare

A50

A STUDY OF WRIST-WORN ACTIVITY MEASUREMENT AS A POTENTIAL REAL-WORLD BIOMARKER FOR LATE-LIFE DEPRESSION

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Introduction. Late-life depression is associated with neuropsychological impairments, motor slowing, and structural brain changes that may impact on quality of life (QoL) and activities of daily living (ADL). However, the quantitatively-assessed real-world correlates of these illness features remain poorly understood. Our aim was to determine whether there was a relationship between lab-based measures and physical activity in naturalistic settings using quantitative analysis of activity levels. Method. A novel wrist-worn device that measured multiple activity indices continuously was worn for seven days by 29 older adults with a diagnosis of major depression and 30 age-matched controls. Participants underwent detailed neuropsychological assessment utilising tests of executive function, attention, processing speed and memory. QoL (SF36; Ware JE et al, 1992. Med. Care, 30, 473–83) and ADL scales (IADL; Lawton M et al., 1969. Gerontologist, 9, 179-86) were also administered. For those who further consented to an MRI scan (15 depressed subjects and 15 controls), regional brain
and white matter hyperintensity volumes (WMH) were calculated. Groups were compared on key variables with partial correlation (controlling for age, sex, IQ and Body Mass Index) used to assess relationships between these variables. Results. Physical activity was significantly reduced in depressed subjects compared to controls (t=3.053, p=0.003), with the main effect being reduced morning rather than afternoon activity. Depressed subjects showed a reduction in fine motor movements (t=3.662, p<0.001). Significant correlations were found between reductions in 24hr activity and impairments in ADL (r=0.51, p=0.006) and QoL (r=0.54, p=0.003), and impaired new learning (r=0.55, p=0.002). There was some evidence of a relationship between activity measures and structural brain volumes. Conclusions. Measurement of 24hr activity over 7 days using a novel wrist-worn device was well tolerated in a community setting. Significant reduction in activity in depressed subjects compared to controls were evident, which correlated with several aspects of neuropsychological function, structural brain differences and functioning. Our findings help demonstrate the real-world impact of impairments associated with late life depression. Data from wearable technology may be a novel and highly informative way of monitoring impairments in the real world. This may have significant application in the longitudinal assessment of patients and should be explored further for its utility in association with treatment response and relapse in clinical trials. Acknowledgements. This study was supported by funding from the Medical Research Council (Life-Long Health and Wellbeing initiative) and Research Capability Funding from Northumberland, Tyne and Wear NHS Foundation Trust.

A51

SSRI PRESCRIPTION PATTERNS IN IRELAND, 2004-2013: IS THERE A NORTH/SOUTH DIVIDE?

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Introduction: There have been growing concerns about the increasing antidepressant use in the island of Ireland, featuring regularly in the media against a backdrop of a changing economic, political and social landscape. SSRIs are the single largest class of antidepressant drugs, with regards to prescriptions and their indications go beyond just treating depression. Individual drugs within the SSRI class have come under the spotlight in recent years due to safety concerns, with guidelines and black box warnings being issued either for the class as a whole or for individual SSRIs. As Ireland is divided into two jurisdictions (Irish Republic and Northern Ireland), it represents a unique opportunity to investigate the prescribing patterns for SSRIs over the last number of years. Thus, the purpose of the current study was to investigate SSRI patterns in the Irish Republic and Northern Ireland over the 10-year period from 2004 to 2013, a period that covers the rise and fall of the “Celtic Tiger” economy, and which saw the population rise by approx. 14% in the Irish Republic and approx. 7% in Northern Ireland. Method: The SSRI prescriptions for the 2004-2013 period were obtained from the Health Service Executive (HSE) in the Irish Republic, and from Health and Social Care (HSC) in Northern Ireland. Results: The total number of SSRI prescriptions increased from 943,464 to 1,514,639 in the Irish Republic (an increase of 61%), and from 715,999 to 1,373,173 in Northern Ireland (an increase of 92%). In both countries, SSRIs accounted for over half of the antidepressants prescribed in 2013, a similar proportion to that seen in 2004. In 2004, both countries prescribed sertraline and escitalopram at a similar proportion (approx. 15-19%), whilst there were marked variations in the prescribing of the other marketed SSRIs. For example fluoxetine was the most commonly prescribed in Northern Ireland (31%), whilst citalopram was most widely prescribed in the Irish Republic (30%); paroxetine was prescribed more often in the Irish Republic (20%), when compared to Northern Ireland (12.3%). In 2013, the most commonly prescribed SSRI in Northern Ireland was citalopram (37%), whilst in the Republic it was the S-enantiomer (44%). The proportion of prescriptions for paroxetine fell markedly in both the Irish Republic (7.5%) and Northern Ireland (3.7%) when compared to 2004. Conclusions: This study demonstrates considerable variation in SSRI prescription across the two jurisdictions of Ireland, suggesting a different emphasis on specific drugs within the SSRI class. There was no funding for this project.

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GSK3BETA: A PLAUSIBLE MECHANISM UNDERLYING HIPPOCAMPAL CHANGES INDUCED BY ERYTHROPOIETIN TREATMENT IN MOOD DISORDERS

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HOW EFFECTIVE IS EMOTION MANIPULATION? A META-ANALYSIS

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Emotional states are thought to be derived from synchronized cognitive, affective, motivational and somatic responses to the appraisal of both external and/or internal events (Scherer, 2005, Social Science Information, 44(4), 695-729). Further it has also been proposed that emotional states are derived from well-operationalized events, such as instrumental reinforcers (Rolls, 2000, Behavioural and Brain Sciences, 23, 177-234). The study of emotion utilizes various methods to manipulate emotional states, however specific studies vary by task and by type(s) of emotion studied and are limited in both statistical power and sensitivity. By examining findings across different perspectives on emotion, we conducted a meta-analysis on the effectiveness of emotional state manipulation in healthy adults. Alongside the traditional affective induction procedures (e.g., emotional scenes, music, erotic pictures, faces, imagery, social content), we included studies using pharmacological manipulations. Here we present preliminary data based on 8 studies. Manipulations on emotional states were selected as long as they provided a valid measure of at least one affective component: subjective reports, physiological measures, the startle response magnitude, choice/preference. Cohen d size effects were derived for positive and negative affect based on the same direction of effect (interaction 1: p=0.040 and 0.061; interaction 2: p=0.0047 and 0.071; Fisher’s trend combined p=0.015 and 0.0017, respectively) in genes that have biological connections with depressive illness, endoplasmic reticulum stress, and PPARgamma function (Gold PW., et al., 2013, Mol Psychiatry, 18, 154-65). Conclusions: Identification of the underlying biological network governed by EPO via GSK3β holds promise for the translation of more effective and targeted mood disorder therapeutic treatments. Financial Sponsorship: GlaxoSmithKline & NIHR Biomedical Research Centre for Mental Health Ethics: Bexley & Greenwich RECAcknowledgements: Authors BI, TN, BW, PM, AR and PM were employees of GlaxoSmithKline when the original data was collected.
role in interpreting and successfully adjusting to the environment (LeDoux, 2012, Neuron, 73, 653-676). This work is supported by a MRC Doctoral Training Grant. The authors declare no competing financial interests.

**A55**

**EFFECTS OF PRENATAL ANXIETY ON INFANT DEVELOPMENT**

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Introduction: A third of women suffer from anxiety in pregnancy with higher rates in the first and third trimester (Lee et al., 2007, Obstetrics & Gynaecology, 110, 1102-1112). A few studies have reported negative effects of pregnancy anxiety on infant behaviour (e.g., Brouwers et al., 2001, Infant Behaviour and Development, 24, 95-106). However, most previous research has only looked at the association between postnatal anxiety and infant development. The aim of this study is to investigate whether babies of mothers who were more anxious in pregnancy are less socially competent and show more dysregulated behaviour in a neonatal assessment at six days postpartum. Method: The State Trait Anxiety Inventory (STAI) was completed by 155 women...
at 25 weeks and by 106 women at 32 weeks’ gestation. The Perceived Stress Scale (PSS) and Pregnancy-Related Anxiety Scale (PRAS) were completed by 113 women at 25 weeks and 107 women at 32 weeks’ gestation. Their babies were assessed at six days postpartum with the Neonatal Behavioural Assessment Scale (NBAS). Results: Analyses controlling for infant gender and infant corrected age showed that babies of mothers who had high state and trait anxiety and high perceived stress at both 25 weeks and 32 weeks’ gestation had significantly poorer scores in the social interactive and autonomic stability clusters of the NBAS (all p values <0.05). Babies of mothers who had high state and trait anxiety and high perceived stress at 25 weeks’ gestation also had significantly poorer scores in the regulation of state cluster of the NBAS (all p values <0.05). There were no significant differences between high and low pregnancy-related anxiety scores at either 25 or 32 weeks in relation to any of the NBAS cluster scores. Conclusion: Our data show early developmental effects of anxiety in pregnancy. New born infants of mothers with high levels of both state and trait anxiety, and high perceived stress at two different time points in pregnancy were less socially interactive and their autonomic systems functioned less optimally. Infants of mothers with high anxiety and perceived stress at 25 weeks were less able to regulate their states. Surprisingly, pregnancy-related anxiety did not predict neonatal performance in the NBAS assessment. Sources of financial sponsorship: none

A56
THE IMPACT OF MATERNAL ANTENATAL DEPRESSION ON DEVELOPMENTAL OUTCOMES IN INFANTS AGED 12 MONTHS
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Background: Research examining the impact of maternal mood on offspring development has mostly been conducted after childbirth with relatively few studies starting during pregnancy. Many women who are depressed following childbirth are also depressed during pregnancy – with estimates of the prevalence of antenatal depression as high as 18% (Gavin et al 2005, Obstetrics & Gynecology, 106, 1071-1083). The few available studies reporting the negative effects of antenatal depression on offspring outcomes (Koutra et al 2012, Social Psychiatry and Psychiatric Epidemiology, 48, 1335-1345, Deave et al, 2008, BJOG, 115, 1043-1051, & Otake et al, 2014, Environmental Health and Preventive Medicine, 19, 30-45) have been conducted on older infants, and have largely utilized self-report measures of depression. The aim of this study was to investigate the effects of diagnosed maternal antenatal depression on infant development at 12 months of age. Method: As part of a prospective cohort study data were collected at 25 weeks of gestation, and at 8 weeks and 12 months postnatally. Maternal depression was assessed using the Structured Clinical Interview for DSM-IV (Michael et al, 2002) at all time-points, and infant development was measured using the Bayley Scales of Infant Development (Bayley, 2006). Of 135 women who were assessed during pregnancy, information on the course of depression and infant outcomes at 12 months was available for 107 participants (79%). Results: Univariate analysis examining the association between maternal antenatal depression and infant development, revealed small effects for expressive language skills and motor development which attenuated following adjustment for antenatal and postnatal risk factors; \( \beta = -0.119, p = 0.274 \) and \( \beta = 0.185, p = 0.088 \), respectively. In contrast, persistent depression (depression both during pregnancy and at 8 weeks postnatal) was associated with lower expressive language (\( \beta = -0.29, p = 0.047 \)) and receptive language (\( \beta = -0.307, p = 0.046 \)) scores when adjusting for confounding risk factors. None of the other domains of infant development (i.e. motor and cognitive development) were associated with maternal antenatal depression. Conclusion: The findings highlight the importance of depression in pregnancy. Exposure to persistent depression during and after pregnancy impacts on child development as early as 12 months of age. Financial Sponsorship: None

A57
MATERNAL DEPRESSION DURING PREGNANCY PREDICTS OFFSPRING ADULTHOOD INFLAMMATION: A 26-YEAR STUDY
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Introduction: Studies demonstrate that offspring exposed to maternal prenatal stress show abnormalities in hypothalamic-pituitary-adrenal (HPA) axis function. Less research has focused on the impact of prenatal stress on immune parameters. We examine the influence of exposure to prenatal maternal depression on immune and HPA axis function. Methods: High-
sensitivity C-reactive protein (hs-CRP) and awakening cortisol were measured at age 25 in 103 young-adult offspring of
the South London Child Development Study, a longitudinal birth cohort of mother-offspring dyads recruited in pregnancy
in 1986. Maternal prenatal depression was assessed in pregnancy (20 and 36 weeks); offspring child maltreatment (birth
to 17 years) was assessed at offspring ages 11, 16 and 25; and clinical depression in offspring (18 to 25 years) was assessed
at age 25. Results: Exposure to maternal prenatal depression predicted significantly elevated offspring hs-CRP at 25 years
(OR=11.8, p=.041), independently of depression in adulthood. In contrast, maternal prenatal depression did not predict
offspring adulthood cortisol; however, exposure to child maltreatment predicted elevated awakening cortisol at 25 years
(B=3.7, p=.003), again independently of depression in adulthood. Conclusions: Fetal exposure to maternal depression during
pregnancy has effects on immune function that persist for up to a quarter of a century after birth. Financial disclosure: The
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National Health Service Foundation Trust and the Institute of Psychiatry, Psychology & Neuroscience, King’s College London
and the Medical Research Council United Kingdom

A58
ASSESSMENT TO TREATMENT OUTCOME OF DEPRESSED PATIENTS WITH EARLY LIFE STRESS
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INTRODUCTION: Depression is a frequent, chronic and recurrent medical condition associated to high levels of functional
inability. Early life stress (ELS) is one of the factors that can considerably impair the therapeutic response (Carr et al. 2013.
Journal of Nervous and Mental Diseases 201, 12, 1007-20, Martins et al 2014. The Journal of nervous and mental disease
was composed by N=53 patients in current depressive episodes from Dia Hospital – unit belonging to Clinics Hospital of
Medicine College of Ribeirao Preto. The presence or absence of ELS was confirmed using Childhood Trauma Questionnaire
(CTQ). The advances made along the treatment regarding depressive symptoms were accessed using Montgomery–Åsberg
Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAM-D-21). The suicide ideation was assessed
using Beck Scale for Suicide Ideation (BSI). Other psychometric instruments were also used to measure the severity of
psychiatric symptoms. In this study, the subjects were divided in two groups – depressive patients with and without ELS –
which were assessed in two different moments - in the admission for the hospital treatment and sixty days later. RESULTS:
66% of the patients sample experienced at least one type of severe ELS, compared to other fraction (34%) of subjects that did
not. There was no difference in MADRS scores between groups with and without ELS in admission (with ELS: 30.5; without
ELS: 30.5; p=0.05), nor sixty days later (with ELS: 18.8; without ELS: 13.3; p=0.05). As well, no difference was found in HAM21
assessment between groups with and without ELS in admission (with ELS: 27.5; without ELS: 25.9; p=0.05), nor sixty days
later (with ELS: 19.3; without ELS: 15.3; p=0.05). Concerning suicide ideation, although no difference was found between
groups in the admission (with ELS: 15.7; without ELS: 12.3; p=0.05), sixty days later there was difference between groups (with
ELS: 11.5; without ELS: 1.5; p<0.001). CONCLUSION: Our data highlighted ELS as an important risk and aggravating factor
for suicide ideation in depressive patients. These data show that ELS impairs therapeutic response of depressive patients,
which will need more complex therapeutic approaches. Conflict of Interest Statement: The authors declare that the research
was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of
interest. Acknowledgments: The study was supported by CNPq, CAPES, FAEP and FAPESP grants.

A59
NEUROPSYCHOLOGICAL PERFORMANCE AND HPA AXIS ACTIVITY IN DEPRESSION RELATED TO EARLY LIFE
STRESS
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Background: Evidence shows HPA axis and cognitive dysfunction as key factors to influence depression. Although, the
association between early stress, endocrine function and cognitive changes in depression needs to be better understood.
Therefore, we aimed to investigate the association between neuropsychological performance and HPA axis functioning in
depressive patients with Early Life Stress (ELS). Methods: Participants were 58 men and women, aged between 21 and 60
years, ELS history was determined according to Childhood Trauma Questionnaire - CTQ. We compared neuropsychological performance among depressed patients with ELS (D-ELS: n=31), depressed patients without ELS (D-NoELS: n=8) during a moderate to severe depressive episode (HAM-D-21 score ≥16) and healthy controls (n=19). The neuropsychological data was assessed through 11 tests divided in four cognitive domains: memory, attention, executive functions and intelligence. Additionally, five saliva samples were collected to measure cortisol levels and Cortisol Awakening Response indicators (CAR) in each subject. Results: D-ELS patients were largely impaired in immediate verbal memory recall and recognition, visuospatial perception, attentional span, selective and divided attention, inhibitory control, verbal fluency, cognitive flexibility and executive IQ compared to healthy controls. Considering D-NoELS patients compared to controls showed deficits on attentional span, selective and divided attention. We could not identify any differences between D-ELS compared D-NoELS, probably due to small sample size of D-NoELS group. The peak cortisol level on CAR was positively correlated to performance on RAVLT (r=0.7), and negatively correlated to CTT – part A (r=-0.84), incongruent part and interference of the Stroop test (r=-0.88; r=-0.88) for D-ELS patients. Conclusions: The increase in cortisol levels was associated with better performance in verbal episodic memory, sustained attention and visual search, greater inhibitory control in depressed patients with ELS. Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest Financial Sponsorship: FAPES, CAPES, CNPq

A60
MINERALOCORTICOID FUNCTION AND TREATMENT RESPONSE IN DEPRESSIVE AND BIPOLAR PATIENTS WITH EARLY LIFE STRESS
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Introduction: Hypothalamic–pituitary–adrenal (HPA) axis dysregulation has been linked with depression and bipolar (Juruena et al 2015, Current Pharmaceutical Design, 21, 1369-78). The aim of these study is improve understanding of the neurobiology of affective patients with Early Life Stress (ELS). This study compares the HPA axis responses to GR, MR agonists and MR antagonist and their association with early life stress (ELS) and treatment outcome (Juruena et al 2013, Journal of Psychopharmacology, 27,12,1169–79; Baes et al 2014.Frontiers in psychiatry 5,1-4). Methods: HPA axis response to placebo, MR agonist, like fludrocortisone (FLUDRO, 0.5 mg), Mixed MR/GR agonist, like prednisolone (PRED.5 mg), MR Antagonist, like Spironolactone (SPIRO,400 mg) and GR agonist dexamethasone (DEX,0.5 mg) were evaluated by cortisol in patients with depression (n = 49), Bipolar (n=36) and healthy controls (n = 40). We assessed clinical severity of depression and history of Childhood Trauma on admission and after 60 days of treatment with Childhood Trauma Questionnaire (CTQ). We divided patients with and without ELS according CTQ score and responders and non-responders to treatment according Montgomery Asberg Depression Rating Scale (MADRS). First we split Depressive Patients in two subgroups: those With ELS (n = 61) and Without ELS (n = 24) in Depressive Patients and HC (n = 40). Then we divided those who did not subsequently respond to treatment (< 50% reduction in MADRS; n = 40) and those who did not respond to subsequent treatment (50% reduction in MADRS; n = 45). Salivary cortisol AUC (nmol X h/L) of Cortisol Awakening Response (awake, 30 min and 60 min after) after Placebo, FLUDRO, PRED, DEX and SPIRO was assessed in all subjects. Results: Awakening salivary cortisol (nmol/L) showed differences regarding time, challenge and its interaction (p<0.001). On FLUDRO, PRED and SPIRO treatments, patients showed lower awakening cortisol than controls. AUC after FLUDRO was lower in patients (p=0.01) mainly in HC vs. Without ELS (p=0.02) and HC vs. With ELS (p=0.04). AUC after PRED was lower in patients (p=0.04) mainly in HC vs. With ELS (p=0.03). AUC after SPIRO was also lower in patients (p<0.01) mainly in HC vs. Without ELS (p<0.01), but there was no difference on DEX. Salivary cortisol AUC was lower in patients after FLUDRO (p<0.01), PRED (p=0.02) and SPIRO (p=0.01) in HC vs. Responder, but not after DEX. Conclusions: These findings showed impaired feedback to an imbalance between GR and MR in patients with depression, bipolar with ELS, leading to hypoactivity of the HPA axis. These data suggest MR function is fundamental in the neurobiology and with ELS and preserved MR function is a predictor for good prognosis and treatment response in this sample Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Acknowledgments: The study was supported by CNPq, CAPES, FAEP and FAPESP grants.
A61
DIFFERENCES IN FUNCTIONING OF HPA AXIS BETWEEN PATIENTS WITH UNIPOLAR AND BIPOLAR DEPRESSIONS ASSESSED BY CHALLENGES USING MINERALOCORTICOID AND GLUCOCORTICOID RECEPTORS AGONIST DRUGS

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Introduction: Unipolar and bipolar depressions are distinct psychiatric disorders. However, in clinical practice, many times, is not simple to make an accurate differential diagnosis to distinguish unipolar and bipolar depression. This fact can lead to wrong diagnosis and incorrect treatment indication for many of these depressive patients (Valiengo et al 2012 Journal of affective disorders 138,1, 149-152). Dysfunction of hypothalamus-pituitary-renal (HPA) axis and impaired cortisol feedback due this hormone binding to mineralocorticoid (MR) and glucocorticoid (GR) receptors have been observed in depressive patients (Juruena 2014 Epilepsy & Behavior 38, 148-159; Baes et al, 2014 Frontiers in Psychiatry 5, 1-). Aim: In order to compare the HPA axis functioning of unipolar and bipolar depressive patients, both groups were assessed using pharmacological challenges with MR and GR agonist drugs. Methods: The sample consisted of n=28 patients with unipolar depression and n= 9 patients with bipolar depression. For diagnostic assessment, MINI International Neuropsychiatric Interview (MINI-Plus) was used. All depressed patients had scores ≥16 in Hamilton Depression Rating Scale (HAM-D21). The neuroendocrine assessment was performed by quantification of salivary cortisol and plasmatic ACTH, after the administration of placebo, dexamethasone (GR agonist), prednisolone (MR/GR agonist), and fludrocortisone (MR agonist) at 10 P.M., on the previous day. The salivary were collected at 10 P.M. right after drug administration, and, in the following day, immediately upon awakening, 30 min later, 60 min later, and before plasma collection, which happened at 9 A.M. Results: Bipolar depressive patients presented significant lower salivary cortisol levels (p=0.01), assessed using area under curve (AUC), and ACTH plasmatic levels (p=0.001), when compared to unipolar depressive patients after prednisolone challenge. No difference between bipolar and unipolar groups for salivary cortisol and ACTH plasmatic levels after placebo, dexamethasone, and fludrocortisone challenges. Conclusion: Our data show that bipolar depressive patients have a significant weaker suppression of cortisol and ACTH levels after mixed MR/GR agonist (prednisolone) drug challenge, than unipolar depressive patients; even though, in placebo, GR (dexamethasone) and MR (fludrocortisone) selective agonist drug challenges, there were not differences between bipolar and unipolar groups for salivary cortisol and plasmatic ACTH levels. Thus, these results suggest that prednisolone may be a potential biomarker for distinguishing unipolar and bipolar depressions. Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Acknowledgments: The study was supported by CNPq, CAPES, FAEPA and FAPESP grants.

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CORTISOL LEVELS IN FINGERNAILS AND NEUROCOGNITIVE PERFORMANCE IN EUTHYMIC BIPOLAR I PATIENTS AND HEALTHY CONTROLS

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Background: Neurocognitive impairment has been found in bipolar patients. However, the cause of this is not fully understood. Hypercortisolaemia is a possible cause, but there is no agreement about this. This may be because previous sampling methods assess acute cortisol levels, while the association between psychopathology and cortisol might be explained by chronic levels. Fingernails can now be used to measure chronic cortisol concentration (CCC). In this study we assessed CCC in euthymic bipolar I patients (BD-1) and matched controls using fingernails to see whether differences in CCC influenced neurocognitive abilities. Methods: Data from Cheung et al.’s (Cheung, E.Y.W. et al., 2013. Cognitive performance is impaired in euthymic Chinese patients with Bipolar I Disorder. Journal of affective disorders, 151(1), pp.156–63. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23871126 [Accessed April 1, 2014]) study was used, which found neurocognitive impairment in euthymic BD-1 patients. For the current study, we included a subsample from 82 people who provided fingernail samples, including 42 BD-1 patients and 40 matched controls. The cortisol was analysed using the Warnock et al.’s (Warnock, F. et al., 2010. Measuring cortisol and DHEA in fingernails: a pilot study. Neuropsychiatric disease and treatment, 6, pp.1–7. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2951060&tool=pmcentrez&rendertype
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 protocol. Results: There was no statistically significant difference in CCC between healthy participants and BD-1 (p = .09). Correlational analyses revealed that the CCC in nails of BD-1 patients were not associated with any clinical illness variables. Multiple logistic regression analyses showed that there was no association between CCC and cognitive impairment in all domains before and after adjustment for age and sex. Conclusions: No difference in CCC indicates that this hormone is not a trait illness biomarker in euthymic BD-1. Furthermore, cortisol does not seem to be implicated in the relationship between neurocognitive impairment and BD-1. Future studies should investigate CCC in different illness phases of BD-1. This research was supported for the Psychiatric Research Trust funding and Chilean Bicentennial Fund Scholarships (Becas Chile). Prof Cleare and Prof Young are supported by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and the Institute of Psychiatry, Psychology and Neuroscience at King's College London.

A63 AN ASSOCIATION BETWEEN CHILDHOOD TRAUMA AND CORTISOL LEVELS IN CHRONIC FATIGUE SYNDROME

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Amounting evidence implicates hypoactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis in the pathophysiology of chronic fatigue syndrome (CFS); whilst not consistently replicated, a blunted cortisol response is generally observed. Similarly, evidence suggests early-life trauma may influence HPA axis functionality later in life. Heim et al. (2009) reported that an observed difference between CFS patients and healthy controls was driven by exposure to childhood trauma (CHT), in that when further examined, a reduced CAR was observed only in individuals with CFS exposed to childhood trauma (CHT), with no significant difference found between CFS patients without exposure and controls (Heim et al., 2009. Arch Gen Psychiatry, 66, pp.72-80). This study aimed to further examine the association between cortisol concentrations and CHT in the CFS patient population. We recruited 20 subjects with a diagnosis of Chronic Fatigue Syndrome (mean±SEM age: 37.6±2.2 years; 40% males), and six healthy control subjects without history of childhood trauma (34.8±5.6 years; 33% males). Salivary cortisol was measured at different time points of the day (awakening and 15, 30 and 60 minutes after awakening, noon and 8pm). Cortisol Awakening Response (CAR) and diurnal cortisol were measured using the Area Under the Curve. Experience of childhood trauma was assessed using the Childhood Experience of Care and Abuse Questionnaire. We ran T-test analyses to examine differences in cortisol levels between groups. No significant differences were observed in the cortisol awakening response or diurnal cortisol levels between patients and controls (p=0.48 and p=0.39, respectively). To examine the effect of CHT on cortisol levels, CFS patients were stratified according to experience of CHT. CAR and diurnal cortisol were not significantly different in CFS patients without CHT compared with healthy controls (p=0.36 and p=0.35, respectively), nor between CFS patients with CHT and healthy controls (p=0.46 and p=0.30 respectively). However, CFS patients with CHT showed a significantly higher CAR (mean±SEM 769.9±50.6 versus 568.3±52.9 nmol min/l, p=0.01) and higher diurnal cortisol levels (59.7±5.0 versus 42.1±3.6 nmol h/l, p=0.01) compared with CFS patients without CHT. Childhood trauma appears to be significantly associated with HPA axis hyper-activity in individuals diagnosed with CFS. This appears to be in contrast to a previous study conducted in CFS patients, while similar to studies in depressed patients finding a greater HPA axis hyper-activity in depressed subjects who experienced childhood trauma. Future studies would need to further clarify the interaction between childhood trauma and HPA axis activity in CFS and possible association with comorbidity of depression. This work represents independent work supported by the Medical Research Council (UK) MR/J002739/1 and the Commission of European Communities Seventh Framework Programme (Collaborative Project Grant Agreement no. 22963, Mood Inflame), and part funded by the NIHR/Wellcome Trust, King's Clinical Research Facility and the National Institute for Health Research (NIHR) Biomedical Research Centre [and Dementia Unit] at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.
CORTISOL LEVELS IN CHRONIC FATIGUE SYNDROME AND INTERFERON-ALPHA INDUCED PERSISTENT FATIGUE: A PILOT STUDY

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To further understanding of the underlying mechanisms involved in the development of Chronic Fatigue Syndrome (CFS), research to date has examined other cohorts expected to develop fatigue after an immune trigger. Up to 40% of patients receiving Interferon (IFN)-alpha therapy for Hepatitis C Viral (HCV) infection report persistent fatigue and other symptoms seen in CFS, six-months after cessation of treatment. Dysfunction of the Hypothalamic-Pituitary-Adrenal (HPA) axis has been implicated in CFS, and though results have been mixed, blunted activity has mainly been observed in these patients. This study aimed to examine the role of HPA axis activity in chronic/persistent fatigue in patients with CFS and in HCV patients who developed fatigue following IFN-alpha treatment. Salivary cortisol was measured at different time points of the day (awakening and 15, 30 and 60 minutes after awakening, noon and 8pm). Cortisol Awakening Response (CAR) and diurnal cortisol were measured using the Area Under the Curve. Fatigue was measured using the Chalder Fatigue Questionnaire (CFQ), at a one-off assessment of CFS patients and controls, and six-months post IFN-alpha treatment in the HCV patient group, and participants stratified according to ‘caseness’. Analyses were conducted in 4 groups: Healthy controls (n = 10; mean±SEM age: 34.6±3.8 years; 50% males); CFS (n = 19; 36.9±2.2 years; 37% males); HCV fatigued (n = 11; 42.6±3.9 years; 91% males) and HCV non-fatigued patients (n = 17; 46.4±3.3 years; 65% males). Depressive symptoms were measured using Inventory of Depressive Symptomatology (IDS). ANCOVA analyses controlling for gender and depressive symptoms were run to examine differences in cortisol levels, and severity of fatigue between groups. Correlation analyses were run to examine associations between severity of fatigue and cortisol levels. No significant differences were observed in the cortisol levels of HCV fatigued patients and HCV non-fatigued patients, or healthy controls. CFS patients had a significantly higher cortisol awakening response (mean±SEM 148.7±42.6 versus 69.7±60.3 nmol min/l, p = .029), and lower diurnal cortisol levels (49.9±2.38 versus 69.52±7.8 nmol h/l, p < .005) compared with HCV fatigued patients. Fatigue symptoms were significantly different between the four groups (F (3,50) = 54.9, p < .001). Severity of fatigue was only associated with diurnal cortisol levels in the HCV fatigued patient group (rs = .700, p = .036). Depressive symptoms were not correlated with any measure of cortisol, in any group. Elevated diurnal cortisol appeared to be associated with elevated levels of fatigue in HCV patients with Interferon-alpha induced persistent fatigue, while this association was not found in the CFS group. Patients with CFS showed lower diurnal cortisol levels compared with HCV patients reporting persistent fatigue. Future research would need to further clarify the interaction of the HPA axis with other biological systems in the development of chronic fatigue. This work represents independent work supported by the Medical Research Council (UK) MR/J002739/1 and the Commission of European Communities Seventh Framework Programme (Collaborative Project Grant Agreement no. 22963, Mood Inflame), and part funded by the NIHR/Wellcome Trust, King’s Clinical Research Facility and the National Institute for Health Research (NIHR) Biomedical Research Centre [and Dementia Unit] at South London and Maudsley NHS Foundation Trust and King’s College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

PROFOUND STRUCTURAL AND FUNCTIONAL ABNORMALITIES IN PATIENTS AFTER LONG-TERM REMISSION FROM CUSHING’S DISEASE: EFFECTS OF PROLONGED HYpercortisolISM

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Introduction: Cushing’s disease (CD) is caused by excessive endogenous cortisol exposure. Patients with long-term remission
of CD have persistent psychological and cognitive impairments, which may be associated with prolonged hypercortisolism. It is unknown whether and to what extent these impairments are accompanied by abnormalities in the brain. We set out to investigate structural and functional abnormalities in patients with long-term remission of CD compared with pair-wise matched healthy controls. Methods: We performed a voxel-based morphometry (VMB) (N=25), a diffusion tensor imaging (DTI) analysis (N=22), we investigated resting-state functional connectivity (RSFC) (N=24) and brain activation during emotion processing using an emotional faces fMRI task paradigm (N=21). We also assessed psychological functioning, cognitive failure, and clinical disease severity. Results: VBM: Patients had smaller grey matter volumes of areas in the anterior cingulate cortex (ACC) (on average 14%, p<.05) and greater volume of the left posterior lobe of the cerebellum (on average 34%, p<.05). As expected, patients with remitted CD reported more depressive symptoms (p=.005), more anxiety (p=.002), more social phobia (p=.034), more apathy (p=.002), and more cognitive failure (p=.023) compared with controls, but the differences in grey matter volumes were not associated with psychological or cognitive measures, nor with clinical severity (Andela et al, 2013, European Journal of Endocrinology, 6:811-19). DTI: The ROI analysis showed FA reductions in patients in all of the hypothesized regions, with the exception of the bilateral hippocampal cingulum. The exploratory whole brain analysis showed multiple regions with lower fractional anisotropy (FA) values throughout the brain. Depression symptom severity in the patient group was negatively associated with FA in the left uncinate fasciculus (p<0.05). Post-hoc analyses showed increased radial and mean diffusivity in the patient group (Van der Werff et al, 2014, NeuroImage Clinical, 4:659-67). RSFC: Patients with remission of CD showed an increased RSFC between the limbic network and the subgenual ACC as well as an increased RSFC of the DMN in the left lateral occipital cortex (p<.05). These findings were not associated with psychiatric symptoms in the patient group (Van der Werff et al, 2015, Neuropsychopharmacology, in press). fMRI: Patients showed less medial prefrontal cortex (mPFC) activation during processing of emotional faces compared to controls (p<.05). In addition, functional coupling between the ventromedial PFC and posterior cingulate cortex was decreased in CD patients (p<.05). Conclusions: Our data indicate that previous prolonged exposure to hypercortisolism is related to persisting changes in brain structure and function. Funding: This study was supported through The Netherlands Organization for Scientific Research – National Initiative Brain and Cognition project (NWO-NIHC, project no. 056-25-010) and through The Netherlands Organization for Scientific Research (NWO-VENI, project no. 016136125). Ethics: The study protocol was approved by the medical ethical committee of the Leiden University Medical Center and done in accordance with the principles of the declaration of Helsinki.

THE PREVALENCE OF TRAUMA AND UNDETECTED POST TRAUMATIC STRESS DISORDER (PTSD) IN A COHORT OF ADULTS WITH A MENTAL ILLNESS

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Introduction: Traumatic events are common in populations with a mental illness and this combined with shared vulnerability factors for the development of Post-Traumatic Stress Disorder (PTSD) and other psychiatric disorders, results in high levels of PTSD within this population, which often goes undetected and untreated. Methods: Data was taken from the National Centre for Mental Health (NCMH). Diagnostic and demographic data was collected from at interview and participants returned a set of self-report questionnaires, which included the Trauma Screening Questionnaire (TSQ) and the Life Events Checklist (LEC). This enabled exploration of the rates of undetected PTSD, as indicated by screening positive for PTSD on the TSQ but not having a documented diagnosis of the disorder. Results: 2,001 participants completed the PTSD questionnaire. 370 participants without a diagnosis of PTSD screened positive for PTSD. To explore whether rates of undetected PTSD are higher in certain disorders, a logistic regression was run with binary outcome of PTSD+ as the dependent variable. Disorders with significant undetected PTSD included depressive disorder recurrent (OR=1.86 95%CI=1.34-2.58), emotionally unstable personality disorder (OR=3.88 95%CI=2.33-6.48), obsessive compulsive disorder (OR=2.66 95%CI=1.45-4.89), agoraphobia (OR=3.85 95%CI=1.46-10.17), bipolar II hypomania (OR=1.76 95%CI=1.10-2.81), and schizophrenia (OR=1.63 95%CI=1.07-2.81). A number of significant predictors of undetected PTSD emerged. Conclusions: Rates of undetected PTSD are high within populations with a mental illness. This has significant clinical implications and suggests the importance of routinely establishing a trauma history and screening for PTSD. NCMH is funded by NISCHR, Welsh Government
THE PREDICTIVE ROLE OF SERUM FACTORS IN INTERFERON-ALPHA (IFN-α)-INDUCED DEPRESSION

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IFN-α, a pro-inflammatory cytokine, is the standard treatment for chronic hepatitis C virus (HCV) infection, which causes high rates of depression (Asnis et al., 2006, Journal of Clinical Gastroenterology, 40, 322-335). However, the biological factors that predispose an individual to the occurrence of depression are still unknown. Previous data have reported an alteration in the serum level of inflammatory and neuroplasticity markers in depressed, when compared with non-depressed patients (Cattaneo et al., 2013, Neuropsychopharmacology, 38, 377-385). There is in fact evidence for blood factors, present in the systemic milieu, to penetrate the most permeable areas of the blood brain barrier and affect neuronal formation and synaptic plasticity (Villeda et al., 2011, Nature, 477, 90-94). Our study proposes to investigate whether co-incubation of human hippocampal progenitor cells (HPCs) with serum from IFN-α-treated HCV patients, collected before the treatment, differently modulate neurogenesis when comparing serum from patients who will and will not later develop depression. Serum samples were collected at baseline from 15 IFN-α-treated HCV patients (mean±SEM age: 36.2±12.8 years; gender: 87% males). The multipotent human hippocampal progenitor cell line HPC03A/07 was used to evaluate the effects of serum. Cells were co-incubated with serum samples under proliferation conditions for 48 hs, followed by differentiating conditions for 7 days. Proliferating cells were examined by immunostaining with bromodeoxyuridine (BrdU) and Ki67 whereas apoptotic cells were evaluated with caspase 3 (CC3). Neuronal differentiation was assessed with doublecortin (Dcx) and microtubule-associated protein 2 (MAP2). Three independent experiments were conducted on three independent cultures. Independent samples t-test was used to investigate differences in the immunostaining outcomes between depressed and non-depressed patients. Under proliferation condition, co-incubation of HPCs with serum from depressed patients significantly increased the number of BrdU+ cells (p=0.03), when compared with serum from non-depressed. However, there was no significant difference in the number of Ki67+ cells (p=0.21) and CC3+ cells (p=0.24) between the two groups. Similarly, under differentiating condition DCX+ cells (p=0.20) and CC3+ cells (p=0.15) did not differ upon treatment with serum from depressed and non-depressed patients. However, the number of Map2+ cells was significantly reduced (p=0.01) with serum from depressed patients, when compared with serum from non-depressed. Our findings show that blood factors contained in serum of HCV patients who will later develop depression enhance the proliferation of new progenitors, but reduce their ability to undergo neuronal maturation. This therefore suggests a possible association between the occurrence of depression and reduced neurogenesis. Future analyses should allow the detection of serum factors involved in the alteration of neurogenesis, which may contribute to the advancement of novel therapeutic strategies for the prevention of IFN-α-induced depression. Financial sponsorship: This work was supported by the Janssen Pharmaceutical NV/Janssen Pharmaceutical Companies of Jonhson&Jonhson, the Medical Research Council (UK) MR/J002739/1, the Commission of European Communities Seventh Framework Programme (Collaborative Project Grant Agreement no. 22963, Mood Inflame) and the NIHR Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London.

SMALL-MOLECULE INHIBITORS AT THE PSD-95/NNOS INTERFACE PROTECT AGAINST GLUTAMATE-INDUCED NEURONAL ATROPHY IN PRIMARY CORTICAL NEURONS

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Glutamate and nitric oxide (NO) are important regulators of dendrite and axon development in the CNS. Excess glutamatergic stimulation is a feature of many pathological conditions and manifests in neuronal atrophy and shrinkage with eventual neurodegeneration and cell death. Glutamate binds to the N-methyl-D-aspartate (NMDA) receptor which is functionally coupled to neuronal NO synthase (nNOS) via the postsynaptic protein 95 kDa (PSD-95). Antagonists of the NMDA-R or inhibitors of nNOS have therapeutic limitations and therefore the ability to modulate NMDA-R function by inhibiting the PSD-95/nNOS interaction may be valuable. This study investigated the effect of two NMDA-R antagonists, ketamine and MK-801, the nNOS inhibitor TRIM and two novel small-molecule inhibitors of the PSD-95/nNOS interface, IC87201 and ZL-006, on neurite outgrowth in vitro. Primary cortical neurons from 1 day old Wistar rat pups were cultured for
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3 days. The effect of excess glutamatergic stimulation on neurite outgrowth was investigated by treating neurons with either glutamate or NMDA (100-500µM) and glycine (10µM) for 24h. The effects of NO were also investigated by treatment with the NO precursor, L-arginine or the NO donor, sodium nitroprusside (SNP) (100-300µM). The effect of MK-801 (10nM), ketamine (10nM), TRIM (100nM; 1-[2-(trifluoromethyl)phenyl] imidazole), IC87201 (10 or 100nM; 2-((1H-benzo[d][1,2,3]triazol-5-ylamino)-methyl)-4,6-dichlorophenol) and ZL006 (10 or 100nM; 4-(3,5-dichloro-2-hydroxy-benzylamino)-2-hydroxybenzoic acid) were examined by pretreatment with NMDA (250 µM)/glycine (10 µM) or L-arginine (300µM) for 1h followed by combined treatment with NMDA/glycine and each compound above for 23h before immunocytochemistry and Sholl analysis. Treatment of cultured primary cortical rat neurons with excess glutamate or NMDA combined with glycine suppressed neurite outgrowth as measured by decreased neuritic length and number of neuritic branches. A similar reduction of neurite outgrowth was observed with L-arginine and SNP, implicating excess NO in mediating neurite regression. The NMDA-R antagonists ketamine and MK-801 counteracted the NMDA/glycine-induced reduction in neurite outgrowth and the nNOS inhibitor TRIM prevented both NMDA/glycine and L-arginine-induced decreases in neurite outgrowth. Furthermore, treatment with the small-molecule inhibitors IC87201 and ZL-006 attenuated NMDA/glycine-induced decreases in neurite outgrowth. In conclusion, targeting the NMDA-R/PSD-95/nNOS interaction downstream of NMDA-R promotes neurotrophic effects by preventing neurite shrinkage in response to excess glutamatergic stimulation. The PSD-95/nNOS interface may be an attractive target for treating deficits in neuronal outgrowth and atrophy associated with excessive glutamatergic neurotransmission in neurodevelopmental, neurodegenerative and neuropsychiatric disorders. This work was funded by the Marie Curie Brain Imaging Return to Health (r’Birth) consortium and the Health Research Board of Ireland.

B02
EVIDENCE THAT NITRIC OXIDE INHIBITS THE ACTIVITY OF DORSAL RAPHE 5-HT NEURONES VIA SOLUBLE GUANYLYL CYCLASE

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The dorsal raphe nucleus (DRN) contains the somata of the 5-HT neurones which innervate the forebrain and which regulate various physiological and psychological functions. Many DRN 5-HT neurones express nitric oxide synthase (NOS), which synthesises the gaseous neurotransmitter nitric oxide (NO). Whilst blockade of NOS in the DRN has been shown to affect sleep, feeding and anxiety and depression-like behaviours, the underlying mechanism is unknown. Coronal slices (350µm) containing the DRN were cut from the brains of adult male Lister hooded rats and perfused with aCSF containing 3µM phenylephrine to evoke 5-HT neuronal firing. Extracellular recordings were made from the ventromedial DRN. 5-HT and the NO donor, diethylammonium (Z)-1-(N,N-diethylamino)diazen-1-ium-1, 2-diolate (DEA-NONOate), were applied via the perfusate for 2 min; the soluble guanylyl cyclase inhibitor, 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ), was applied for 5 min before and 2 min during reapplication of DEA-NONOate. Firing rates during drug application were compared with those immediately before. Neurones firing regularly at ≤5 Hz and inhibited by 5-HT (25-100µM) were considered 5-HT phenotype: their mean firing rate was 1.50 ± 0.17 (35) Hz (range 0.54-4.81 Hz). Six neurones with relatively high basal firing 6.71 Hz (range 4.67-8.92 Hz) which were excited by 5 HT (25-100 µM) or showed only small inhibitory response (≤ 25%) at 100 µM were designated as non-5-HT phenotype. All 5 HT neurones tested were inhibited by DEA NONOate. Responses to both 30 and 100 µM DEA-NONOate were statistically significant (paired t tests, p<0.01). Although inhibition was greater at higher concentrations (29.2 ± 9.3 (29), 37.1 ± 9.5 (7), 47.6 ±10.3 (5) % inhibition at 30, 100, and 300 µM), the response to DEA-NONOate was not significantly concentration dependent (ANOVA n.s.). Non-5-HT neurones in the DRN were unaffected by DEA NONO (30-300 µM) (3.0 ± 4.5 (6) % inhibition, n.s.). ODQ (3-30 µM) alone did not alter 5-HT neuronal firing (1.96 ± 0.50 versus 2.15 ± 0.48 Hz (5) before vs during ODQ) but significantly reduced the inhibitory response to DEA-NONOate (30 or 300 µM) (52.7 ± 13.9 (5) versus 3.5 ± 7.3 (5) % inhibition in absence versus presence of ODQ; paired t test, p<0.05). Following washout of ODQ, the response to DEA-NONOate partially recovered. Our data indicate that 5-HT neurones, but not non-5-HT neurones, in the DRN are inhibited by NO via its receptor soluble guanylyl cyclase. This is a potential mechanism by which NO modulators influence behaviours. This work was funded by Newcastle University.
**Bo3**

AN ASSESSMENT OF METABOLISM, BEHAVIOUR AND EXERCISE IN THE PCD5J MOUSE MODEL OF SPONTANEOUS NEURODEGENERATION

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Introduction: The Purkinje cell degeneration (pcd5j) strain is a spontaneous mouse model of neurodegeneration with an early well-defined, progressive loss of cerebellar Purkinje neurons. A natural disease model, it conveys advantages over knockout or transgenic mice, which often only partially demonstrate neurodegeneration. Given its aetiology in human ageing, and the extent of contributory factors, it's difficult to separate the effects of neuronal loss from the ageing phenotype. Here, we investigated the effects of neurodegeneration on metabolic and behavioural indices in the pcd5j strain. Methods: Male and female pcd5j +/-, pcd5j +/− and WT littermates (n=5-14 per group) were subjected to testing at 1, 2 and 3 months of age. On Day 1, mice were tested for spontaneous alternation in a Y-maze to assess short term spatial working memory. On Day 2, mice were tested for locomotor and anxiety-related behaviour in an open field arena (30 mins). These data were analysed using a three-way ANOVA (age x sex x genotype). On Day 3, motor coordination was evaluated using the Rotarod, and the latency to fall was analysed using a two-way repeated measures ANOVA (genotype x trial). For days 3-4, mice were placed in the Comprehensive Lab Animal Monitoring Systems (CLAMS) to record food intake, metabolic rate and locomotor activity. These measures were analysed using a two-way repeated measures ANOVA (genotype x time of day). Results: CLAMS results showed that pcd5j +/- mice of both sexes are significantly less at 2 and 3 months of age (p < 0.001); this was associated with a trend towards increased metabolic rate. CLAMS and open field data revealed no differences in locomotor activity, but fall latency was significantly reduced in pcd5j +/+ mice (p< 0.01) in Rotarod trials. Additionally, pcd5j +/- mice of both sexes showed increased anxiety-like behaviour at 2 months (p= 0.05). Spontaneous alternation was only impaired in pcd5j +/+ females at 3 months of age (p= 0.001) although pcd5j +/+ mice visited less arms at all ages (p < 0.0001). Conclusion: Purkinje cell degeneration has clear suppressive effects on appetite in association with motor coordination impairments, while also altering short term spatial working memory and anxiety-related behaviour in an age-dependent manner. Pcd5j mice are therefore an interesting model for understanding of how neurodegeneration impacts on food intake and metabolism. All work was funded by the University of Nottingham.

**Bo4**

PHARMACOLOGICAL BLOCKADE OF GPR55 IN THE ANTERIOR CINGULATE CORTEX REDUCES FORMALIN-EVOKED NOCICEPTIVE BEHAVIOR IN RATS

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The G-protein coupled receptor GPR55, a putative novel cannabinoid receptor, modulates nociceptive processing in animal models of inflammatory and neuropathic pain (Staton et al., 2008, Pain, 139(1): p. 225-36). Given the expression of GPR55 in the anterior cingulate cortex (ACC) (Henstridge et al., 2011, Mol Endocrinol, 25(11): p. 1835-48), a key brain region involved in the cognitive-affective dimension of pain, we hypothesised that selective blockade of GPR55 signalling in the ACC, would reduce formalin-evoked nociceptive behaviour in rats. The aim of this study was to investigate the behavioural and molecular effects of direct administration of the selective GPR55 receptor antagonist CID16020046 into the ACC on formalin-evoked nociceptive behaviour in rats. Adult male Sprague-Dawley rats (225-250g, n=6-8 per group) were bilaterally implanted with stainless steel guide cannulae just above the ACC under isofluorane anaesthesia and allowed 7-8 days to recover. Rats received bilateral microinjections of either CID16020046 (10 µM /0.5µL) or vehicle into the ACC, 10 minutes prior to intraplantar injection of formalin (50µL, 2.5%). Nociceptive behaviour was assessed for 60 minutes using Ethovision XT software. Post-mortem brain tissues were harvested for histological verification of injection sites and measurement of extracellular signal regulated kinase (ERK) phosphorylation in the ACC. The ipsi- and contra-lateral dorsal horn of the spinal cord was dissected and analysed for the expression of the immediate early gene marker of neuronal activity, c-fos, using qRT-PCR. Microinjection of CID16020046 into the ACC reduced second phase formalin-evoked nociceptive behaviour compared with vehicle-treated controls (treatment: F(11,132)=4.95, p=0.046; treatment x time: F(1,12)=2.06, p=0.028). Furthermore, CID 16020046 treatment was associated with a reduction in phosphorylation of ERK, a downstream target of GPR55 activation, in the ACC (CID vs Veh: 100.0 ± 13.31% vs 61.37 ± 13.48%, p=0.06). Intra-ACC administration of CID16020046...
abolished the formalin-induced increases in ipsilateral spinal cord expression of mRNA coding for c-fos, relative to the contralateral side (CID: ipsi vs contra = 55.26 ± 28.60% vs 69.06 ± 18.14%, p<0.05) and Vehicle (ipsi vs contra= 100.0 ± 18.02% vs 44.75 ± 9.067%, p<0.05). These data suggest that endogenous activation of GPR55 signalling and ERK phosphorylation in the ACC may facilitate formalin-evoked nociceptive behaviour. The attenuation of formalin-evoked spinal c-fos expression by CID16020046 suggests modulatory effects of GPR55 signalling in the ACC on the descending pain pathway. Acknowledgements: This work was funded by a grant from Science Foundation Ireland (10/IN.1/B2976).

**B05**

**INDUCTION OF NEUROPATHIC PAIN DOES NOT AFFECT BASELINE ATTENTION BUT DOES INFLUENCE ATTENTIONAL CHANGES SEEN WITH GABAPENTIN AND AMPHETAMINE**

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Pain is attention demanding. Hypotheses suggest that pain competes for limited cognitive resources, decreasing attention available for goal-directed tasks, causing attentional deficits seen in some pain patients (Legrain et al., 2009 Pain 144, 230-232). Here the 5-choice serial reaction time task (5-CSRTT) was used to investigate effects of pain and subsequent analgesia with gabapentin or putative cognitive enhancement with amphetamine on attentional processing in a rodent model of chronic neuropathic pain. 24 male Lister hooded rats were trained in the 5-CSRTT. To increase cognitive demand a variable inter-trial interval and short stimulus duration were used throughout. Once trained, rats received either partial saphenous nerve injury (PSNI) or sham surgery. Baseline attention was retested one week after surgery. Oral gabapentin (0, 50mg/kg, t=-60mins) then oral amphetamine (o, 3mg/kg, t=-30mins) were tested in separate counterbalanced study designs. Variables recorded were analysed using repeated measures ANOVA with a DOSE within-subjects factor and GROUP between-subjects factor. Analysis of the baseline data did not reveal any significant difference in subject performance pre- and post-surgery or between sham and PSNI groups post-surgery. Gabapentin had a trend DOSE effect on accuracy (F(1,21)=4.296 p=0.051) and a significant effect on correct latency (F(1,21)=10.582 p=0.004). However, gabapentin effects appeared to differ depending on the pain state of the animal. In sham animals accuracy was reduced (p=0.028) and correct latency was unaffected. In contrast, in PSNI animals accuracy tended to be increased (p=0.051) and correct latency was significantly increased (p=0.004). There was a trend towards a GROUP effect on omissions (F(1,21)=4.107 p=0.056) but no post-hoc effects were seen. Amphetamine also induced different effects in the two groups. 3mg/kg decreased accuracy only in PSNI (p=0.031) but decreased correct latency in both groups (sham (p=0.029), PSNI (p<0.0001)) but increased correct latency in PSNI animals only (p=0.050). 1mg/kg decreased accuracy only in PSNI (p=0.031) but decreased correct latency in both groups (sham (p=0.007), PSNI (p=0.035)). This dose also decreased omissions in shams (p=0.02). There was a significant DOSE x GROUP interaction on correct latency (F(2,44)=4.548 p=0.024). In contrast with baseline data, shams had a longer correct latency than PSNI after vehicle (p=0.039). These preliminary data suggest that PSNI-induced pain does not cause attentional deficits in the 5CSRTT, but may influence the effects of different drug treatments. Gabapentin impaired sham but enhanced PSNI group accuracy, suggesting a detrimental effect on attention could be outweighed by analgesic effects. Enhanced sensitivity of PSNI animals to amphetamine may suggest psychostimulants decrease cognitive performance in chronic pain sufferers. This research was supported by Biotechnology and Biological Sciences Research Council (BBSRC) PhD studentship awarded to CE Phelps.

**B06**

**AFFECTIVE PAIN AND ANXIETY-RELATED BEHAVIOUR AS A RESULT OF INFLAMMATORY PAIN IN MICE**

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Chronic pain is estimated to affect every fifth adult on a global level and is often associated with anxiety. Reliable and translational preclinical methods are of major importance in the development and testing of new treatments. Traditionally, pain assessment in animals has been limited to tests relying mainly on reflexive behaviours and do not address the affective component of pain sufficiently. The place escape/avoidance paradigm (PEAP) has been used to assess the affective component of pain in rats. In the current study a mouse version of PEAP was developed and possible confounders were investigated, namely anxiety-like behaviour, locomotor activity, and hedonic levels. Inflammatory pain was induced in mice (female C57BL/6, 18-22g, n=21 for both treatment groups) by intraplantar injections of Complete Freund's Adjuvant (CFA). Mechanical sensitivity was measured before CFA injection and on day 1, 14 and 28 after CFA using a Dynamic Plantar Aesthesiometer. A paradigm to assess
the affective component of pain in mice was developed (mPEAP) by modifying the PEAP setup known from rat studies. Anxiety-like behaviour, locomotor activity and anhedonia was assessed with the elevated zero maze (EZM), an open field setup and a saccharin preference test, respectively. All procedures were approved by the Danish Animal Experiments Inspectorate. CFA significantly reduced the paw withdrawal latency on day 1, 14, and 28 days (RM-ANOVA; F1,42=185.08; p<0.001). In the mPEAP, CFA-treated animals spent more time in the light area (RM-ANOVA; F1,40=6.60; p=0.014), indicating that stimulation of the CFA-treated paw is aversive. In the EZM there was a significant effect of CFA on latency to enter open quadrants and on time spent in open (ANOVA; latency: F1,39=4.48; p=0.041, time in open: F1,39=9.01; p=0.005), indicating an anxiety-like response to CFA treatment. There was no effect of CFA on locomotor activity but a significant decrease in saccharin preference on day 2 after treatment (p=0.028). Intraplantar CFA injection resulted in mechanical hypersensitivity in the entire period. CFA-treated mice spent significantly more time in light in the mPEAP compared to saline-treated animals. This suggests that the PEAP can also be applied in mice to study the aversive component of pain. CFA treatment was also associated with increased anxiety-like behaviour and anhedonia on day 2. Further studies are needed to elucidate if changes in anxiety-like behaviour have an impact on PEAP behaviour in mice. The study is funded by Department of Drug Design and Pharmacology, University of Copenhagen.

Co1

UNALTERED SUSCEPTIBILITY TO NEUROINFLAMMATION IN PRE-SYMPTOMATIC APPSWE/PS1ΔE9 MICE, FOCUS ON GENOTYPE AND SEX DIFFERENCES

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Alzheimer’s disease is a progressive brain disorder characterized by amyloid plaques and neurofibrillary tangles, and is more prevalent in women. Neuroinflammation is one of the main events responsible for the cognitive decline and involves the activation of microglia and astrocytes. Lipopolysaccharide (LPS) is used to trigger acute neuroinflammation response through the binding to the microglial exclusive toll-like receptors-4 (TLRs-4) and is associated with a transient sickness syndrome. We assessed the susceptibility of Alzheimer’s disease (AD) mouse model to LPS by analysing daily living activity, locomotor activity, spatial working memory and glial cells activation 4 hours post-injection, with a particular focus on sex differences. 4.5 month-old female (n=12) and male (n=10) APPswe/PS1ΔE9 and wild-type littermates (n=12 males and 10 females) were used in the study. Sickness syndrome was assessed using the food burrowing test. The spontaneous alternation test was used to measure locomotor activity and spatial working memory. Baseline behavioural performance was evaluated on on the first two days of the experiment. On Day 3, mice received an injection of LPS (100µg/kg, i.v.) or vehicle (PBS) and were assessed behaviourally 4 hours later. Brain tissue was collected for immunostaining of Iba-1 and GFAP to assess microglia and astrocytes density and activation in the hippocampus, respectively. The data were analysed with two-way ANOVA with repeated measures followed Tukey’s post hoc analysis where appropriate. LPS suppressed food burrowing (p=0.0054) and locomotor activity (p=0.001) regardless of genotype or sex, while an improvement in spatial working memory was evident in LPS treated APPswe/PS1ΔE9 female only (p=0.0322). LPS had no effect on microglia and astrocytes, but a higher microglia density in CA2 (p=0.0233), CA3 (p=0.0005) and DG (p=0.0233) and lower microglia activation (p=0.019) were observed in APPswe/PS1ΔE9 female compared to wild-type female. In addition, wild-type female showed reduced microglial density in CA3 (p=0.044) and DG (p=0.009) but higher microglia activation compared to wild-type male (p=0.0209). These data shows that 100µg/kg LPS did not reveal a higher susceptibility of APPswe/PS1ΔE9 mice compared to wild-type mice, regardless of sex. Indeed, LPS induced suppression of daily living and locomotor activity to a similar extent in both genotypes and sex. But improvement in spatial working memory was observed in APPswe/PS1ΔE9 female, suggesting a beneficial effect of microglia stimulation. Further work needs to be done to clarify the mechanisms underlying this beneficial effect of microglia on behaviour, in response to an immune challenge. Founded by UoN, European Union Master Scholarship.

Co2

POSSIBLE COMPENSATORY INCREASE IN PRE-SYNAPTIC PROTEINS IN ADULTS AT HIGHER GENETIC RISK OF ALZHEIMER’S DISEASE

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Introduction: Alzheimer’s disease (AD) has a devastating effect on patients and carers and the prevalence is estimated to quadruple by 2050. Variation in the APOE gene is the major genetic risk factor for the most common form of AD, late onset AD. The human APOE gene has 3 variants, ε2, ε3 and ε4, encoding apolipoprotein E isoforms E2, E3 and E4. E4 heterozygotes have a threefold increase in risk and homozygotes a tenfold increase. The mechanisms remain unclear but may involve
cumulative repair and maintenance inefficiencies. Previous studies of ε4 allele carriers found early neuropathological changes of AD, and cognitive changes have been found even in early middle age. ε4 possession in the absence of dementia was also linked to higher levels of Alzheimer’s pathology at autopsy. Pre-synaptic proteins shown to be decreased in LOAD include synaptophysin (a marker of neuronal content) and SNAP-25 (part of the SNARE complex involved in vesicle fusion). It is currently unclear when ε4-related changes in brain structure and function begin and which changes occur first. We hypothesised that ε4 allele possession in adults aged < 75 is associated with reduced pre-synaptic proteins. Methods: We measured synaptophysin and SNAP-25 by ELISA in superior temporal cortex and hippocampus from 103 individuals with no history of memory problems and no autopsy evidence of AD or any other disease causing dementia. APOE genotyping was performed by liquid phase two SNP one reaction genotyping. We corrected for neuronal content by ELISA measurement of neuron-specific enolase. Previous studies showed good post-mortem preservation of synaptophysin and SNAP-25. Results: There was a trend towards a reduction of neuronal content in ε4 allele carriers (50% reduction, p=0.077). In ε4 allele carriers, although synaptophysin and SNAP-25 were lower per unit volume of cortex, they were higher in both brain areas in relation to neuronal content. The relative increase was particularly marked in the superior temporal gyrus (synaptophysin p=0.032, SNAP-25 p=0.045). Conclusion: A relative increase was found in both synaptic proteins in the superior temporal gyrus, which may reflect a compensatory response to decreased neuronal content. These findings are in contrast to previous animal work suggesting that synaptophysin decreases very early in the disease process, but in keeping with the Cambridge later life study which found increased synaptophysin in individuals with Braak stages III and IV. Very few of these studies had corrected for neuronal content. More research is required to confirm these findings. This work was supported by a research training fellowship from the Wellcome Trust.

C03

INVESTIGATING THE EFFECTS OF AMPAKINE-MEDIATED FACILITATION OF NEUROTRANSMISSION AND ASSOCIATIVE RECOGNITION MEMORY

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The medial prefrontal cortex (mPFC) plays a key role in associative recognition memory by integrating object and location information (Barker et al 2007, J.Neurosci,27,2948-2957). Glutamatergic neurotransmission is critical for facilitating memory processes with positive allosteric modulation of AMPA receptors (AMPAkines) a potential therapeutic target for memory impairments (Damgaard et al 2010, Behav.Brain.Res,144-150). AMPAkines, CX546 and CX516, enhance excitatory neurotransmission by affecting either the amplitude (CX516) or duration (CX546) of synaptic currents (Arai et al 2004, Neurosci,123,1011-1024). In this study we have investigated whether these different actions impact on their in vivo effects in a rodent task of associative recognition memory. Male Lister-Hooded rats (n=15) were implanted with bilateral cannula to facilitate micro-infusion to the mPFC. Animals received drug doses (CX546, CX516, 0.0-0.3µg/µL) according to a within-subject counterbalanced Latin square design, with the experimenter blind to treatment. Animals performed an object-in-place (OIP) task, involving the exploration of four distinct objects in specific locations (sample phase). After a one hour delay animals were exposed to the previous objects except two objects had switched locations (test phase). If recognition memory is intact (discrimination ratio >0), animals will spend longer exploring objects in novel locations versus objects in previously experienced (familiar) positions. Objects/locations were counterbalanced across the cohort. Drugs were administered immediately post sample phase or prior to the test phase to investigate effects on the encoding or retrieval of information. Data were analysed using separate repeated-measures ANOVA for each drug with dose as a within-subject factor. CX546 impaired discrimination performance when administered prior to the test phase (F(2,28)=4.79 p=0.016), and tended to disrupt encoding (F(2,28)=3.05 p=0.063). Animals could not discriminate between novel/familiar object locations, irrespective of dose or time point of administration. CX516 treatment had no effect on recognition memory, with animals showing significant levels of discrimination across both time points. Overall exploration time during the sample or test phases were unaffected by drug treatment. Our findings support evidence that retrieval of associative recognition memory is dependent on excitatory neurotransmission (Barker, Warburton 2008, J.Neurosci,28,2837-2844). Our results show that CX546 but not CX516, impairs long term recognition memory, specifically memory retrieval. These results suggest that the way in which glutamatergic neurotransmission is modulated is crucial to its efficacy in this task, with impairments associated with AMPAkines that prolong rather than enhance the amplitude of synaptic responses. This has important considerations for the development of AMPAkines as cognitive enhancers. This work was supported by funding from the MRC.
C04
THE DORSOLATERAL STRIATUM COULD MEDIATE STRAIN-SPECIFIC EFFECTS OF CHRONIC STRESS ON THE RETENTION OF COPING BEHAVIOUR IN FORCED SWIMMING TEST
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Chronic stress (CS) has negative effect on cognitive processing. We have previously reported strain-specific coping differences to CS in mice, thus stressed DBA/2 (DBA) mice, but not C57BL/6 (C57) showed impaired retention of coping behaviour (i.e., immobility) in the forced swimming test (FST) (Alcaro et al., 2002 Psychopharmacology, 164, 138-43). Here, we evaluate whether this strain difference was due to interference with expression, acquisition or retention of the immobility response. The effects of CS on early gene activation in the dorsal hippocampus (DH) and the dorsolateral striatum (DLS), two important regions in memory formation, was also investigated. Seven week-old (25 g) male DBA and C57 mice underwent CS using a food restriction (FR) protocol (Cabib et al., 2000 Science, 289, 463–5) or were fed ad libitum (FF) (n=8 per group). Two days after the FR protocol half of the animals (n=4 per group) were sacrificed and early gene activation in the DH and DLS was measured using c-fos immunolabeling. The other half of the animals underwent a 10 min FST session and were sacrificed 50 minutes later for the c-fos immunolabeling. In a second study (n=8 per group), DBA and C57 mice were again subjected to FR or FF and immobility was measured in a 10 min FST. Twenty-four hours later immobility was measured again to assess retention. Data were analysed using a two-way or one-way ANOVA where appropriate. C-fos was increased in DH in both strains following FST [p<0.05] and this was further increased by CS [DBA: p<0.01; C57: p<0.05]. In the DLS CS decreased c-fos expression in DBA mice only [p<0.05]. In the FST all the groups demonstrate successful acquisition, as indicated by a significant increase of immobility during the 10 minute training period (DBA-FF: 0-5 min 35±17, 5-10 min 100±26; DBA-FR: 0-5 min 32±15, 5-10 min 86±20; C57-FF: 0-5 min 156±18, 5-10 min 233±14; C57-FR: 0-5 min 151±16, 5-10 min 215±20). Twenty-four hours later CS impaired the retention of the immobility response in DBA mice [p<0.05] (test FF: 110±27; FR 50±20) but had no effect in C57 mice. These results suggest a strain-specific effect of CS on retention coping behaviour in mice that might be mediated by altered DLS activity, a structure involved in retention of immobility response (Colelli et al, 2014 Neurobiol Learn Mem. 111, 49-55). These findings encourage further investigation on the interaction between CS and genetic background in the development of depressive-like behaviour. This work was funded by “Sapienza” University of Rome. All the experiments were conducted according to the Italian national law (DL 116/92) on the use of animals for research.

C05
PRECLINICAL EVIDENCE FOR COGNITIVE EFFECTS OF VORTIOXETINE AND POSSIBLE UNDERLYING MECHANISMS
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Introduction: Vortioxetine is an antidepressant with multimodal activity: it is a serotonin (5-HT)1D, 5-HT3, and 5-HT7 receptor antagonist, a 5-HT1B receptor partial agonist, a 5-HT1A receptor agonist and a 5-HT uptake inhibitor in cellular assays. In clinical studies, vortioxetine improved cognitive outcomes in patients with major depressive disorder (Katona C. et al., 2012, Int Clin Psychopharmacol, 27(4): 215-23; McIntyre RS. et al., 2014, Int J Neuropsychopharmacol, 17(10):1557-67; Mahableshwarkar AR. et al., 2015, Neuropsychopharmacology, doi: 10.1038/npp.2015.52 ). Here we summarize the preclinical evidence for cognitive effects of vortioxetine and a mechanistic hypothesis for its pharmacological actions. Methods: Vortioxetine was studied in various rodent models of memory impairment using different behavioral tests, including novel object recognition, object placement, spontaneous alternation, fear conditioning, social memory and attentional set-shifting. In a quantitative EEG
study, vortioxetine dose-dependently increased the oscillatory power in freely-moving rats (increases: Theta 67%, Gamma 50%). In electrophysiology studies, vortioxetine (20µM) blocked the serotonin (5-HT)-induced inhibitory post-synaptic currents (sIPSC) in CA1 pyramidal cells (%change in amplitude: 5-HT 107±25%, 5-HT+VOR 40±15%) and enhanced long-term potentiation (LTP, %change in field excitatory postsynaptic potential (fEPSP) slope, VEH: 125-140%, VOR: 150-175%) in hippocampal slices. Vortioxetine also increased hippocampal mRNA levels of neuroplasticity-related genes (Nfkb1, Fos, Fmr1, Camk2a, Arc, Shank1, Nlgn2, Rab3a). Conclusion: Consistent with clinical findings, vortioxetine improves cognitive functions in a variety of preclinical models. Vortioxetine enhances neurotransmission and is likely to increase neuroplasticity in relevant brain regions. We hypothesize that the effects of vortioxetine on cognitive functions are mediated via modulation of GABA and glutamate neurotransmission. This work is supported by H. Lundbeck A/S and the Takeda Pharmaceutical Company, Ltd.

Co6

A SYNTHETIC ANALogue OF Cerebrosterol Acts as a positIve allosterIc modulator of the NMDA receptor

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NMDA receptor dysfunction is associated with neurological and psychiatric disorders such as Huntington’s disease and schizophrenia. Cognitive deficits often precede the positive symptoms of these disorders but treatments for these are limited. We recently discovered that the synthetic steroid, Org49209, is a positive allosteric modulator (PAM) of the NMDA receptor. This synthetic steroid has a very similar structure to the endogenous neurosteroid, cerebrosterol which we have also shown to be a PAM of the NMDA receptor. Both steroids are subject to endogenous sulfation, which alters their effects as PAMs. Here we used a single cell calcium-imaging technique to investigate the influence of Org49209 and sulfated Org49209 (Org49230) on NMDA-induced increases of intracellular calcium ([Ca2+]i) recorded from mouse cerebellar granule cells (CGCs) maintained in cell culture (DIV 6-20). Cells were pre-loaded with the fluorescent calcium indicator dye, FURA -2AM, and the alteration in fluorescence used to determine the change in [Ca2+]i produced by a submaximal concentration of NMDA (30 µM), both before and after application of the steroid. Org49209 induced a concentration-dependent increase in the NMDA response of 18.7% (± 7.2) (100nM, n=6); 22.1% (± 9.5) (300nM, n=5); and 36.4% (± 8.7) (1mM, n=5). The enhancement of the NMDA response by Org49230 was more than twice as great, being 53.9% (±11.3) (100nM, n=6); 65.4% (±4.5) (300nM, n=5); and 79.1% (±5.4) (1mM, n=5), demonstrating that not only does sulfation maintain potency, it enhances the efficacy of the steroid precursor. All results are significantly different to the NMDA evoked response, using a repeated measures ANOVA (p<0.001). These results are consistent with the potency of cerebrosterol and cerebrosterol sulfate, and with the increased efficacy observed following sulfation of the endogenous neurosteroids. Changes in cerebrosterol levels have been hypothesized to contribute to the cognitive decline in conditions such as Alzheimer’s or Huntington’s disease, where altered cerebrosterol levels are being investigated for use as disease biomarkers. Given the established role of NMDA receptor function in the synaptic mechanisms underpinning learning and memory, the synthetic cerebrosterol analogues Org49209 and Org49230 provide valuable tools to further explore the role of NMDA-modulatory steroids in health and disease states. Casmira Brazaitis is supported by a SULSA/MSD studentship.

Co7

THE COMBINED EFFECT OF COMT INHIBITION AND THC ON A RAT MODEL OF ATTENTIONAL SET SHIFTING

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Catechol-O-methyltransferase (COMT) modulates prefrontal cortex (PFC) dopamine and PFC activity. The human COMT gene contains a functional polymorphism (Val158Met) that influences enzyme activity: the ancestral Val158 allele has three-to fourfold greater activity than the Met158 allele. Human studies suggest that the COMT Val158Met polymorphism modulates the effects of cannabis use: the Met158 allele may protect against the negative cognitive effects of cannabis or Δ-9-tetrahydrocannabinol (THC), its primary psychoactive compound, compared with the Val158 allele. We investigated, in rats, whether pharmacologically lowering COMT activity, using the brain-penetrant inhibitor tolcapone, might protect against the negative cognitive effects of THC. Male Lister-hooded rats (200-250g) were maintained at 90% of their free
feathering weight. On the day of testing, each animal received two i.p. injections: tolcapone (30mg/kg) or its vehicle, followed one hour later by THC (2.5mg/kg) or its vehicle. Rats were tested on the attentional set-shifting task 30 minutes later. Rats were housed in groups of four and were randomised, within-cages, to one of the 4 drug groups (vehicle-vehicle, vehicle-THC, tolcapone-vehicle or tolcapone-THC; n=7 per group). The experimenter was blind to drug treatment. The number of trials to criterion (six consecutive correct) for each stage of the task was analysed using repeated-measures ANOVA with LSD post hoc tests. Vehicle-THC animals performed significantly more poorly (across all stages) than those given vehicle-vehicle (p=0.036). However, rats given either tolcapone-vehicle (p=0.713) or tolcapone-THC (p=0.984) did not differ from vehicle-vehicle controls. Tolcapone-THC and Vehicle-THC groups differed at trend level (p=0.081). These data suggest that tolcapone might protect against the negative effects of THC on cognitive function. These findings are broadly consistent with human data linking the high activity Val158 allele with a poorer cognitive response to THC, compared with Met158. Furthermore, our data indicate that rodent models may be useful for clarifying the neural mechanisms underlying the reported gene-environment interaction between COMT and THC/cannabis. All experiments were conducted in accordance with the UK Animals (Scientific Procedures) Act 1986 and associated Home Office Guidelines. This research was supported by a Royal Society fellowship awarded to EMT.

Co8
REVERSAL OF PCP-INDUCED COGNITIVE DEFICIT WITH DONEPEZIL: RELEVANCE TO SCHIZOPHRENIA AND THE RDOC INITIATIVE

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Background: Schizophrenia is a neuropsychiatric disorder characterised by cognitive decline, positive and negative symptoms. The acetylcholinesterase inhibitor donepezil and the non-competitive NMDA receptor antagonist memantine are two of the few drugs approved for the symptomatic treatment of Alzheimer's disease. However these drugs have also been shown recently to ameliorate cognitive deficits in schizophrenia (Zhu W. et al, 2014, Neuropsychiatric Disease and Treatment, 10: 1317–1323). Clinically the Research Domain Criteria project (RDoC) is proposing a new disease classification according to behavioural dimension: instead of starting with a disease definition and seeking its underlying neurobiological mechanisms, RDoC begins with current understandings of behaviour-brain relationships and links them to clinical phenomena. Drug targets can therefore be focused on treating the same endophenotype in multiple diseases, to develop new treatments for neurological disorders (http://www.nimh.nih.gov/research-priorities/rdoc/nimh-research-domain-criteria-rdoc.shtml). AIM: The aim of these studies is twofold: (i) to develop a schizophrenia-relevant mouse model of cognitive impairment in a spatial memory task using the non-competitive NMDA receptor antagonist phencyclidine (PCP); (ii) to back translate the recent clinical data with donepezil. Methods: Study 1: 30 male C57Bl/6 mice aged 78 weeks were treated with PCP at 0.5, 0.75 or 1 mg/kg or vehicle (0.9% saline). Study 2: 40 male C57Bl/6 mice aged 7-8 weeks were treated with vehicle alone, PCP at 1mg/kg & vehicle, or PCP and 0.1, 0.3, or 0.5 mg/kg donepezil. Thirty minutes following dosing, spatial memory was assessed using a two-chamber spatial recognition box. Animals were allowed to explore one side for 5mins before being placed back in home cages for a 30min inter trial interval (ITI). Animals were then placed back in the apparatus and allowed to freely explore the whole arena for 5mins. Data were analysed using a paired t-test and one-way ANOVA. Results: Animals dosed with vehicle spent significantly longer exploring the novel vs familiar side of the arena (p<0.001), indicating they remember after a 30min ITI. PCP significantly disrupted this at 1mg/kg without affecting locomotor activity. Donepezil reversed PCP-induced deficits, significantly increasing exploration time in the novel vs familiar side at 0.1 and 0.3 mg/kg (p<0.05 and p<0.01 respectively). Conclusion: These data demonstrate that PCP effectively induces spatial memory deficits in mice that can be reversed with donepezil. This assay provides a valid way to assess putative cognitive enhancers in a spatial paradigm. More interestingly, these data demonstrate that targeting specific cognitive endophenotypes shared by multiple psychiatric disorders is a valid strategy, providing a potential new approach in the treatment of CNS disorders from a personalized medicine standpoint. Financial sponsorship:Takeda Cambridge Ltd.

Co9
PROBING INTRINSIC NETWORK DYSFUNCTION WITH KETAMINE: DISRUPTION OF TASK-INDUCED MODULATION OF DEFAULT MODE OXYGEN FUNCTIONAL CONNECTIVITY IN THE FREELY-MOVING RAT

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Imaging studies have shown that regions of the brain engage in organized patterns of correlated activity forming resting
state networks (RSNs), which are disrupted in numerous neuropsychiatric diseases. Previous reports have demonstrated task-induced decreases in functional connectivity between a default mode network (DMN) node pair, but not within a distinct lateral cortical network pair, using an in vivo oxygen amperometry approach in freely-moving animals. This study assessed the pharmacological modulation of oxygen functional connectivity within and between these two RSNs following administration of the NMDA antagonist ketamine. Male Wistar rats (284-318 g) were implanted with carbon paste electrodes in four different brain regions, 2 DMN nodes - the prelimbic prefrontal cortex (PRL) and the retrosplenial cortex (RSC), and two lateral cortical network (LCN) nodes - anterior secondary motor cortex (M2) and primary somatosensory cortex, jaw region (S1J). Implanted rats were then trained in a blocked design of four 15 minute alternating periods of an instrumental responding task (variable interval 30s schedule) and rest (unscheduled spontaneous behaviour). Once acquired, animals were dosed with either vehicle, or 10mg/kg S(+)-ketamine s.c in a within-subjects, cross-over design 15min before the session. Linear correlations of oxygen signal slow fluctuations (0.01-0.1Hz) were performed and the average ‘rest’ and ‘task’ correlations calculated for each node pair under the 2 treatment conditions. Broadband correlation values were analysed by a Repeated Measures ANOVA with node pair (6 pairings), treatment (veh, ket) and block (rest, task) as within-subjects factors, followed by specific planned comparisons as required. At baseline, significantly higher correlations were observed for signals recorded in node pairs within a defined network (r = 0.56 - 0.63), compared to those between networks (r = 0.12 - 0.19) (F1,16 = 133.61, p <0.001). The DMN pair was specifically sensitive to behavioural state, where significant reductions in connectivity were observed during task (r = 0.52) compared to rest blocks (r = 0.63) (F1,16 = 13.01, p = 0.002). Task modulation of DMN connectivity was abolished by ketamine (r = 0.56 rest, r = 0.51 task) (F1,16 = 15.9, p = 0.022). Further, ketamine also significantly increased between-network functional connectivity (r = 0.30 - 0.36) compared to vehicle (r = 0.05 - 0.22) (F1,16 = 28.58, p <0.001). Ketamine induced a pattern of effects on functional connectivity suggestive of an overall disruption of intrinsic network integrity, and specifically disrupted the sensitivity of a DMN node pair to behavioural state. Pharmacological modulation of intrinsic networks, as measured by in vivo oxygen amperometry in freely-moving animals, offers novel translational endpoints that may usefully predict human rsfMRI outcomes. All authors are employees of Eli lilly & Co.

C10
VALIDATION OF AN AUTOMATED COGNITIVE ASSESSMENT INSTRUMENT

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Cantab computerised cognitive tests have been used in 150 clinical trials worldwide, and have been demonstrated to be sensitive to sustained and acute pharmacological manipulation in patient populations and volunteers. Technological advances now enable the possibility of high-frequency, large-scale measurement of neurocognitive function outside the laboratory, including in clinical trials. However, increased automation of cognitive assessment should still produce equally high quality data as that from face-to-face testing. This study compared cognitive performance measured using Cantab tests delivered on an iPad to the established Cantab software delivered on a Motion touchscreen tablet. Compared to the original Cantab tests, the iPad Cantab tests were shorter (average 20-25 min (Motion) versus 15 min (iPad)), had updated graphics. Importantly, test instructions in the new version of Cantab were delivered using an automated voiceover, whereas in the original Cantab a rater read a standardised script. Eighty-one healthy individuals aged 19 to 67 (M± SD: 40.4 ± 14.7) completed tests from Cantab Research Suite and Cantab Connect Research at 3 time points. Tests assessed psychomotor processing (Cantab Reaction Time: RTI), episodic memory (Cantab Paired Associates Learning: PAL), and executive function (Cantab Spatial Working Memory: SWM). There was a strong correspondence between performance on the two platforms for RTI (r81= 0.80, p < 0.001), PAL (r81= 0.75, p < 0.001) and SWM (r81= 0.84, p < 0.001). The test re-test Test re-test over one week showed good repeatability. > 95% of individuals fell within the limits of agreements, i.e. over 95% of the differences were less than two standard deviations, across all levels of performance. Our results demonstrate that the new iPad Cantab tests have good test-retest properties and good correspondence with the established Cantab technology. Accurate remote assessment using automated administration will facilitate larger-scale studies, making it logistically easier and cheaper to run large-scale studies and long-term monitoring of drug safety and efficacy. Funding: Study was funded by Cambridge Cognition and conducted independently at the University of Maastricht.
C11
THE ACUTE EFFECTS OF CANNABIS AND COCAINE ON PERFORMANCE MONITORING
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Introduction: The use of drugs such as cocaine and cannabis is often associated with risky and unsafe behavior. Performance-monitoring is a central cognitive process that is important for safe and efficient behavior. However, how drugs affect this cognitive process has not been systematically investigated. The aim of the current study was to investigate how administration of cocaine and cannabis alters common electrophysiological and behavioural indices of performance monitoring: the error-related negativity (ERN), the error positivity (Pe) and post-error slowing. Methods: The sample consisted of sixty-one regular polydrug users who received cocaine or cannabis in a double-blind, double-dummy, placebo-controlled randomized three-way crossover design. All subjects performed a modified version of the Eriksen flanker task. The ERN and Pe were measured using EEG for both correct and incorrect response types. In addition, post-error slowing was measured as a measure of behavioral adaptation. The results were analysed with linear mixed models. Ethical approval was obtained for the study and all participants provided written informed consent. Results: The analyses revealed a significant main effect of response type indicating that the ERN was larger to errors vs correct responses (F1,620.125= 516.29, p<0.001). More importantly, there was a significant drugs x response type interaction (F2,620.125= 9.66, p<0.001). Pairwise comparisons showed that the ERN was larger in the cocaine compared to placebo (p=0.001) and smaller in the cannabis compared to the placebo condition (p<0.001). The amplitude of the Pe was also larger for incorrect vs correct responses (F1,619.978= 104.84, p<0.001). However, no interaction with drugs was observed in relation to the Pe (p=0.79). Likewise, the drugs did not differentially affect post-error slowing (p=0.90). Conclusions: The impaired performance monitoring after cannabis is consistent with an impairing effect of cannabis on executive functioning. The effect of cocaine agrees with the cognitive enhancing effects of the drug on human cognition. Critically, the results show that cocaine and cannabis have opposite effects in the acute phase. Furthermore, these opposite effects are restricted to the early phases of performance monitoring, while the late appraisal and behavioral adaptation phases remain unaffected by the drugs. Sources of financial sponsorship: This study was supported by a grant received from The Netherlands Organisation for Health Research and Development (31160206).

C12
AN FMRI STUDY TO THE EFFECTS OF LSD ON THE SUBJECTIVE RESPONSE TO MUSIC
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Introduction: Music and psychedelic drugs are potent ways to modulate affective states, and humans have used these tools throughout history and often in a combined format. In western psychiatry in the 1950s and 1960s, music listening was a key component in pioneering clinical trials with the classic psychedelic drug lysergic acid diethylamide (LSD). It was believed that music acts synergistically with LSD to enhance emotion, to ease access to personal memories, and to enhance eye-closed mental imagery. Recent placebo-controlled clinical trials demonstrated safety and efficacy of psychedelic-assisted psychotherapy, and the significance of music is maintained in the respective therapeutic model. The present study sought to study the brain mechanisms underlying the interaction of LSD with music. Due significant involvement of the parahippocampus (PHC) in both the subjective effects of psychedelics and of music, a prior hypothesis was held that the PHC plays an important role in enhancing some of the subjective effects of music under LSD. Method: Twelve participants underwent fMRI scanning on two separate occasions. In a randomized order, they received LSD (75 mcg) on one occasion, and placebo on the other. One 8-minute music listening block was always presented in between two 8-minute resting
state blocks without music. Primary outcomes included a seed-based functional connectivity analysis of the PHC for the contrast music > rest for LSD > placebo. This was followed by a dynamic causal modelling (DCM) study to assess changes in effective connectivity between the PHC and the visual cortex. Results: Increased functional connectivity was found of the bilateral PHC with the visual cortex. DCM showed that in response to music, input to the visual cortex from the PHC was enhance under LSD. The magnitude of this modulation significantly predicted enhancement of eyes-closed visual imagery and recollection of personal memories. Conclusions: LSD enhances some of the subjective effects of music via enhancing information flow from the PHC to visual cortex. This research received financial and intellectual support from the Beckley Foundation and was conducted as part of a wider Beckley-Imperial research programme.

C13
THE PARADOXICAL PSYCHOLOGICAL EFFECTS OF LSD
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Introduction: Lysergic acid diethylamide (LSD) is a potent serotonergic hallucinogen or psychedelic that modulates consciousness in a marked and novel way. This study sought to examine the acute and mid-term subjective effects of LSD in a controlled study. Methods: Twenty healthy volunteers participated in this within-subjects study. Participants received LSD (75µg, i.v.) on one occasion and placebo (saline i.v.) on another, in a balanced order, with at least 2 weeks separating sessions. Acute subjective effects were measured using the Altered States of Consciousness (ASC) questionnaire and the Psychotomimetic States Inventory (PSI). Mid-term effects were assessed at baseline (pre-LSD/placebo) and two weeks after LSD/placebo via an optimism scale (the Life Orientation Test, LOT-R), the NEO PI-R personality inventory and the Peter's Delusions Inventory (PDI). Results: LSD produced robust psychological effects; including heightened mood (on the “blissful state” scale of the ASC, Cohen's d=1.65, p < .01) but also high scores on the PSI (all sub scales p<.01), an index of psychosis-like symptoms. Increased optimism (t=2.91, df=18, p=0.009) and trait openness (t=1.95, df=19, p=0.03) were observed two weeks after LSD (and not placebo) and there was no change in delusional thinking. Conclusions: The present findings reinforce the view that psychedelics elicit psychosis-like symptoms acutely and yet improve psychological wellbeing in the mid to long-term. It is proposed that acute alterations in mood are secondary to a more fundamental modulation of orderliness or ‘entropy’ of cognition. Moreover, it is proposed that increased cognitive entropy subsequent to 5-HT2AR stimulation, promotes emotional lability during intoxication and leaves a residue of ‘loosened cognition’ in the mid to long-term that is conducive to improvements in psychological wellbeing. This research received financial and intellectual support from the Beckley Foundation and was conducted as part of a wider Beckley-Imperial research programme.

D01
THE GENERATION AND MOLECULAR CHARACTERISATION OF A NOVEL CYFIP1+/- KNOCKOUT RAT AS A MODEL OF NEUROPSYCHIATRIC DISORDER RISK
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CYFIP1 is associated with increased risk to neuropsychiatric disorders such as schizophrenia (Stefansson et al., 2008, Nature, 455: 232-236) and ASD (Burnside et al., 2011, Human Genetics, 130:517-528). A key biological function of CYFIP1 is to repress the translation of neuronal mRNA targets. One such mRNA target is ARC, which is rapidly transported to the dendrites upon synaptic activation, whilst ARC-related pathways have been implicated in schizophrenia risk (Kirov et al., 2012, Molecular Psychiatry, 17:142-153). Genomic studies therefore imply a convergent biological mechanism at the synapse consisting of Cyfip1 and Arc (Hall et al., 2014, Biological Psychiatry, 77:52-58), whilst we have generated and characterised a novel, preclinical animal model of Cyfip1 heterozygous gene reduction. Cyfip1+/− heterozygous knockout rats (Long Evans) were generated via a CRISPR/Cas9 targeting strategy (SAGE laboratories). Brains from adult males and females were extracted (2 months old), as were wild-type littermate controls (n=7/genotype). Prefrontal cortical (n=7/genotype) and hippocampal regions (n=6/7 for WT/Het, respectively) were dissected from each hemi-brain and either prepared for i) quantitative real-time PCR analysis of Cyfip1 and Arc mRNA (utilising Gapdh, Hprt as housekeeper genes and the ΔΔCt method to quantify fold change) or ii) homogenised in a synaptoneurosome preparation (Syn-PER) to isolate pre- and post-synaptic terminals followed by standardised Western blotting techniques and semi-quantitative densitometric analysis. Statistical comparisons were made using an independent T-test (including a Shapiro-Wilk test and Levene's test). qPCR revealed a reduction in Cyfip1 mRNA in the Cyfip1+/− heterozygous knockout rats compared with wild-type littermate controls in both the hippocampus and prefrontal cortex (t(5.62)


= 3.065, P = 0.024 and t(12) = 3.667, P = 0.003, respectively). Additionally, Cyfip1+/- heterozygous knockout rats show a reduction in Cyfip1 protein expression in prefrontal cortical synaptoneurosomes (45.3 ± 5.1% compared with wildtype expression, t(9) = 5.118, P = 0.001), but no such change in equivalent hippocampal synaptoneurosomes. Further, whilst Arc mRNA levels did not alter between Cyfip1+/- knockout and wild-type littermates in either the prefrontal cortex or hippocampus, there was a reduction in Arc protein in prefrontal cortical synaptoneurosomes (t(9) = 5.314, P = 0.0001). Firstly, we validated the Cyfip1+/- knockout rat as a model of reduced Cyfip1 gene dosage, with functional consequences on synaptic Cyfip1 protein levels in the prefrontal cortex. Paradoxically, under basal conditions, reduced Cyfip1 leads to reduced synaptic Arc protein expression within the prefrontal cortex and could subsequently impact upon synaptic plasticity events, of relevance to neuropsychiatric disorders. The work was funded by the Wellcome Trust and the Brain & Behavior Research Foundation.

Do2
L-TYPE VOLTAGE GATED CALCIUM CHANNELS ARE NECESSARY FOR THE CONSOLIDATION OF ASSOCIATIVE MEMORY, EXTINCTION AND LATENT INHIBITION

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Polymorphisms in CACNA1C, which encodes the alpha-1 subunit of Cav1.2 L-type voltage-gated calcium channels (LVGCC), have been found to show genome-wide significant association with schizophrenia and other psychiatric illnesses (Smoller et al., 2013, Lancet, 9875:1371-9). Calcium influx mediated by LVGCCs and subsequent expression of specific activity-dependent genes (Tabuchi et al (2000) J Biol Chem 275, 17269-75) is necessary for forms of synaptic plasticity and learning. Associative memory and other hippocampal-dependent processes have been found to be impaired in psychiatric disorders (Pohlack et al (2011) Mol. Psychiatry, 16:1072-3). The role of LVGCCs, and of Cav1.2 specifically, in cognitive processes affected in schizophrenia are not fully understood. By investigating the effects of inhibiting LVGCCs and genetic knockdown of CACNA1C in a novel heterozygous ethological rat model, we aim to understand the possible molecular mechanisms that link genetic risk and learning and memory deficits associated with psychiatric illnesses. Targeted infusions of diltiazem were used to investigate effects of pharmacological inhibition of LVGCCs on hippocampal-dependent contextual fear conditioning (CFC) and extinction. RT-qPCR was used to assess expression of CACNA1C and LVGCC-regulated genes to characterise the validity of our rat model as a tool for investigating psychiatric disorders. Intrahippocampal diltiazem had no effects on behaviour during CFC (F(1,12)=0.32, P=0.582), but attenuated fear memory at recall 1 day later compared to rats infused with PBS(F(1,10)=6.798, P=0.026). Infusion of diltiazem prior to extinction training had no effect on within-session extinction, however conditioned fear responses were preserved when tested 1 and 7 days later(F(1,13)=8.92, P=0.011). In addition, infusion of diltiazem prior to 4 hour context pre-exposure 1 day before conditioning prevented the inhibition of CFC (F(1,10)=9.286, P=0.012). Heterozygous CACNA1C rats show a 55% reduction in CACNA1C expression (t(7)=2.622, P=0.034). In addition, an associated change in BDNF expression in the PFC and hippocampus is indicated. Our results are consistent with LVGCCs being necessary for the consolidation of associative memory, extinction and latent inhibition, but not acquisition or recall. This concurs with similar findings in the amygdala for cued fear learning and extinction, suggesting a conserved role for LVGCCs in the consolidation of associative learning. Effects on latent inhibition suggest there may be shared molecular processes involved in prior and subsequent inhibitory learning. Our results begin to connect genetic risk to specific learning related symptoms. The transgenic CACNA1C rats show construct validity and further analysis of this novel model may help reveal the biological basis of schizophrenia. Funded by Wellcome Trust

Do3
DNA METHYLATION ALTERATIONS IN PARVALBUMIN GENE IN SCHIZOPHRENIA AND IN RATS UNDERGOING PCP TREATMENT

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Introduction: Schizophrenia exhibits a subtle brain pathology in which deficits in specific GABAergic neuronal subtypes are apparent. Subchronic phencyclidine (PCP) administration to rats and several developmental interventions in animals can produce changes in the brain that model some symptoms of the disease as well as deficits of GABAergic neurons expressing the calcium binding protein parvalbumin (PV) (Abdul-Monim et al., 2008; J Psychopharm 21). We hypothesise that epigenetic factors may contribute to the deficit in PV expression seen in both schizophrenia and these animal models. One such factor could be hypermethylation of the promoter sequence of the PV gene resulting in relative decrease of PV expression. Thus
we undertook to determine whether there was elevated DNA methylation in the promoter sequences of the human PV gene in schizophrenia and the rat PV gene following subchronic PCP administration. Methods: We identified equivalent DNA sequences in the 5′ regions of the human and rat PV genes that contained likely transcription factor binding sequences, and developed a pyrosequencing method for determination of methylation at each of four (human) and two (rat) CpG sites within these sequences following bisulphite reaction. DNA was extracted from hippocampus and prefrontal cortex (PFC) from two series of post-mortem brain tissue (n=25 and 15 patients with schizophrenia; n=15 and 15 controls respectively) and from rats administered either PCP (5mg/kg per day for 7 days; n=10) or vehicle (saline; n=10). The t-test was used for statistical analysis. Results: We found higher methylation in PFC at CpG1 (p=0.029) and hippocampus at CpG2 (p=0.007), associated with rat PCP administration. In post-mortem brain samples, methylation in the hippocampus was consistently increased across all four CpG sites in both series, reaching significance at CpG3 in one series (p=0.016) and at CpG2 (p=0.003) and CpG4 (p=0.0008) in the other. No significant differences were found in PFC. Conclusion: Both subchronic PCP administration to rats and schizophrenia in humans result in a hypermethylation of DNA in equivalent promoter sequences of the PV gene. These results support our hypothesis that environmental or developmental effects on DNA methylation contribute to the deficits in PV expression in both the disease and its animal models. Financial Support: Cnpq (Brazilian Government)

**Do4**

**EFFECT OF VARIATION IN THE COMT GENE ON THC-EVOKED CHANGES IN ACCUMBENS DOPAMINE RELEASE AND BEHAVIOURAL REINFORCEMENT IN MICE**

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The primary psychoactive component of cannabis, delta-9-tetrahydrocannabinol (THC), is thought to interact with a polymorphism in the catechol-O-methyltransferase (COMT) gene (Val158Met) to increase the risk for psychosis and cognitive impairments. Dopaminergic mechanisms are a plausible candidate for mediating this interaction. We used transgenic mice that model the Val158Met polymorphism to investigate the effects of altered COMT activity and acute THC administration on regional brain dopamine release and behavioural reinforcement. Microdialysis coupled with high performance liquid chromatography was used to examine the effects of THC (3mg/kg i.p.) on extracellular dopamine and its metabolites, DOPAC and HVA, in frontal cortex, dorsal striatum and nucleus accumbens in freely moving mice carrying the COMT Met allele (COMT-Met), and their wild type littermates (C57Bl/6, male, 8-10 weeks, n=6-10). Compared to wild type mice, COMT-Met mice had lowered COMT activity as evident by increased DOPAC and decreased HVA in all 3 brain areas. There was no effect of genotype on basal dopamine levels. Compared to vehicle, THC increased dopamine in the nucleus accumbens by 25% in wild type (p=0.01) but not in COMT-Met mice (p=0.58; drug × genotype interaction p=0.03). In comparison, cortical and striatal dopamine levels were not significantly altered by THC, irrespective of genotype. In order to examine the behavioural correlates of the observed neurochemical effect, COMT-Met mice and their wild type littermates were run on a progressive ratio task, a task commonly used to assess the effects of drugs on the efficacy of reinforcers, following administration of vehicle or THC (0.3, 1 or 3 mg/kg) in a latin square design. The behavioural experiments have been completed and the results are being analysed. The current data suggest that genetic variation in COMT activity influences the effect of THC on nucleus accumbens dopamine function. Our data therefore provide a potential mechanism for the reported interaction between COMT Val158Met genotype and cannabis/THC relevant in determining psychosis risk and cognitive impairments. It will be of interest to examine the behavioural correlates of this neurochemical effect. This research was funded by the Royal Society (EMT) and the Wellcome Trust (KS).

**Do5**

**EFFICACY OF AUT6, A NOVEL AND SELECTIVE KV3 CHANNEL MODULATOR, TO ALLEVIATE COGNITIVE AND NEUROBIOLOGICAL DYSFUNCTION IN A SUB-CHRONIC PHENCYCLIDINE RAT MODEL OF SCHIZOPHRENIA SYMPTOMATOLOGY**

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Introduction: The voltage gated potassium channel Kv3.1, mainly located on parvalbumin (PV) GABAergic interneurons, is closely involved in brain circuitry thought to be affected in schizophrenia. Acute treatment with AUT6, a novel Kv3.1
modulator restores deficits in two cognitive domains (recognition memory and problem solving) and social behaviour in the sub-chronic phencyclidine (PCP) rat model of schizophrenia. Kv3 channel modulators may thus provide treatment for these unmet clinical needs in schizophrenia. Our aim was to explore efficacy of chronic treatment with AUT6 to improve cognitive and neurobiological deficits in the PCP model. Methods: Adult female hooded-Lister rats received PCP (2 mg/kg; n=30) or vehicle (n=10) i.p. twice daily for 7 days. After 6-weeks washout, rats (n=10/group) received AUT6 (60 mg/kg; p.o.; PCP-AUT6 group) or vehicle (VEH-VEH and PCP-VEH groups) for 21 days or AUT6 for 21 days plus 7 days washout (PCP-AUT6wo group). Rats were tested for memory performance in the novel object recognition (NOR) test on days 1, 7, 14 and 21 for all groups, and also on days 22 and 28 for the PCP-AUT6wo group. On day 21 (or day 28 for PCP-AUT6wo group), rats were sacrificed and PV and Kv3.1b channel positive cell densities quantified using immunohistochemistry. Results: A significant memory deficit in NOR at each time point was observed in PCP-VEH group (p<0.05; Cohen’s d=0). This deficit was reversed by concomitant AUT6 treatment on days 1, 7, 14 and 21 (p<0.01; d=2.08) but not following 1-day of washout in PCP-AUT6wo group (p<0.05; d=0.36). The NOR deficit was associated with a significant reduction in PV density in the hippocampus (p<0.01) and infralimbic cortex (p<0.05) in the PCP-VEH group. This neuronal deficit was significantly reversed by AUT6 (p<0.05 and p<0.01, respectively) but not after a 7-day washout. Kv3.1 channel-positive cell density was significantly reduced in the prefrontal cortex (p<0.05) in the PCP-AUT6 group. No Kv3.1 density changes were observed in other groups (p>0.05). We also verified that Kv3.1 channels were co-localised on PV interneurons in rat and human brain control tissues. Conclusion: Chronic treatment with AUT6 provided sustained improvement of cognitive and neuropathological deficits in a validated animal model of schizophrenia symptomatology. Efficacy of AUT6 to restore cognitive function was associated with reversal of the PV deficit observed in the PCP rats. The modulation of Kv3 channels on PV neurons could thus be an important novel approach for improving cognitive deficits in schizophrenia and could restore neuronal function. Sources of financial sponsorship: the work is supported by Innovate UK and Autifony Therapeutics Limited. Declaration of interest form: J. Neill has received expenses to attend conferences and fees for lecturing and consultancy work (including attending advisory boards) from the manufacturers of various antipsychotic drugs

Do6
A GLYT1 INHIBITOR, RO4993850, SELECTIVELY INCREASES C-FOS EXPRESSION IN THE RAT PREFRONTAL CORTEX
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Glycine Transporter (GlyT1) inhibitors represent a novel treatment approach for disorders involving NMDA receptor hypofunction, such as schizophrenia. By regulating synaptic levels of the NMDA receptor co-agonist, glycine, GlyT1 inhibitors indirectly increase NMDA receptor activity. Previous studies have shown this approach attenuates deficits in learning and memory in a variety of rodent and non-human primate tasks but the precise brain loci mediating these effects following systemic administration are unknown. This study therefore focused on the impact of RO4993850 (an analogue of the GlyT1 inhibitor, Bitopertin) on c-fos expression (an index of neuronal activation) in selected brain regions including the prelimbic (PrL) and orbitofrontal (OFC) cortices, nucleus accumbens and amygdala. 24 group-housed adult male Lister-hooded rats (175-200g, Charles River UK) were habituated to handling before receiving a single i.p. injection of vehicle (2ml/kg) or RO4993850 (1 or 3mg/kg); these doses have previously been shown to attenuate deficits in a Novel Object Discrimination paradigm. Rats were left undisturbed in the home cage for 2h post-injection and transcardially perfused with 4% paraformaldehyde solution under isoflurane anaesthesia. Brains were dissected and used for c-fos immunohistochemistry. c-Fos immunoreactivity and positive nuclei were visualized with 3, 3’-diaminobenzidine and quantified using ImageJ software (NIH). Differences in c-fos counts between treatment groups were analysed using one-way ANOVA (Sidak post-hoc) for each brain region of interest. Compared to vehicle, RO4993850 caused a significant increase in the number of c-fos immunoreactive cells in the rostral dorso-lateral (F(2,22)=13.710, p<0.001), lateral (F(2,23)=7.647, p=0.03), ventral (F(2,23)=6.877, p=0.05), and caudal ventral (F(2,20)=13.536, p<0.001) and lateral (F(2,20)=21.750, p<0.001) OFC. Further analysis revealed this increased pattern of c-fos activation to be dose-dependent, with significance achieved between both low and high doses in the rostral dorso-lateral (p<0.001), and caudal lateral (p=0.006) OFC. RO4993850 also increased c-fos expression in the rostral (F(2,23)=2.784, p=0.085) and caudal (F(2,20)=3.349, p=0.058) PrL, infralimbic (F(2,20)=7.231, p=0.005), and limbic cortices (CG1) (F(2,20)=4.785, p=0.022). However, RO4993850 failed to produce any concomitant substantial elevation in c-fos expression in the nucleus accumbens or basomedial amygdala although a small but significant increase at the low dose occurred in the basolateral amygdala (F(2,21)=4.696, p=0.022). This pattern of c-fos activation induced by RO4993850 administration suggests it may cause preferential activation of neurons in the prefrontal cortex. This possibly represents differential activation of mesocortical and mesolimbic dopaminergic neuronal pathways, potentially contributing to the enhancement of learning and memory associated with GlyT1 inhibitors. Study funded by F. Hoffman La Roche. Ltd
Do7
MICE HAPLOINSUFFICIENT FOR MAP2K7, A SCHIZOPHRENIA RISK GENE, SHOW IMPAIRED ASSOCIATIVE LEARNING ABILITY AND ATTENTIONAL DEFICITS: IMPACT OF MINOCYCLINE

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Developing effective therapies to treat psychiatric disorders relies on animal models with appropriate face and construct validity. We investigated mice haploinsufficient for Map2k7 (Map2k7+/-), a gene functionally associated with schizophrenia (Winchester et al., 2012 Human Molecular Genetics 21:4910-4921), in two cognitive tasks that closely resemble those used to examine human subjects, and in which schizophrenia patients show deficits: the 5-choice serial reaction time task (5-CSRTT) for attention and paired associates learning (PAL) for object-in-place memory. Performance in both tasks was assessed before and after administration of minocycline (5-CSRTT requires mice to respond via nose poke to a brief light stimulus in one of five spatial locations for a large number of trials, and PAL necessitates mice to learn and report the correct location of three different images on a touchscreen. Mice were trained on either the 5-CSRTT in a 9-hole operant chamber (Med Associates) (16 Map2k7(+/+) (9 male), 15 wild-type littersmates (WT; 8 male)) or PAL in a touchscreen chamber (Campden Instruments) (10 Map2k7(+/+) (5 male), 10 WT (5 male)) until their performance stabilised. All mice were then given minocycline in their drinking water for 7 days (5mg/ml; 86mg/kg/day on average received) and re-tested on the 5-CSRTT/PAL on days 4 and 7. Mice were 8-10 weeks old at the start of both experiments and weighed between 26-32g. The last 5 sessions of stable performance were analysed by repeated measures ANOVA with session as the within subjects factor and genotype as the between subjects factor. In the 5-CSRTT, while accuracy was unimpaired, Map2k7+/- mice missed significantly more target stimuli than WT mice (F(1,154)=42.36; p<0.001) and all mice showed improvement in % missed after minocycline treatment, from Map2k7+/+: 7.8±3.1% to 11.8±1.7%; WT: 12.6±1.3% to 10.1±1.7% (F(2,58)=2.95; p=0.06) with no genotype x treatment interaction. In the PAL task, Map2k7+/- mice made less correct responses (p<0.001; f(1,72)=17.84) and significantly more inter-trial interval touches than WT mice (p=0.007; f(1,72)=7.71). Overall, Map2k7+/- mice display attentional deficits in the 5-CSRTT that shows signs of improvement with administration of minocycline, and exhibit significant impairment in PAL performance comparable to schizophrenia patients. Our results show promise for Map2k7+/- mice being an informative and translatable model of some aspects of schizophrenia, with potential for aiding future development of improved therapies. This study was financially supported by the Medical Research Council and we thank Prof. Penninger for the gift of the mice. All work was conducted under the Animals (Scientific Procedures) Act 1986.

Do8
HAPLOINSUFFICIENCY OF THE SCHIZOPHRENIA RISK GENE MITOGEN-ACTIVATED PROTEIN KINASE 7 (MAP2K7) ATTENUATES THE CEREBRAL METABOLIC RESPONSE TO DEXTROAMPHETAMINE

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MAP2K7 has recently been identified as a candidate risk gene for schizophrenia and decreased expression levels are seen in the brain of schizophrenia patients (Winchester et al., 2012, Human Molecular Genetics 21:4910-4921). The encoded protein, MKK7, is involved in JNK pathway activation, but we currently have little understanding of how MAP2K7 deficiency impacts brain and neurotransmitter system functioning to increase the risk of schizophrenia. Here we measure cerebral metabolism in 58 brain regions in Map2k7 haploinsufficient (Map2k7+/-) mice (n=23; male n=10, female n=13) and their wild-type (WT, n=29; male n=13, female n=16) littersmates (aged 3-6 months) using 14C-2-deoxyglucose imaging (Dawson et al., 2014, Neuropsychopharmacology 39:1786-1798). Cerebral metabolism was determined under basal conditions (saline-treated, WT n=18, Map2k7+/- n=12) and in mice treated with dextroamphetamine (5mg/kg, intraperitoneal, WT n=11, Map2k7+/ n=11). Data were analysed using ANOVA with sex, genotype and treatment as independent variables. Post-hoc Tukey’s HSD was used to test group differences when significant interactions were found. Significance was set at p<0.05. While Map2k7 haploinsufficiency did not alter constitutive metabolism in any of the brain regions analysed, the cerebral metabolic response to dextroamphetamine was significantly attenuated in Map2k7+/ mice. In WT animals dextroamphetamine induced significant hypermetabolism in the prefrontal cortex (anterior prelimbic [aPrL], p=0.0016; cingulate [Cg1] p=0.0015, Tukey’s), hippocampus (dorsal subiculum [DS] p=0.001, Tukey’s) and thalamus (mediodorsal [MD] p=0.001; dorsal reticular [dRT] p=0.001, Tukey’s). These effects were significantly attenuated in Map2k7+/- mice (ANOVA genotype x treatment; aPrL F(1,44)=7.469, p=0.009; Cg1 F(1,44)=7.427, p=0.009; DS F(1,44)=12.326, p=0.001; MD F(1,44)=6.975, p=0.0114; dRT F(1,44)=6.926, p=0.009. While these changes were not statistically significant, they suggest potential beneficial effects of Map2k7+/- mice for investigating the impact of novel antipsychotics on the cerebral metabolic response to dextroamphetamine treatment.
p = 0.017) where dextroamphetamine failed to induce hypermetabolism in Map2k7+/− mice (treatment: aPrL p = 0.999; Cg1 p = 0.999; DS p = 0.079, Tukey’s) or reduced the magnitude of the response (treatment: MD p = 0.045; dRT p = 0.0045, Tukey’s). In these regions there was no significant evidence that this interaction was influenced by sex. However, in the ventral tegmental area (VTA) and retrosplenial cortex (RSC) the metabolic response to dextroamphetamine was significantly attenuated in female but not in male Map2k7+/− mice (ANOVA sex x genotype x treatment: VTA F(1,44) = 5.517, p = 0.023; RSC F(1,44) = 5.075, p = 0.0234. ANOVA genotype x treatment: females: VTA F(1,25) = 18.733, p = 0.001; RSC F(1,25) = 13.525, p = 0.001, males: VTA F(1,19) = 0.530, p = 0.476; RSC F(1,19) = 0.327, p = 0.574). Map2k7 haploinsufficiency attenuates the response to dextroamphetamine in neural systems known to be dysfunctional in schizophrenia. These data suggest that Map2k7 haploinsufficiency alters the functioning of the monoaminergic (dopamine, noradrenaline, serotonin) neurotransmitter systems, which may contribute to its influence on the risk of developing schizophrenia. Acknowledgments: We thank Prof. Penninger (Institute of Molecular Biotechnology, Vienna) for the gift of the Map2k7+/− mice. Financial Sponsorship: This work was supported by the Psychiatric Research Institute of Neuroscience in Glasgow (PsyRING).

**D09**

**VALIDATION OF A MATERNAL IMMUNE ACTIVATION (MIA) MODEL OF SCHIZOPHRENIA: EFFECTS OF STRAIN AND DOSE OF POLY I:C ON INFLAMMATORY PROFILES OF RATS**

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**Introduction:** There is accumulating evidence for the role of neuroinflammatory processes in the aetiology of neuropsychiatric disorders. In fact, maternal immune activation (MIA) through administration of the viral-mimetic polyriboinosinic-polyribocytidylic acid (poly-I:C) is a key model for neurodevelopmental disorders such as schizophrenia. However, MIA studies predominantly use mice despite the benefits of rats for robust behavioural and developmental neuroimaging read-outs. Furthermore, differences in dose, strain and route of administration exist in the literature, which may contribute to the behavioural and neurochemical variations observed in the offspring. This study aimed to establish a strain and dose of poly I:C that induces a robust systemic inflammatory challenge in rats for MIA studies.

**Methods:** Acute systemic inflammation was induced in female Wistar, hooded-Lister and Sprague Dawley rats (n=8; 182-281g; 10-weeks old) intraperitoneally (i.p) with poly I:C (5, 10 or 15mg/kg) or saline. Subsequently, chronic inflammation was induced in female Wistar rats (n=8) by poly I:C i.p. (2.5, 5 or 10mg/kg) or saline over 5 consecutive days. Changes in core body temperature and body weight were measured prior to treatment, 3h and 6h post-poly I:C. Blood samples were taken following poly I:C administration at 3h and changes in IL-6, TNFα, IL-1β expression measured in the plasma by ELISA. Behavioural consequences of chronic poly I:C treatment were assessed by open field activity and social interaction 7 days post-poly I:C.

**Results:** Acute administration of poly I:C at 10mg/kg produced a significant increase in IL-6 in Wistar (P<0.001), hooded-Lister (P<0.05) and Sprague Dawley rats (P<0.05) at 3h post injection but not at higher doses. TNFα was significantly increased in Wistar (P<0.05), hooded-Lister (P<0.01), and Sprague dawley rats (P<0.05) at 3h post- injection but not at higher doses. TNFα was significantly increased in Wistar (P<0.05) and Sprague dawley rats (P<0.05) only. Acute poly I:C evoked an increase in body temperature in all strains at 3h (P<0.001) in the absence of any weight loss. Similarly, chronic inflammation was induced in female Wistar rats (n=8) by poly I:C i.p. (2.5, 5 or 10mg/kg) or saline over 5 consecutive days. Changes in core body temperature and body weight were measured prior to treatment, 3h and 6h post-poly I:C. Blood samples were taken following poly I:C administration at 3h and changes in IL-6, TNFα, IL-1β expression measured in the plasma by ELISA. Behavioural consequences of chronic poly I:C treatment were assessed by open field activity and social interaction 7 days post-poly I:C.

**Results:** Acute administration of poly I:C at 10mg/kg produced a significant increase in IL-6 and TNFα (P<0.001) in plasma samples on day 1, however, no marked cytokine expression was observed in response to poly I:C on days 3 and 5 or at lower doses. Chronic poly I:C elicited an increase in body temperature in all strains at 3h (P<0.001) in the absence of any weight loss. Similarly, chronic administration of poly I:C (10mg/kg) elicited a significant increase in IL-6 and TNFα (P<0.001) in plasma samples on day 1, however, no marked cytokine expression was observed in response to poly I:C on days 3 and 5 or at lower doses. Chronic poly I:C elicited an increase in temperature on all days (P<0.001) but did not cause any changes in open field or social interaction 7 days post-poly I:C injection. Conclusions: These data demonstrate that, under our experimental conditions, acute administration of 10mg/kg poly I:C (i.p) to female Wistar rats is the optimal dosing schedule and strain to induce a robust systemic inflammatory response for MIA studies. Sources of financial sponsorship: the work is supported by Roche and the University of Manchester MRC Confidence in Concept scheme.

**D10**

**IMPACT OF CHRONIC ANTIPSYCHOTIC TREATMENT ON THE RAT NIGROSTRIATAL DOPAMINERGIC SYSTEM AND RELATIONSHIP TO VACUOUS CHEWING MOVEMENTS**

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Tardive dyskinesia (TD) is a known adverse effect of chronic antipsychotic drug (APD) treatment, characterised by involuntary, repetitive, purposeless facial movements. Neuropathological changes in dopaminergic (DA) neurons in the ventral midbrain have been implicated in other forms of dyskinesia, particularly Parkinsonism (Bergman et al.1990, Science;249(4975): 1436-1438). Degeneration of the substantia nigra is also reported in patients with TD (Christensen et al.1970, Acta Psychiatr Scand;46: 14-23). We hypothesised similar degeneration would therefore be present in rats chronically treated with APD that show TD-like behaviour. Brain tissue from Sprague-Dawley rats (250±10g) treated with vehicle (n=8), haloperidol (2mg/kg/day; n=8) and olanzapine (10mg/kg/day; n=8) were generated previously (Vernon et al.2011, Biological Psychiatry;69(10): 936-944), were sectioned (interval and thickness; 1:12 at 59um) and immunostained for tyrosine hydroxylase (TH), a marker for DA neurons. The number and density of TH+ cells in the substantia nigra pars compacta (SNPC) were estimated using unbiased stereology (optical fractionator) and correlated to vacuous chewing movement scores (VCMs), a robust rodent analogue of TD (Andreassen and Jørgensen1995, Life Sciences;57(24): 2263-2272). Cell counts were analysed using one-way analysis of variance with post-hoc Bonferroni’s multiple comparisons test. Correlations were measured using Spearman’s Rho. The mean estimate of TH+ cells in haloperidol, olanzapine and vehicle-treated animals was 1349±SEM 108.4, 1366±SEM 123.4 and 1920±SEM 228.3 respectively; a significant difference overall (F(2,19)=4.271, p=0.0294), however post-hoc analysis reveals only haloperidol is significant to control (p<0.05). Median VCMs for haloperidol, olanzapine and vehicle-treated animals were 4±SEM 1.698, 15±SEM 1.217 and 0.5±SEM 0.4773 respectively; a significant difference between vehicle vs. olanzapine, and haloperidol vs. olanzapine (p=0.0003). No correlation was found between VCM scores and TH+ cells in both haloperidol-treated (Spearman’s r=-0.4579, p=0.2675) and olanzapine-treated animals (Spearman’s r=-0.085, p=0.8401). Chronic treatment with haloperidol decreases the number of TH+ cells in the SNPC, although a downward trend is seen with olanzapine. However there were no significant correlations between this and VCMs within our sample, likely due to the small sample size. Additional studies with a larger sample range of APD doses is required to thoroughly assess any potential correlation. This study was funded by a grant from the Medical Research Council (G1002198), whom we thank for their generous financial support. All animal experiments were performed under Home Office Project Licence 70/7085, approved by the local ethical review committee of King’s College London and in accordance with the Home Office Scientific Procedures (Animals) act 1986 and EU directive 2010/63/EU.

**D11**

**POSTSYNAPTIC DENSITY PROTEINS IN NEURONAL PLASTICITY AND PSYCHIATRIC DISEASE**

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Introduction: Proteins within the postsynaptic density (PSD) are involved in mediating the intracellular signalling cascades that lead to synaptic plasticity. Alterations in PSD proteins could underpin abnormal synaptic plasticity demonstrated in neuropsychiatric disorders such as schizophrenia. Since PSD Homer proteins are involved in the restructuring of the PSD following neuronal stimulation, we evaluated their potential involvement in memory consolidation following contextual fear conditioning, using in situ hybridization and immunoblotting. Methods: Adult male Lister Hooded rats were placed into a novel context for 2 min before receiving a 0.5mA foot shock. Freezing behaviour was quantified in the 1 min following foot shock and for 2 min (recall) or 10 min (extinction) in the same context 48 hours later. Brains were dissected 0.5, 2, 4 or 24 hours after conditioning, recall or extinction. For expression analysis, brains were sectioned at 14µm and washed with radiolabeled oligonucleotide probes targeted to Homer1a, Ania-3 or long Homers, before exposure to x-ray film. For protein quantification, hippocampi were homogenised and centrifuged to produce synaptosomal fractions. This is the first time quantification, hippocampi were homogenised and centrifuged to produce synaptosomal fractions. This is the first time that the differential time course of multiple activity-induced Homer1 isoforms has been examined. Knockdown experiments involved the surgical implantation of a bilateral cannula and administration of anti-Homerta and/or anti-Ania-3 antisense into the hippocampus prior to contextual fear conditioning or extinction. Results: Fear-conditioned rats displayed a transient increase in the expression of short Homer1 isoforms, Homerta (160% naïve controls, P<0.001 (ANOVA)) and Ania-3 (225%, P<0.001), in CA1, CA3 and dentate gyrus regions of the hippocampus. Interestingly, following the recall or extinction of fear memory, a similar pattern of expression of the two isoforms was observed (Homerta: 160%, P<0.001, Ania-3: 210%, P<0.001). Whilst levels of Homerta were elevated for at least 4 hours, Ania-3 expression peaked around 30 min but returned to baseline by 2 hours after consolidation, recall or extinction. Western blot confirmed a corresponding increase in short Homer protein after contextual fear conditioning (130%, P<0.05). Anti-Homerta antisense had no effect on the acquisition or consolidation of contextual fear conditioning. Conclusions: The results suggest distinct roles for activity-induced Homer1 proteins in memory consolidation and support their involvement in synaptic plasticity mechanisms relevant to psychiatric disease. This work is funded by the Wellcome Trust.
D12
SUB-CHRONIC PCP TREATED RATS DEMONSTRATE PESSIMISM IN A TASK OF OPTIMISTIC COGNITIVE BIAS: A NOVEL APPROACH FOR INVESTIGATING THE DISRUPTION OF ANTICIPATORY MOTIVATION IN SCHIZOPHRENIA

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Introduction: The deficit in anticipatory motivation for pleasurable activities is considered to be one of the main negative symptoms of schizophrenia. Sub-chronic treatment with phencyclidine (PCP), a non-competitive NMDA receptor antagonist, has been widely used by us and other researchers for modelling cognitive deficits in the disease (Neill JC, et al, 2014, Eur Neuropsychopharmacol, 24(5): 419-3). However, to date there is no validated method for investigating anticipatory motivation experienced in the disease in an animal model. Our aim is to address this issue by exploring the cognitive bias of PCP treated rats using a novel task for optimistic cognitive bias (Brydges NM, et al, 2011, Animal Behaviour 81, 169-75).

Methods: Adult female hooded-Lister rats (160-200 g) were divided into saline and PCP groups (n=10, each). The protocol was adapted from that described by Brydges et. al (2011). In this task, rats were introduced to white chocolate drops as high value rewards and 1/2 honey nut cheerios as low value rewards and trained to associate each reward with a particular grade of sandpaper (fine or coarse) on the floor of the apparatus. After training, rats were subjected to a pre-treatment test for determination of their natural optimistic bias which was defined when an animal made a choice for the high value reward, chocolate, when introduced to an ambiguous stimulus (medium grade of sandpaper). PCP (2 mg/kg; i.p.) or saline (0.1 ml/100g; i.p.) was administered twice a day for 7 days followed by wash-out (7 days). Then both groups were finally subjected to post-treatment testing. Data were analysed by Student’s t-test and one-way ANOVA. Results: The time taken to choose the correct bowl in chocolate vs cheerio trials (p<0.01) revealed that chocolate had more reward value than cheerios. Rats took less time to leave the tunnel (p<0.01), choose the first (saline, p<0.001; PCP, p<0.01) and correct bowl (both groups, p<0.001) within the distinct phases. Thus, in the pre-treatment test, the cognitive bias was in favor of optimism in both groups. However, after the treatment, the number of optimistic choices was significantly decreased in the PCP group compared to the saline group (p<0.01) which exhibited no change in optimistic bias after the treatment. Conclusions: These preliminary data suggest that optimistic bias, as evaluated in a modified version of the sandpaper task was negatively affected by sub-chronic PCP administration. Therefore it may be used as a novel test for investigating the efficacy of novel compounds to reduce blunted affect, a core negative symptom of schizophrenia. This study was funded by b-neuro, Manchester Pharmacy School, University of Manchester

D13
INFLUENCE OF ANTIPSYCHOTICS ON MOOD: VALIDATING THE AFFECTIVE BIAS TEST IN THE SUB-CHRONIC PCP MODEL OF SCHIZOPHRENIA.

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Introduction: Deficit in affective processing, one of the negative symptoms of schizophrenia, compromises successful social interaction and influences the functional outcome of the patients (Hooker et al., 2011, Journal of Abnormal Psychology, 120, 98-107; Stuart et al., 2013, Neuropsychopharmacology, 38, 1625-1635). Treating such deficits has proven to be difficult and remains an unmet clinical need. This is partly due to the lack of valid animal models of the disease and clinically relevant neuropsychological tests with high translational power. The current study aims to investigate the influence of antipsychotics risperidone and haloperidol on affective states and to explore a novel animal behavioural test for negative symptoms.

Methods: 40 adult female Lister-hooded rats were trained to dig in bowls to retrieve a food reward prior to pairing. Sub-chronic phencyclidine (PCP) -treated rats (n=20) were divided into cohorts, each receiving a different drug pairing. Each cohort underwent four pairing sessions (Sessions 1 and 3 performed under drug treatment; Sessions 2 and 4 performed under vehicle treatment), where rats chose between two bowls, one always rewarded (bowl A for sessions 1 and 3; bowl B for sessions 2 and 4) compared to another empty one (bowl C for all sessions). This was followed by a test session on day 5 where the rats were presented with the two previously rewarded bowls (A and B) over 30 trials. Choosing bowl A was considered as a response associated with a drug-induced positive bias. A vehicle control (n=10) and a sub-chronic PCP control group (n=10) underwent the same procedure, with bowl A containing a higher food reward value. Results: The vehicle control
rats showed a significant preference for bowl A rather than B (p=0.035). This preference was absent in control sub-chronic PCP rats (P=0.41). In drug treated cohorts, no change in the affective state was detected in sub-chronic PCP rats receiving haloperidol (0.05 mg/kg) and risperidone (0.1 mg/kg) treatment. Conclusion: This current experiment and previous findings obtained in our laboratory point to the validity of the affective bias test as a measure of affective state. The antipsychotics which have been previously shown to induce a positive bias in vehicle rats, failed to induce such an effect in PCP-treated rats. The extreme effect of PCP treatment on neurobiology of affective system would thus prevent the antipsychotics to exert their influence. More investigations need to be conducted to evaluate influence of antipsychotic treatment on affective state. This project was supported by the in vivo training initiative award from British Association of Psychopharmacology.

D14
INVESTIGATION OF THE BEHAVIOURAL ARCHITECTURE OF PHENCYCLIDINE IN RATS MONITORED IN THE HOME CAGE

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Social behaviours are key parameters in preclinical models of social deficit relevant to schizophrenia and autism. Short-term testing in specific paradigms, between unfamiliar animals, and focussing on the model animal may not reveal deficits in normal social situations, and misses the opportunity for employing normal animals to detect abnormal behaviour in disease model cagemates. However, sustained monitoring of animals in the home-cage in groups is technically difficult. We have previously presented results from our rodent tracking system which pairs high-quality video with synchronised reads from a radio-frequency identification (RFID) baseplate, allowing tracking of group-housed animals continuously in their home-cage and overlaying of videos with individual identification for manual scoring (Brett et al, 2014, J Psychopharm, 2014, 28, Supp A114). Automatic measures demonstrated altered distance travelled and separation between animals after phencyclidine (PCP) treatment. Here we present further analysis focussing on social behaviours. 18 male Sprague-Dawley rats (10-12 wks) group-housed in 3s (lights on/off 03.45/15.45) implanted with RFID transponders were monitored for 72 hrs following an initial saline injection 15 min before lights off. At 24 hrs, one randomly selected rat per cage received 5 mgkg-1 PCP ip and the others saline (one PCP condition); at 48 hrs all received 5 mgkg-1 PCP. The present data derives from detailed scoring of 3 cages in the one PCP condition for 30 min beginning 15 min after injection, at peak PCP activity and at the onset of the dark period. Individual behaviours were manually scored using ActualTrack software and compared by unpaired t-tests (control vs PCP). Social behaviours (control towards control, control towards PCP, PCP towards control) were similarly scored and analysed by one-way ANOVA. PCP-treated and control animals showed radically different behaviour patterns. Control animals spent 10±5s eating, 294±75s grooming and 411±100s lying down, whereas PCP-treated animals spent 0s eating, 12±6s grooming (p=0.019) and 62±3s lying down (p=0.014). PCP-treated animals showed modest stereotypical head-weaving (46±98) and rotating (25±28) behaviours, which were absent in the control animals. Remarkably little social behaviour was present, and behaviour towards the PCP-treated animal was not different in the parameters investigated. Work is ongoing to develop algorithms for automatic scoring of social behaviours. However the limited social behaviour in these established adult social groups suggests that PCP models of social deficit might best be studied in more socially active subjects such as adolescent male rats. Funding sources: NC3Rs Rodent Big Brother Challenge; Scottish Funding Council Innovation Voucher

D15
SELECTIVELY ALTERED ASSOCIATIVE LEARNING IN THE DUAL-HIT POST-NATAL PCP/SOCIAL ISOLATION RAT MODEL OF SCHIZOPHRENIA

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Introduction: Reinforcement learning frameworks propose that aberrant learning can lead to false beliefs, unshakable habits, and attentional biases that ultimately shape mood and behaviour. These frameworks aim to explain psychiatric symptoms in terms of alterations in associative learning (mediated by prediction errors), and alterations in decision making (mediated by the tendency to exploit or explore). In this experiment we investigated whether dual-hit post-natal phencyclidine (PCP) and post-weaning social isolation (a model of adverse early-life biological and environmental interaction relevant to schizophrenia) produces abnormalities in variants of reversal learning that require different associative learning
mechanisms. Methods: Twenty-four male Lister-hooded pups received either s.c. saline (2 mL/kg) or PCP HCl (10 mg/kg) on post-natal days (PND) 7, 9 and 11. Upon weaning (PND 24), PCP-treated rats were housed individually (n=12), and vehicle treated rats (n=12) in groups of four. Locomotor activity and novel object recognition were assessed six weeks later. From week seven, rats were food restricted and trained on an appetitive two-stimulus touchscreen visual discrimination. After acquisition, rats were assigned to either the perseverence test (where the S+ becomes S- and a novel S+ is introduced, n=11) or learned irrelevance test (where the S- becomes S+ and a novel S- is introduced, n=12). To control for treatment effects on novelty per se we then performed a novelty bias test (where a novel S- is introduced), followed by extinction (where neither the S+ nor the S- is rewarded). Results: Consistent with the development of the syndrome, PCP-isolates displayed initial hyperactivity in a novel arena (F(1, 21)=7.85, p=0.011). During acquisition of the visual discrimination, there was no effect of PCP-isolation on the number of sessions to criterion (χ²=0.34, d.f.=1, p=0.56). On the perseverence task, PCP-isolates reached criterian significantly faster than the group-housed animals (χ²=10.42, d.f.=1, p=0.001), making significantly more correct responses (F(1, 8)=7.94, p=0.023) and fewer errors (F(1, 8)=8.65, p=0.019). On the learned irrelevance task there was no difference between the groups in the number of sessions to criterion (χ²=0.31, d.f.=1, p=0.58), correct responses (F(1, 10)<0.01, p=0.93) or errors (F(1, 10)<0.01, p=0.99). There was also no difference between the groups in any measure on the novelty bias task or extinction (all p>0.5), regardless of prior task. There was no effect of PCP-isolation on any latency measure in any task. Conclusion: Rats who receive a dual-hit of post-natal PCP and post-weaning social isolation display augmented associative learning indicative of enhanced positive prediction error signalling with no changes in negative prediction error signalling. These findings suggest that a combination of early-life glutamatergic disruption and social isolation can produce selective abnormalities in associative learning in adulthood. MDR was funded by the University of Nottingham.

D16
UNDERLYING NEURAL MECHANISMS LINKING RISK FACTORS FOR PSYCHOSIS AND EMOTION PROCESSING
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Introduction: Psychotic disorders are associated with environmental risk factors such as migration, urbanicity, childhood adversity and current life stressors. Individuals with psychotic disorders also display differences in emotion processing. The neurobiological basis for this difference in emotion processing has been studied, and it has been shown that individuals with schizophrenia display reduced activation of the amygdala when viewing emotional faces compared to healthy controls. It is not known if altered emotional processing develops as a secondary consequence of the emerging symptoms and neurobiological changes associated with the development of schizophrenia, or whether these alterations are independently linked to environmental risk factors. This is an important distinction, as if the changes are directly linked to exposure to the risk factors, this suggests that they are an early neurobiological change in the mechanistic pathway leading to the onset of the disorder. Methods: 12 individuals with a history of high exposure to psychosocial stressors (HPSS) and 12 with a low exposure (LPSS) were scanned using a 3T MRI scanner to measure BOLD response while viewing faces displaying different emotions. Subjects were aged 18-45, with no history of mental illness. The HPSS group had ≥2 of the following inclusion criteria: (i) Inner London upbringing or current dwelling (ii) 1st or 2nd generation migrant (iii) History of childhood adversity (iv) Current adult adversity. The LPSS group were living in a rural setting AND had never lived in inner London for more than 6 months AND had no history of childhood adversity AND had no significant life events in the 6 months prior to the study. Images were preprocessed and analysed using SPM8. Results: Individuals in the LPSS demonstrated an increased amygdala and insula BOLD response to fearful faces (contrasted with fixation cross) compared to the HPSS group (p<0.001, uncorrected). The maximum between group difference was in the right amygdala (d=1.34). Conclusions: These results support the hypothesis that environmental risk factors play a role in some of the neurobiological features observed in schizophrenia. Furthermore they suggest that these changes occur prior to the onset of any form of mental disorder. Ethical approval was granted by the National Research Ethics Service Committee London –West London Sources of financial sponsorship: The study was funded by the Medical Research Council (MC-A656-5QD30). Dr McCutcheon’s research is supported by the National Institute for Health Research.
D17

REGULATION OF PRE-SYNAPTIC DOPAMINE BY APOMORPHINE IN MAN: AN 18F-DOPA PET STUDY

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Introduction: The neuropeptide dopamine has been implicated in a number of neuropsychiatric disorders, including the Addictions, Parkinson’s Disease and Schizophrenia. In recent years there has been renewed interest in measures of pre-synaptic dopamine, especially in psychosis research, evidence showing elevated dopamine synthesis capacity (DSC), as measured by 18F-DOPA PET, in people at high risk of psychosis who develop psychosis, compared to those who do not (Howes et al, 2011, The American Journal of Psychiatry 168,1311–17.) Meta-analytic evidence has suggested that dopamine dysfunction in schizophrenia occurs at a pre-synaptic level, as opposed to involving dopamine transporters or at a post-synaptic level. Current antipsychotic treatments have limited efficacy, and are thought to exert their effects at post-synaptic D2 receptors. A potential therapeutic agent would directly target pre-synaptic dopamine. Apomorphine, a potent D1 and D2 agonist, is thought to exert its effect through autoreceptors. Unlike other dopamine agonists it does not increase the incidence of psychotic symptoms in healthy people or disease states (Dépatie, L, and Lal S. “2001, Journal of Psychiatry & Neuroscience: 26, 203–20.) Animal and indirect in-vivo evidence suggests Apomorphine may decrease DSC, with animal PET data suggesting baseline DSC may predict response to Apomorphine (Torstenson, R et al, 1998. Neuropharmacology 37: 989–95). To date, there has been no direct in-vitro examination of this.

Methods: 12 healthy male volunteers (mean age 26.42, SD 5.14), 10 right-handed, underwent 3,4-dihydroxy-6-[18F]-fluoro-l-phenylalanine ([18F]-DOPA) PET scans on two separate occasions. 10 participants received either placebo (saline) or apomorphine, given sub-cutaneiously, immediately preceding F-DOPA injection. 2 subjects did not receive placebo. 8 subjects received Apomorphine at a dose of 0.005mg/kg. To control for the possible effects of regression to the mean, we examined a similar dataset from our group, who had been scanned on two occasions, using F-DOPA, carrying out similar analyses. Results: At group level there was no statistically significant difference in influx rate constant (Ki values) of 18 F-DOPA between those receiving Apomorphine (Mean=11.99 l/minx10^-3, SD=1.14 l/minx10^-3), and not receiving Apomorphine (Mean 12.23, SD=1.03); t (11)=0.645, p=0.532 (two-tailed). There was a positive correlation between baseline Ki and percentage change with Apomorphine, r= 0.71, n=12, p=0.01 (two-tailed). This was more pronounced in the group receiving the lower dose of Apomorphine (0.005mg/kg), r=0.87, n=8, p=0.005. No significant correlation was found between baseline scan and difference between the two scans, r=0.37, n=8, p=0.37. Conclusions: Apomorphine, given at low dose, has a significant effect on pre-synaptic dopamine, dependant on baseline levels. This merits further investigation. This work was funded by an MRC Grant to Dr Oliver Howes.

D18

SEX DIFFERENCES IN DOPAMINE SYNTHESIS CAPACITY: AN 18F-DOPA PET STUDY

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Introduction: Recently it has been found that men have greater intra-hemispheric structural connectivity than women, whilst women have greater inter-hemispheric connectivity than men (Ingalhalikar et al. 2013, Proc Natl Acad Sci U S A 111(2):823-8). It remains unknown whether this finding may also be reflected in neurochemistry. Only one study has previously examined sex differences in dopamine synthesis capacity (DSC) in exclusively healthy subjects (Laakso et al. 2002, Biological Psychiatry 52(7):759-63) and reported that women had significantly greater DSC compared to men in the caudate and putamen. We sought to address this by replicating the finding of Laakso et al. and testing the hypotheses that, compared to men, women would exhibit greater DSC correlation between the left and right striatum. Methods: We compared dopamine synthesis capacity in 31 men and 19 age-matched women. Dopamine synthesis capacity (indexed as the influx rate constant Kicer) was measured with positron emission tomography and 3,4-dihydroxy-6-[(18F)-fluoro-l-phenylalanine ([18F]-DOPA) in the striatum, and its anatomical and functional subdivisions. Results: There were no statistically significant differences in DCS
between men and women in the substantia, the whole striatum \((p=.56)\) or any of its functional or anatomical subdivisions \((p>.05)\). Women displayed a greater left-right correlation \((r=.94, p<.001)\) compared to men \((r=.80, p<.001)\). The difference in correlations between women and men was statistically significant \((z=2.09, p=.037)\). Conclusions: These findings indicate that women have greater correlation in DSC between the left and right whole striatum compared to men. These findings may be due to increased inter-hemispheric structural connectivity and cross-hemispheric participation in women. It is possible that these findings may be of relevance to sexually dimorphic behaviours. Study funded by an MRC grant to Dr Howes, an MRC grant to Prof Curran and Dr Morgan and an NIHR grant to Kings College London.

**D19**

**EEG EFFECTS OF THC AND CBD IN HEALTHY VOLUNTEERS**

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Introduction: The cannabis plant contains over 120 different compounds known as cannabinoids. Its main cannabinoid, Δ9-tetrahydrocannabinol (THC), is linked to an increased risk of psychosis, cognitive impairment and dependence. In a previous study our group showed that intravenously administered THC induced reduction to EEG power and coherence compared to placebo, and bi-frontal coherence was inversely correlated with positive psychotic symptoms. Cannabidiol (CBD) is a non-psychoactive cannabinoid which has been found to counter the effects of THC and may possess antipsychotic properties. The aim of the present study was to explore the protective effects of CBD on THC-induced EEG-abnormalities. Methods: This was a double-blind, placebo controlled, between subject study of forty five healthy volunteers on the effects of CBD pre-treatment (600mg, oral) on THC-induced (1.5mg IV) EEG-abnormalities. EEG was recorded during engagement in the n-back task (up to 3-back) at baseline, 2h post- capsule (CBD/placebo) administration and post-THC (3.5h post-capsule). EEG data was analyzed for amplitude and coherence in the delta (1-3.5 Hz), theta (3.5-7 Hz), alpha (8-13 Hz) and beta (14-25 Hz). Results: Administration of THC induced positive psychotic reactions in 11 out of 24 in the placebo group and 3 out of 21 in the CBD group, a significant group difference \((\chi^2=5.201, p<.05)\). THC significantly decreased theta amplitude \((p<.001)\) and coherence \((p<.001)\), an effect which CBD did not inhibit. However, unlike our previous study, change in theta coherence was not correlated to change in positive psychotic symptoms. THC also increased delta \((p<.001)\) and alpha amplitude \((p<.001)\), effects which were absent in the CBD group. Conclusions: THC produces reliable EEG abnormalities specifically in the theta band. However, these abnormalities were unrelated to psychotic symptoms as found in a previous study. CBD did not inhibit changes to theta, in spite of CBD significantly reducing the psychotogenic effects of THC. CBD did reduce THC-induced increases to delta and alpha amplitude. Further research is needed to elucidate the psychopharmacological interactions of THC and CBD. This research was funded by grants from the MRC and the Beckley foundation.

**D20**

**INFERRING SUBJECTS’ PRECISION ESTIMATES USING A BAYESIAN MODEL OF PURSUIT: A PHYSIOLOGICAL VALIDATION WITH MEG**

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Introduction: Subjects with schizophrenia are thought to have lower synaptic gain in high hierarchical areas of cortex, and higher synaptic gain in primary sensory areas, relative to normal subjects. Given the brain instantiates a hierarchical Bayesian model, this imbalance of synaptic gain is likely to lead to decreased precision (inverse variance) of representations at the top of the model, and increased precision of representations at the bottom. We have shown that characteristic oculomotor pursuit abnormalities (e.g. decreased pursuit velocity) in schizophrenia can be reproduced by decreasing the high/low precision ratio in a hierarchical Bayesian model of pursuit (Adams et al., 2012, PLoS One, 7(10):e47502). We have also shown that this model can be inverted using empirical pursuit data (Adams et al., 2015, J Neurosci Methods, 242:1-14). This work suggested that fluctuations in target motion makes subjects increase their sensory level precision: i.e. they attend more to the target's sensory attributes. Precision is thought to be encoded by the gain of cortical superficial pyramidal cells, which can be estimated from magnetoencephalographic (MEG) data. This paper demonstrates the construct validity of estimating the precision of subjects' beliefs during pursuit, by correlating sensory precision with its neural substrate. Methods: 17 non-psychiatric subjects viewed a sinusoidal target, with or without random fluctuations in its motion. Eye trajectories and MEG data were recorded concurrently. The target was periodically occluded, and its leaving the occluder caused a visual evoked response field (ERF). Dynamic causal modelling (a Bayesian model inversion scheme) was used to invert models of
eye trajectories and the ERGs. We compared changes in the synaptic gain of the DCM of MEG data to changes in precision in the DCM of pursuit data. Results: DCM of MEG responses revealed that adding noise to target motion increases the gain of superficial pyramidal cells in V1 (across subjects). Furthermore, across individual subjects the increase in sensory precision inferred by our behavioural model correlates ($r = -0.57, p = 0.0174$) with the mean decrease in self-inhibition (i.e. increase in gain) in V1. Conclusions: We have demonstrated that synaptic gain in V1 strongly correlates with sensory level precision, estimated from subjects’ oculomotor pursuit. This paradigm could therefore be used to assess abnormalities in the neural encoding of precision by schizophrenic subjects. Financial acknowledgements: This work was funded by the Wellcome Trust Grant 088130/Z/09/Z. The Wellcome Trust Centre for Neuroimaging is supported by core funding from Wellcome Trust Grant 091593/Z/10/Z.

D21
MICROGLIA, PSYCHOSIS AND MEDICATION; A TRANSLATIONAL INVESTIGATION
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Background: Microglial changes are thought to contribute to the neurobiology of schizophrenia. Positron emission tomography (PET) has demonstrated an elevated microglial signal in patients with established schizophrenia (Doorduin et al., 2009; van Berckel et al., 2008), however it is unclear whether this is primary to the disorder or secondary to other factors. It is also unclear how microglial activity is affected in vivo by antipsychotic medication. Methods: We use $^{[11C]}$PBR28 PET to image microglia in patients with schizophrenia, unmedicated ultra-high risk for psychosis subjects (UHR) and matched controls to determine whether microglial signal is elevated and associated with subclinical psychotic features in UHR and schizophrenia. We also dose rats with haloperidol (0.05 mg/kg/day) to study the effects of medication, independent of psychosis. We test inflammatory context specificity in naïve and lipopolysaccharide (LPS) injected rats. Microglial cell changes are quantified using confocal microscopy and automated custom software. Microglial changes are compared with peripheral cytokines. To assess the underlying mechanisms, we investigate apoptosis and proliferation. Results: UHR and schizophrenia subjects demonstrated elevated grey matter (p<0.01), temporal (p<0.01) and frontal (p<0.05) $^{[11C]}$PBR28 signal, when compared with controls. UHR PBR28 signal and symptoms were correlated (r=0.730 p<0.05). Rats dosed with haloperidol demonstrated a reduction in brain volume (p<0.01) compared to controls. Microglial density (p<0.01), soma area (p<0.001) and Iba-1 soma stain intensity (p<0.05) were elevated by 50% with LPS. In LPS treated animals, haloperidol restored these to control levels. In naïve animals, these parameters were reduced by 40% with respect to controls (p<0.01). Microglial branches became more complex with LPS treatment (p<0.001), however haloperidol did not restore this. Peripheral CXCL1 and TNFα were elevated by LPS (p<0.01), however in both naïve and LPS animals, haloperidol did not alter these levels. There was a reduction in total number of apoptotic cells with haloperidol in naïve tissue (p<0.01). We are currently in the process of assessing proliferation and inflammatory associated transcriptional changes. Conclusions: Microglial activity, as measured using $^{[11C]}$PBR28, is elevated in UHR and schizophrenia and correlates with symptom severity in UHR subjects. The evidence from our haloperidol investigation suggests an anti-inflammatory effect of medication, however microglial cell reduction is not attributed to apoptosis. More work is needed to determine the true relationship between the preclinical microglial stain results and the clinical PET signal. This study was funded by King’s College London and Medical Research Council grants

D22
GLUTAMATE IN SCHIZOPHRENIA: A META-ANALYSIS OF PROTON MAGNETIC RESONANCE SPECTROSCOPY STUDIES
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Introduction: An increasing literature of proton resonance spectroscopy (1H-MRS) studies has measured glutamatergic metabolites in vivo in selected brain regions of schizophrenia patients. We present a meta-analysis of results from the medial frontal cortex, striatum and medial temporal lobe. Methods: Electronic databases were searched to identify journal articles reporting 1H-MRS glutamate, its metabolite glutamine or Glx (total glutamate+glutamine) in At-risk subjects, first-episode psychosis or schizophrenia patients in comparison to healthy volunteers (HVs). Hedges’ g effect sizes were calculated for each brain region. Results: 59 eligible studies were identified. In the medial frontal region, glutamine...
levels were significantly higher in patients in comparison to HVs \( (g=0.35, 95\% CI 0.03\) to 0.67, \( p=0.04) \), which was no longer significant when At-risk subjects were excluded. Glutamine was higher in unmedicated patients relative to HVs \( (g=0.84, 95\% CI 0.38\) to 1.30, \( p=0.001) \) and no difference was seen in medicated patients. Medial frontal Glx levels did not differ in patients relative to HVs, however higher Glx levels were found in At-risk subjects \( (g=0.26, 95\% CI 0.06\) to 0.46, \( p=0.01) \). No differences between schizophrenia patients and HVs were seen, regardless of medication status. Glutamate levels did not differ in patients relative to HVs, nor when At-risk and schizophrenia patients were analysed separately. In the striatum, patients possessed higher glutamate \( (g=-0.63, 95\% CI 0.15\) to 1.11, \( p=0.01) \) and Glx levels \( (g=0.39, 95\% CI 0.09\) to 0.69, \( p=0.01) \) compared to HVs. When analysed separately, Glx levels were higher in schizophrenia patients relative to HVs \( (g=0.57, 95\% CI 0.26\) to 0.88, \( p<0.001) \), whereas At-risk subjects did not differ. In the medial temporal lobe, Glx levels were higher in patients relative to HVs \( (g=0.32, 95\% CI 0.12\) to 0.52, \( p=0.002) \). Elevated Glx levels were specific to schizophrenia patients regardless of medication status and were not seen in At-risk subjects. Glutamine levels were higher in patients relative to HVs \( (g=0.41, 95\% CI 0.02\) to 0.80, \( p=0.04) \). Conclusions: Glx in the striatum and medial temporal lobe were higher in schizophrenia patients regardless of medication status, but did not differ between At-risk subjects and healthy volunteers. Glutamine and Glx elevations in the medial frontal cortex may be specific to the earlier stages of schizophrenia, in antipsychotic-naïve patients and At-risk subjects respectively. Future treatments for schizophrenia may act to normalise these glutamatergic abnormalities. This work is funded by the Medical Research Council.

**D23**

**METABOLIC OUTCOMES AND SERUM OREXIN-A LEVELS IN CHRONIC PATIENTS WITH SCHIZOPHRENIA**

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Objectives: The metabolic abnormalities induced by antipsychotic treatment represent a major issue for patients with schizophrenia. However, the underlying mechanism remains unclear. Recent evidence has shown that orexin-A, a neuropeptide mainly secreted in the lateral hypothalamus, is involved in the regulation of arousal and energy homeostasis as well as in protecting from insulin resistance and obesity in mice. Serum levels of orexin-A linearly correlate with its CSF levels, suggesting an integration between central and peripheral metabolic signals. Orexin-induced sympathetic arousal and thermogenesis effects are reduced by antipsychotics. Preclinical studies have shown that antipsychotics with significantly weight gain liability increase activity of orexin neurons, while those without weight gain liability do not. The aim of our study is to clarify the association between serum orexin-A levels and metabolic abnormalities induced by antipsychotics in patients with schizophrenia.

Methods: This is a cross-sectional study. Patients with schizophrenia who received either less obesogenic antipsychotics (including aripiprazole, amisulpride, ziprasidone or haloperidol) (group1) or clozapine (group 2) for more than 6 months were enrolled. Anthropometrical measurements, fasting glucose, lipid, and insulin levels were assessed. Serum orexin-A levels were assayed by commercial ELISA kit. Student’s t-test, Chi-square test, Pearson's test and linear regression were used for comparable variables. Results: A total of 160 patients were recruited, 51 in group 1 (mean age 39.3± 9.2 y-o, 32% in male) and 109 in group 2 (mean age 42.0± 9.3 y-o, 56% in male). Group 2 patients had higher diastolic blood pressure (DBP), higher fasting blood sugar (AC sugar), and lower high density lipoprotein (HDL) comparing with group 1. Serum orexin-A levels were significantly lower in group 2 when comparing with group 1. In the whole group, serum orexin-A levels were positively correlated with HDL \( (R=0.21, p<0.01) \) and HBA1c \( (R=0.18, p=0.03) \). In patients treated with clozapine, serum orexin-A level were negatively correlated with systolic blood pressure (SBP) \( (R=-0.32, p<0.01) \). After adjustment for antipsychotic group, age and gender by regression model, orexin-A still correlated negatively with SBP \( (beta=-0.17, p<0.05) \) and positively with HDL \( (beta=0.17, p<0.05) \). Conclusions: Different APs affect metabolic outcomes and serum orexin-A levels in different ways. Higher orexin-A is associated with better lipid and blood pressure profiles, while its role on glucose regulation remains controversial. In summary, our results support a role of the orexin system in antipsychotic induced metabolic abnormalities. Further prospective studies would need to clarify the causal-relationship between orexin-A and metabolic abnormalities. * This study is supported by Ministry of Science and Technology,Taiwan and Health Bureau of Taipei City Government, Taiwan
A FOUR YEAR MIRROR-IMAGE STUDY COMPARING RISPERIDONE LONG ACTING INJECTION WITH FIRST GENERATION ANTIPSYCHOTIC DEPOT INJECTIONS IN TERMS OF EFFECTIVENESS, COST EFFECTIVENESS AND TOLERABILITY

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Introduction: Risperidone long acting injection has been available since 2002. Some studies have demonstrated that it is associated with a reduction in requirement for inpatient care, and hence is a cost-effective treatment. There are, however, few studies comparing risperidone long acting injection with first generation antipsychotic depot injections. We therefore wished to compare treatment with risperidone long acting injections with first generation antipsychotic depot injections, in terms of effectiveness, cost-effectiveness and tolerability. Methods: We undertook an observational, retrospective four-year mirror study for patients who started treatment with risperidone long acting injection between May 2010 and January 2012 (n=36) and for matched patients who were treated with a first generation depot antipsychotic (n=37). Notes were reviewed to identify number of days of inpatient care, home treatment and cost of care for the 2 years preceding and following the commencement of the long acting injection. Use of concomitant medication, and discontinuation of the long acting injection were also examined. Results: Patients treated with first generation depot spent on average 28 days less in inpatient or home treatment care than those patients receiving risperidone long acting injection (p=0.036), were approximately 14 times less likely to discontinue treatment (p<0.001) and required £9027 less spent on direct healthcare (p=0.011). Patients treated with risperidone long acting injection were more likely to receive concomitant oral antipsychotic medication (p=0.038). There was no difference between the groups in terms of the requirement for antimuscarinic medication. Conclusions: First generation antipsychotic depot were superior to risperidone long acting injection with respect to use of inpatient and home treatment care, discontinuation and direct healthcare costs. Financial sponsorship: This study was part-funded by the University of Birmingham. No other financial support was received.

PALIPERIDONE LONG-ACTING INJECTION: A NATURALISTIC 6-MONTH OUTCOME STUDY

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Introduction: Pragmatic and naturalistic outcome studies have provided useful insights into the effectiveness of antipsychotics in clinical practice (e.g Lieberman et al. N Eng J Med 2005; 353:1209-1223). The aim of the present study was to assess the effectiveness of paliperidone long-acting injection (PLAI) in a real world setting using treatment discontinuation at six months as an outcome measure. Method: Patients initiated on PLAI between its UK launch and October 2014 in a single health board in Wales were identified from pharmacy records. Outcomes of patients with a diagnosis of schizophrenia or schizoaffective disorder were included. Demographic factors which may have influenced outcome were analysed using Fisher’s Exact test, and reasons for treatment discontinuation noted. Previous treatment with clozapine was considered an indicator of treatment refractory illness. Data were collected by retrospective case-note review. Results: Sixty-two patients received PLAI, of whom 12 had a diagnosis other than schizophrenia or schizoaffective disorder, and two were lost to follow-up. Therefore, six month outcome data were available for 48 patients (seven previously received clozapine). The majority of patients (n=37; 77%) were switched to PLAI from oral or long-acting injectable risperidone. Thirty-four (71%) patients remained on treatment at six months (three previously received clozapine). Treatment discontinuation was not predicted by previous clozapine treatment (P=0.17), inpatient status on initiation (P=0.52), or switching to PLAI from risperidone vs other antipsychotics (P=1.0). The most common reasons for discontinuation of PLAI were perceived lack of effect (n=8; 17%), and adverse effects (n=3; 6%). Conclusions: The proportion of patients remaining on treatment in our study (71%) was comparable to that reported at the six month time-point of a one year naturalistic study (Attard et al. Acta Psychiatrica Scand 2014; 130:46-51). The most common reason for discontinuation in our study and that of Attard et al. (at one year) was perceived lack of effect. In contrast to the study of Attard, neither switching to PLAI from risperidone, nor initiation as an inpatient predicted outcome in our study. The shorter duration of follow-up and smaller number of subjects may explain this difference. The authors declare no financial sponsorship. Acknowledgement: The authors thank Mrs W. Davies for the opportunity to conduct this work.
D26

LURASIDONE DOSE OPTIMIZATION IN PATIENTS WITH SCHIZOPHRENIA: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Introduction: Lurasidone is an atypical antipsychotic agent approved for the treatment of patients with acute schizophrenia at once-daily doses of 37-148 mg (equivalent to 40-160 mg with the hydrochloride salt). Study objectives were to evaluate the efficacy of low-dose luradone in this population and to assess the potential benefit of dose escalation in patients who failed to demonstrate clinically meaningful symptom improvement after 2 weeks of standard dosing. Methods: Adults (aged 18-75 years) were randomized to receive fixed-dose luradone 18.5 mg/d, luradone 74 mg/d, or placebo. Early nonresponders to luradone 74 mg/d (patients with <20% Positive and Negative Syndrome Scale [PANSS] score decrease after 2 weeks) were re-randomized in a 1:1 ratio to unite fixed-dose luradone 18.5 mg/d or 148 mg/d for the remaining 4 weeks of the study. Results: Data from 411 patients (63.7% male; mean age, 40.8 years) were included in the intent-to-treat (ITT) analysis (lurasidone 18.5 mg/d, n=101; luradone 74 mg/d, n=198; placebo, n=112). Reductions from baseline to Week 6 in total PANSS score were -14.5 in the placebo group, -17.6 in patients receiving luradone 18.5 mg/d (P=0.26 vs placebo), and -24.9 in patients receiving luradone 74-148 mg/d (P<0.001; effect size=0.63). Of the 198 patients initiated at luradone 74 mg/d, 95 were classified as early nonresponders and re-randomized to luradone 74 mg/d or 148 mg/d for the remainder of the study. Improvement in PANSS total score from Week 2 to Week 6 in patients increased to luradone 148 mg/d (n=43) was significantly greater than improvement in patients continued on luradone 74 mg/d (n=52; -16.6 vs -8.9; P=0.023; effect size=0.52). Treatment response (≥30% decrease in PANSS total score) at study endpoint was observed in 53.5% of early nonresponders escalated to luradone 148 mg/d and 38.5% continued on 74 mg/d. The most common adverse events occurring more often with luradone (dose groups combined) than placebo were akathisia (8.7% vs 1.8%), nausea (6.4% vs 3.6%), and vomiting (3.7% vs 0.9%). Conclusions: Lurasidone 18.5 mg/d did not demonstrate improvement in schizophrenia symptoms versus placebo, thus confirming 37 mg/d as the minimum effective dose. This study is the first rigorous demonstration of the clinical value of dose escalation in early nonresponders with schizophrenia; luradone dose increase to 148 mg/d provided significant benefit with no observed reduction in safety/tolerability. ClinicalTrials.gov identifier: NCT01821378. Sponsored by Sunovion Pharmaceuticals Inc.

D27

SCREENING FOR CARdio-METABOLIC RISK FACTORS IN PEOPLE ON CONTINUING ANTIPSYCHOTIC MEDICATION: A SIX-YEAR, UK QUALITY IMPROVEMENT PROGRAMME

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There is a consensus across evidence-based guidelines that patients on continuing antipsychotic medication should receive regular metabolic monitoring and adequate treatment of any cardio-metabolic risk factors identified. The Prescribing Observatory for Mental Health conducted a national, audit-based, quality improvement programme (QIP) designed to increase the frequency and quality of screening for hypertension, central obesity, raised plasma glucose level and dyslipidaemia in such patients. Key elements of the QIP were the provision of customised feedback to participating mental health services after each audit, including benchmarked data on their relative and absolute performance against an evidence-based practice standard, and the provision of bespoke change interventions. Six clinical audits in adult, assertive outreach, community psychiatric services in the UK were conducted between 2006 and 2012. Twenty-one mental health Trusts participated in the baseline audit in 2006, submitting screening data for 1,966 patients, while 32 Trusts participated in the 2012 audit, submitting data on 1,591 patients. Over the six years of the QIP, successive audit samples showed an increase in the proportion of patients for whom all four relevant measures (blood pressure, obesity, plasma glucose level, plasma lipid profile) had been documented in the clinical records in the previous year, from just over one in ten patients (11%) in 2006 to just over one in three (34%) by 2012. The proportion of patients with no evidence of any such screening fell from almost half (46%) of the patients to one in seven (14%) over the same period. The findings suggest that audit-based QIPs can help improve clinical practice in relation to physical healthcare screening, although this QIP was conducted in the context of other national initiatives raising awareness of the need for such monitoring over the six-year period. Contributing to any success attributable to the QIP were the use of a widely-accepted practice standard and the development of educational and facilitative change interventions designed to directly address barriers to physical healthcare monitoring that had been
originally identified by participating clinical teams. Nevertheless, the findings also reveal that only a minority of community psychiatric patients prescribed antipsychotic medication is screened for cardio-metabolic risk factors in accordance with best practice recommendations and therefore potentially remediable causes of cardiovascular disease and diabetes remain undetected and untreated. POMH-UK is funded solely from subscriptions from member health services.

D28
CARDIORESPIRATORY FITNESS AND SCHIZOPHRENIA: EMERGING RESEARCH QUESTIONS
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Introduction: Premature mortality in schizophrenia has attracted recent research interest. The WHO Global Health Risks report (2009) highlighted physical inactivity as the 4th most important global mortality risk factor. However, research has focused on features of the metabolic syndrome in relation to the observed reduced life expectancy in those with schizophrenia. Cardiorespiratory fitness (CRF) is an important health-related component of physical fitness and is highly correlated with cardiovascular and all-cause mortality in the general population (Kodama et al, 2009, JAMA 301 (19), 2024-2035). Few studies have explored CRF in established schizophrenia (Beebe, 2006. Applied Nursing Research, 19(1), 43 -47). Koivukangas et al (2010), (Schizophrenia Research,116 (2),152-158) showed that teenagers who went on to develop schizophrenia had lowered CRF. CRF levels in schizophrenia patients have been found to be lower than in sedentary adults. Reduced peak oxygen (VO2) uptake has implications for cardiovascular health and quality of life in patients with schizophrenia (Heggelund et al, 2011, BMC Psychiatry, 11:188). Method We undertook a systematic review of the relationship between CRF and schizophrenia. . A meta- analysis was not possible due to widely disparate measures of CRF. Results: Our systematic review demonstrates both clinically and experimentally this is an under researched area. The current review adds further to the view that schizophrenia is not solely a disorder of the brain but is associated with extracerebral manifestations such as lower cardiorespiratory fitness (CRF) and metabolic abnormalities which may predate frank psychosis. However, the review suggests more questions than it answers. These include the relationship between lower CRF and symptom clusters such as negative symptoms and cognitive impairment. Whether low CRF is a risk factor for premature death as it is in the general population? Practically it would be important to determine whether improvement in CRF is accompanied by an improvement in mental state, social function and improved longevity. Currently, there are large gaps in our knowledge of CRF in schizophrenia and this needs to be addressed. The focus on BMI, lipids and diabetes needs to be widened to include CRF if we are to gain a balanced understanding of schizophrenia and health risks associated with it. This research is self funded.

D29
WORKING MEMORY DEFICITS IN CHRONIC SCHIZOPHRENIA, BIPOLAR DISORDER AND FAMILY MEMBERS (WITH/ WITHOUT) DISC-1 TRANSLLOCATION
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Introduction: Working memory (WM) has been identified as one of the most stable neuropsychological impairments observed in schizophrenia (Lee & Park, 2005, Journal of Abnormal Psychology, vol.114, p599-611; Forbes et al., 2009, Psychological Medicine, vol.39, p889-905). It has also been hypothesised as the leading cause of the generalised cognitive symptoms observed in the disorder (Goldman-Rakic, 1994, Journal of Neuropsychiatry and Clinical Neurosciences, vol.6, p348-357). Recently, studies suggested that the degree of WM impairment, both in schizophrenia and healthy controls was predictive of delusional ideation (Freeman et al., 2014, Psychological Medicine, p1-8) and therefore may be relevant to psychosis. Aims: The aims of this study were to: 1) compare the WM performances of healthy controls (n=43) against those of patients with Chronic Schizophrenia (n=24), Bipolar Disorder (n=15), and Family Members of the Disrupted-In-Schizophrenia 1 translocation carriers (n=24; DISC-1: risk factor for developing major mental illness); 2) identify whether different sub-types of working memory impairments emerged within each patient group. Methods: We used the spatial working memory task from the Cambridge Neuropsychological Test Automated Battery (CANTAB) to test the retention and manipulation of visuospatial information with increasing memory load. DISC-1 translocation status of family members was unknown at the time of recruitment but following sequencing revealed that 11 of the 24 family members were translocation carriers. Results: Similarly to previous studies using the CANTAB spatial working memory task (e.g: Park & Holzman, 1992, Archives General Psychiatry vol.49, p975-982), we found significant impairments of memory retention with increasing
memory load in chronic schizophrenia, bipolar disorder and family members (F(4,104)=4.919, p<0.01). No significant differences were found between the patient groups (Monte-Carlo Permutation tests; p>0.05). However, we did not observe an association between DISC-1 translocation status and working memory performances (Monte-Carlo permutation tests, p>0.05). Conclusion: This study suggests that patients with Bipolar disorder and Chronic Schizophrenia have similar deficits in WM retention as WM load increases. Surprisingly however, DISC-1 family members and patients were equally affected by WM deficits, and translocation status did not appear to be associated with the degree of WM deficits. Further research is necessary in order to identify the causes of WM deficits in family members as they may be similar to those of patients. The lead author was funded by the MRC, BBSRC, and the EPSRC. This study was approved by the Psychiatry and Clinical Psychology subcommittee of the Lothian research ethics committee.

D30

SEASON OF BIRTH AND HEAD CIRCUMFERENCE IN SCHIZOPHRENIA AND HEALTHY CONTROLS - FINDINGS FROM EPILUX-D

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Introduction: There is a well-established season of birth effect in schizophrenia with increased incidence of the disease in those born late winter to early spring (Reviewed in McGrath et al. 2002). It has been hypothesised that this could be due to the interaction of differing levels of environmental light with genetic and hormonal factors affecting neurodevelopment (Quested, 1996), mediated in a delay paradigm and possibly interacting with drivers to cerebral lateralisation. It could be such a delay in neurodevelopment that is reflected in smaller birth head circumferences in pre-schizophrenic neonates. The latter study also found adult head circumference to be larger in schizophrenic patients than controls (Cantor-Graae et al 1998). This would then potentially represent a failure of dendritic pruning as a consequence of missing a relevant time window in the developmental trajectory.

Methods: Data were collected in an epidemiological controlled study of adults (18-65 years) with information about diagnosis (SADS-L and OPCRIT), ethnicity, place of birth, month of birth enabling division into seasonal quartiles, (adult) head circumference (mean of three measurements), finger length, height, weight and family history in men and women with schizophrenia n = 110 (84 male, 26 female) and healthy controls n = 135 (79 male, 56 female).

Results: Univariate Analysis of Variance found there was a significant interaction between head circumference, gender and a diagnosis of schizophrenia vs controls p = 0.045 (controlling for height). In men mean head circumference was greater in the schizophrenic group than the control group except for season two (months February to April). In women mean head circumference was lower in the schizophrenic group for all seasons.

Conclusions: Season of birth appears to affect head circumference in some male schizophrenics differently to controls. This could be via an effect of environmental light on neurodevelopment. The lack of a similar effect in women supports the above theory invoking a complex aetiology of the condition with some cases being more familial and others more environmental in origin. Whilst this study has a significant finding, family history and specific sunshine data by month and region need to be incorporated. Developing the work with a larger epidemiological dataset would enable fuller testing of a likely underlying gene environmental model. This study was approved by the South Central Oxford A REC: Ref number O 03.017 and was funded by Oxford Health NHS Foundation Trust.

E01

METHYLPHENIDATE IMPROVES THE PERFORMANCE OF NK1R-/ MICE IN THE 5-CHOICE CONTINUOUS-PERFORMANCE TEST

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Mice lacking functional neurokinin-1 receptors (NK1R-/-) are hyperactive compared with their wildtype counterparts. They also express inattentiveness (omission errors) and excessive motor impulsivity (premature responses) in the 5-Choice Serial Reaction-Time Task (5-CSRTT; Yan et al. 2011, PLoS ONE 6:e17586). This abnormal behavioural profile resembles that of patients with Attention Deficit Hyperactivity Disorder (ADHD). Here, we compared the performance of these mice in the 5-Choice Continuous-Performance Test (5C-CPT), which is a refinement of the 5-CSRTT. By including both Go and No-Go signals, consistent with human CFTs, the 5C-CPT captures another form of impulsive behaviour, response disinhibition (false alarms), in addition to premature responses. We aimed to establish whether NK1R-/-/ mice display both types of impulsivity in this test and also whether their performance is improved by methylphenidate, which is a first-line
treatment for ADHD. Male wildtype and NK1R−/− mice (N=12 per group; aged 6-7 weeks; 30-34 g) were first trained on the 5C-CPT to baseline criteria (training procedure adapted from: Young et al. 2009, 4(1):e4227). Animals were then tested, once-weekly, under several test conditions: baseline (no injection: ‘NI-1) or 30 min following administration of saline (10 mL/kg), methylphenidate (3, 10, & 30 mg/kg i.p.), or a second session under baseline conditions (NI-2). This sequence of tests was counterbalanced across subjects There was no difference in either false alarms or premature responses when the baseline performance of the two genotypes was tested for the first time (NI-1). However, premature responses were strongly dependent on whether mice were tested in the morning or afternoon. In subsequent tests, methylphenidate reduced the incidence of premature responses and false alarms (c.f., vehicle injection), but increased omission errors (i.e., exacerbated inattentiveness), in both genotypes, especially at the highest dose. Methylphenidate also reduced perseveration by NK1R−/− mice but not wildtypes [F(3,63)=11.29; P<0.001]. We infer that a lack of functional NK1R does not aggravate impulsive behaviour ( premature responses or false alarms) in the 5C-CPT. Moreover, the efficacy of methylphenidate in reducing impulsive behaviour by both NK1R−/− mice and wildtypes, together with the reduction of perseveration by NK1R−/− mice, only, (regarded as analogous to compulsive checking in ADHD), suggests that the beneficial effects of methylphenidate on these behaviours do not require functional NK1R. This experiment was authorised under 2010/63/EU and funded by MRC PhD awards to KP & AP.

E02

ENHANCEMENT OF SELECTIVE ATTENTION IN LOW ATTENTIVE RATS BY EVP-6124, AN a7 NICOTINIC RECEPTOR PARTIAL AGONIST

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The 5-choice continuous performance task (5C-CPT) is a novel translational test for assessing sustained attention, vigilance and response inhibition based on the human CPT (Young et al. 2013, Psychiatry Research, 212(3), 183-91). EVP-6124 is a selective a7 nicotinic receptor partial agonist that improves performance in rodents in a test of natural forgetting (Huang et al. 2014, Psychopharmacology 231(23), 4541-51). A recent study suggests a normalising effect on EEG event related potentials in schizophrenia patients (Preskorn et al.2014, J Psychiatric Practice 20(1), 12-24) however, effects on attention remain to be determined. This study aimed to examine effects of EVP-6124 on attention and impulsive action in rats separated by performance for attentive measures in the 5C-CPT. 40 female Lister-hooded rats were trained in the 5C-CPT to a stable baseline (Barnes et al. 2012, Psychopharmacology, 220,129-141). Animals were then divided into high and low attentive groups (HA and LA; n=10) by upper/lower quartile of accuracy and sensitivity index (SI) and tested on a variable stimulus duration (SD of 0.75, 1.25, 2 s; over 250 trials or 1 hour). EVP-6124 0.1, 0.3 and 1 mg/kg p.o. or vehicle was given 30 min prior to testing in a within subjects design. Data were analysed using a repeated measures ANOVA with LSD planned comparisons. For LA animals EVP-6124 significantly improved accuracy (sustained attention) at 1.25 s SD at all 3 doses (p<0.05-0.001) and at 2 s SD at 0.3 mg/kg (p<0.001), 0.3 mg/kg increased SI (vigilance) at 0.75 and 1.25 s SD, (p<0.05). 1mg/kg significantly reduced pFA (response disinhibition) at 0.75 s SD (p<0.05). In HA animals 1 mg/kg significantly reduced SI at 0.75 and 1.25 s SD. This is the first study to show EVP-6124 improves sustained attention, vigilance and response inhibition in LA animals. Effects of nicotine to improve attention and vigilance are well documented, but this has previously been more closely linked to activation of a4β2 nicotinic receptors. EVP-6124 increases dopamine release in the prefrontal cortex which may explain its effects to enhance sustained attention (Huang et al. 2014, Psychopharmacology 231(23),4541-51). EVP-6124 also increases acetylcholine release in the basal ganglia and cortex which may increase the representation of less salient stimuli represented here by short SD trials. In conclusion, these results support a role for a7 nicotinic receptor mechanisms in enhancing attention in disorders such as attention deficit hyperactivity disorder schizophrenia and Alzheimer’s disease. Conflicts of Interest: JCN has received expenses to attend conferences and fees for lecturing and consultancy work (including attending advisory boards) from the manufacturers of various neuropsychiatric drugs. Funding Information: Work was funded by B-Neuro
THE TVA MODEL APPLIED TO MICE PERFORMING THE 5-CHOICE SERIAL REACTION TIME TASK

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Introduction: Bundesen’s theory of visual attention (TVA) (Bundesen, C. 1990, Psychological Review, 97, 523–547) explains a wide range of findings in the human attention literature. Defined by a set of simple equations, it allows a componential analysis of attentional functions. It has been widely used to study attentional function associated with various types of brain damage and neuropsychiatric conditions (Habekost, T., 2015, Frontiers in Psychology, 6:290). However, whether the human-based TVA can be used to describe attention in rodents remains to be investigated. In rodents the 5-choice serial reaction time task (5-CSRTT) is a widely employed paradigm to study the neurobiology and pharmacology of attention and impulsivity by presenting light stimuli of variable duration at different intervals. Objective: To investigate the applicability of the TVA model to describe the performance pattern showed my mice in the 5-CSRTT. Methods: 5-CSRTT: Sixteen C57BL/6 male mice (7-14 months of age; single/grouped housed; 21-29g) were trained for the 5-CSRTT and tested in 60-minute sessions during two consecutive days. Unmasked stimuli of 200, 400, 700, 1100 and 1800 milliseconds were pseudo-randomly presented with fixed inter-trial intervals of five seconds. TVA modeling: The mean score was calculated and represented as a function of stimulus-duration time. Specifically, the TVA parameters of visual processing speed (C) and perception thresholds (t0) were calculated. Results: The non-linear performance pattern shown by mice completing the 5-CSRTT was successfully modeled by TVA on an individual level. The model assumes that with a certain probability in each animal an attentional lapse occurs, explaining why scores do not approach 100% as in humans. In the remaining trials the animal’s encoding of the visual stimulus is assumed to follow the equation described by TVA. The probability of a correct report follows an exponential function of the exposure duration t: 1 − exp(−C*(t − t0)). Discussion: The TVA model has shown cross-species validity to study attention in both humans and mice, adding a translational value to the model. This finding will improve the ability to model attentional processes in rodents and increase the understanding of the neurobiology and pharmacology of attention. All testing procedures were in accordance with European Communities Council Directive of 24 November 1986 (86/609/EEC) and the Danish Animal Experimentation Act. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this abstract. Funding: 2013-2017 Strategic Founds of the University of Copenhagen (UCPH’s 2016 FUNDS): “Attention to Dopamine: From Psychological Functions to Molecular Mechanisms.”

DEFICITS IN SOCIAL BEHAVIOUR IN LOW ATTENTIVE RATS AS A MODEL FOR IMPAIRED SOCIAL FUNCTION IN ADULTS WITH ADHD

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Introduction: In addition to the core symptoms of ADHD (inattention, impulsivity and hyperactivity), people with ADHD also have deficits in social cognition, known to significantly impair quality of life. Understanding the mechanisms underlying social cognition and thus social functioning in ADHD is vital to improve current treatment approaches; animal models offer this opportunity. We have recently shown using the 5-choice continuous performance task (5C-CPT) that low-attentive rats (LA) can provide a translational model of ADHD. Therefore in the current study we aimed: firstly, to investigate the social behaviour of adult LA animals compared to HA animals. Secondly, to provide further validation for the LA group as a model of ADHD. Methods: Adult female Lister-hooded rats (n=40) were trained for 60 sessions in the 5C-CPT, and then divided into two groups (high attentive; HA and LA) based on set criteria Tomlinson et al 2014. For the social interaction test pairs of unfamiliar rats were placed in the test arena. The pairs consisted of 8 pairs of HA rats (n=16) and 7 pairs (n=14) of LA rats, thus one LA rat was placed with another unfamiliar LA rat and one HA rat was placed with another unfamiliar HA rat. Social behaviours (following, sniffing, exploration of an inanimate object and avoiding) were recorded on video for subsequent blind scoring. The social behaviours of one rat of each pair were blind scored, and the groups were compared using a one-way ANOVA. Results: LA animals spent significantly less time engaging in sniffing (p<0.001) and following (p<0.05) the unfamiliar conspecific compared with HA animals. The other measures investigated (exploring an object and avoiding) did not differ between groups. Conclusions: Impairments in interpersonal and social functioning are well-established features of ADHD. We have recently shown in humans that emotion recognition in adults with ADHD is due to a specific impairment
in social perception and not due to general cognitive dysfunction (inattention and/or impulsivity) (Tomlinson A, et al. Methylphenidate normalises facial emotional recognition deficits in adults with ADHD. Submitted for publication in British Journal of Psychiatry (2015)). Using a translational animal model of ADHD we are able to explore the underlying mechanisms of social impairments in ADHD. This work has shown that, in addition to impairments in vigilance and sustained attention, the LA animals also show impairments in active social interactions. Further analysis of the neurobiological basis of this behaviour may enhance our understanding of mechanisms underlying social dysfunction in ADHD. (Tomlinson A, et al. Pay Attention: Modeling the Inattentive and Impulsive Subtypes of Adult ADHD in the Rat - Using the 5-Choice Continuous Performance Task (5C-CPT). European Journal of Neuropsychopharmacology, 2014, 24(8), p1371-80) The study was funded as part of a PhD project for A Tomlinson. JCN has received expenses to attend conferences and fees for lecturing and consultancy work (including attending advisory boards) from the manufacturers of various neuropsychiatric drugs.

E05
USING THE VALPROATE (VPA) RAT MODEL TO UNDERSTAND THE INTERACTION BETWEEN BRAIN AND GUT WITHIN AUTISTIC SPECTRUM DISORDER (ASD)

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Introduction: Autistic spectrum disorder (ASD) is a neurodevelopmental condition that affects central and peripheral neurodevelopment, neurobiology and behaviour. Current aetiological understanding is limited, although the heterogeneity within patient cohorts supports a complex interaction of genetic and environmental mechanisms. Recently focus has been given to the role of environmental risk factors in ASD (Goyal and Miyan 2014, Front Endocrinol, 5: 29). Valproate (VPA) exposure has been associated with a higher incidence of ASD in humans and ASD-like behaviours in rodent offspring. Considering the incidence of comorbid gastrointestinal (GI) dysfunction in ASD patients, it is of particular importance to explore developmental changes in the neuro-immune circuitry of the GI system in animal models. Methods: Pregnant Wistar rats were treated with 500mg/kg VPA or saline on gestational day 12. Male pups underwent behavioural testing at adolescence. At postnatal day 80 male rats (n=6/group) were sacrificed and the GI tissue collected for immunohistochemical analysis. In a preliminary study, anti beta-tubulin staining on the GI tract was used to quantify nerve fibres innervating the gut. The gut tissue was dissected to obtain samples of small intestine (duodenum, jejunum and ileum) and colon for comprehensive analysis of the entire tract. Faecal pellets were taken from the animals before sacrifice and the DNA extracted for metagenomic sequencing of the gut microbiota present in VPA vs. control rats. Results: In male offspring at post-natal day 80, a trend of increased nerve fibre staining within the small intestine was observed. Neural innervation to the large intestine measured in mucosa and muscle was significantly increased in VPA vs. control rats (%area stained 2.54 vs. 1.78 respectively, p<0.05). The composition of gut microbiota was altered at the phylum level in adult offspring of VPA treated mothers. Metagenomic sequencing of faecal samples revealed a significant reduction of the acidobacteria phylum in VPA treated rats vs. control (p<0.01). Conclusion: These preliminary data are the first to show that a single prenatal exposure to VPA increases neural innervation to the GI tract which is correlated with effects on the GI bacterial environment. Increased nervous supply may provide abnormal feedback from the gut to the brain, resulting in the aberrant behaviours produced in ASD. Increased understanding of this gut-brain interaction within ASD is particularly important given the incidence of comorbid GI abnormalities seen in the clinic. Further research in this area may stimulate the development of novel therapeutic treatments for specific patient cohorts. Sources of financial sponsorship: The work is support by the Neuroscience Research Institute at the University of Manchester

E06
THE CONSEQUENCES OF PRENATAL OR POSTNATAL METHAMPHETAMINE EXPOSURE ON ADULT BEHAVIOUR IN RATS

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In recent years, there has been a growing concern about methamphetamine (MA) use during pregnancy and/or lactation in humans. However, there are limited preclinical studies investigating MA’s potential harm at these different exposure times. Moreover, even fewer studies have examined the effects in later life after prenatal or postnatal exposure in offspring.
Thus, the aim of this study was to determine if prenatal or postnatal MA exposure in rats at a pharmacological dose affects behaviour in adult life. Pregnant Sprague-Dawley dams (n=8-10 dams/group, 250-300g) received MA (3.75mg/kg) or control (distilled water) daily via oral gavage either from gestation day 7-21 or postnatal day (PND) 1-21. Maternal body weight, food and water consumption were recorded daily. Later in life, offspring were tested in commonly used paradigms of anxiety, depression, cognitive function and locomotor activity namely the elevated plus maze (EPM) and open field test (OF) during the adolescent (PND 28) and adult (PND 56, 85, 113) periods and also the Morris water maze (MWM), forced swim test (FST) and home cage activity (HCA) in the adult period (PND 56). Data were analysed using either Repeated-Measures ANOVA and Two-way ANOVA or Friedman's ANOVA and Kruskal-Wallis with relevant post-hoc tests, with the level of significance set at p<0.05. Maternal weight gain was significantly reduced in the prenatal and postnatal MA groups with a concomitant significant reduction in food intake. No significant impairments were observed in the adolescent or adult measures of anxiety (EPM and OF), cognitive performance (MWM) or locomotor activity (HCA). In the adult period however the postnatal MA male (but not female) group displayed significantly decreased time spent immobile and increased time spent climbing in the FST (i.e. less “depressive-like” behaviour). There was also a trend for the prenatal MA male group that showed increased time spent immobile and decreased time spent climbing (i.e. more “depressive-like” behaviour). This study demonstrates that MA can have a profound long lasting effect on rats that are exposed to the drug via the breast milk. If extrapolated to the clinical scenario, this will give cause for concern regarding the risks associated with this drug of abuse during the postnatal period. This project was supported by a PhD fellowship awarded by the College of Medicine, NUI, Galway, Ireland.

E07
ANXIETY IN PREGNANCY AND ADHD OUTCOMES IN CHILDREN
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The possibility of an environmental effect being passed on in utero is the main tenet of the fetal programming hypothesis. Accumulating evidence suggests depression in mothers is associated with higher rates of mental health problems in their offspring. However the specific effects of anxiety in pregnancy on the child are less understood. ADHD is one of the most commonly diagnosed mental health conditions in childhood. The relationship of anxiety in pregnancy to ADHD in offspring remains elusive. Using data from the ALSPAC cohort (n=14541, mother-child pairs), we examined the association between anxiety symptoms in pregnancy and outcomes of ADHD in children at 7 and 13 years. Prenatal anxiety and depression were measured using 23 items from three relevant subscales of the Crown Crisp Experiential Index (CCEI) at 18 and 32 weeks of pregnancy. The CCEI was factor analysed and two latent factors were identified; one relating to somatic anxiety symptoms and one dominated by depressive symptoms. The relationship between the somatic anxiety factor and outcomes of ADHD in the children was explored using logistic regression (unadjusted, and adjusted for maternal factors [age, alcohol use, smoking], child related factors [including birthweight, birth order, gender] and socio-demographic factors [social status, education, ethnic background]). ADHD was identified using the Development and Well-Being Assessment (DAWBA) at 7 years and the Strength and Difficulties Questionnaire (SDQ) hyperactivity subscale at 13 years, using two standard deviations above the mean as a cut off. An association was found between the CCEI somatic anxiety factor and any ADHD diagnosis by DAWBA at age 7 years: OR=1.775 (95% CI =1.239 - 2.543), p<0.01 (unadjusted) and 1.579 (1.007 - 2.476), p<0.05 (after adjustment). For SDQ hyperactivity at 13 years, the OR was 1.607 (1.239 - 2.082), p <0.01(unadjusted), but fell to 1.217 (0.876-1.691), p= 0.325 after adjustment. Fetal programming of the brain remains an intriguing hypothesis. While the impact of depression in pregnancy has already attracted interest, our results suggest that somatic symptoms of anxiety may predispose to ADHD but after adjustment the effect is observable only at 7 y. High attrition in the cohort may have attenuated the effect, since children and families with higher stress levels and diagnoses of ADHD are lost to follow up more frequently. The study conforms to the ethical standards established by the ALSPAC law and ethics committee as stated in http://www.bristol.ac.uk/alspac/researchers/data-access/ethics/. No funding was required.

E08
EVIDENCE FOR ABERRANT PRECISION SETTING IN AUTISM: BEHAVIOUR, COMPUTATIONAL MODELLING AND NORADRENERGIC FUNCTION
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New theories of brain function in Autism Spectrum Disorder (ASD) propose that an imbalance of the precision (or gain)
ascribed to sensory inputs, relative to top-down predictions of those inputs, might underlie the perceptual atypicalities in the disorder (Lawson et al, 2014, Front. Hum. Neuro., 8, 302). Precision itself rests on the optimal representation of environmental uncertainty and the action of neuromodulators, such as noradrenaline. Here we employ computational models of behaviour and indices of central noradrenergic function to explore aberrant precision setting in ASD. Adults with ASD (n=21) and age and ability-matched neurotypical controls (NT, n=18) took part in a probabilistic associative learning task. Participants heard either a high or low tone, followed by a briefly presented image, and were required to make a button press response indicating whether the image was a face or a house. The probabilistic associations between the tone and the images changed over time. Concurrent pupillometry provided trial-by-trial biomarker of central noradrenergic function (Samuels et al., 2008, Curr Neuropsychopharmacology, 6, 1-19). Data were modelled using the Hierarchical Gaussian Filter (Mathys et al., 2014, Front. Hum. Neuro., 8, 825), allowing the quantification of individual learning under different levels of uncertainty. NT adults showed a slowing of reaction time (F(2,34)=17.8, p=0.001) and an increase in error rates in response to images of increasing outcome unexpectedness (OU) (F(2,34)=6.2, p=0.005), whereas ASD adults showed no modulation of error rates (F<1), and a significantly reduced RT modulation as a function of OU (t(37))=2.29, p=0.028. NT adults also showed a trend towards the predicted pupil dilation to increasing OU (F(1,16)=3.20, p=0.09), whereas ASD adults did not (F(1,10)=1.9, p=0.19). Modelling of the RT data suggests that group status can be predicted from model parameters that characterise the influence of ‘high-level’ environmental uncertainty on RT (Chi-square=13.2, p=0.001, df=2). These data provide evidence that adults with ASD are less able than NT adults to use the probabilistic structure in the environment to guide behaviour. Such a pattern of responses is consistent with reduced sensitivity to environmental uncertainty, which itself determines the precision (gain) that one should ascribe to sensory inputs, relative to top-down predictions of those inputs. An absence of pupillometric response to OU further suggests aberrant neural precision (central noradrenergic function) in ASD. This study was supported by the Wellcome Trust (#100227). Ethical approval was provided by the UCL Research Ethics Committee (4357/002).

E09
A MULTIMODAL META-ANALYTIC COMPARISON OF STRUCTURAL AND FUNCTIONAL BRAIN ABNORMALITIES IN ADHD AND OCD

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Introduction: Attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD) patients share performance deficits during inhibitory control tasks. In ADHD, inhibitory control deficits are hypothesized to result in difficulty regulating impulsive behaviours, whereas in OCD, these deficits are hypothesized to underlie difficulties in controlling obsessions and compulsions. However, the extent to which these shared behavioural deficits are associated with shared or disorder-specific alterations in underlying inhibitory control networks is unclear. Methods: Effect-Size Signed Differential Mapping (ES-SDM) was used to perform a meta-analysis of structural and functional abnormalities in ADHD and OCD patients. Included studies compared ADHD or OCD patient groups against healthy controls using whole-brain voxel-based morphometry (VBM) to investigate brain structure, or using functional magnetic resonance imaging (fMRI) to investigate brain function during tasks of inhibitory control. Direct quantitative comparisons of structural and functional neural abnormalities in ADHD and OCD relative to healthy controls were performed while covarying for age and gender. Within each disorder, multimodal analyses were used to elucidate regions with overlapping functional and structural abnormalities. Results: Structurally, OCD patients (N of 729) showed disorder-specific decreases in rostro-dorsomedial prefrontal cortex grey matter (GM). Compared with healthy controls, both patient groups showed GM deficits in medial orbitofrontal cortex (mOFC), although these were significantly greater in OCD. Patient groups showed opposing findings in basal ganglia GM, which was increased in OCD patients and decreased in ADHD patients (N of 686) relative to controls. In fMRI studies, performance of inhibitory control tasks was associated with disorder-specific underactivation in ADHD patients (N of 449) in bilateral inferior frontal gyri, anterior insula, putamen, superior temporal gyri and supplementary motor area, while OCD patients (N of 292) showed disorder-specific underactivation in rostro-dorsomedial prefrontal cortex, right caudate, left postcentral gyrus and cerebellum. Multimodal analyses revealed overlapping function-structure abnormalities in ventrolateral–prefronto-insula–striatal regions in ADHD and rostrodorsal–prefronto-cingulo–striatal regions in OCD. Conclusions: Together, the findings suggest that inhibitory control deficits are associated with disorder-dissociated patterns of functional and structural abnormalities in ADHD and OCD, suggesting that distinct neurocognitive mechanisms may underlie these deficits in the two disorders. LJN is supported by an IOP-MRC PhD studentship.
E10
THE EFFECTS OF ACUTE FLUOXETINE ADMINISTRATION ON FUNCTIONAL ABNORMALITIES DURING TEMPORAL DISCOUNTING IN CHILDREN WITH ADHD

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Temporal discounting (TD) is the rate at which a subjective value of reward decreases with increasing time delay. Steeper TD is associated with impulsiveness and Attention Deficit Hyperactivity Disorder (ADHD). The role of the selective serotonin reuptake inhibitor (SSRI) fluoxetine in ADHD is relatively unexplored, but evidence supports involvement in impulsivity, TD and ADHD. This study examines whether a single acute dose of fluoxetine ameliorates atypical neurofunctional response in ADHD during TD. 12 boys with ADHD and 20 controls (15.09+/−1.76y) completed a TD task requiring participants to choose between receiving a certain amount of hypothetical money now or receiving £100 in either one week, month or year in an fMRI scanner. ADHD patients were scanned twice in a placebo-controlled randomised design under either Fluoxetine or placebo. Controls were scanned once, off medication. Activations to delayed vs immediate reward choices were modeled, with the modulatory effects of medication on the ADHD group's activations to delayed choices as the primary effect of interest. Repeated-measures whole-brain analysis (p<0.005) within patients revealed significant upregulation with fluoxetine in right inferior frontal cortex, insula, precentral gyrus and basal ganglia. This activation correlated with better TD performance within patients. Comparisons between controls and patients under either drug condition revealed normalization with fluoxetine in the activation of right insula and pre and postcentral gyrus and parietal lobe which was reduced in patients under placebo. Furthermore, there was a significant difference in TD behaviour between patients on placebo and controls (F(df=1,30)=4.11, p=0.05), but this difference was no longer significant when comparing patients on fluoxetine and controls (F(df=1,30)=2.41, p=n.s.). Inferior frontal, insular and striatal dysfunction is typical in ADHD during TD and other tasks and is consistently modified with psychostimulants. The findings show that serotonin agonists may have a similar upregulatory effect to psychostimulants in inferior fronto-insular-striatal regions and may alter discounting behaviour in ADHD in the context of impulsivity and TD. This study and CC were supported by the UK Department of Health via the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) for Mental Health at South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, King's College London. The research leading to these results has also received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115300, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007 - 2013) and EFPIA companies’ in kind contribution.

E11
THE NATIONAL CENTRE FOR MENTAL HEALTH

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Introduction: The National Centre for Mental Health (NCMH) was established in 2011 and is Wales' first biomedical research centre investigating the aetiology and treatment of mental illness across the lifespan. NCMH aims to facilitate and undertake high quality mental health research in order to better understand the causes, triggers, diagnosis and treatment of mental illness across the lifespan, from childhood to older age. The centre also strives to raise awareness of mental health issues and improve understanding of mental illness amongst patients, carers, professionals and the public whilst promoting and encouraging participation in research. Methods: NCMH works closely with clinical and non-clinical teams to recruit participants into the portfolio study. Participants are recruited through systematic and non-systematic methods. Non-systematic methods employed include bus and radio advertisements, print adverts in newspapers including the Western Mail, South Wales Echo, Big Issue and a sponsored editorial in Health Check Wales. Systematic methods include recruitment through community mental health teams and secondary care services, primary care mailouts and focussed recruitment (for example veterans, women in pregnancy from antenatal clinics and children and families from specialist ADHD and ASD clinics). Study participation involves a short interview capturing information including demographic details, mental health history, family history and treatment history, a blood or saliva sample and self-report questionnaires. NCMH has a major role in education and improving understanding of mental illness and this is achieved in a number of ways. The NCMH website (www.ncmh.info) comprises information about our research, education and public engagement as well as patient
and carer information leaflets, on-line tools and resources and topical blogs. The NCMH website has had 56,814 visitors thus far. NCMH has also developed training tools, for example a DVD training midwives on identifying and managing maternal mental illness and psychotropic medication charts used widely amongst general practitioners. Results: NCMH has recruited 4358 participants to the portfolio study creating a pan-Wales mental health database across a lifespan ranging from 5 years to 96 years old using systematic and non-systematic recruitment methods. Conclusion: Establishing a pan-Wales mental health database will allow us to investigate causes and treatment of mental illness through large datasets, across the lifespan and across research domains. Through our education, training and public engagement strategy, we hope to continue to raise awareness of mental illness and improve understanding of mental health and the importance of research amongst patients, carers and the public. Funding: NISCHR, Welsh Government

E12

SERVICE EVALUATION OF MEDICINES INFORMATION GIVEN TO PATIENTS

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Background: A Care Quality Commission (CQC) inspection highlighted that patients did not receive necessary information regarding their treatment. This study aimed to evaluate the current provision of medicines information and whether the implementation of a medicines booklet would improve information delivery. 1. To evaluate the provision of medicines information services 2. To evaluate acceptability of a draft medicines booklet at patient discharge 3. Developing a strategy to improve information provision inline with CQC standards. Methods: Focus group and semi-structured interview methodology was used to explore participant perspectives and experiences of receiving and/or delivering medicines information. Participant groups included service users, ward managers, and healthcare professionals (HCPs). Study participants were recruited via a gatekeeper using purposive sampling. All potential patients participants were/had been an inpatient on a mental health ward, and all staff members worked in a mental health trust. Inductive thematic analysis was used. As this was a service evaluation NRES was not required but the study was conducted using NRES principles. Results: Two focus groups and 6 interviews were completed; with a total of 22 participants. There were 10 inpatients, 4 occupational therapists; 2 ward nurses, 1 ward manager, 1 community psychiatric nurse, 2 psychiatrists and 2 pharmacists. Five themes emerged: medication, information, patient individuality, healthcare, and service development. Patient participants preferred the booklet at first prescribing, not at discharge: “in the beginning would have been better than later” (P2, FG1). Patient participants valued involvement in their care: “they actually discussed it with me and have asked me for any ideas what I might think about them. It’s kind of like a joint decision and I think that’s really good.” (P6, FG2) Few patients were aware of community pharmacy support services they could access on discharge: “I didn’t know there was one” (P2, FG2). Key Findings 1. Patients should receive information tailored to their individual needs. 2. An adaptation of the medicines information booklet was thought to be beneficial by patients and HCPs. 3. Patients valued a shared decision making approach as it provided patients with a feeling of importance in and control over their own care. 4. Clear strategies for signposting patients to community pharmacies need to be developed Conclusion: This study demonstrated a need for a number of improvements in the delivery of patient medicines information. The most important being the provision of information provided to be tailored according to individual need. This study was supported by a small HEFCE educational grant

F01

VARENICLINE, THE CLINICALLY EFFECTIVE SMOKING CESSION AGENT, RESTORES PROBABILITY RESPONSE REVERSAL PERFORMANCE DURING WITHDRAWAL FROM NICOTINE.

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Cognitive deficits associated with nicotine withdrawal have been shown to be a factor associated with relapse of tobacco smoking. Previous work has shown that the probabilistic reversal learning (PRL) task can assess cognitive flexibility in rats. This task involves making nose pokes in one of two holes; pokes into the active hole result in a food pellet reward on 80% of the trials. Upon retrieval of the food pellet, the next trial was initiated with the correct hole reversed after eight correct trials. The aims of this experiment was to examine cognitive deficits associated with nicotine withdrawal and investigate if varenicline, a nAChR α4β2 partial agonist, and nicotine can restore these impairments in the PRL task. Male hooded Lister rats (n = 32) were trained in the PRL task. The animals were made dependent on nicotine via osmotic mini-pumps implanted subcutaneously for 7 days (3.16mg/kg/day). Cognitive flexibility was measured via reversals, latency to respond, omissions, duration of trial and omissions. Upon removal of the osmotic mini-pumps, withdrawal was characterised by significant reduction in the number of reversals (p<0.05), an increase in latency to respond (p<0.01) and increases in omissions (p<0.05),
which were all time dependent. Nicotine (0.2 mg/kg SC) or varenicline (0.3 & 1.0 mg/kg SC) administered 10-min prior to PRL test sessions during the peak periods withdrawal, relieved the performance deficits. At 24 hours withdrawal, nicotine and varenicline (1 mg/kg) prevented onset of withdrawal by maintaining reversals, in addition to reducing latency of responding as a high dose of varenicline only, reduced omissions. These results confirm the role of nicotine to induce dependence and its withdrawal to disrupt PRL performance. Furthermore, demonstration that current smoking cessation treatments can restore withdrawal-induced disrupted performance provides a valuable model to develop putative new treatments for smoking cessation. Funding statement: Newcastle University vacation scholarship and BAP in vivo initiative award

**F02**

**DIFFERENTIAL INVOLVEMENT OF 5-HT1A AND 5-HT1B RECEPTORS IN THE LOCOMOTOR STIMULANT AND HYPOTHERMIC EFFECTS OF MEPHEDRONINE IN THE RAT**

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The recreationally used synthetic cathinone 4-methylmethcathinone (mephedrone) has similar psychoactive effects to 3,4-methylenedioxymethamphetamine (MDMA) and both are non-selective substrates for monoamine transporters (Simmler et al. 2013 Br J Pharmacol 168:458-70). 5-HT is involved in the hyperlocomotor and hypothermic effects of mephedrone in rats (King et al. 2014 Eur Neuropsychopharmacol 24:S217) and this study investigated the involvement of 5-HT1A, 5-HT1B and 5-HT7 receptors (with known roles in locomotion/thermoregulation), using selective antagonists (WAY-100635, GR127935, and SB-258719, respectively). Adult male Lister hooded rats (190-280g; CRUK) were habituated (40-60min) to individual Perspex arenas, then received saline vehicle (1ml/kg i.p.), WAY-100635 maleate (0.5mg/kg, Tocris; Rusyniak et al. 2007 J Pharmacol Exp Ther 323:477-87), GR 127935 HCl (3mg/kg, Tocris; Fletcher et al. 2002 Psychopharmacology 162:282-91) or SB-258719 HCl (10mg/kg, Tocris; Graf et al. 2004 Neurosci Lett 359:45-48), followed 30 min later by saline vehicle (1ml/kg i.p.) or mephedrone HCl (10mg/kg, Ascent Scientific). Locomotor activity for 1h post-mephedrone (Shortall et al. 2013 Eur Neuropsychopharmacol 23:1085-95) or rectal temperature for 2h post-mephedrone (Shortall et al. 2013 Br J Pharmacol 168:966-77) were measured as previously described (n=8 in each case). Time-course data were analysed by 3-way repeated measures ANOVA and total activity post-mephedrone by 2-way ANOVA, each with Bonferroni post-hoc. There were significant time x pre-treatment x treatment interactions for the effects of GR 127935 on ambulation (F(17,476)=2.145, P=0.005) and WAY-100635 on hypothermia (F(7,196)=2.837, P=0.008), while that for ambulation approached significance (F(17,476)=1.566, P=0.069).

Mephedrone caused significant hyperactivity (P<0.01-0.0001) 10-40min post-injection which was shortened to 10-15min by GR127935 + mephedrone-treated rats exhibited lower ambulation than mephedrone alone from 15-35min post-injection (P<0.05-0.01), and 43% fewer beam breaks during the entire post-mephedrone period (P<0.01). WAY-100635 + mephedrone-treated rats exhibited lower ambulation than mephedrone alone 15min post-injection (P<0.05). Mephedrone caused significant hypothermia 20-40min post-injection (−1.2±0.2°C from baseline; P<0.001 versus vehicle + vehicle) which was absent following WAY-100635 pre-treatment (−0.6±0.2°C from baseline; P>0.05 versus other treatment combinations). 5-HT plays an important role in the hyperlocomotor and hypothermic effects of mephedrone, which are mediated in part via 5-HT1A and 5-HT1B receptors. This finding is consistent with similar observations on MDMA (Fletcher et al. 2002; Rusyniak et al. 2007). Low affinity of mephedrone for the 5-HT1A receptor (Ki>20µM; Simmler et al. 2013) makes any direct effect unlikely but affinity for 5-HT1B receptors has yet to be determined. CAM is a Brazilian undergraduate funded by the Science Without Borders scheme.

**F03**

**PHARMACOLOGY OF LSD IN HEALTHY HUMAN SUBJECTS**

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Introduction: The pharmacokinetics of oral lysergic acid diethylamide (LSD) are unknown despite its common recreational use and clinical studies with LSD. Methods: We characterized the pharmacokinetic profile, subjective, and autonomic effects of a single oral dose of LSD (200 µg) in 16 healthy subjects (eight male, eight female). Results: Maximal concentrations of LSD (mean ± SD: 4.5 ± 1.4 ng/ml) were reached 1.7 ± 1 h after administration. Elimination was linear up to 12h with a half-life of 3.6 ± 0.9 h. Plasma LSD concentrations were quantified (> 0.1 ng/ml) in all of the subjects up to 12 h after administration. One percent of the orally administered LSD was eliminated in urine as LSD, and 14% was eliminated as 2-oxo-3-hydroxy-LSD within 24 h. No sex differences were observed in the pharmacokinetic profiles of LSD. LSD produced pronounced...
alterations in waking consciousness that lasted 12h. LSD also increased subjective well-being, happiness, closeness to others, and openness. LSD significantly increased blood pressure, heart rate, body temperature, and pupil size. The acute subjective and sympathomimetic responses to LSD were closely associated with the concentrations in plasma and exhibited no acute tolerance. Conclusion: In addition to marked hallucinogenic effects, LSD exerts empathogenic mood effects. LSD can safely be used in a controlled clinical setting but it produces sympathomimetic stimulation. These first pharmacokinetic data of oral LSD assessed in a controlled setting are essential for further clinical studies and serve as a reference for the assessment of intoxications with LSD. The study was funded by the University Hospital Basel, Switzerland, and the Swiss National Science Foundation (grant no. 320030_1449493).

**F04**

RETRIEVAL DEPENDENT CHANGES IN MEMORY FOR ADAPTIVE REAPPRAISALS RELATED TO ALCOHOL IN HEAVY DRINKERS: A MODEL FOR A RECONSOLIDATION-BASED COGNITIVE THERAPY?

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Introduction: Reconsolidation is implicated in the strengthening and modification of long-term memories. ‘Reappraisal’ is an emotion regulation procedure used in cognitive behavioural therapy, which engenders less threatening or more adaptive meanings to ‘maladaptive thoughts.’ Effective cognitive therapy relies on patients being able to effectively access these new meanings. Here we examine whether retrieval procedures designed to destabilise alcohol memories can increase accessibility of newly learned ‘reappraisals’ related to moderating alcohol consumption in heavy social drinkers. Methods: On Day 1 participants either retrieved alcohol-related memories using one of two retrieval procedures - Value Prediction-Error (n=15) or Expectancy Prediction-Error (n=16) - or did not retrieve alcohol memories (Control; n=16). After this, participants identified six personally-relevant ‘unhelpful thoughts,’ which related to their reasons for drinking excessively. They then generated alternative, more balanced thoughts (reappraisals) for each of the six unhelpful thoughts. Memory for these reappraisals was assessed at the end of Day 1 and again one week later (Day 8). Alcohol craving and drinking behaviour (over the previous 7 days) were assessed on both days. Results: All three groups showed ceiling level recall of reappraisals on Day 1 (98% recall accuracy) indicating excellent learning in all groups. Although recall of reappraisals on Day 8 was not significantly different by group (p = .118), planned comparisons revealed that percentage recall of reappraisals was significantly higher in the Value PE group (M = 91.1%, SD = 12.38) than the Control group (M = 78.1%, SD = 19.92) [t (29) = -2.162, p = .039] on Day 8. Conclusions: This preliminary study employs an emotion regulation strategy commonly used in cognitive therapy (reappraisal) in the context of memory retrieval procedures designed to cause memories to become unstable and susceptible to modification (reconsolidation). We found preliminary evidence that using a Value Prediction-Error during retrieval, prior to generating new, adaptive reappraisals related to moderate drinking, resulted in improved retention of these adaptive reappraisals at Day 8. While this did not translate into a change in behaviour during the short interval of the experiment, the results raise the possibility that reconsolidation-based adaptive memory modification using reappraisal might improve outcomes in cognitive therapy for alcohol problems by making adaptive cognitions related to the negative effects of alcohol (or the positive effects of moderation/abstaining) more accessible. SKK and RKD receive funding from the MRC.

**F05**

LIFELAB: A REACTION-TIME STUDY OF COGNITIVE BIASES TO ALCOHOL BRANDS IN SCHOOL STUDENTS FROM HIGH, MEDIUM AND LOW DEPRIVATION AREAS

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Introduction: Attentional bias is a well-described process in the maintenance of addictive behaviour (Field & Miles Cox, 2008, Drug and Alcohol Dependence, 97, 1-20). Adolescent heavy drinkers demonstrate biases towards alcohol with lower alcohol intake than non-heavy drinkers (Field et al. 2007, Addiction, 102, 579-586). We sought to examine attentional biases in alcohol vs. non-alcohol related brands, across high and low socioeconomic status. Data was collected in LifeLab, an educational intervention aiming to change young people’s health attitudes and behaviours. Methods: 186 students (91M/95F; Mage=13.5, SDage = .53) from 13 secondary schools completed a brand game on an iPad application. Students were instructed to correctly identify 12 alcohol brands, 6 non-alcohol brands and 3 control images presented in parallel across 3 blocks of 7 images. Accuracy and reaction time for correct identification were scored for each brand. Demographic data and data relating to alcohol exposure and consumption was also collected for each student through use of an iPad survey. We categorized schools into three groups (high, medium and low deprivation) using 6 standard indicators. Due to low numbers
in the low deprivation schools, these low and medium deprivation schools were collapsed into a single group for analysis. Results: Mixed-model ANCOVA examined effects of school-deprivation (high vs. low/medium) x Brand (alcohol vs. non-alcohol) with age, gender, alcohol exposure and consumption included as covariates. All students were more accurate for non-alcohol (M=.92, SD=.15) vs. alcohol (M=.68, SD=.22) brands, F(1,182)=6.15, p<.01, regardless of school group, F(1,182)=1.54, p=.22. All students were quicker to correctly identify non-alcohol than alcohol brands, with an interaction between school deprivation and brand type, F(2,181)=14.87, p<.001. Students from higher deprivation schools were quicker to identify alcohol brands vs. students from medium/low deprivation (Mdiff=.17s, p=.009) but not non-alcohol brands (Mdiff=.07s, p=.10). Students were more accurate at identifying alcohol brands if they were exposed more to alcohol in their life (r=.25) and personally consumed more alcohol (r=.23), p=.001. Discussion: These findings suggest that attentional biases in young people may be affected by socioeconomic factors, such as peer- and adult alcohol exposure, with implications for the development of addictive behaviours in later life. Further research should clarify the degree to which increased susceptibility to alcohol advertising might be moderated in order to reduce the higher burden of alcohol related disease in lower socioeconomic groups. Financial Support: The study was funded by the University of Southampton, University Hospital Southampton, NHS Foundation Trust and NIHR Southampton Biomedical Research Centre in Nutrition. Ethical approval was received from Uni. Southampton Ethics and Research Governance.

**F06**

**LIFELAB: EXPLORING THE LINK BETWEEN SOCIOECONOMIC STATUS AND ALCOHOL AWARENESS AND CONSUMPTION IN SECONDARY SCHOOL STUDENTS**

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Introduction: It is well recognised that lower socioeconomic status is associated with worse health outcomes. Health behaviours such as smoking and alcohol consumption play a role in determining health inequalities (Mckenbach et al., 2008, New England Journal of Medicine, 358:2468-2481). In some cases (eg. smoking) these behaviours start before adulthood. However, the case for alcohol consumption is less clear. (Hanson, Chen, 2007, Journal of Behavioral Medicine, 30:263-285). We explored the relationship between socioeconomic status, alcohol awareness and alcohol consumption. Data was collected in the LifeLab facility in Southampton General Hospital, an innovative educational intervention aiming to change young people's health attitudes and behaviours. Methods: 407 students (177 boys /230 girls) from 13 secondary schools in Hampshire, UK, completed an iPad survey whilst at the LifeLab centre. The survey collected demographic details and data on exposure to alcohol, personal consumption and alcohol unit awareness. Students were also asked to list three consequences of drinking alcohol. Answers were categorised into physical, psychological, social and other consequences using operationalized criteria. Uncertainties were settled through consensus with a second author. Six standard indicators of deprivation were used to divide schools into three groups: high, medium and low deprivation. Results: Consequences most commonly stated were physical (69%), followed by psychological (14%), and social (3%). There was no effect of school deprivation on students' understanding of the alcohol percentage of different drinks. Students from high deprivation schools reported significantly less exposure to alcohol than medium and low deprivation (F(2,403) = 7.60, p = .001) and significantly less personal consumption (F(2,403) = 7.60, p = .001). Exploratory analysis found that increased exposure to alcohol was related to increased consumption (r=.55, p<.001) and reduced awareness of the social consequences of alcohol (r=-.13, p = .007). Conclusions: The identified associations between socioeconomic status, personal consumption and exposure to alcohol has implications for the role of alcohol in determining health inequalities. Further research should examine effects of the LifeLab education programme on future drinking behaviour and health outcomes. Sources of financial sponsorship: The study was funded by the University of Southampton, University Hospital Southampton, NHS Foundation Trust and NIHR Southampton Biomedical Research Centre in Nutrition.

**F07**

**STOPPING HAND AND EYE MOVEMENTS DURING ACUTE ALCOHOL INTOXICATION**

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Background: Alcohol impairs response inhibition, but it remains unknown how general or specific such impairments are. Indeed it remains contested whether there exists a general inhibition system in the human brain, or whether inhibition systems are embedded in, and thus specific to, the planning mechanisms for each response modality. Further, alcohol-
induced impairments have not been disambiguated between proactive and reactive inhibition mechanisms, and nor have the contributions of attention- or action-updating impairments to ‘inhibition’ deficits been investigated. This study employed two tasks, a saccadic stop-signal reaction time (SSRT) task and manual SSRT. It is predicted that alcohol will affect saccadic SSRT but it is unknown and of primary interest whether this effect is similar to that for manual task. Methods: 16 Participants (8 male, mean age 23.1 years) completed both a manual and a saccadic stop signal task before and after a 0.8g/kg dose of alcohol and, on a separate day, before and after a placebo. Blocks in which participants were required to ignore the signal to stop or make an additional ‘dual’ response were be included to obtain measures of proactive inhibition, attentional and action-updating effects as well as whether these too are affected by alcohol, or whether the impairment is specific to reactive manual response inhibition. Results: Bayesian analyses assessing the difference in alcohol induced impairments to SSRT in the manual and saccadic domains suggests there is substantial evidence for the null hypothesis (B = 0.26), indicating no difference in the effect of alcohol on response inhibition across response modalities. Conclusions: These first phase findings indicate that alcohol affects a response inhibition system that is not specific to the manual domain providing support for a domain general response inhibition network in the brain. This work was supported by Alcohol Research UK. Ethical approval was gained from the School of Psychology ethics board at Cardiff University.

**Fo8**

**THE AD-LIBITUM ALCOHOL ‘TASTE TEST’: INVESTIGATION OF ITS CONSTRUCT VALIDITY AND POTENTIAL CONFOUNDS**

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Introduction: The motivation to drink alcohol can be unobtrusively measured in the laboratory in the guise of a ‘taste test’ in which participants rate the taste of alcoholic drinks whilst their intake is monitored. The method is used to investigate experimental manipulations of the motivation to drink and establish proof-of-concept for novel behavioural interventions. However, little is known about its construct validity (relationship to typical drinking habits) or the variables that may compromise its validity. Method: We re-analysed data from 11 published and unpublished studies that used an ad-libitum taste test. To investigate construct validity, we correlated alcohol intake with typical alcohol consumption, subjective craving, scores on the Alcohol Use Disorders Identification Test, and perceived pleasantness of the drinks. We also investigated the influence of time of day and participant awareness of the purpose of the taste test on alcohol consumption. Results: We identified 753 participants (447 female) with a mean age of 20.81 (± 3.10) years. Males (40.24 % ± 27.63) drank significantly more alcohol than females (30.73% ± 24.79) during ad-libitum sessions (p<.001). When controlling for experimental condition, individual differences in typical alcohol consumption ($\beta = 0.09$, p = .05; 95% CI [0.02 to 0.016]), craving ($\beta = 0.35$ p < 0.001; 95% CI [0.14 to 0.55]) and drink pleasantness ($\beta = .14$, p < .001; 95% CI [0.06 to 0.22]) all significantly predicted the volume of alcohol consumed. Participant awareness and time of day were not related to alcohol intake after controlling for these variables. Conclusions: The construct validity of the ad-libitum taste test was supported, with significant predictive relationships observed between typical weekly alcohol consumption, craving and pleasantness ratings of the drinks provided. There was no evidence that alcohol intake was sensitive to time of day or participant awareness of the purpose of the taste test. We conclude that the ad-libitum taste test method is a valid method for the assessment of alcohol intake in the laboratory. This research has no financial sponsorship.

**F09**

**EFFECTS OF SLOT MACHINE GAMBLING ON AD LIBITUM ALCOHOL CONSUMPTION: A LABORATORY STUDY**

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Introduction: Alcohol consumption and gambling frequently co-occur, and disordered gambling and alcohol use disorders are highly comorbid. While past studies have examined the effect of a standardized alcohol load on subsequent gambling behaviour, only one prior study has tested the reverse pathway, showing that video lottery terminal play increased subsequent alcohol consumption (Stewart SH et al, 2002, Addictive Behaviors, 27, 819-835). Methods: This study investigated whether 30 minutes of slot machine play (in a ‘casino lab’ housing four live terminals) influenced subsequent alcohol consumption during a resting period (30 minutes) when beer and non-alcoholic soft drinks were available. Participants were male University students who were both social drinkers and had some prior gambling experience. Participants were
tested in groups of 2-3 subjects, with groups counterbalanced to either the gambling condition or a control condition who watched a movie for 30 minutes. In the ad libitum session, beverages were dispensed by a researcher in order to measure volume consumed and preclude participants exceeding intoxication limits, based on breath alcohol monitoring. Results: We compared 20 participants in the gambling condition against 17 participants in the movie condition. All participants consumed at least one alcoholic beverage in the ad libitum session. The gambling condition was associated with a greater number of beverages requested (M = 3.0, SD = 0.6; movie M = 2.4, SD = 0.6, t(33) = 1.35, p = .05), alcoholic volume consumed (gambling M = 877ml, SD = 183; movie M = 651ml, SD = 187, t(33) = 1.35, p = .001), and an increase in the self-reported intention to drink alcohol (gambling M = 0.23 SD = 0.4, movie M = -0.12, SD = 0.3, t(28) = 2.48, p = .019). There were no differences in the subjective response to alcohol between the two conditions (p > .05). Conclusions: Our study extends the earlier report by Stewart et al (2002) showing that gambling behavior potentiates subsequent alcohol intake. These effects are specific to alcoholic beverages, although the subjective response to alcohol was not altered. In light of other data showing that alcohol administration increases risky gambling, these findings highlight a feedback loop with relevance to public policy (availability of alcohol in gambling venues) and public messaging regarding alcohol use during online gambling at home. Funding: The Centre for Gambling Research at UBC is supported by a grant from the Province of BC government and the British Columbia Lottery Corporation (UBC F15-00758). JTW is supported a studentship from the University of Cambridge Poynton Trust. Approvals: This project was approved by the Behavioural Research Ethics Board at the University of British Columbia (H14-02803).

**F10**

**EFFECT OF GLASS MARKINGS ON DRINKING RATE IN SOCIAL ALCOHOL DRINKERS**

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Excessive alcohol use is associated with personal and societal harms (British Medical Association, 2008, Alcohol misuse: tackling the UK epidemic, London). Alcohol consumption has been shown to be sensitive to changes in price (Huang C., 2003, Econometric models of alcohol demand in the United Kingdom, H.M. Customs and Excise, London.) and availability (Room et al., 2005, Lancet, 365(9458), 519-30). Another area showing promise is glassware; research has suggested that beer consumed from a straight glass is consumed slower compared to a curved glass, potentially because of volume perceptual error (Attwood et al., 2012, PloS one, 7(8), e43007). The aim of these studies was to explore the influence of different types of accurate volume information on the rate of consumption of alcoholic beverages. Study 1: Experimental design was a 2 × 2 between-subjects model with factors of glass marking (marked, unmarked) and beer strength (low 3.8% ABV, standard 4.8% ABV). Social alcohol consumers (n = 159; 80 female) were randomised to drink either low or standard strength lager from either a marked or unmarked glass. The marked glass had its midpoint marked with a band of yellow tape and a small transparent sticker stating “midpoint”. The primary outcome measure was total drinking time. Baseline and post-consumption measures of mood and craving were obtained. Study 2: Protocol was registered prior to study (osf.io/z8s9r). The design was the same as Study 1, but with only one beer strength used. Social alcohol consumers (n = 160; 80 female) participated and standard strength lager was used (5% ABV). The marked glass had its ¼, ½, and ¾ volume points marked with black adhesive stickers. All other aspects of Study 1 remained identical. Linear regressions were used to test the effect of glass marking on consumption time, adjusted for age and sex. Outliers were removed based on residing 1.5*IQR’s above or below the upper or lower quartiles. Participants in the marked glass condition had slower drinking times compared to those in the unmarked glass condition in both studies. There was no statistical evidence for a difference in Study 1 (mean difference 0.49, 95% CI -0.82 to 1.80, p = .462), but there was some statistical evidence for a difference in Study 2 (mean difference 1.37, 95% CI 0.04 to 2.70, p = .043). There was no statistical evidence for changes in mood or craving over the course of either study (p > .01). The volume information in Study 2 appears to influence the rate of drinking of alcoholic beverages. The specific design of the information may also have an influence. This may represent a modifiable target for public health interventions. This study was funded by the University of Bristol with support from the Medical Research Council Integrative Epidemiology Unit at the University of Bristol, the National Institute for Health Research’s School of Public Health Research, and the UK Centre for Tobacco and Alcohol Studies. Both studies were reviewed and approved by the Faculty of Science Research Ethics Committee at the University of Bristol (Study 1 reference: 310108288, Study 2 reference: 25091410961).
F11

COMPULSIVITY AS A TRANS-DIAGNOSTIC TRAIT

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Introduction: Researchers have suggested dispensing with traditional categorical assessment of psychiatric disturbance, in favor of defining trans-diagnostic psychiatric traits that may be of greater biological relevance. The present study tested if compulsivity is such a trait; being present across diagnostic categories and associated with normal variation in a well-defined neurobiological process, model-based (i.e. goal-directed) learning. Method: Two independent experiments were carried out to test this hypothesis, each conducted online via Amazon’s Mechanical Turk. In Experiment 1, data from 548 subjects were included in a proof-of-principle study that assessed if obsessive-compulsive symptoms (but not depression or anxiety) tracked model-based deficits in the general population, while controlling for variation in age, gender and IQ (assessed using progressive matrices). In Experiment 2, 1413 subjects completed the measures listed above, in addition to completing a broader range of self-report clinical questionnaires that varied in the extent to which they measure putatively ‘compulsive’ (addiction, eating disorders, impulsivity) and ‘non-compulsive’ (apathy, social anxiety) psychiatric symptoms. Results: In Experiment 1, using mixed-effects modeling of trial-by-trial behavior, we found that deficits in model-based learning were associated with normal variation in obsessive-compulsive (p=.049), but not depressive (p=.439) or anxious traits (p=.777). In Experiment 2, we replicated this result, finding that similar deficits in model-based learning were associated with total scores on questionnaires assessing obsessive-compulsive disorder (p=.020), addiction (p=.029), eating disorders (p<.001) and impulsivity (p=.007), but not with depression (p=.385), trait anxiety (p=.498), apathy (p=.953) and social anxiety (p=.496). We conducted a factor analysis using responses to individual questionnaire items to test for the presence of a latent factor that linked compulsive symptoms across disorders. We found clear evidence for a ‘compulsive’ factor, which cut across existing diagnostic categories, and this factor was a highly significant predictor of goal-directed deficits (p<.001). Using this approach, we were able to establish the specificity of this effect with respect to non-compulsive psychiatric features, namely an ‘anxious-depressive’ factor and ‘social anxiety’ factor. Neither of these factors were related to model-based deficits, and planned pairwise contrasts indicated that their effect sizes were significantly smaller than that of compulsivity (p=.002 and p<.001, respectively). Conclusion: Compulsivity is a trans-diagnostic trait that is selectively associated with deficits in model-based (goal-directed) learning. These data provide support for the feasibility and importance of a dimensional approach to psychiatry, laying the foundation for a promising new course for psychiatric research. Funding: Sir Henry Wellcome Postdoctoral Fellowship (101521/Z/12/Z) to CMG.

F12

RECREATIONAL COCAINE USE IS ASSOCIATED WITH INHIBITORY CONTROL DEFICITS

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Introduction: Evidence has linked chronic cocaine use with various neuropsychological deficits in particular inhibitory deficits; however relatively few studies have investigated the effects of recreational (non-dependent) use (e.g Colzato et al, 2007,2009; Soar et al, 2012; Sellaro et al, 2013). The present study aimed to further explore whether recreational cocaine users show deficits in inhibitory control relative to non-cocaine polydrug users. Methods: Using a quasi-experimental between groups design, recreational cocaine users (n = 20; 10 males) and non-cocaine poly-drug users (n= 20; 10 males) were compared on the Stroop and Stop Signal Task. Questionnaires assessing psychological health and drug use were also completed. Results: Recreational cocaine users had a lower stop latency (p=0.04) and made more stop errors (p=0.03) on the Stop Signal Task relative to polydrug controls. There was a significant interaction between congruency and drug group on Stroop accuracy (p=0.03), with cocaine users showing poorer Stroop performance than polydrug controls. Recreational Cocaine users also reported significantly poorer psychology health, higher nicotine, alcohol, cannabis and ecstasy use relative to polydrug controls. Conclusions: Recreational cocaine users show a pattern of inhibitory response deficits consistent with previous literature in chronic users. Thus even at recreational levels, cocaine use may be sufficient to induce general inhibitory processes across a number of tasks, possibly as a result of dopaminergic alterations. However, as is commonly the case in recreational drug users, polydrug use was higher in the cocaine group, thus the influence of other drug use and psychological health needs to be considered. UEL ethical approval was granted and this research was supported by internal funds only.
A RANDOMISED CONTROLLED TRIAL OF ACUTE CANNABINOID ADMINISTRATION: THC AND CBD HAVE OPPOSITE EFFECTS ON AUDITORY MISMATCH NEGATIVITY

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Introduction: Previous research suggests Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), the main constituents of cannabis, have opposite effects on cognition and brain function. THC has generally been found to be cognitively impairing and have anxiogenic, paranoia inducing, psychotogenic properties. In contrast, CBD has been reported to ameliorate adverse effects of THC. In the current double blind crossover, placebo-controlled study, we examined the acute effects of THC and CBD alone and in combination on a candidate endophenotype for schizophrenia, the mismatch negativity (MMN). MMN is reduced in amplitude in patients with schizophrenia and subserved by NMDA receptor function. Our aim was to explore mechanisms by which THC may trigger and CBD may ameliorate psychotic-like brain phenomena. Methods: Thirty-six healthy volunteers (31 male) comprising 18 experienced cannabis-users and 18 non-naïve controls/irregular-users (median lifetime use 307 versus 24, respectively), underwent 5 randomised drug sessions with a one week washout: 1. Placebo; 2. THC(8mg); 3. CBD(400mg); 4. CBD(4mg)+THC(8mg)[LoCBD+THC]; 5. CBD(400mg)+THC(12mg)[HiCBD+THC]. Drugs were dissolved in 100% ethanol (which served as placebo) and vaporised using a Volcano® Vaporiser. Participants completed a multifrequency auditory oddball paradigm with duration and frequency deviants (6% each). MMN amplitude was analysed at Fz. Results: A 5(Drug)x2(MMN-type)x2(Group) repeated-measures ANOVA revealed a significant DrugxMMN-type interaction (F=6.12, p<.001) and DrugxGroup interaction (F=2.89, p<.025). CBD attenuated while THC enhanced freqMMN, more so in users than controls, and CBD enhanced durMMN in controls but not users. In the comparison of the three THC conditions, freqMMN was more consistently affected, where a significant DrugxGroup interaction indicated that HiCBD+THC significantly attenuated freqMMN relative to THC-alone and LoCBD+THC in users particularly, while trend differences in controls indicated that LoCBD+THC compared to THC tended to reduce both freqMMN and durMMN. Conclusions: THC and CBD have opposite effects on frequency MMN, while the pattern of effects is less clear for duration MMN. These findings suggest that different neurobiological interactions with the endocannabinoid system may subserve frequency and duration MMN. Further, the effects of CBD on MMN were not typically in the direction expected with regard to potential antipsychotic properties and when combined with THC differed according to dose, prior exposure to cannabis and the nature of the MMN investigated. Acknowledgements: This study (CT12/003) was approved by the University of Wollongong and Illawarra Shoalhaven Local Health District Health and Medical Human Research Ethics Committee. Funded by the National Health and Medical Research Council of Australia (Project Grant 1007593) and the Australian Research Council (FT110100752). Drugs were supplied by STI Pharmaceuticals and the Volcano® Vaporiser was provided by Storz & Bickel.

I WAS GONNA PUT IN THE EFFORT AND DEVELOP A RESPONSE BIAS - BUT THEN I GOT HIGH: ACUTE AND CHRONIC EFFECTS OF CANNABIS ON REWARD-PROCESSING

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Introduction: Both the acute and chronic effects of dependence-forming drugs (e.g. cannabis) have been associated with deficits in various aspects of reward-processing. Recently, two behavioural tasks have successfully been used to assess effort-related-decision-making and the development of a rewarded response-bias: namely, the Effort-Expenditure-for-Rewards-Task (EEfRT) and the Probabilistic-Reward-Task (PRT), respectively. However, the relationships between these aspects of reward-processing and cannabis use have not been thoroughly investigated. We had two main aims: (i) to investigate the acute effects of three types of cannabis (THC-only, THC+CBD and placebo) on effort-related-decision-making (ii) to investigate the effects of cannabis dependence on effort-related-decision-making and the development of a rewarded response-bias. Methods: In experiment 1, using a repeated-measures design, participants (n=16, 7 male) received one of three types of vaporized cannabis (containing: 8mg of THC; 8mg of THC + 10mg CBD; or placebo) and subsequently completed the EEfRT. In experiment 2, using a between-subjects design, two groups were compared: people dependent upon cannabis (n=20) and poly-drug using controls (n=20) who were not dependent on any drug. Participants completed the EEfRT and PRT in a non-intoxicated state. Results: In experiment 1, relative to placebo, both types of cannabis reduced the likelihood of participants making a high-effort/large-reward choice (p=0.042 THC-only; p=0.068 THC+CBD). There was no evidence
for a difference between the cannabis types on effort-related-decision-making. In experiment 2, compared to poly-drug using controls, the cannabis-dependent group demonstrated a weaker overall response bias ($p=0.032$). Moreover, only the poly-drug using controls’ response bias improved from block 1 to block 2 ($p<0.001$). Exploratory analyses indicated that these group differences might be associated with depression and tobacco use. However, the results from experiment 2 suggests cannabis dependence was not associated with impaired effort-related-decision-making. On the other hand, cannabis dependence was associated with an impaired ability to acquire a rewarded response-bias, but this may be explained by comorbid depression and tobacco use. Will Lawn’s PhD is funded by the BBSRC.

**F15**

**ASSESSING THE TRANSLATIONAL FEASIBILITY OF PHARMACOLOGICALLY WEAKENING DRUG MEMORIES WITH MEMANTINE IN QUITTING SMOKERS**

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Introduction: Preclinical reconsolidation research offers the first realistic opportunity to pharmacologically weaken the maladaptive memory structures that support relapse in drug addicts. N-Methyl D-Aspartate receptor (NMDAR) antagonism is a highly effective means of blocking drug memory reconsolidation. However, no research using this approach exists in human addicts. We therefore sought to assess the potential and clinical outcomes of blocking the reconsolidation of cue-smoking memories with memantine in quitting smokers. Methods: 59 dependent and motivated to quit smokers were randomised to one of three groups receiving: 1) Memantine with or 2) without reactivation of associative cue-smoking memories or 3) reactivation with placebo on their target quit day in a double-blind manner. Participants aimed to abstain from smoking for as long as possible. Levels of smoking and FTND score were assessed prior to intervention and up to a year later. Primary outcome was latency to relapse. Subjective craving measures and attentional bias were assessed in-lab. Results: All study groups successfully reduced their smoking at one week [$F(1,56) = 10.586$, $p = 0.002$, $\eta^2= 0.159$] up to three months [$t(58) = 6.04$, $p< 0.001$, $r = 0.62$]. Memantine in combination with smoking memory reactivation did not reduce smoking, cue reactivity or attentional capture by smoking cues compared to the control groups. [$F(2, 56) = 0.355$, $p = 0.703$, $\eta^2=0.01$]

Conclusions: Memantine did not weaken maladaptive cue-smoking memories when these were reactivated. This failure to translate rodent research to humans highlights critical areas of research priority needed to assess the treatment potential of reconsolidation blockade in human addicts. Primary among these are tolerable drugs that reliably block reward memory reconsolidation and retrieval procedures that reliably destabilise strongly trained memories. This research was funded by a Medical Research Council grant awarded to RKD, SKK and HVC and an Economic and Social Research Council grant awarded to RKD.

**F16**

**DO E-CIGARETTE USERS ALTER THEIR PUFFING BEHAVIOURS WHEN GIVEN LOWER NICOTINE CONCENTRATIONS?**

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Introduction: To reverse tobacco-related withdrawal symptoms and reduce craving, smokers need to maintain a constant plasma nicotine level via continued nicotine intake. Early studies show that smokers will increase their puffing frequency and intensity when given ‘lighter’ tobacco cigarettes (i.e. lower nicotine content), whether this is also the case with e-cigarette use has not been empirically explored. When the EU-TPD (European Union’s Tobacco Product Directive) comes into effect (May 2016), all e-cigarettes containing nicotine concentrations above 20mg/mL will require medicines licensing, potentially restricting access to adequate nicotine concentration needed by users. Determining whether and how users can compensate for this reduced nicotine concentration therefore has practical, clinical and regulatory significance. Aims: To explore puffing topography in regular e-cigarette users under two conditions, their ‘habitual nicotine concentration’ and a ‘lower nicotine concentration’. Methods: A within-participant design study with two conditions: ‘high’ (18mg/mL) and
'low concentration' (6mg/mL) nicotine e-liquid. On 2 separate days, 5 regular e-cigarette users used an 'e-Vic' tank system with a dual coil atomiser ad libitum for 45 minutes. Puffing topography ('numbers of puffs', 'puff duration' and 'Intervals between puffs' (IPI)) was captured via video-recordings and in-built e-cigarette puff counter. Other measurements included 'amount of e-liquid consumed', 'nicotine exposure' (volume consumed timed by nicotine concentration), 'urge to vape' (craving) and 'withdrawal symptoms' (at baseline and post-vaping). Results: Data were analysed using Bootstrapped t-tests. Nicotine exposure was lower (t (4) = 3.10, p = .036), and amount of e-liquid consumed was higher in the 'low' compared with the 'high' condition, t (4) = -6.29, p = .003. Mean puff number and puff duration were also greater and IPI was shorter in the 'low concentration' but these fell short of statistical significance (p > .05). 'Urge to vape' and 'withdrawal symptoms' did not differ between conditions (p > .05). Conclusion: These findings, although in need of replication in a larger sample, suggest that if nicotine concentration is restricted, e-cigarette users attempt to compensate by increasing their puffing frequency and duration, thereby consuming more liquid. Although nicotine exposure was higher in the 'high' condition, urge to vape and withdrawal symptoms did not differ, suggesting compensatory puffing behaviour can effectively alleviate craving and withdrawal symptoms. Whether compensatory puffing behaviour affects toxicant exposure is an important question for future investigation. Funding: This pilot study was funded by the University of East London. Ethics approval was granted by the university’s research ethics committee.

F17

THE BRAIN MORPHOLOGY OF DRUGS OF ABUSE

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Numerous studies have applied voxel-based morphometry to reveal widespread alterations in grey matter (GM) volume associated with various forms of substance-dependence, such as alcohol, cocaine, heroin, and nicotine. Building a consensus view from these studies is difficult due to several factors such as polydrug use, distinct demographic profiles, and co-dependencies. In this study we use a unique MRI database of polydrug users and healthy subjects, and model the different drugs of abuse and confounds, to identify the unique variability associated with each. A group of 152 subjects from the ICCAM study [ ICCAM Consortium, http://www.bbmh.manchester.ac.uk/iccam/], containing 67 healthy subjects and overlapping subsets of 62 alcohol, 44 cocaine, and 39 opioid dependent users were analysed. From the 152 subjects, 94 were smokers. The T1 anatomical images from all subjects were linearly and non-linearly registered to a custom template following the SPM-DARTEL protocol, and the registered modulated GM segmentations smoothed (8 mm FWHM). These were then fitted to a linear model with the following descriptors: alcohol, cocaine, opioid, nicotine, gender, and age. Besides age, all the other descriptors given were binary (e.g. 0=non-alcohol dependent, 1=alcohol dependent). As expected, age showed a larger global reduction of GM volume than any of the studied drugs. After accounting for age and gender (i.e. only examining the variance uniquely attributable to the specific drugs of abuse), alcohol further showed a general decrease of GM volume. This was observed within lobules V and VI of the cerebellum bilaterally, right amygdala, bilateral putamen, bilateral precentral gyrus, and posterior cingulate cortex, at a confidence interval (CF) of 99%. To a lesser extent, opioid and cocaine also showed decreased GM volume at bilateral precentral gyrus and right Heschl’s gyrus respectively, at CF=99%. Finally, nicotine showed both reductions and increases of GM volume, with the major increases at middle frontal gyrus bilaterally and right occipital pole, and decreases at inferior temporal gyrus bilaterally, at CF=99%. In this work we modelled, within the same framework, the unique variability associated with several drugs of abuse, while accounting for the effects of gender, age, and remaining drugs of abuse. Interactions between drugs have not been explicitly modelled. Results showed distinct effects for alcohol, cocaine, opioids, and nicotine, which may be due to specific properties of the different substances, or associated lifestyles. This work was supported by the MRC and the Edmond J. Safra Philanthropic Foundation.
**F18**

**AMYGDALA-MIDBRAIN CONNECTIVITY CHANGES MAY BE ASSOCIATED WITH NEUROADAPTATIONS LINKED TO CHRONIC ALCOHOL EXPOSURE**

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Animal models of alcohol dependence have identified the amygdala as a putative site of persistent neuroadaptations, which mediate withdrawal, intake-escalation and relapse (Koob G. 2009 Brain Research 1293(1),1,61-75). However, the cumulative impact of chronic alcohol consumption on human amygdala function is less well understood. We performed resting state functional connectivity analysis to test the hypothesis that abstinent alcohol dependent patients would show alterations in amygdala network interactions, proportionate to their cumulative lifetime exposure to alcohol. Abstinent alcohol dependent patients (n=23, 5 female,19 smokers, age 45.6±8.0 years, abstinence 9.8±10.7 months, lifetime exposure to heavy/dependent alcohol consumption 21.8±9.4 years) and healthy controls (n=39, 32 female,20 smokers, age 44.3±7.4) were scanned with eyes closed at rest for six minutes (TR=2), during the first visit within a multi-centre, multi-session study (ICCAM Consortium, http://www.bbbmh.manchester.ac.uk/ICCAM/cluster/platform). All patients fulfilled DSM-IV criteria for alcohol-dependence, were free from any current primary Axis-I Psychiatric Disorder, and tested negative for alcohol and drugs of abuse on the study day. Groups did not significantly differ for age, IQ, motion in scanner, digit-span, handedness, heart rate, blood pressure, cigarettes smoked per day and cigarette package years amongst smokers. Preprocessing included despiking, motion correction, boundary based registration, non-linear registration (ANTs), motion scrubbing, bandpass filtering and removal of nuisance variables (6 motion, local white matter, draining vessels, and ventricle CSF), and smoothing (6 mm FWHM). Resting state connectivity was modelled in the framework of a voxelwise GLM (FSL Feat), using a bilateral amygdala seed. A whole-brain voxelwise comparison of amygdala connectivity between healthy and alcohol dependent patients was undertaken to identify regions where patients had significantly reduced or increased connectivity relative to controls. Subsequently, we selected a region based on the criteria that it showed both altered amygdala connectivity in patients, and a biologically plausible link to substance-dependence, and tested it for a potential association with lifetime duration of heavy/dependent drinking, within the patient group. Alcohol dependent patients revealed significantly increased amygdala connectivity in the midbrain (SN/VTA) and hypothalamus, whilst also showing significantly decreased amygdala connectivity in the right lateral occipital cortex (Z>2.3, p<0.05 corrected). Amygdala-midbrain connectivity within the alcohol dependent group significantly correlated with lifetime duration of heavy/dependent drinking (r2=0.20, p<0.05). Increased connectivity between amygdala and midbrain (SN-VTA) may provide a marker of neuroadaptations driven by long-term chronic alcohol use, and may serve as a potential target for pharmacological interventions for relapse prevention. This work was funded by the MRC and NIHR BRC.

**F19**

**PROBING GABA-B RECEPTOR FUNCTION IN MAN; A PHARMACOKINETIC AND PHARMACODYNAMIC STUDY OF BACLOFEN IN HEALTHY VOLUNTEERS**

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Although evidence suggests a role for γ-aminobutyric acid type B (GABA-B) receptor agonists in addiction and its treatment, characterization of this receptor system in clinical addiction is limited. In particular it is unclear why some, but not all, patients tolerate or require high doses for treatment of alcohol dependence. This pharmacokinetic and pharmacodynamic study was designed to assess the effects of the GABA-B agonist baclofen on brain function in healthy volunteers, before starting to study its effects in addiction. Eight healthy male volunteers completed a double blind, placebo-controlled, randomised 3-way crossover study, in which they received a single dose of 10mg or 60mg baclofen or placebo (vitamin C 100mg), with an interval of at least 1 week between each study day. Subjective and objective measurements were taken at baseline and at 0.5, 1, 2, 3, 4 and 6 hours after dosing. Objective measures included EEG, blood samples for analysis of plasma baclofen levels, heart rate and blood pressure. As part of this pilot study plasma baclofen analysis techniques have
been developed to optimise accurate assessment of plasma baclofen levels, using liquid chromatograph mass-spectrometry. Participants completed a number of subjective rating scales including: the Subjective High Assessment Questionnaire (SHAS), visual analogue scales for ‘sleepy’, ‘relaxed’, ‘tense’ and ‘alert’ and a drawing task assessing motor coordination. For the high dose, changes in objective and variables compared with baseline reached a peak at 2-3 hours post dosing compared with placebo. Changes after the low dose were less evident. EEG data demonstrated a significant increase in EEG theta activity, particularly with eyes open (P<0.05) compared with placebo at the 60mg dose, but little change at the lower dose. Subjective data indicated a significant increase (p<0.05) in total SHAS scores and in individual items including feeling ‘drunk or intoxicated’, ‘effects of alcohol’ and ‘muddled or confused’, compared with placebo. Systolic blood pressure was increased at the 2 hour time point after the higher dose. The relationship of these changes to plasma baclofen concentration will be presented. The findings from this study will be used to inform future studies investigating the sensitivity of GABA-B receptors in alcohol and opiate addicts. The study was financially supported by the UK Medical Research Council (MRC G1002226) and National Institute for Health Research (NIHR)/Wellcome Trust Imperial Clinical Research Facility.

F20
REGIONAL GABAA AND OPIOID RECEPTOR CO-DISTRIBUTION AND NETWORK MODELLING WITH MULTI-LIGAND PET
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Introduction: Research into cognitive functions as well as neurological and psychiatric disorders usually implicates more than one neurotransmitter and receptor system. With the understanding that these systems interact locally as well as through larger networks, recent focus has been on integrating research from previously disparate fields to gain deeper knowledge of how the functions and disorders arise. Positron emission tomography can directly measure density of specific receptor sites in the brain and here we develop methods to further the analysis of PET data when more than one ligand is used to investigate the same disorder, the same cohort of subjects, or both. Methods: Previously acquired healthy volunteer data from 3 PET studies with [11C]flumazenil, [11C]Ro15-4513 and [11C]carfentanil, to label GABAA, GABAA α5 and µ-opioid receptors respectively, were quantified pharmacokinetically at a regional and voxelwise level. Of the cohorts involved, a subset of 8 individuals were scanned with both [11C]Ro15-4513 and [11C]carfentanil. Co-distribution of the different receptors was quantified using techniques developed for fluorescence microscopy, including the Manders overlap coefficient (MOC), and the Costes automated threshold search (T). Inter-regional correlation matrices were created to investigate within- and between-ligand putative networks. Results: Regional codistribution between all ligands was very high. For [11C]flumazenil and [11C]Ro15-4513, MOC=0.96, T=0.078, for [11C]Ro15-4513 and [11C]carfentanil, MOC=0.96, T=0.084, for [11C]flumazenil and [11C]carfentanil, MOC=0.94, T=0.067. Inter-regional correlation matrices revealed largely positive relationships between all regions for both [11C]Ro15-4513 and [11C]carfentanil, except for interesting negative relationships in GABAA α5 binding between most regions and the pre-caudate, supplementary motor area and thalamus, and µ-opioid binding between most regions and the cerebellum and caudate. With individuals scanned with both ligands, the strongest positive relationships between GABAA α5 and µ-opioid binding were seen in the pre-caudate and thalamus, with negative relationships in the amygdala and hippocampus. Correlation matrices revealed a strong negative relationship between opioid binding in the cerebellum and GABAA α5 binding in the rest of the brain, as well as a slight positive relationship between thalamic opioid signal and cortical GABAA α5. Conclusion: Colocalisation and network correlation methods provide interesting insight into the relationships between neurotransmitter systems. We are using this approach to investigate the covariance of one receptor system with another within the population and to compare patterns between different groups to provide a greater understanding of brain function. Acknowledgements: The study was financially supported by the UK Medical Research Council (MRC G1002226) and National Institute for Health Research (NIHR) Imperial Biomedical Research Centre.
F21
NEURAL CORRELATES OF LSD-INDUCED VISUAL HALLUCINATIONS

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Lysergic acid diethylamide (LSD) is a hallucinogen and classic psychedelic drug. The altered state of consciousness produced by LSD is characterized by visual hallucinations. Using fMRI, it is possible to measure resting-state functional connectivity (RSFC) by correlating the BOLD time course of a region of interest (ROI) with activity in the rest of the brain. We hypothesized that closed eyes RSFC of the primary visual cortex with the rest of the brain will change under the influence of LSD. We measured changes in RSFC between the primary visual cortex (V1) and the rest of the brain under the influence of LSD in a balanced order, within-subjects, placebo-controlled design. Twenty healthy subjects received 75 micrograms of LSD and separately saline (placebo) via intravenous infusion. Five subjects were discarded from the analysis due to high level of head movement. Therefore, fifteen subjects were included in the analysis (four females), mean age 31±7.95. Subjects had two 7 minutes fMRI (BOLD) scans (eyes-closed ‘resting-state’) in each condition. LSD produced marked changes in V1-RSFC. Specifically, increased RSFC was observed between V1 and the bilateral striatum, insular cortex, operculum cortex, orbitofrontal cortex, inferior frontal gyrus, superior and middle temporal gyrus, supramarginal gyrus, angular gyrus, paracingulate gyrus and medial posterior thalamus. Furthermore, these increases correlated positively with the subjective ratings of complex visual hallucinations (r²=0.461, p=0.005). There were no statistically significant decreases in V1-RSFC under LSD. Since V1 is centrally involved in visual processing, these results imply that increased communication between V1 and several brain regions may underlie LSD’s characteristic effects on visual perception. The results may have implications for the neurobiology of visual hallucinations and visual processing more generally. This was the first modern neuroimaging study with LSD. That the drug produced robust effects and was well tolerated by the participants augurs well for the future of human LSD research. The study received financial and intellectual support from the Beckley Foundation. The study was approved by a National Health Service research ethics committee.

F22
ONE-MONTH USE OF VERY LOW NICOTINE CONTENT CIGARETTES AND NICOTINE PATCH REDUCES AMYGDALA REACTIVITY TO SMOKING CUES

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Introduction. Smoking very low nicotine content cigarettes (VLNCs; typically < .1 mg nicotine yield) while wearing a transdermal nicotine patch (NRT) in the weeks leading up to the target quit date has been shown to reduce smoking behavior and nicotine dependence; and result in better cessation outcomes. By making nicotine administration non-contingent with smoking behavior, new associations between behavior and drug effects are created (instrumental extinction). In a small, uncontrolled pilot study (McClernon et al., 2007, Addiction Biology, 12, 503-512) we found evidence that VLNCs+NRT decrease brain activation to conditioned smoking cues in the amygdala, a brain region associated with the acquisition and extinction of learned reward. The objective of the present study was to investigate the effects of VLNCs+NRT on brain reactivity to smoking cues with the hypothesis that smoking VLNCs+NRT (EXT group) would reduce amygdalar reactivity to these cues relative to a group of smokers who continued to smoke their usual brand (UB Group). Methods. Eighty-nine (n=89) adult, treatment-seeking regular smokers were randomly assigned to: EXT (n=46) in which they smoked VLNCs while wearing a 21 mg/d nicotine patch for one month prior to their quit date or UB (n=43) in which they smoked their usual brand of cigarettes up to the quit date. Following the quit date, both groups received standard nicotine replacement therapy. Brain cue-reactivity was measured using fMRI prior to randomization, following pretreatment but prior to the quit date, and within 12-24 hrs after quitting smoking. 83% (n=38) and 86% (n=37) of subjects assigned to EXT and UB, respectively, completed all three scans. Results. Consistent with prior research, compared to UB, EXT resulted in significantly reduced breath CO levels, F=7.33, p<.001; and FTND scores, F=16.6, p<.001 in the 4 weeks prior to quitting smoking; and greater days to lapse, chi-square= 4.26, p=.04, hazard ratio=1.72. Preliminary analyses indicated that smokers in the EXT group, relative to the UB group, exhibited decreased amygdala activation to smoking cues (relative to baseline) following pretreatment (Cohen’s d = -.22) and post-quit (d = -.64). Conclusions. The results of this study are consistent with the hypothesis that
VLNCs plus NRT devalue smoking, which may in turn mediate their combined effects on nicotine dependence and cessation outcomes. Implications for further refining VLNCs-based interventions will be discussed. This research was supported by R01 DA025876 (FJM).

F23
ELECTRONIC CIGARETTES AS A RESEARCH TOOL: INVESTIGATION OF THE NEURAL EFFECTS OF ‘SMOKING’ WITH fMRI
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Introduction: Cigarette addiction is a major global health issue, and may be maintained by the behavioural and sensory aspects of smoking, as well as the pharmacological effects of nicotine. The latter has been well studied, however practical and safety issues have largely precluded studies of the former with modern methods. Electronic cigarettes are a relatively novel technology which provide a close simulation of smoking, without many of the associated practical and safety issues. The objective was to evaluate the feasibility of performing fMRI scans while subjects actively ‘smoked’ e-cigarettes. Methods: An initial evaluation stage tested different brands of e-cigarettes for their safety profile in the MRI environment and effects on image quality using a MRI phantom and one subject (Author MW). Magnetic susceptibility and the effect on image quality of different brands varied widely, however several contained no ferrous material and produced no obvious image artefacts. Subsequently a small pilot study was carried out using 11 participants (all regular or occasional smokers). The subjects completed a visual-cued smoking task that contained 20 smoking trials (with an ITI that varied randomly between 25, 30, and 35 seconds; 10 minutes in total). A custom-built optical device recorded the light-output of the e-cigarette’s LED in order to monitor task performance, and physiological data (pulse-oximetry, respiration) were also recorded. Standard EPI sequences were used to give BOLD contrast, and data analysis was performed with standard parameters, with all statistical images thresholded at z=2.3 (p=0.05, corrected for multiple comparisons) at the group (random effects) level. Results: A network of brain regions was significantly activated by smoking events, including left motor cortex and right cerebellum; most likely related to hand and facial movements that occurred on smoking trials. Also active were several thalamic and sub-cortical areas (putamen, ventral striatum), and the anterior insula bilaterally. These may reflect sensory or physiological aspects of smoking, such as flavour perception or reward processing. Conclusion: Electronic cigarettes are a viable method of studying the neural correlates of ‘smoking’ with fMRI and we have shown for the first time the brain correlates of actively ‘smoking’. This study potentially enables a fruitful new avenue of neuroscientific addiction research, using e-cigarettes and fMRI. This work was supported (in terms of general resources and scanner time) by Imanova Ltd.

F24
NEURAL CORRELATES OF CIGARETTE HEALTH WARNING AVOIDANCE AMONG SMOKERS
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Background: Eye-tracking technology has demonstrated that daily smokers actively avoid cigarette package health warnings. This avoidance may be a result of two different biases. Through repeated exposure to warnings, a pre-cognitive perceptual bias may develop, leading to the reduced attentional salience of the warnings. Alternatively (or additionally), avoidance behaviours may be a result of higher order cognitive biases, such as reduced emotional processing. Using electroencephalography (EEG), the aim of this study was to distinguish between these two possibilities. Understanding the mechanisms underlying health warning avoidance will be important in preventing this avoidance with effective health warning design. Method: Non-smokers (n = 20) and daily smokers (n = 20) attended a single EEG testing session where they completed a battery of tasks involving viewing cigarette package health warnings and control stimuli. These elicited the Event Related Potentials of interest: visual P1, visual Mismatch Negativity (vMMN), a proxy measure of early sensory processing, the P3a, an index of selective attentional orientation and the Late Positive Potential (LPP), a measure of higher order cognitive biases. Results: Non-smokers and daily smokers showed a similar P1 and vMMN response to health warning stimuli. By contrast, non-smokers showed an increased P3a amplitude (F(1,38) = 4.26, p = 0.046) and a larger LPP (F(1,38) = 5.16, p = 0.029) as compared to daily smokers. Conclusion: We find no difference in P1 or vMMN between non-smokers and daily smokers, indicating that there is no early perceptual bias in smokers’ visual perception of health warnings. By contrast, we see both a difference in the P3a response and the LPP response between these groups when viewing health warnings. Together these findings suggest that daily smokers are less sensitive to the emotional content of cigarette health warnings,
indicating that in order to design effective warnings, their content and framing should be changed to increase their emotional salience, and help to counteract the higher order cognitive bias observed. Funding: This research was supported by the Medical Research Council Integrative Epidemiology Unit (MC_UU_12013/6), which is funded by the Medical Research Council and the University of Bristol.

F25
STATE-TRAIT INTERACTION OF HUNGER ON STRIATAL RESPONSE TO ANTICIPATORY MONETARY REWARD
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Introduction: Obesity is associated with alterations in the neurocircuitry involved in reward processing that may not be food modality specific. Certain eating behaviour traits influence food intake, but their neurobiological effects on reward processing are poorly understood. We examined the interaction of: (i) trait hunger using the hunger sub-scale of the Three-Factor Eating Questionnaire (TFEQ-Hunger, Stunkard & Messick, 1985, J Psychosom Res 29:71-83), a behaviour that may be associated with food overconsumption and obesity, and (ii) state hunger (nutritional state), on anticipatory monetary reward brain responses. Methods: Eighteen healthy non-obese volunteers (10 male; age mean ± SD = 29.6 ± 9.1 years, BMI 23.7 ± 2.8 kg/m2) completed a Monetary Incentive Delay (MID) task during an fMRI scan twice in a randomised crossover design: (i) after an overnight fast (Fasted), and (ii) 70 mins after a 1200 kCal breakfast (Fed). Results: Subjects were hungrier on the Fasted compared to the Fed visit as determined by 10-cm visual analogue scale ratings (6.8 ± 1.9 vs. 2.6 ± 1.8, P<0.001). TFEQ-Hunger scores were positively correlated with BOLD signal in the caudate in response to anticipation of winning money when participants were Fasted (r= +0.48, P=0.04), but not when Fed (r= -0.33, P=0.18), with a significant state-trait interaction (P=0.035). Conclusions: These results suggest a state-trait interaction of hunger to increase striatal response to anticipatory monetary reward, demonstrating the cross-modal influences of nutrition and eating behaviour on reward processing.

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F26
EXTERNAL EATING IS ASSOCIATED WITH GREATER ENDOGENOUS OPIOID RELEASE FOLLOWING AMPHETAMINE ADMINISTRATION IN NON-OBESE MEN: A [11C]CARFENTANIL PET STUDY
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Introduction: Brain opioid systems are important in the regulation of food intake and body weight. Mu-opioid receptor (MOR) antagonists can reduce food intake and hedonic, reward and motivational responses, while obesity has been associated with reduced MOR availability using [11C]Carfentanil positron emission tomography (PET). Eating when exposed to appetizing stimuli is a behavioural trait that may promote overconsumption of energy dense foods and development of obesity. This can be measured by the ‘external eating’ subscale of the Dutch Eating Behaviour Questionnaire (DEBQ-External, Van Strien et al., 1986, Int J Eat Disord 5:295-315). However, its neurobiological basis is uncertain. Here we examined the relationship between external eating and brain opioid systems using PET imaging of MOR. Methods: An established [11C]Carfentanil PET paradigm was used to investigate the relationship between external eating and MOR availability at (i) baseline and (ii) endogenous opioid release following amphetamine administration (Colasanti et al., 2012, Biol Psychiatry 72:371-7). Nine healthy non-obese male volunteers (age mean ± SD 33.1 ± 6.5y) underwent two PET scans: one
before and one 3h after the oral administration of 0.5mg/kg d-amphetamine (Mick I et al., 2014, Int J Neuropsychopharm 17:2069-74). MOR binding potential (BPND) values were determined by applying the simplified reference tissue model (SRTM) to the regional time activity data with occipital lobe as the reference region. Linear regression was performed to calculate Pearson correlation coefficients r between DEBQ-External trait scores and baseline MOR BPND, and change in BPND following amphetamine administration, reflecting endogenous opioid release, in a priori ROIs: nucleus accumbens, caudate, putamen, thalamus, anterior cingulate and frontal lobe. Results: There was no significant correlation of DEBQ-External score with baseline [11C]Carfentanil BPND in any ROI. DEBQ-External score was however positively correlated with the amount of endogenous opioids released by amphetamine (change in [11C]Carfentanil BPND between pre- and post-amphetamine scans) in the nucleus accumbens (r= +0.92, P=0.001 uncorrected, P=0.006 Bonferroni corrected), caudate (R= +0.85, P=0.003 uncorr, P=0.018 corr), putamen (r= +0.75, P=0.02 uncorr, P=0.12 corr), and thalamus (r=+0.70, P=0.04 uncorr, P=0.16 corr). Conclusions: The finding of greater endogenous opioid release after amphetamine administration suggests greater sensitivity of the dopaminergic-opioid system in non-obese subjects with higher external eating behaviour. Funding: The study was financially supported by the UK Medical Research Council (MRC G1002226) and National Institute for Health Research (NIHR) Imperial Biomedical Research Centre, and approved by the West London Research Ethics Committee and the Administration of Radioactive Substances Advisory Committee, UK.

F27

A SURVEY OF ENERGY DRINK CONSUMPTION PATTERNS AND MOTIVATIONS FOR USE AMONG UK STUDENTS

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Introduction: Despite the rise in energy drink sales and the British media attention regarding its use, there is currently a lack of research examining energy drink consumption patterns and the motives for consumption among UK students. As part of a larger survey on the consumption of energy drinks mixed with alcohol among the UK student population, data were collected on the prevalence and frequency of energy drink use (without alcohol) and the reasons that underlie consumption.

Method: An online survey was advertised via UK university student union social media platforms. Responses (N = 1873, age 18-30 years old, Male =721 Female = 1152) were received from universities across the UK. As part of the survey students were asked questions regarding the frequency and quantity (typical and greatest) of energy drinks consumed on one occasion across different time frames (month and year), as well as questions regarding the motivations for energy drink consumption.

Results: Fifty one percent of students (N = 950) reported that they had previously consumed energy drinks. On average these students usually consumed 1.7 standard size energy drinks (250ml, 80mg caffeine) on one occasion and at least one energy drink on 4.5 days in the previous month. On average, the greatest number of energy drinks consumed on one occasion in the past month and year were 2.2 and 3.7 standard energy drinks respectively, less than the recommended daily upper limit for caffeine intake (<400mg/day, Nawrot et al, 2003, Food Additives and Contaminants, 20, 1-30). The motives reported for consuming energy drinks included “To keep me awake” (59%), “I like the taste” (54%), “It gives me energy” (46%), “It increases alertness” (44%), “It helps me concentrate better” (23%) and “It makes me less sleepy when driving” (12%). Conclusion: This first known UK wide student survey found that energy drink consumption is a popular practice among UK students. However, on average energy drinks are consumed in moderation do not exceed current caffeine guidelines (United Kingdom Committee on Toxicity, 2012, Statement on the interaction of caffeine and alcohol and their combined effects on health and behaviour). The majority of students consume energy drinks due to their appreciation of energy drink taste and the expectations regarding the positive effects of the drinks functional ingredients. Although energy drink consumption by itself does not appear to pose a public health problem, further research is required to examine total caffeine consumption from all sources among the student population. Financial sponsorship: Red Bull GmbH Ethical Approval: University of the West of England Ethics committee.
F28

SELF-REPORTED PROBLEM EATING BEHAVIOURS IN PATHOLOGICAL GAMBLERS: INVESTIGATING LINKS WITH IMPULSIVITY

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Introduction: Pathological gambling is characterised by a preoccupation with gambling that interferes with financial, family or social life. It is classified by the ICD10 as a disorder of impulse control and affects 9/1,000 people in the UK with a further 70/1,000 at risk of becoming pathological gamblers [PG] (Royal College of Psychiatrists, 2011). Problem eating is another example of an impulse control disorder that includes both pathological bingeing, and emotional eating behaviours. Since greater impulsivity is associated with both gambling (Steel et al. 1998) and problem eating (Yeomans et al. 2008), we sought to examine their relationship in pathological gamblers recruited for a neuroimaging study.

Method: 20 male pathological gamblers (PG, age 27-45y, BMI 20.2-30.8kg/m2) from the National Problem Gambling clinic, and 22 healthy males (age 26-41y, BMI 20.1-29.6 kg/m2) were recruited. Subjects completed the Barratt Impulsiveness Questionnaire (BIS; an assessment of motor, attentional and non-planning aspects of impulsivity), Canadian Problem Gambling Inventory (CPGI; a measure of Gambling Severity), Dutch Eating Behaviour Questionnaire (DEBQ; which examines dietary Restraint, and Emotional and External eating), and Three Factor Eating Questionnaire (TFEQ; examining dietary Restraint, Disinhibition and Hunger).

Results: PGs scored significantly higher (p<0.05) than controls on BIS, however there were no significant differences between the groups in any DEBQ or TFEQ score (p>0.05). In PGs there was a significant positive correlation (r=+0.69, p<0.005) between gambling severity and impulsivity. However there was no correlation between gambling severity and DEBQ or TFEQ scores in either group (p>0.5). BIS was positively correlated with TFEQ-Hunger in controls (r=+0.61, p<0.005), but not in the PG group (r=-0.1, p>0.5, difference between groups p<0.05). Similarly, there was a positive correlation between impulsivity and DEBQ-emotional eating in controls (r=+0.43, p<0.01) but not in the PG group (r=-0.1, p>0.5, difference between groups p<0.05).

Conclusion: These findings demonstrate that there is no relationship between gambling severity and pathological eating behaviours in pathological gamblers in treatment. Although problem eating behaviours have been correlated with levels of impulsivity in healthy participants (Lyke and Spinolla 2004), as seen in the controls in the current study, this relationship was absent in PGs. This suggests that there is a distinct psychopathology between the two impulse control disorders of PG and problem eating.

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IMPULSIVITY AND COGNITIVE DISTORTIONS IN PATHOLOGICAL GAMBLERS AND UNAFFECTED BIOLOGICAL SIBLINGS

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Background: Pathological gambling (PG), now classified as a behavioural addiction in DSM-5, is associated with increased levels of gambling-related cognitive distortions and impulsivity. However, it is not known if these characteristics represent a pre-existing vulnerability, or are a consequence of the addiction itself. The present study aimed to identify the role of impulsivity and gambling distortions as a risk factor for pathological gambling by comparing unaffected biological siblings of PGs, an (unrelated) PG group, and healthy controls (HCs) without any family history of PG.

Methods: PGs attending the National Problem Gambling Clinic (n=20, all male) were compared with HCs (n=18). A third group of unaffected biological siblings (n=37, 8 male, 9 female) were compared with a matched HC group (n=17). In both cases, the HCs did not differ in age, gender, smoking status, and IQ. Trait impulsivity was assessed using the UPPS-P impulsivity scale, comprising 5 facets: sensation seeking, premeditation, perseverance and positive and negative urgency. The Gambling-Related Cognitions Scale (GRCS) was used to assess cognitive distortions. Results: Preliminary analyses show that compared to HCs, PGs displayed elevated impulsivity on several UPPS-P subscales, including the negative urgency subscale, t(36)=-4.06, p<0.001, and
significantly elevated cognitive distortions, t(36)=8.48, p<0.001. Compared to HCs, siblings showed no significant difference on any of the UPPS subscales and they did not differ from HCs in terms of degree of cognitive distortions t(30)=0.77, p=0.45. Within the PGs, negative and positive urgency correlated with the level of cognitive distortions (r=0.60). Conclusions: We have replicated our previous research, with a new sample, showing PGs display elevated cognitive distortions and impulsivity, particularly on the negative urgency subscale (Michalczuk R, Bowden-Jones H, et al 2011). Impulsivity and cognitive distortions in pathological gamblers attending the UK National Problem Gambling Clinic: a preliminary report. Psychological Medicine, 41, 2625-2635). Compared to HCs, siblings do not show any alterations in impulsivity or cognitive distortions. The absence of an observed effect could suggest that these characteristics are a consequence of the addiction, rather than a risk factor. However this is based on self-reported questionnaires and these findings may not hold when we incorporate task based measures. Research was funded by the Medical Research Council (Grant code: RG63092) and National Institute for Health Research (NIHR) Imperial Biomedical Research Centre.

F30

PREFERENCES IN CANNABIS SMOKING: REASONS BEHIND THEM AND DO THEY AFFECT THE TYPE OF CANNABIS SMOKED?

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Background: The concentrations of two major active ingredients found in cannabis; delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), vary considerably across different types of cannabis worldwide. Although high THC, low CBD cannabis (commonly known as 'skunk') is the most available type in the UK, it has also been linked to an increased risk of mental health problems such as psychosis (Di Forti, M., et al. 2014. Schizophrenia bulletin 40.6: 1509-1517). Little is known about the relationship between users’ preference for type of cannabis and what is smoked. This exploratory study had the following aims: (1) To ascertain users’ preference and the main factors influencing it, (2) to determine whether preference for a type of cannabis relates to THC and CBD concentrations in the cannabis smoked. Methods: 456 (daily and recreational) cannabis users were recruited and assessed in their own homes. Participants were asked about their preference for cannabis type (‘no preference’, ‘hash/resin’, ‘herbal’, ‘skunk’, ‘other’) and to choose the main reason for this preference (‘effects’, ‘price’, ‘supply’, ‘quality’, ‘physical health’, ‘mental health’, ‘other’). An analysis was carried out on participants’ own cannabis samples to determine THC and CBD concentrations (%). Results: The majority of users reported preferring ‘skunk’ type cannabis (35.1%), compared to ‘herbal’ (23.2%), ‘hash’ (18.1%) or ‘other’ (21.4%). A significant proportion of participants stated no preference for a particular type of cannabis (21.4%). Regarding reasons behind a majority preference for ‘skunk’, the results suggest that the main factors influencing preference are ‘quality’ (stated by 50.28% of ‘skunk’ inclined participants) and ‘effects’ (35.52%) of skunk type cannabis over other varieties. Furthermore, ‘supply’ was only reported as the main deciding factor for preference by 11.17% of ‘skunk’ inclined participants. THC concentrations varied significantly according to preferred variety of cannabis, in which ‘skunk’ inclined participants had samples of cannabis containing higher concentrations of THC (p = 0.003). No such association was found for CBD. Conclusion: This study indicates that ‘skunk’ may be more popular than other types of cannabis as well as being the most available in the UK. Preliminary results show that this preference may be driven by the quality and effects linked to ‘skunk’ type cannabis over availability (‘supply’). Importantly, the preference for a particular type of cannabis (‘hash/resin’, ‘herbal’, ‘skunk’, ‘other’) may influence users’ pharmacological content. These findings are crucial in harm-reduction education and future legislation. This study was supported by the Medical Research Council.

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ASSOCIATIONS BETWEEN CANNABIS POTENCY, PROFILE OF EFFECTS, AND SEVERITY OF DEPENDENCE

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Introduction: In the last decade, cannabis use has decreased in England and Wales, whilst demand for cannabis treatment in drug services continues to rise. This could be in part due to increased availability of high potency cannabis over the same time period. Methods: Adults residing in the United Kingdom were questioned about their drug use, including three common types of cannabis (high potency: skunk; low potency: other grass, resin) through an online survey. Cannabis types were profiled and examined for possible associations between frequency of use and (i) cannabis dependence, (ii) cannabis-related concerns. Results: Frequent use of high potency cannabis predicted a greater severity of dependence (days of skunk use per month: b=0.093, 95% CI: 0.047, 0.138, P<0.001). By contrast, use of low potency cannabis was not associated with dependence...
(days of other grass use per month: \( b=0.019, 95\% \text{ CI: } -0.029, 0.067, P=0.455 \); days of resin use per month \( b=0.027, 95\% \text{ CI: } -0.018, 0.069, P=0.191 \)). Frequency of cannabis use (all types) did not predict severity of cannabis-related concerns. The profile of high potency cannabis was clearly distinct from low potency varieties by its marked effects on memory and paranoia. It also produced the best high, was preferred, and most available. Conclusions: High potency cannabis use is associated with an increased severity of dependence. Its profile is strongly defined by negative effects (memory, paranoia), but also positive characteristics (best high, preferred type), which may be important when considering clinical or public health interventions focusing on cannabis potency. Funding: This study was self-funded.

**F32**

**THE EFFECTS OF CONCURRENT LIFETIME ALCOHOL AND CANNABIS USE ON ANXIETY AND WORKING MEMORY USING THE ICCAM DATA SET**

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Introduction: There has been mounting evidence to suggest that cannabis use may have a number of beneficial effects, such as the attenuation of cell death observed in rodent models of alcoholism and also of some cognitive deficits associated with long term alcohol use in humans. Using the ICCAM study (http://www.bbmh.manchester.ac.uk/ICCAM) dataset of healthy controls and abstinent alcohol dependent subjects, we tested the hypothesis that concurrent alcohol and cannabis use may confer some protection from the adverse effects of alcohol with regard to anxiety and working memory. Methods: The ICCAM data-set was divided into those with a history of heavy/deepndent use of both cannabis and alcohol (n=43), those with a history of heavy dependent alcohol use but no cannabis use (n=37) and controls with no heavy cannabis or alcohol use (n=61). The first group was stratified along a continuum using a measure termed the concurrence ratio (CR). This was the number of years in which the subject was using both cannabis and alcohol divided by the total number of years that they were using alcohol. Two outcomes were assessed: the CANTAB Spatial Working Memory Task (SWM) and the Spielberger Trait Anxiety Inventory (STAI). SWM data were available from fewer participants: heavy/deepndent use of both cannabis and alcohol (n=32) heavy/deepndent alcohol use but no cannabis use (n=24) and healthy controls (n=30). Results: No significant difference (p>0.05) was found in STAI scores between the users of both alcohol and cannabis and users of alcohol without cannabis. However, a significant, negative Spearman’s correlation coefficient (\( r=-0.36 \)) (p=0.02) was found between STAI scores and CR. There was no significant correlation between lifetime alcohol exposure and CR, however there was a significant positive correlation between lifetime cannabis exposure and CR. No statistically significant difference was found between the groups in the SWM analysis. Conclusions: We show here that concurrent cannabis use in alcohol dependent subjects may protect against the anxiogenic effects of alcohol but not the working memory deficits. This suggests that the interaction between alcohol and cannabis on clinical outcomes may vary. These results therefore provide some support for the hypothesis that cannabis, if used concurrently with alcohol, may protect against some of the detrimental effects of long term alcohol use in humans. More research needs to be conducted to ascertain the underlying mechanisms and impact in other domains. Funding: ICCAM is independent research funded by the Medical Research Council as part of their addiction initiative (grant number G0000018). GlaxoSmithKline kindly funded the functional and structural MRI scans that took place at Imperial College and provided the GSKa98809 and vofopitant medication.

**F33**

**EVIDENCE FOR A CAUSAL EFFECT OF COFFEE CONSUMPTION ON HEAVINESS OF SMOKING AND SMOKING CESSATION: A TWO-SAMPLE MENDELIAN RANDOMISATION ANALYSIS**

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Introduction: Coffee consumption is associated with a range of smoking behaviours. Given the widespread use of coffee worldwide, and the substantial health burden posed by smoking, determining the causal impact of coffee consumption on smoking behaviour is of clear public health importance. However, traditional observational studies do not allow us
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EFFECTS OF CAFFEINE AND SLEEP RESTRICTION ON RISK TAKING
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Introduction: Caffeine is probably the most widely consumed drug being present in foods and beverages throughout the world. Sleep restriction has been associated with subjective fatigue and impaired cognitive function, including increased risk taking. This study set out to examine whether caffeine would improve mood, risk taking performance and inhibitory control after sleep restriction. Method: Fourteen participants (6 female) aged 18-22 were assessed the day following sleep restriction and sleep restriction though improved when caffeine was consumed in this state, but poorer performance with caffeine after normal sleep. Caffeine reduced risk taking with the BART (balloons popped) after sleep restriction, but showed increases in the non-sleep restricted condition with a greater number of balloons popped. A similar significant effect was also seen with the stop signal task, a measure of response inhibition, with performance decreased after sleep restriction though improved when caffeine was consumed in this state, but poorer performance with caffeine after normal sleep. Discussion: Caffeine is regularly consumed to reverse the effects of sleep loss and fatigue, through increasing subjective alertness, and with the belief that this is accompanied by improved performance. These results have shown that caffeine may be beneficial when fatigued after sleep restriction. However, after normal sleep, the stimulant effect of caffeine can have adverse effects, perhaps through hyper-arousal, with impaired response inhibition as well as showing increased risk taking. These preliminary results from this relatively new area of research suggest that caffeine may impair these important aspects of performance after normal sleep – when participants are not fatigued. No financial sponsorship was received for this study. Ethical Approval: University of the West of England Ethics committee.
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MEPHEDRONE AND MDMA: COMPARATIVE PSYCHOBIOLOGICAL EFFECTS AS REPORTED BY TWO COHORTS OF RECREATIONAL POLYDRUG USERS

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Aims: to compare the effects of mephedrone and MDMA, as self-reported for the longest single sessions of recreational usage. Methods: 152 MDMA users (mean age = 25.6 years, 94 males, 58 females), and 81 Mephedrone users (mean age = 25.4 years, 46 males, 35 females), were recruited through snowballing on social network sites. They completed a standard online questionnaire, for either Mephedrone or MDMA. The identical sets of questions covered the average amount taken per session, the longest duration of usage in the last 12-months, subjective effects while on-drug, and recovery effects in the days afterwards. Results: Mephedrone users reported a significantly longer maximum session of use in the last 12-months (mean 37.9 hours), than MDMA users (mean 24.4 hours). Mephedrone users also reported a significantly greater average amount used per session. There were also indications of low acute pharmacodynamic tolerance to mephedrone, since successive doses were reported to retain their subjective efficacy over time. The majority of on-drug subjective ratings did not differ between drugs, with similar increases in entactogenic effects such as euphoria, talkativeness, and feeling close to others. Although mephedrone users reported significantly more issues with sleeping, anger and anxiety. In relation to post-drug recovery, mephedrone users reported more craving, nasal irritation, paranoia and relationship difficulties. Mephedrone users also rated general recovery effects as more severe over the 7-day period following use, with more days before feeling normal. Their more severe recovery issues may reflect their longer periods of acute usage. Conclusions: The acute effects of MDMA and Mephedrone were broadly similar. However the recovery period for mephedrone was more enduring, possibly due to the longer duration of acute session usage, and putatively less acute pharmacodynamic tolerance. No financial sponsorship was sought for this research.

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DRUG TERM USAGE AND CHANGING TRENDS IN HIP-HOP LYRICS

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Background: Hip-hop culture emerged in the late 1970s in New York City, USA (Sule & Inkster, 2014, The Lancet Psychiatry, 1, 494-495). Since the genre's conception, drug terms have been referenced regularly in hip-hop lyrics. During the early 1980s, NYC experienced a crack epidemic that was described by socially conscious hip-hop artists by means of 'street epidemiology'. In the early 1990s, hip-hop music gained global mainstream popularity and other drug terms (e.g., ‘chronic’ i.e., cannabis) became frequently referenced in the lyrics. From conception to current trends, hip-hop lyrics have reflected a dynamic history of changes in drug culture. This study investigates the usage of a set of drug terms appearing in hip-hop lyrics and how usage has changed across time since the culture's conception. Method: We performed electronic searches using the Rap Genius ‘Rap Stats’ database (http://genius.com/rapstats; verified annotations and text, SameOldShawn). Frequency plots of words appearing in hip-hop song lyrics from 1988 through the present day were generated. Word frequency was defined as total number of hip-hop songs containing a drug term per year divided by total number of hip-hop songs recorded/produced per year. Searches were performed using street terminology (e.g., brown, molly...) and medical/pharmacological terminology (e.g., heroin, ecstasy...). Results: We detected several changing trends across time, some relating closely to changes in sociopolitical and geographical influences. We observed a rise in the frequency of the street term ‘molly’ (i.e., ecstasy, MDMA) emerging approximately in 2010 that continues to increase. Hip-hop culture was once predominantly affiliated with African American listeners, but now reaches broader demographics, particularly suburban listeners. In addition, we observed increased use of street terms ‘crunk’ and ‘sizzurp’ in the early 2000s peaking around 2005; this maps with the emergence and dominance of America’s southern commercial hip-hop scene, which heavily promoted the use of these substances. Furthermore, we observed the emergence and rise of pharmaceutical/prescription drug terms used in lyrics in the early-to-mid 2000s. The hip-hop artist Eminem soared in popularity during this time and he commonly referenced such terms in his lyrics. The rise in the term ‘cannabis’ was indicative of the onset of the Golden Age of hip-hop in the early-to-mid 1990s and then peaked again late 2000s, possibly relating to sociopolitical changes (e.g., decriminalization/medical recreational use etc.). Conclusions: Hip-hop lyrics may provide informative indicators of changing trends in hip-hop drug culture. Evaluating these trends may provide potential insights for more targeted and context-relevant interventions. Financial Sponsorship: no funding received.
**F37**

**“KNOW YOUR OWN NUMBER” – IMPROVING ALCOHOL SPECIFIC HEALTH LITERACY IN NHS STAFF AND VOLUNTEERS**

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Introduction: Alcohol-related harm costs the National Health Service £3.5 billion annually associated with 1.2 million hospital admissions. Epidemiological data suggests that interventions to reduce alcohol consumption will reduce alcohol related harms (Rehm, Nutt, 2014, Journal of Psychopharmacology, 28:3-7). Previous studies have shown that clinical staff experience a lack of confidence and poor knowledge in estimating alcohol units (Searle et al., 2009, Journal of Psychopharmacology, 23:A75), reducing their ability to assess potential alcohol health-harms in patients; leading to missed opportunities for interventions. Improving alcohol-specific health literacy in staff and volunteers working in hospitals may improve outcomes for patients. This audit assessed the knowledge and confidence of staff and volunteers at a large acute hospital before and after a ‘know your own number’ intervention. Methods: A representative sample of staff from across departments and disciplines University Hospital Southampton were asked to estimate the alcohol units in 4 commonly consumed drinks and rate their confidence in speaking to patients about alcohol use (via iPad questionnaire). A ‘know your number’ intervention, delivered by the research nurses teaching people about alcohol units was then carried out and the audit repeated. Results: The baseline audit of 482 staff and 127 volunteers showed only 2.5% of staff and none of the volunteers were able to accurately estimate all four drinks. 11.2% of staff felt very confident discussing alcohol with patients, only 5.6% of whom were able to correctly answer the questions on alcohol units. A re-audit on 465 staff and 59 volunteers showed 5.4% of staff and 1.7% of volunteers were able to calculate alcohol units. 9% of staff felt confident discussing alcohol with patients of whom 21.4% correctly answered the 4 questions. Of the staff who had received the educational package (N=91), 15.4% could answer all 4 questions compared to 2.9% (N=374) of staff not receiving the intervention -X2 (29.6 (4df), p<0.001). 16.5% of staff felt very confident in talking to patients about alcohol compared with 7.2% who had not received training -X2 (11.6 (2df), p<0.05). Conclusion: The majority of staff and volunteers have a limited knowledge of alcohol units, and potentially misplaced confidence in their ability. This significantly improved in those receiving the ‘know your numbers’ intervention, but remained low. Sources of Financial Sponsorship The study was funded by the Wessex Academic Health Science Network

**F38**

**MEDICALLY ASSISTED WITHDRAWAL FROM ALCOHOL: AN AUDIT OF PRACTICE IN ACUTE ADULT PSYCHIATRIC WARDS IN THE UK CONDUCTED BY THE PRESCRIBING OBSERVATORY FOR MENTAL HEALTH (POMH-UK)**

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Patients with alcohol dependence are often admitted to acute adult psychiatric wards, with alcohol-related problems as a primary or more usually a secondary reason. Thus, mental health staff should be competent in the management of alcohol withdrawal and alcohol-related complications. As part of a POMH-UK quality improvement programme, a UK audit of the management of medically-assisted withdrawal from alcohol was conducted in acute adult psychiatric settings in 2014. Clinical practice standards were derived from NICE guideline recommendations regarding the diagnosis, assessment and management of harmful drinking and alcohol dependence and related complications, and were agreed by a panel of clinical experts in addiction. Forty-three Trusts participated, submitting data for 1,197 patients: the majority (70%) under the care of a general adult psychiatrist rather than a specialist. Only a quarter were undergoing detoxification for the first time. An alcohol history and a physical examination were documented for 80% and 90% of the total national sample respectively. In 20% of cases, care was discussed with a physician. Only a third had a full documented assessment for Wernicke’s encephalopathy, 15% of whom had at least one sign or symptom of this condition. Parenteral thiamine was prescribed in 58% of cases. Relapse prevention medication was prescribed for 15% of patients under the care of a general adult psychiatrist. Continuing care for alcohol-related problems at discharge was most commonly provided by NHS specialist alcohol services. Our findings suggest that cases of alcohol detoxification undertaken by general adult psychiatrists on acute adult psychiatric wards are often medically complex. Screening for Wernicke’s encephalopathy was relatively poor, thus clinically significant signs and symptoms are likely to have
been missed and to have remained untreated in a proportion of patients. The quality of care would likely be enhanced if there were more specialists or appropriate training in addictions within mental health services. Each participating Trust was provided with audit data on their performance in relation to the practice standards, benchmarked against the other Trusts that took part. Thus, Trusts have had the opportunity to review their local practice with respect to aspects of care that fall short of the standards, or where the Trust, or teams within the Trust, appear to be outliers in terms of their practice. On the basis of the audit findings, POMH-UK has produced an educational change intervention and made this available to participating Trusts to support their local action plans. POMH-UK is supported solely by subscriptions from member health services.

F39
THE EFFECT OF DEPRESSION AND ANXIETY SYMPTOMS ON RESPONSES TO ANTICIPATION OF REWARD IN PATHOLOGICAL GAMBLERS

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Introduction: Depression and anxiety commonly occur in those with pathological gambling (Petry et al 2005 J Clin Psychiatry 66:564-74). Previously it has been shown in healthy controls that depression reduces responses in reward-related areas of the brain (Pizzagalli et al 2009 Am J Psychiatry 166:702-10). We therefore hypothesised that in pathological gamblers (PG), higher ratings of depression and anxiety would be associated with reduced responses to reward anticipation. Methods: 20 male (age (mean±SD): 34.5±7.4yrs) PG (DSM-IV) in treatment and 22 (Age: 33.23±8.2yrs) healthy volunteers (HV) were recruited. Participants had no current or past history of substance dependence (except nicotine) and no neurological or other psychiatric disorders. Participants completed Beck Depression Inventory (BDI) and the Spielberger State and Trait Anxiety Inventories (SSAI, STAI), and during an fMRI task, the monetary incentive delay (MID) task. The fMRI protocol was part of a larger study involving PET and further fMRI tasks (ICCAM protocol: www.bbmh.manchester.ac.uk/iccam/cluster/). The BOLD response was measured in two regions of interest (ROI): striatal (5mm sphere including parts of caudate, putamen, nucleus accumbens, globus pallidus) and bilateral anterior insula. Data were analysed using Mann-Whitney U and Spearman Rho tests in SPSS. Results: PGs had significantly higher anxiety (STAI, SSAI) and depression (BDI) scores compared with HVs (HV vs PG: STAI: 32.4±10.2 vs 43.1±11.5; SSAI: 26.2±5.5 vs 38.1±14.5; BDI: 1.3±2.6 vs 11.7±11.3; all p<0.05). There was no significant difference between BOLD response in PG compared with HV in either ROI (p>0.05). No significant correlations were found between depression or anxiety ratings and BOLD responses in either ROI during anticipation of reward during the MID task in the PGs. In the HV group there were significant negative correlations between SSAI and BOLD response in the striatal ROI (r=-0.584, p=0.005) and the bilateral anterior insula (r=-0.439, p=0.046) and between STAI and response in the striatal ROI (r=-0.470, p=0.032). Conclusion: Consistent with our hypothesis, PG had higher ratings of anxiety and depression compared with HV. However, contrary to our hypothesis, ratings of anxiety and depression had no association with BOLD response during anticipation of reward in the PG group. Interestingly in the HV group, lower anxiety was associated with a greater BOLD response during anticipation. It may be that since any PG with a psychiatric comorbidity was excluded, the levels of anxiety and depression were not sufficient to moderate BOLD response to anticipation of reward. Financial support: MRC funded grant (G0002226).

Go1
EFFECT OF AN AMPA POSITIVE ALLOSTERIC MODULATOR IN THE BEHAVIOURAL EFFECTS OF CITALOPRAM IN MOUSE ANTIDEPRESSANT AND ANXIOLYTIC MODELS

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Introduction: Anxiety and depression are highly prevalent, co-morbid disorders (Bystritsky, 2004, Molecular Psychiatry, 11(9), 805-14). Both respond to drugs that affect the monoaminergic systems. Current treatment options are limited by poor efficacy and slow onset of action (Farach et al., 2012, Journal of Anxiety Disorders, 26, 833-843). One possible target of antidepressant drugs is α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptors (AMPARs). AMPA positive allosteric modulators (APAMs) have shown to act antidepressant-like and synergistically boost conventional antidepressants’ effects in the forced swim test (FST), a test predictive of antidepressant efficacy (Li et al., 2001, Neuropharmacology, 40(8), 1028-33; O’Neill & Witkin, 2007, Current Drug Targets , 8, 603-20). Chronic treatment with
antidepressants increases AMPAR-mediated neurotransmission (Svenningsson et al., 2005, Proc. Natl. Acad. Sci. U.S.A., 99(5), 3182-7), suggesting that conventional antidepressants produce their antidepressant actions through increased AMPA neurotransmission (Farley et al., 2010, Int J Neuropsychopharmacol. 13(9): 1207-18). APAMs have been less studied in tests of anxiety-like action. Methods: NMRI female mice, aged 2-5 months of age and weighing 25-29g, were intraperitoneally administrated a conventional antidepressant, the selective-serotonin reuptake inhibitor citalopram (0-30 mg/kg) and the APAM LY 451646 (0-3 mg/kg). The antidepressant-like and anxiolytic-like effects of both, in combination, were tested using the FST and three validated anxiety-related animal models: elevated zero maze (EZM), marble burying test (MBT) and novelty-induced hypophagia paradigm (NIP). Results: The combination studies revealed that LY 451646 significantly blocked the anxiolytic-like effect of citalopram in the MBT by increasing the number of marbles buried (minimum effective dose: 0.625 mg/kg, P < 0.001). LY 451646 caused a decrease in the latency to enter the open areas, a decrease in the number of entries and time spent in the open areas in the EZM (MED: 3 mg/kg, P < 0.01). This APAM PAM also enhanced the total distance swimming effects of citalopram in the FST with sub-active (LY: 1 mg/kg, P < 0.05) and threshold (LY: 3 mg/kg, P < 0.001) doses without altering locomotive activity. Conclusions: This data suggests that AMPAR neurotransmission enhancement has a contrasting role in anxiety and depression, this having ramifications in the search for AMPA-based novel anxiolytic and antidepressant treatments. This data suggests AMPAR potentiation may facilitate antidepressant-like effects of citalopram while blocking citalopram's anxiolytic-like effects. All testing procedures were in accordance with European Communities Council Directive of 24 November 1986 (86/609/EEC) and the Danish Animal Experimentation Act. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this abstract. Financial Sponsorship: Danish Research Council, The Carlsberg Foundation.

Go2

THE EFFECTS OF STATE ANXIETY ON LEARNING SOCIAL EVALUATION: AN EXPERIMENTAL MANIPULATION WITH 7.5% CARBON DIOXIDE INHALATION

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Background: Positive self-concept is protective for mental health and may be maintained via cognitive processes that bias incoming self-referential information in a positive direction. When learning social evaluation, low anxious individuals tend to rate themselves as being more liked than others, and make fewer errors learning when they are liked than disliked. Social anxiety is associated with a loss of this positive self-referential bias. However, it is unclear whether this effect is driven by differences in state or trait anxiety as both are elevated in social anxiety. We therefore examined the effects of state anxiety via 7.5% CO2 inhalation on social evaluation learning. Methods: Forty-eight (24 female) healthy volunteers with a mean age of 23 years (range 19 - 50) attended a test session undertaking two inhalations (medical air and 7.5% CO2 , counterbalanced) whilst completing an instrumental social evaluation learning task. Participants used trial-and-error to learn four social rules: self-liked, self-disliked, other-liked, and other-disliked. Outcome was errors to criterion (8 consecutive correct answers), modelled as a function of gas (air, CO2), condition (self, other), and rule (like, dislike) to test for main effects using multi-level Poisson regression. We then added gas × condition, gas × rule, and gas × condition × rule to the model to test for interactions. Results: Individuals had a higher error rate in the dislike rule condition (.39, 95% CI .30, .49, p < 0.001), the other-referential condition (.11, 95% CI .01, .20, p = 0.026) and the CO2 gas inhalation (.29, 95% CI .19, .38, P<0.001). There was a gas × condition × rule interaction (P = 0.003), with the rule effect strongest in the self-referential condition, where it did not vary with gas inhalation. By contrast, the difference between rules was smaller in the other-referential condition, and there was a substantial increase in errors in the CO2 inhalation, which was relatively uniform across both rules. The CO2 inhalation increased state anxiety, blood pressure and heart rate (all p's <0.001). Conclusions: Positive self-referential bias (i.e., fewer errors learning self-like than self-dislike) in social evaluation learning seems robust to fluctuations in state anxiety. In contrast, state anxiety seems to impair learning of other-referential evaluation. This suggests that variations in self-referential bias arise due to trait rather than state characteristics. Funding: KSB is funded by the National Institute for Health Research School for Primary Care Research (NIHR SPQR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The NIHR SPQR is a partnership between the Universities of Birmingham, Bristol, Keele, Manchester, Nottingham, Oxford, Southampton and University College London. MRM is a member of the UK Centre for Tobacco Control Studies, a UKCRC Public Health Research: Centre of Excellence. Funding from British Heart Foundation, Cancer Research UK, Economic and Social Research Council, Medical Research Council, and the National Institute for Health Research, under the auspices of the UK Clinical Research Collaboration, is gratefully acknowledged.
Go4

EFFECT OF PREFRONTAL TRANSCRANIAL DIRECT CURRENT STIMULATION ON ATTENTION TO THREAT IN A CARBON DIOXIDE INHALATION EXPERIMENTAL MODEL OF ANXIETY

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Rationale: Neuropsychological models of anxiety suggest that deficits in prefrontal mechanisms underlie maladaptive biases in attention control and hypervigilance to threat. 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 over targeted cortical areas, and may represent an alternative treatment option for patients with mood and anxiety disorders. We evaluated the effect of 20 minutes of 2mA prefrontal tDCS on subjective anxiety, autonomic arousal and attention to threat in the 7.5% carbon dioxide (CO2) inhalation human experimental model of anxiety. Method: 36 healthy volunteers were screened for physical and mental wellbeing and randomized to receive either 20 minute 2mA active tDCS (anode over left PFC, cathode over right PFC; n = 18; 12 females; mean age = 21.4 years) or non-active sham control stimulation (n = 18; 10 females; mean age = 21.3 years). Active and control groups did not differ on standardized questionnaire measures of trait anxiety or attention control, nor on baseline measures of state anxiety, alertness, heart-rate or blood pressure. Scalp electrodes were placed bilaterally over prefrontal sites and stimulation was double-blind. Post-stimulation, participants inhaled air enriched with 7.5% CO2 for twenty minutes and completed a concurrent eye-tracking attention task in which they had to control attention toward (prosaccade) or away (antisaccade) from negative and neutral images. Anxiety (questionnaire) and autonomic arousal (blood pressure and heart rate) were assessed at baseline and after each inhalation. Participants completed a high-load working memory task (WM) and low-load choice reaction time task (CRT) during the twenty minute inhalation of i) normal air and ii) air enriched with 7.5% CO2 (inhalation order blind and counterbalanced). Concurrent pupil dilation was captured with an Eyelink 1000 remote eye-tracker. This study was approved by University of Southampton School of Psychology Ethics Committee. Results: One way repeated measures ANOVA indicates that inhalation of 7.5% CO2 produced significant increases in state anxiety [F (2,38)=12.3, p<.001] and systolic blood pressure [F(2,38)=3.65, p<.035], compared to inhalation of normal air and pre-test baseline. Paired sample t-tests compared the effect of CO2 challenge on processing effectiveness (accuracy) and performance efficiency (reaction time RT) during high WM and low CR load tasks. During the high load working memory task 7.5% CO2 inhalation reduced performance efficiency (increased reaction times) compared to the air condition [t (29) = 2.608, p =0.014], but did not affect performance accuracy [t (29) = 1.941, p =0.062]. CO2 challenge did not affect performance efficiency nor effectiveness in the low load task. A similar pattern was observed in the pupillometry data - CO2 challenge increased pupil dilation during response preparation in the high load working memory task, but did not modulate pupil diameter in the low load CRT. Conclusions: This is the first study of the effects of 7.5% CO2 inhalation on cognitive processing using pupillometry. The effects of 7.5% CO2 on anxiety, autonomic arousal, processing efficiency and pupil diameter during conditions of high cognitive load is consistent with attention control models of anxiety, and evidence of CO2-induced deficits in attention control in related paradigms (e.g. antisaccade task). The study highlights the use of pupillometry as a complementary measure of cognitive processing efficiency that is sensitive to manipulations of cognitive load and anxiety. Acknowledgements: The project is funded by the Strategic Interdisciplinary Research Development Fund at the University of Southampton.
These findings complement evidence that in unchallenged non-anxious individuals tDCS can improve executive control, reduce vigilance to threat and augment the experimental training of attentional biases. Consequently prefrontal tDCS might usefully target discrete cognitive biases that contribute to the maintenance of anxiety disorders. JM funded by a University of Southampton VC-award to MG and DSB.

**Go5**

**TRAIT ANXIETY IS ASSOCIATED WITH RESPONSE TO 7.5% CARBON DIOXIDE CHALLENGE**

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The 7.5% carbon dioxide (CO2) inhalation model is used to provoke acute anxiety, for example to investigate the effects of anxiety on cognitive processes. This paradigm has been widely used in both clinical and healthy volunteers. However, previous studies have suggested individuals vary in their sensitivity to the 7.5 CO2 challenge. As little is known about the relationship of baseline trait anxiety with response to 7.5% CO2 challenge, it is possible trait anxiety may account for some inter-individual variability in response. We examined data from 15 different 7.5% CO2 challenge studies to determine whether trait anxiety and anxiety sensitivity are related to subjective or physiological response. All studies were used a repeated-measures design, with inhalation of 7.5% CO2-enriched air or medical air as the within-subjects factor. Participants completed the Spielberger State-Trait Anxiety Inventory state (STAI-S) and trait (STAI-T) sub-scales and the Anxiety Sensitivity Inventory (ASI) at baseline. Measures of subjective (STAI-S and PANAS) and physiological (blood pressure and pulse) response were completed at baseline and immediately after each inhalation. High trait anxious individuals have a greater subjective (STAI-S) response to the placebo (B 0.45, 95% CI 0.35 to 0.54, p < 0.001) (medical air) condition than to the CO2 (B 0.23, 95% CI 0.10 to 0.37, p = 0.001) (Pdiff= 0.010). Anxiety sensitive individuals display the same heightened response to placebo (B0.22, 95% CI 0.14 to 0.31, p < 0.001) over CO2 (B 0.04, 95% CI -0.08 to 0.15, p = 0.542) (Pdiff= 0.004). Our results suggest the inhalation of 7.5% CO2-enriched air may have similar subjective and physiological effects across all participants, whereas the anticipatory anxiety associated with the procedure is greater in high trait anxious and anxiety sensitive individuals (leading to a relatively stronger response in the air condition). These results have important implications for the design and conduct of future 7.5% CO2 challenge studies, which may need to be taken into account either during recruitment or in the resulting analyses. The greater subjective response in the air condition relative to the 7.5% CO2 condition means it may be more difficult to demonstrate an effect of 7.5% CO2 inhalation relative to air in high trait or anxiety sensitive individuals. Therefore, the impact of a pharmacological agent may be more difficult to detect. This may mean that important effects are missed if, by chance, a sample with a substantial proportion of high trait anxiety participants is recruited. Funding Funding from the Medical Research Council, the Economics and Social Research Council, the National Alliance for Research on Schizophrenia and Depression, the Centre for Defence Enterprise, and the University of Bristol is gratefully acknowledged.

**Go6**

**EFFECTS OF 7.5% CARBON-DIOXIDE INHALATION ON FORCE EXERTION AND TEMPORAL ACCURACY IN HEALTHY VOLUNTEERS**

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Introduction: Accurate execution of force and timing plays an important role in many actions, and deficits in this ability can impair desired motor control. Anxiety may negatively impact on force and temporal accuracy. Previous research has indicated that anxiety increases force exertion, which may be detrimental to a number of behaviours that rely on appropriate force exertion, and impairs temporal accuracy by increasing an individual's internal 'timekeeping' clock, leading to asynchrony. However, past research has used trait anxious individuals, negative images or an audience to induce anxiety, and found mixed results for force and temporal accuracy. To address this, we used the validated 7.5% carbon-dioxide (CO2) inhalation model to induce continuous anxiety whilst participants performed a force measuring and timekeeping task.

Methods: Thirty-two right-handed healthy volunteers (50% male) took part in a single study session consisting of one air and one 7.5% CO2-enriched air inhalation (counterbalanced). Participants tapped to a metronome on a force sensor which measured force exertion and temporal accuracy (asynchrony). Subjective measures of anxiety (STAI-S) and physiological measures (heart rate and blood pressure) were taken after each inhalation. Results: CO2 inhalation resulted in increased state anxiety (t(31) = 8.52, p < .001, d = 3.06), systolic blood pressure (t(31) = 4.77, p < .001, d = 1.71) and heart rate (t(31) = 5.73, p < .001,
Anxiety disorders are associated with disrupted cognitive processing, including in the domains of working memory and decision-making. However, it is unclear how acute stress affects cognition, or how it interacts with trait anxiety. In order to investigate this question, we implemented a translational acute stress paradigm (threat of unpredictable shock: ToS) in a group of healthy participants with a range of trait anxiety scores, as measured by the state-trait anxiety inventory (STAI). Participants (N=56; 25 males; mean age: 24, SD: 5.7) encompassing a range of STAI scores (mean = 38.9; range = 20-61) completed a gambling task, embedded within an emotional working memory task. During each trial participants memorised from two experimental studies that used the 7.5% CO2 inhalation model to test the effects of state anxiety on emotional face processing. In study one, twenty healthy volunteers (50% male) attended a single session and completed 20-minute inhalations of 7.5% CO2 and placebo (medical air). During each inhalation participants completed a six alternate forced choice task that required them to identify emotions in facial images. All six primary emotional expressions were presented (i.e., happy, sad, fearful, surprised, angry and disgusted). Dependent variables were global accuracy (i.e., across all emotions) and sensitivity (derived from hits and false alarm data) for each emotional expression. Study two (n = 42, 50% male) was a direct replication of study one to assess the reproducibility of the effects. Study one found a global processing deficit of anxiety with few correct identifications in the CO2 condition (mean difference = 10.7, SD = 10.8; t(19) = 4.8, p < 0.001, dz = 0.99). Sensitivity analysis split by emotion indicated a gas by emotion interaction (F(5, 95) = 2.80, p = 0.021, ηp2 = 0.13) with reduced sensitivity in the CO2 condition across all emotions except happiness. Study two replicated the global processing deficit in the CO2 condition (mean difference = 11.1, SD = 15.6; t(41) = 4.6, p < 0.001, dz = 0.71), but there was no evidence of a gas by emotion interaction in the sensitivity analysis (p = 0.37). In this study, anxiety (CO2 condition) was associated with lower sensitivity to all emotions, including happiness. These findings are among the first to experimentally investigate the effects of state anxiety on emotional face processing. State anxiety is associated with global detriments in emotional face processing, particularly for negative emotional expression (including surprise). As facial emotional processing is a key component of social competency and interaction, impaired processing may lead to poor social functioning during periods of high state anxiety. These findings have particularly importance for trait anxious individuals who are particularly prone to experiencing state anxiety. Funding: This work was supported by the MRC Integrative Epidemiology Unit at the University of Bristol (MC_UU_12013/6).
significant threat (safe, threat) by emotion (happy, fearful, neutral, object) by trait anxiety interaction (F(3,159)=3.34, p=0.021, η²=0.059). Post-hoc analysis revealed ToS made highly anxious participants remember the locations of threat congruent faces (fearful) relatively more accurately (r=0.316, p=0.019). The opposite association was found for neutral faces (r=-0.304, p=0.024) suggesting highly anxious participants encoded neutral face locations relatively more accurately under safe conditions. The difference between these two correlations was significant (Steiger’s Z=3.34, p<0.001). No significant main effects or interactions were identified with respect to the propensity accept gambles, or model-based parameters such as loss aversion or choice consistency. High anxiety participants under acute stress showed improved working memory for threat-congruent but not neutral faces. However, economic decision-making did not appear to be affected by ToS. These results are important in relation to memory biases in anxiety. Our results may be important for development of new therapies aimed at the cognitive features of anxiety. Future research should aim to replicate these findings in a clinical population, and further aim to disentangle the complex relationship between anxiety, acute stress and memory. This research was funded by a UCL Grand Challenge Studentship (CJC), a Medical Research Council studentship (CH) and the Wellcome Trust (JPR).

G09
EVALUATING THE ANXIOLYTIC POTENTIAL OF QUETIAPINE IN THE 7.5% CARBON DIOXIDE EXPERIMENTAL MODEL OF ANXIETY

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Introduction: Inhalation of 7.5% carbon dioxide (CO2) induces subjective, autonomic and neurocognitive features of anxiety in healthy subjects (Garner et al., 2011, Neuropsychopharmacology 36:1557–1562). CO2 challenge is considered a translational model of generalised anxiety disorder (GAD) with potential for testing putative anxiolytic compounds (Bailey et al., 2011, J Psychopharmacol. 25(9):1199–1206). Quetiapine is a second-generation antipsychotic that has demonstrated efficacy in reducing GAD symptoms in clinical populations (Baldwin et al., 2014, J Psychopharmacol. 28(5):403–439). We tested whether quetiapine can reduce subjective, autonomic and neuropsychological response to 7.5% CO2 challenge in healthy adults compared to placebo. Methods: 24 healthy volunteers were randomised to 2 weeks of quetiapine (25mg titrated to 50mg on day 3) or pill placebo (double-blind). On day 14 participants completed two 20-minute inhalations – normal air, and air enriched with 7.5% CO2. During each inhalation participants completed an eye-tracking antisaccade attention task (Garner et al., 2011). Subjective anxiety, heart rate and blood pressure were recorded at baseline and after each inhalation. Results: Mixed-design analysis of variance (ANOVA) tested the effect of drug and inhalation gas on subjective and autonomic outcome measures. CO2 significantly increased heart rate and systolic blood pressure (p<0.001) similarly in both drug and placebo groups. CO2-challenge increased subjective anxiety in both groups, however this effect was significantly lower in the quetiapine relative to placebo group on visual analogue scale measures of anxiety (p=0.014). CO2-challenge impaired attention control (increased erroneous eye-movement on antisaccade trials) irrespective of drug-group. Conclusions: Our results replicate the expected effects of CO2 inhalation on autonomic, subjective and neurocognitive features of anxiety. We provide some evidence that quetiapine reduces subjective anxiety following CO2 challenge. Our findings complement evidence that quetiapine is effective in producing response and remission in patients with GAD (LaLonde et al., 2011, J Clin Psychopharmacol. 31(3):326–33). The study was approved by the University of Southampton Research Ethics and Governance Office, and funded by MRC grant MR/J011754 awarded to MG, DSB and MRM.

G10
SHORT TERM DIAZEPAM TREATMENT IN HEALTHY VOLUNTEERS MODULATES EMOTIONAL ATTENTION AND REDUCES BASELINE STARTLE RESPONSES

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Despite concerns about tolerance and dependency, benzodiazepine drugs continue to be prescribed quite frequently, especially where selective serotonin reuptake inhibitors fail to provide symptomatic relief or when rapid treatment effects are essential. Understanding the neuropsychological mechanisms of these drugs is therefore important, and a number of studies have considered the effects of a single dose of diazepam in healthy volunteers on emotional processing measures relevant to anxiety disorders (eg Murphy et al, 2009, Psychopharmacology, 199, 503-513). Findings from single dose studies, however, have been rather inconsistent and we therefore reasoned that repeated dosing might generate more reliable effects.
Healthy volunteers were randomised to receive seven or eight day’s treatment with 15 mg diazepam (5 mg morning; 10 mg evening). On the penultimate or final day of treatment participants underwent behavioural testing using a well validated battery of tasks measuring emotional processing (see Harmer et al, 2004, Am J Psych, 166, 1178-1184). In addition, attention to threat was measured using an emotional dot probe task with happy and fearful faces presented at short (100 ms) and long (1000 ms) duration. The groups were well matched at baseline for age, IQ, neuroticism and a number of subjective measures. On the day of testing, visual analogue scales indicated that participants in the diazepam group were more drowsy (p=0.01) and tended to be less alert and more sad. Diazepam treatment modulated the allocation of attention to fearful but not happy faces (p<0.01). Whilst the placebo treated group showed the expected vigilant-avoidant pattern of attention towards fearful faces at short duration and away at the longer duration, this pattern was reversed in the drug treated group. Diazepam also reduced baseline startle responses (p<0.05). Diazepam treatment enhanced the processing of positive vs negative stimuli in the emotional categorisation task (p<0.05), but did not affect measures of emotional memory or the recognitions of facial expressions of emotion (all p values >0.10). Cognitive theories of anxiety emphasize the importance of early vigilance to threat followed by its later avoidance which prevents habituation. In this study, diazepam promoted vigilance to threat at the longer stimulus duration. Remediating later avoidance of threat may therefore be a neuropsychological mechanism of benzodiazepine treatment. These results replicate findings of reductions in baseline startle responses following diazepam treatment (eg Murphy et al, 2009, Psychopharmacology, 199, 503-513; Baas et al, 2002, Psychopharmacology, 161, 223-247), although it remains unclear whether this effect could be secondary to the sedative and muscle relaxant properties of the drug.

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G11
THE NMDA RECEPTOR ANTAGONIST MEMANTINE IMPROVES ATTENTION CONTROL IN A CARBON DIOXIDE EXPERIMENTAL HUMAN MODEL OF ANXIETY
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Introduction: Inhalation of 7.5% carbon dioxide (CO2) for 20 minutes increases subjective and physiological symptoms of anxiety and induces neuropsychological biases that characterise the anxiety phenotype. Some anxiolytics (e.g. lorazepam and paroxetine) can attenuate the subjective response to 7.5% CO2 and suggest 7.5% challenge as a useful, translational model for treatment evaluation. The moderate-affinity NMDA receptor antagonist memantine is clinically used in Alzheimer’s disease and has positive effects across cognitive and behavioural symptoms. Pre-clinical studies suggest memantine may also have therapeutic potential in other conditions, for example, memantine has an anxiolytic effect in animal paradigms. However, the anxiolytic effect of memantine in humans is unclear. We tested whether memantine can reduce anxiety and neuropsychological deficits during CO2 challenge. Method: 36 healthy volunteers were randomised to receive either a 2-week course of memantine (smg titrated to 10mg on day 7) or placebo (balanced for gender, administration double-blind). On day 14 participants completed an eye-tracking attention task in which they had to control attention toward (prosaccade) or away (antisaccade) from negative and neutral images during inhalation of 7.5% CO2 and air. Anxiety (questionnaire) and autonomic arousal (blood pressure and heart rate) were assessed at baseline and after each inhalation. Results: 7.5% CO2 significantly increased anxiety, heart rate and blood pressure, irrespective of drug group (p’s < .01). Participants made significantly more antisaccade errors during CO2 vs. air, consistent with our previous findings, F(1,27) = 5.02, p = .03. Notably, the memantine group made significantly fewer antisaccade errors compared to placebo, particularly during CO2-inhalation, F(1,27) = 5.07, p = .03. Discussion: Findings suggest that prior administration of memantine reduces the maladaptive effects of CO2 on attention control. This positive effect occurred in the absence of changes in anxiety and autonomic arousal. Future research should test whether memantine can target deficits in attention control that characterize clinical anxiety disorders, and perseverative patterns of negative thinking (e.g. rumination and worry). Funded by MRC grant MR/J011754 awarded to MG, DSB and MRM.

G12
DEVELOPING A RELIABLE, NON-SUBJECTIVE MEASURE OF ANXIOUS RESPONDING: A TEST RETEST RELIABILITY STUDY OF INHIBITORY CONTROL UNDER THREAT OF SHOCK
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Stress is a key factor precipitating the onset of affective episodes for many individuals. However, large individual differences exist and a substantial portion of people cope effectively with life-stressors. Classical measures of stress reactivity, e.g.
questionnaires, are limited in that they are not able to directly identify underlying abnormal mechanisms in anxiety and mood disorders. The goal of this work is to develop a stable, non-subjective measure to evaluate the effect of acute anxiety/ stress on cognition. Healthy participants (N = 50) completed a simple cognitive task, in which they were required to withhold a response to infrequent no-go stimuli, across two-testing sessions separated by at least thirteen-days. A translational, within-subject, subject-mind induction technique was used to induce a transient, anxious state similar to that in pathological anxiety (Robinson et al., 2014, Lancet Psychiatry 1(4) 294–302). Participants completed the task under alternating conditions of threat (where they were at risk of receiving an unpredictable electric shock) and safe conditions (absence of shock). The stability of the stress-induced changes was explored by comparing the subjects' performance between-sessions. An adapted drift diffusion model was also fitted to reaction times to go stimuli. Under threat of shock, subjects were a) more accurate on no-go trials (F(1,49) = 9.1, p = 0.004) and b) made slower responses to Go trials (F(1,49) = 6.7, p = 0.012) Critically, the effect of anxiety induction on go reaction times was reliable across both testing sessions (r = 0.43, p = 0.002). These stress induced changes were compared against self-report measures of depression and anxiety but were not found to track self-reported symptoms in this healthy sample. The drift diffusion model suggested that reaction time changes were driven by significantly increased ‘non-decision time’ under threat (F(1,49)=8.1,p=0.007). Our results suggest that acute stress induced via threat of shock reliably affects task performance. Specifically, we replicate prior work demonstrating improved inhibitory control (i.e. no-go accuracy) under threat of shock (Robinson et al., 2013, Front Hum Neurosci. 7:69; Grillon et al., 2015, In Press), but expand these findings to demonstrate that slower reaction times to go trials under threat (perhaps driven by increased non-decision - i.e. motor and perception - time) may be a reliable measure of individual anxious responding. This paradigm may therefore hold promise as a reliable, non-subjective measure of anxiety or stress responding. Funded by an MRC Career Development Award to OJR (MR/K024280/1).

### G13

**HOW DOES MINDFULNESS TARGET ANXIETY? THE EFFECT OF FOCUSED ATTENTION AND OPEN-MONITORING MEDITATION ON NEGATIVE THOUGHT INTRUSIONS**

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**Introduction:** Mindfulness based cognitive-behavioural interventions have shown efficacy in the treatment of anxiety disorders (see Khoury et al. 2013, Clinical Psychology Review, 33, 763-71), but the anxiolytic mechanisms of action remain unclear. Evidence from experimental studies suggests that component mindfulness exercises such as focused attention and open-monitoring can improve attentional functioning (e.g. Ainsworth et al. 2013: Psychiatry Research, 210, 1226-1231), and reduce subjective distress in a human experimental model of anxiety (CO2 challenge – Ainsworth et al. Journal of Psychiatric Research, in press). We extended this work to examine whether two types of brief mindfulness intervention (vs. active control) can reduce negative thought intrusions activated by a worry-induction procedure. Methods: 77 volunteer students were randomly allocated to three intervention groups: focused attention (FA: N=27), open-monitoring meditation (OM: N=26) and progressive muscle relaxation (PMR: N=24). Individuals in each group engaged in a 10-minute guided practice, before completing a behavioural measure of intrusive thought that required participants to control their attention during two focus periods separated by a five-minute period of self-referential worry. Thought intrusions were sampled throughout the pre- and post-worry periods. Results: Groups did not differ in baseline thought-intrusion frequency (before the worry task), Fs(2,76) < .77. Mixed-model ANCOVA examined the effects of Group (FA vs. OM vs. PMR) x Emotion (negative vs. neutral vs. positive) x Time (pre vs. post-worry) with age, gender and worry topic included as covariates. A significant three-way interaction [F(4,148) = 4.21, p = .003, ηG² = .02] was characterized by robust increases in negative thought intrusions following self-referential worry in the PMR group (Mdiff =+1.87) and the FA group (Mdiff = +0.88) but not in OM (Mdiff = +0.23). Worry induction did not change the frequency of positive or neutral thought intrusions. Questionnaire measures of trait anxiety and worry, mindfulness and attention control were not associated with changes in thought intrusions. Dispositional worry was associated with increased negative and neutral intrusions before and after the worry task (rs > .25, ps < .03). Conclusions: Our findings suggest that brief mindfulness interventions might target anxiety by reducing negative elaborative processes that maintain worry. Initial evidence of a differential effect between FA and OM mindfulness requires replication, and should be further examined using convergent experimental measures of attention control and mind-wandering before, during and after periods of worry. Source of Financial Sponsorship This work was entirely supported by the University of Southampton, School of Psychology and approved by Uni. Southampton Ethics & Research Governance.
G14

STRUCTURAL BRAIN CHANGES DUE TO COGNITIVE-BEHAVIOURAL GROUP-THERAPY IN SOCIAL ANXIETY DISORDER

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Social anxiety disorder (SAD) is a frequent anxiety disorder with a high heritability and a typical begin in early adolescence. Functional neurobiological characteristics of SAD are hyper(re)active limbic, frontal and parietal brain regions (meta-analysis: Brühl, et al. 2014 Neuroscience Biobehavioral Reviews, 47, 260-280), involved in emotional and attentional processes. At the structural level, some studies that compare healthy subject with SAD patients found increased cortical thickness in frontal, parietal and other brain areas in SAD patients (e.g. Brühl, et al., 2014, Human Brain Mapping, 35, 2966-77). Cognitive-behavioural therapy (CBT) is the gold-standard psychotherapeutic treatment for SAD. At the neurofunctional level, parieto-occipital and amygdala hyperactivations typically normalize after CBT in SAD. At the structural level, pharmacotherapy with escitalopram decreased/normalized cortical thickness in SAD in bilateral dorsal temporal cortex (Cassimjee, et al., 2010, Metabolic Brain Disorders, 25, 369-374). In spider phobia, successful CBT normalized brain volume in cortical midline and amygdala (Schiene, et al., 2014, Journal of Anxiety Disorders, 28, 276-279). But until now information about structural changes in SAD associated with psychotherapy and treatment response is scarce. Therefore, we investigated the change in cortical volume in SAD after 10 weeks of CBT in a group setting (CBGT). Twenty-four patients suffering from SAD underwent structural 3T MRI before and after CBGT. Structural brain changes were investigated using surface based morphometry implemented in FreeSurfer (http://surfer.nmr.mgh.harvard.edu/). Morphometry was compared between pre and post therapy (Reuter, et al., 2012, NeuroImage, 61, 1402-1418). Furthermore, correlations between the change in morphometry and the change in SAD symptoms (Liebowitz Social Anxiety Scale (LSAS)) were computed. Clinically, CBGT resulted in a significant reduction of SAD symptoms (change in LSAS: p < .0005). Structurally, the cortical volume was reduced after therapy in the left inferior parietal cortex (p = .0002, d = 1.66). Treatment success as reflected in the reduction of LSAS was correlated with cortical volume reduction in bilateral superior dorsomedial prefrontal cortex (p = .0001, r = 0.652). In conclusion, we found a normalizing effect of CBGT on parietal cortex volume, whereas symptom improvement was correlated with a normalization of frontal cortex volume. The dissociation between neurobiological effects of treatment and individual treatment success could point to different processes: Treatment affecting primarily parietal, attention-related regions whereas treatment success, i.e. symptom improvement is associated with changes in prefrontal regions, typically involved in emotion regulation. This study was funded by the Swiss National Science Foundation (SNSF grant No. 320030_133009). ABB received a fellowship from the Swiss National Science Foundation (PA00P3_145749).

G15

QUANTIFYING ANXIOUS RESPONDING: THE IMPACT OF THREAT OF SHOCK ON REINFORCEMENT LEARNING DURING A FOUR ARMED BANDIT TASK

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Being in a situation in which something unpleasant might happen can be anxiety-provoking and stressful. There are, however, strong individual differences in how people respond to stressful situations which may, in turn, underpin vulnerability to stress-related disorders. At present, clinical categorizations of stress-related disorders are based on subjective self-report rather than any mechanistic understanding. Such categorization may ultimately contribute to poor treatment outcomes. In this study we therefore sought to quantify anxiety and stress-responding in a non-subjective manner. In addition to asking healthy individuals (N=86) to subjectively rate their anxious traits, we placed them in safe and stressful (threat of unpredictable electrical shock) environments and asked them complete a four armed bandit task. Chosen bandits were followed by fearful or happy faces (or both/neither) with fluctuating independent probabilities whilst subjects attempted to maximise their receipt of happy faces. We applied a Bayesian model fitting procedure to a reinforcement learning model comprising six parameters: decision weights (sensitivity, or choice bias according to past outcomes) and decay rates (how quickly past outcomes are forgotten) for reward (happy faces), punishment (fearful faces) and choice
repetition (i.e. perseveration). Decision weights revealed a bias towards repeating rewarded and avoiding punished actions (p<0.001), stress did not impact this (p=0.9). Threat of shock did, however, significantly reduce punishment (p=0.004) but not reward (p=0.4) decay rate (F(1,85)=9, p=0.004), meaning that under stress these healthy subjects more rapidly 'forgot' past punishments. We also saw an interaction between stress, decision-weight valence and self-reported trait anxiety symptoms (F(1,83)=5, p=0.02) driven by a significant correlation between threat-potentiated (threat minus safe) punishment (r=0.2, p=0.04) but not reward (r=-0.1, p=0.2) decision weights. This means that more anxious individuals are less likely, when stressed, to avoid options that have recently been associated with fearful faces. In this healthy sample, stress reduced the weight assigned to previous punishments whilst leaving overall sensitivity to punishments intact. This may explain prior work demonstrating increased punishment prediction errors under stress in healthy individuals. In addition, trait anxiety might reflect a reduced propensity to avoid negative outcomes when stressed, which is consistent with our prior work using gambling tasks. Critically, the mechanisms underpinning these effects are considerably more experimentally tractable than self-report questionnaires and may ultimately improve our ability to diagnose and treat mood and anxiety disorders. Funded by an MRC Career Development Award to OJR (MR/K024280/1)

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**G16**

REDUCED SEROTONIN ENHANCES NEURAL SENSITIVITY TO THREAT UNDERMINING FLEXIBLE ADAPTATION

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Introduction: Although there is clear involvement of serotonin in threat learning and anxiety related disorders, there has been limited research into the role of serotonin to flexibly adapt to changing threatening stimuli. The present study sought to determine the effects of tryptophan depletion on a threat reversal paradigm. Methods: We tested twenty-seven healthy subjects (15 subjects following dietary depletion of the serotonin precursor tryptophan (ATD) and 12 controls matched for gender and age). A threat discrimination (CS+ vs CS-) reversal paradigm with angry faces was used combined with fMRI and skin conductance measurements (SCRs), where the CS+ co-terminated with a mild shock to the wrist on approximately 35% of the trials during learning. Halfway through the experiment the contingencies were reversed (unannounced reversal stage) where the previously non-reinforced stimulus now sometimes co-terminates with the US and the previously reinforced stimulus was now safe. Results: During reversal ATD subjects showed impaired discrimination for the CS+ vs CS- as measured by SCRs compared to subjects who received placebo (P<0.05). Our fMRI data did not show any group differences for the contrast CS+ > CS-. Comparing the CS+ or CS- versus background (intertrial fixation cross) we found the following significant whole brain group differences (Z threshold clusters of 2.3 and P<0.05): ATD subjects compared to placebo for the contrast CS+ vs background (fixation cross) showed significantly higher activity in the lingual gyrus, while for the contrast CS- vs background ATD subjects showed higher activity in lingual gyrus, precuneus, insula and dACC. During the reversal stage, ATD subjects versus placebo showed for CS+ vs background higher recruitment of the lingual gyrus. Conclusion: These results provide strong support for a specific influence of serotonin on the processing angry faces, which affected the ability of ATD subjects to show differential responding during reversal to the CS+ face compared to the CS- face, during which responses to both faces remained strong as measured by SCRs. The neural correlates showed that ATD increased responding in the lingual gyrus (involved in face processing) for the CS+ during learning and reversal, while for the CS- under ATD there was increased processing in face areas as well as areas of general emotional processing. Taken together these results indicate that decreased serotonin can lead to generalized responding to threatening faces, resulting in a generalized responses when flexible adaption is needed, which is of great relevance to anxiety related disorders. This work was funded by a Wellcome Trust grant (089589/Z/09/Z). Research was completed within the University of Cambridge Behavioural and Clinical Neuroscience Institute (BCNI) funded by a joint award from the Medical Research Council and the Wellcome Trust (G0001354).
G17
TRYPTOPHAN DEPLETION ENHANCES CARDIOVASCULAR RESPONSES TO STRESS IN RECOVERED PATIENTS WITH ANXIETY DISORDERS
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SSRI antidepressants may improve outcome of cardiovascular disorders such as ischaemic heart disease, however it is unknown if serotonin has direct cardioprotective effects. Previous research found that serotonin manipulation through acute tryptophan depletion (aTD) increased the cardiovascular and psychological response to stress challenge in SSRI and CBT treated patients with anxiety disorders. 58 clinically-remitted participants (30 female; mean age (SD) 37.6 (12.1); SSRI-remitted panic disorder (SSRI-PD), social anxiety disorder (SAнд), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), generalised anxiety disorder (GAD), and CBT-remitted panic disorder (CBT-PD)) were studied under a standard aTD vs control (nD), double-blind procedure. Measurement of systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) were taken prior to and during a disorder specific stress challenge. Difference scores were calculated using (during challenge – pre-challenge on aTD day) – (during challenge – pre-challenge on nD day), with a positive difference score indicating greater stress induced increases in BP on the aTD day. Data were analysed using single sample t-tests. Significant reductions in plasma tryptophan concentration ranged from 66-92%. The difference scores for SBP [t(57)=3.1, p=0.003, diff=6.9 mmHg, 95% confidence interval (CI) 2.4 to 11.5 mmHg] and DBP [t(57)=2.4, p=0.019, diff=5.4 mmHg, 95% CI 0.9 to 9.8 mmHg] were significantly greater than 0, reflecting the greater challenge induced increase in BP observed on the aTD day compared with the nD day. Inspection of the data suggested this was driven by the PD-SSRI, PD-CBT, SAнд and PTSD group responses. Data were split post hoc into two groups: "fear" (PD groups, SAند and PTSD) and "anxiety" (OCD and GAD). The “fear" group [SBP t(36)=3.9, p=0.001, diff=10.7, 95% CI 5.1 to 16.3; DBP t(36)=2.7, p=0.009, diff=7.6, 95% CI 2.0 to 13.3] but not the “anxiety” group [SBP t(20)=0.1, p=0.925, diff=0.4, 95% CI -7.0 to 7.8; DBP t(20)=0.370, p 0.715, diff=3.9, 95% CI -6.2 to 8.9] showed aTD – nD differences significantly greater than 0. HR analysis found no difference between days [t(54) = -0.44, p = .663, diff = -0.8 mmHg, 95% CI -4.6 to -2.3 mmHg]. In participants with treated anxiety disorders, tryptophan depletion was associated with a greater pressor response following stress challenge on the aTD compared with the nD day. This effect appeared to be confined to the “fear” disorders. Our data suggest serotonin is important in the regulation of the cardiovascular human stress response, at least in treated patients with panic, social anxiety and PTSD. Ethics approvals: Social anxiety, panic disorder CBT and panic disorder SSRI studies: United Bristol Healthcare Trust, UK. GAD: United Bristol Healthcare Trust, UK; University of Western Australia Human Research Ethics Committee, and South Metropolitan Area Health Service Human Research Ethics Committee Australia. OCD: University of Western Australia Human Research Ethics Committee and South Metropolitan Area Health Service Human Research Ethics Committee, Australia. PTSD: Research Ethics Committee of the Hospital das Clínicas, University of São Paulo School of Medicine, São Paulo, Brazil. Financial support: Social anxiety: SmithKline Beecham UK and Wellcome Trust (Project Grant 058425) Panic disorder SSRI: SmithKline Beecham and Wellcome Trust. Panic disorder CBT: Wellcome Trust and Avon and Wiltshire Partnership Trust. GAD: Raine Medical Research Foundation Priming Grant, Perth, Australia and Wellcome Trust Project Grant, Bristol, UK OGD: Raine Medical Research Foundation Priming Grant, Perth, Australia PTSD: Fundação de Amparo à Pesquisa do Estado de São Paulo (State of SãoPau lo Research Foundation; Grant Nos. 2008/04122-5 and 99/00170-4

G18
EMOTION-INDUCED MODULATION OF ECONOMIC DECISIONS IN CLINICAL ANXIETY
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Influential theories in both mental health and economics posit that emotions drive people’s choices. This suggests that if we manipulate a person’s emotions, we should be able to alter their decisions. In a previous study (Charpentier et al, 2014, Journal of Psychopharmacology, 28(8):A79), we demonstrated that the influence of emotional face primes on risk-taking varied according to trait anxiety, with low anxious individuals taking fewer risks under emotional conditions. We suggested that this represents a potential mechanism for resilience to anxiety. However, whether individuals with clinical
Introduction: Obsessive-compulsive disorder (OCD) is typically a chronic and distressing mental disorder, which is often comorbid with major depression and anxiety disorders. Disturbances of serotonergic and dopaminergic function are known to be important in the pathophysiology of the condition, but the role of potential disturbances in hypothalamo-pituitary-adrenal (HPA) axis function has not been investigated extensively. We therefore wished to evaluate current knowledge of HPA function in OCD. Method: Search of publications describing original research findings in patients with a primary diagnosis of OCD, using the terms obsessive-compulsive disorder, OCD, cortisol, hypercortisolism, and glucocorticoid, for journal articles published until December 2014. Duplications, reviews, letters, single case reports and articles in languages other than English were excluded from analysis. Meta-analysis of findings was not attempted due to differences in study design. Results: A total of 125 potentially relevant papers were identified: after exclusion, 77 papers (some examining multiple aspects of HTA function) remained, some reporting multiple investigations. Among 17 studies of plasma or salivary cortisol levels (either in single assay or across 24 hours) in unchallenged OCD patients, 13 studies found significant elevation of cortisol, when compared to healthy controls (4 found no significant differences). Among 13 studies involving dexamethasone suppression, 9 studies found a greater proportion of dexamethasone non-suppression in OCD patients, when compared to healthy controls: in 5 of these studies this was either dependent upon (3 studies) or influenced by (2 studies) comorbid depression. A total of 33 reports examined the cortisol response to pharmacological challenge, mainly exploring serotonergic or noradrenergic function: the largest number relating to m-CPP challenge (12 reports), but with inconsistent results. Eight studies investigated cortisol levels in response to psychological or behavioural challenge: with inconsistent evidence of associated changes in cortisol levels. Eight studies examined the influence of (or change in) cortisol levels on response to pharmacological treatment, and together provide no consistent evidence that treatment outcome is either predicted by baseline or change in cortisol parameters. Conclusion: Variations in study design and the small sample size in most reports hinder interpretation, but there is much data indicating that OCD is associated with hypercortisolism: findings relating to dexamethasone suppression are inconsistent, and the influence of coexisting depression is uncertain. Investigations involving pharmacological and psychological challenge have produced inconsistent results, and studies of the effects of pharmacological treatment on cortisol levels have also yielded inconsistent findings. Funding: Presenting/first author is supported by KSS Deanery. No specific funding was sought for this project.
G20
THE COGNITIVE PROFILE OF EARLY-ONSET OBSESSIVE-COMPULSIVE DISORDER. DOES AGE MATTER?
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Obsessive-compulsive disorder (OCD) is a psychiatric condition characterised by recurrent distressing thoughts and acts. Importantly, the majority of patients experience an onset of symptoms before the age of 18. However, most of the research has focused on adult patients, while adolescent OCD is rarely investigated. There are notable differences between juvenile and adult OCD. Teenagers generally have less insight into their disorder than adult patients and whilst there are no gender differences in adults, 2-3 times more boys than girls suffer from OCD. The aim of this study was to investigate the cognitive profile of adolescent OCD. 27 juvenile OCD patients (21 females) without additional Axis I disorders and 27 healthy volunteers matched for age, gender, and intelligence were recruited. The Cambridge Neuropsychological Test Automated Battery (CANTAB) was used to assess visual memory (Pattern Recognition Memory), cognitive flexibility (Intra-Extra Dimensional Set Shift), and decision-making (Cambridge Gambling Task). To examine effects of group, analyses of variance (ANOVA) were performed using IBM SPSS 21. Adolescent OCD patients took significantly more time to complete the memory task (OCD = 2186.46 (521.54) msec, Control = 1804.58 (364.99) msec, p<.005) yet their performance was worse (correct responses: OCD 82.56 (13.48) %, Control = 91.98 (8.00) %, p<.005). In addition, OCD patients made significantly less rational decisions (OCD = 91.97 (11.15) %, Control = 99.15 (2.18) %, p<.005). Finally, cognitive flexibility was not impaired, but patients showed a general learning deficit. A follow-up analysis showed this effect to be driven by the younger subgroup of patients. The older the patients were, the greater was their impairment of cognitive flexibility (Pearson's correlation, r=.46, p<.05). A longer response time on memory tasks has previously, but inconsistently, been reported for adult OCD patients. In contrast, reduced cognitive flexibility is characteristic of adult OCD patients (Chamberlain, S. R. et al., 2006, Am. J. Psychiatry 163, 1282–1284); however, the young patients in this sample did not show this impairment perhaps because their learning impairment precluded formation of a stable attentional set or prepotent tendency. These differences suggest that early- and late-onset OCD might be two subtypes of the disorder. This work was funded by a Wellcome Trust Senior Investigator Award (Ref: 104631/Z/14/Z) to Prof. Trevor Robbins. Julia Gottwald is financially supported by a BCNI MRC PhD scholarship and St John's College, Cambridge. The study was approved by the NRES Committee East of England - Essex (REC ref: 10/H0301/49).

G21
PERSONALIZED PSYCHIATRY – PHARMACOGENETIC MARKERS OF ANTIDEPRESSANT RESPONSE
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Background: Personalized medicine utilizing genetic testing has recently received much attention given that the variability of response and tolerability to psychotropic medications are partly due to an individual's genetic variations. This has led to increasing research to investigate the role of specific genetic factors on psychotropic medication response and utility of testing in the clinical realm (Zai et al., 2014, Pharmacogenomics, 15, 1147-1157). Antidepressant medications are the first-line pharmacological treatment for mood, anxiety, and obsessive-compulsive and related disorders. However, 20-50% of patients show poor or minimal response to these medications. Purpose: We aimed to investigate the genetics of antidepressant response in patients with obsessive-compulsive disorder (OCD) in two ethnic groups. Hypothesis: We postulated that different genetic variations across known OCD candidate genes may predict antidepressant response in OCD patients with different ethnic background. Method: We examined two independent and ethnically different OCD samples. The Canadian sample comprises of 222 Caucasian OCD subjects and we investigated 32 single nucleotide polymorphisms (SNPs) across 14 OCD candidate genes and their regulatory regions with antidepressant response data using a custom-made 32-SNP QuantStudio Flex Real-Time PCR System Chip. Individuals were grouped into those who improved following an adequate
trial of antidepressant as compared with those who reported “minimal” improvement, “no change”, or “worsening” using the Clinical Global Impression – Improvement scale. Pearson χ² test was performed to detect differences in the number of responders versus non-responders across genotype groups. The Brazilian sample consists of 192 Brazilian OCD individuals and 45 SNPs across 18 OCD candidate genes were genotyped. Of the 192 Brazilian OCD participants, 74 completed an adequate antidepressant trial and change of the Yale-Brown Obsessive-Compulsive Scale severity scores pre- and post-treatment were compared between genotype distributions of each examined SNP. Results: For the Canadian sample, interesting associations (P<0.05) were detected for the serotonin genes, HTR2A and HTR1B, in antidepressant response. For the Brazilian sample, significant associations were detected for a gabaergic system gene, GABRA3, and antidepressant response (P<0.05). Conclusions: These variants may be clinically useful in predicting treatment resistance versus response in patients with OCD, thereby, reducing their duration of suffering via trial-and-error method of prescribing and improving clinical outcome. Funding: Dr. Zai is supported by funding from the Canadian Institutes of Health Research (CIHR) Postdoctoral Fellowship and the W. Garfield Weston Doctoral Fellowship. The research is supported by grant from the Ontario Mental Health Foundation and private donation from the Frederick W. Thompson family.

GUEST

GENETICALLY DETERMINED DIFFERENCES IN THE IMMEDIATE TRANSCRIPTOME RESPONSE TO STRESS PREDICT RISK-RELATED BRAIN FUNCTION AND PSYCHIATRIC DISORDERS

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Depression risk is exacerbated by genetic factors and stress exposure; however, the biological mechanisms through which these factors interact to confer depression risk are poorly understood. One putative biological mechanism implicates variability in the ability of cortisol, released in response to stress, to trigger a cascade of adaptive genomic and non-genomic processes through glucocorticoid receptor (GR) activation. Here, we demonstrate that common genetic variants in long-range enhancer elements modulate the immediate transcriptional response to GR activation in human blood cells. These functional genetic variants increase risk for depression and co-heritable psychiatric disorders. Moreover, these common risk variants are associated with overgeneralized amygdala reactivity, a trans-diagnostic psychiatric intermediate biological phenotype and an important stress hormone response trigger. Network modeling and animal experiments suggest that these genetically determined differences in GR-induced transcriptional activation may mediate risk for depression and other psychiatric disorders by altering a network of functionally related stress-sensitive genes.

JOINT01

PSYCHOLOGICAL MECHANISMS OF ANTIDEPRESSANT DRUG ACTION

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Cognitive and pharmacological approaches to depression are often considered independently from one another and can be viewed as competing explanations. However, recent evidence challenges this division and shows that antidepressants affect cognitive mechanisms important for the maintenance of depression very early in treatment. For example, a single dose of an antidepressant reduces negative affective bias in depression by increasing the recognition of positive facial expressions and enhancing memory for positive vs negative information (Harmer et al., (2009) Am J Psychiatry. 2009 Oct;166(10):1178-84). At a neural level, these early changes in emotional processing are related to re-tuning fronto-limbic circuitry important for the detection and response to biologically salient information. Hence, 7 days treatment with the SSRI escitalopram reduced neural response to negative facial expressions in depressed patients compared to double blind administration of placebo (Godlewska et al (2012) Psychol Med. 2012 Dec;42(12):2609-17). Although these changes in neurocognitive processing occur before clinical changes in depression are seen, they are predictive of later clinical response. These results are therefore consistent with the view that antidepressants work via early correction of negative bias and the delay in response reflects the need for changes in processing to interact with everyday events, stressors and cues. As such, antidepressants may not be direct mood enhancers but affect the cognitive mechanisms important for maintenance of depression. These changes are seen with a range of different antidepressant agents, including those acting via different neurochemical targets such as ketamine and St Johns Wort. Early changes in emotional processing with psychological treatment have been studied less but a single session of cognitive behavioural therapy for panic disorder with agoraphobia was associated with reduced processing of threat before therapeutic response and this early change predicted subsequent recovery (Reinecke et al (2013) Biol Psychiatry. 2013 Jun 1;73(11):1064-70). These results suggest that effective treatments may target the processing of emotional information and that this may transcend traditional treatment divisions or boundaries. This approach offers a framework by which novel treatment approaches may be formulated and screened. In particular, this approach offers hypotheses about how to best combine psychological and pharmacological strategies for depression and anxiety.
JOINT02
TARGETING CORE PSYCHOLOGICAL DYSFUNCTIONS IN ADDICTION
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Addiction can be successfully treated with pharmacotherapy, psychological treatments such as cognitive behavior therapy (CBT), or novel interventions such as cognitive bias modification. Unfortunately there is enormous variability in patient response to treatment, with multiple relapses the norm before patients eventually recover. Therefore it is important to develop and evaluate novel treatments for addiction, and to tailor treatment to individual patient characteristics if possible. I will argue that we can maximise the speed and efficiency of the development of novel treatments if we focus on psychological dysfunctions that play a key role in addiction. I use the example of poor impulse control because it is associated with addiction and clearly implicated in its onset and in relapse to substance use after treatment. I will demonstrate that impulse control can be targeted and improved by conventional cognitive behaviour therapy (Ryan, F. (2013). Cognitive Therapy for Addiction: Motivation and Change. Wiley-Blackwell), but also by computerised cognitive training interventions (Jones, A., & Field, M. (2013). Experimental and Clinical Psychopharmacology, 21(1), 8-16), and medications such as modafinil (Schmaal, L., et al., (2014). Psychological Medicine, 44(13), 2787-2798). Moreover, improvements in impulse control that arise as a result of these treatments may be associated with recovery from addiction. There is no reason not to combine these different types of treatment, and further research is required to investigate if a combination of pharmacotherapy and psychological treatments can maximise improvements in impulse control, and if this would translate into improved treatment outcome. Furthermore, some addicted patients recover without formal treatment, and changes in impulse control may be associated with their recovery. I conclude that this general approach can be applied to other important psychological dysfunctions in addiction, such as affect regulation and automatic responses to substance-related cues. Financial sponsorship: Some of the research described was supported by a research grant from the Medical Research Council awarded to Matt Field, reference MR/K001558.

JOINT03
EXPERIMENTAL PSYCHOPATHOLOGY AND INTRUSIVE EMOTIONAL MEMORY
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Emotional, intrusive memories “flash upon the inward eye” causing distress across mental disorders. They can flash back to the past or flash-forward to the future. Intrusive memories of trauma are the hallmark of post-traumatic stress disorder (PTSD). “Flashforwards” to future suicidal acts or manic pursuits occur in bipolar disorder (Hales, et al., 2011, Bipolar Disorders, 13, 651-661). My group is interested in the form taken by intrusive memories – that is, mental imagery - using an experimental psychopathology approach. Experimental psychopathology involves laboratory-based research aimed at discovering and explaining the aetiology and maintenance of psychopathological processes, potentially contributing to the amelioration of dysfunction through intervention and prevention. Neuroscience reveals that mental imagery involves an experience like perception in the absence of a percept: seeing in our mind’s eye, hearing with our mind’s ear and so forth. Imagery recruits similar brain areas to perception, enhances memory and learning, and has a powerful impact on emotion. We discuss two areas introducing an imagery approach to treatment innovation. (I) We lack preventative interventions after a trauma. We can exploit the properties of imagery (its vividness can be dampened by imagery-competing tasks) plus memory reconsolidation (it is labile when reactivated). After experimental trauma, using a cognitive blockade of memory reactivation plus the computer game “Tetris”, reduced the frequency of intrusive memories (James et al, in press, Psychological Science). Brief cognitive task protocols may provide a “cognitive vaccine” to prevent post-traumatic stress symptoms. (II) Bipolar disorder treatments require improvement. We have hypothesized that bipolar disorder is characterised by an excessive use of mental imagery. Bipolar anxiety is highly prevalent, involving “flash-forwards” to future scenarios. We have developed a new treatment protocol to tackle such imagery, and thereby improve overall mood stability. These examples drew on cognitive science and neuroscience, animal and human work, pharmacology and CBT perspectives in their development. More broadly, bridging between different levels of mechanisms (Holmes et al, 2014, Nature, 511, 287-289) - behavioural, cognitive, neural and molecular and so forth, may offer treatment innovations, including those that look little like existing ones.
JOINT04
EXPERIMENTAL MEDICINE APPROACHES IN ANXIETY DISORDERS
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Although a large number of pharmacological and psychological approaches have been found efficacious in the short-term and long-term treatment of patients with anxiety disorders, many treatment-seeking patients will not respond to current interventions, despite having features suggestive of a good prognosis. Others will respond, but then stop pharmacological or psychological treatment early because of untoward effects such as treatment-emergent sexual dysfunction, drowsiness and weight gain, or reluctance to continue with previously successful homework tasks and techniques. Guidance from the British Association for Psychopharmacology summarizes treatment options for patients with anxiety disorders including those who have not responded to (or proved intolerant of) first-line treatments (Baldwin et al., J Psychopharmacol 2014; 28: 403-39). There is certainly much scope for refining animal models of anxiety disorders and the methods for establishing likely anxiolytic properties (Haller et al., Neurosci Biobehav Rev 2013; 37: 2318-30): but it has been argued that successful further development of novel anxiolytics is dependent upon a refined biomarker approach combining genetic, cognitive and neuroimaging measures (Insel et al., Neurosci Biobehav Rev 2013; 37: 2438-44). Confirming the potential benefit of novel treatments in the necessary large randomised controlled trials is a time-consuming and costly endeavor: so experimental medicine studies in healthy volunteers represent a useful ‘proof-of-concept’ approach for determining whether to proceed to these expensive pivotal efficacy studies. Investigations of challenge of healthy volunteers with inhalation of air ‘enriched’ with 7.5% carbon dioxide (CO2) suggest this technique provides a robust experimental medicine model of generalized anxiety, mirroring the subjective, autonomic and cognitive features of GAD. Prior administration of duloxetine, memantine, instruction in mindfulness techniques, and use of transcranial direct current stimulation can all mitigate against at least some of the effects of CO2 challenge: and suggest this model may be useful in the evaluation of potential innovative pharmacotherapies or psychotherapies at the proof-of-concept stage. No funding was sought or obtained.

PD01
PHARMACOGENOMICS IN PSYCHIATRY: RESPONSE TO ANTIDEPRESSANTS AND ANTIPSYCHOTICS-INDUCED TARDIVE DYSKINESIA
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Background: Personalized medicine utilizing genetic testing has recently received much attention given that the variability of response and tolerability to psychotropic medications are partly due to an individual’s genetic variations. This has led to increasing research to investigate the role of specific genetic factors on psychotropic medication response/tolerability and utility of testing in the clinical realm. Antidepressant and antipsychotic medications are first-line pharmacological treatment for mood, anxiety, obsessive-compulsive and related, and psychotic disorders respectively. However, approximately 20-50% of patients show poor or minimal response to these medications. Furthermore, antidepressant and antipsychotic medications have significant and sometimes rare serious adverse effects. Tardive dyskinesia (TD) is a side effect of long-term antipsychotic treatment that is characterized by involuntary movements. Purpose: We aimed to investigate the genetics of antidepressant response in patients with obsessive-compulsive disorder (OCD) and antipsychotic-induced TD in patients with schizophrenia. Hypothesis: We postulated that genetic variations within candidate genes may predict antidepressant response in OCD patients and antipsychotic-induced TD in schizophrenia patients. Method: We examined two independent OCD samples and one schizophrenia sample. In the 222-Canadian OCD sample, we investigated 32 single nucleotide polymorphisms (SNPs) across 14 OCD candidate genes and their regulatory regions with antidepressant response data using a custom-made 32-SNP QuantStudio Flex Real-Time PCR System Chip. Individuals were grouped into those who improved following an adequate trial of antidepressant as compared with those who reported “minimal” improvement, “no change”, or “worsening” using the Clinical Global Impression – Improvement scale. Pearson chi-square test was performed to detect differences in the number of responders versus non-responders across genotype groups. For the 192-Brazilian OCD sample, 45 SNPs across 18 candidate genes were genotyped. Of 192 OCD patients, 74 completed an adequate antidepressant trial
and change of pre- and post-treatment Yale-Brown Obsessive-Compulsive Scale severity scores were compared between the genotype distributions. For the third sample, we genotyped three SNPs within the neuregulin (NRG1) and its receptor (ERBB4) genes in 196 European schizophrenia patients and TD severity was measured using the Abnormal Involuntary Movement Scale (AIMS). Results: For the Canadian sample, interesting associations (P<0.05) were detected for the serotonin genes, HTR2A and HTR1B, in antidepressant response. For the Brazilian sample, significant associations were detected for a gabaergic system gene, GABRA3, and antidepressant response. For TD, our preliminary findings revealed that the ERBB4 gene was associated with TD (P=0.016). Conclusion: The serotonergic and gabaergic system genes may be clinically useful in predicting treatment resistance versus response in patients with OCD across different ethnic groups, thereby, reducing their duration of suffering from the traditional trial-and-error method of prescribing and improving clinical outcome. Our results suggested that ERBB4 may play a role in TD. Future study with larger sample size is required to replicate these findings. Funding: Dr. G. Zai is supported by funding from the Canadian Institutes of Health Research (CIHR) Postdoctoral Fellowship and the W. Garfield Weston Doctoral Fellowship, Toronto, Canada. The research is supported by a grant from the Ontario Mental Health Foundation (Richter MA & Kennedy JL), a Schizophrenia grant from the Canadian Institutes of Health Research (MOP-115097; Kennedy JL), a grant from the Sao Paulo Research Foundation (FAPESP nº 2005-55628-8; Miguel EC & Shavitt RG), and a private donation from the Frederick W. Thompson family (Richter MA).

PD02

PHARMACOGENOMICS OF LITHIUM

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Introduction: Lithium remains the mainstay of bipolar disorder (BD) treatment as it is effective in the acute phases of illness (manic and depressive) and in the prevention of manic, and at least in part, depressive recurrences. Naturalistic analyses show that approximately one third of BD patients achieve complete remission on lithium. Lithium response is a heritable sub-type of BD: it has been shown to be familial and it is associated with family history of BD. Consequently, researchers have focused on the search for genetic determinants of lithium response initially using candidate gene approaches and case-control study design. The failure in the identification of reliable predictors of lithium response determined the shift towards more hypothesis-free approaches such as genome-wide association studies (GWAS). To date, three GWAS of lithium response in BD have been carried out, although no replicable findings have been found. The ongoing GWAS carried out by the Consortium of Lithium Genetics (ConLiGen) will provide results from the largest cohort of BD patients assessed uniformly for lithium response. The aim of this presentation is 1) to provide an overview of the most recent findings on lithium pharmacogenomics, and 2) to focus on the impact of phenotypic definition of lithium response on GWAS findings. Methods: Genome-wide association data of lithium response were gathered from previously published studies. The inter-rater agreement [Kappa (k)] and reliability [intra-class correlation coefficient (ICC)] of lithium response assessment with the Alda scale of a two-stage case-vignette rating procedure performed by 29 ConLiGen sites was analyzed before and after training. The distributional properties of the treatment response scores available for 1,308 BD patients were analyzed using mixture modeling. Results: Genome-wide association studies have so far implicated ACCN1, GRIA2, GADLi genes in lithium-responsive BD. Substantial and moderate agreement was shown across ConLiGen sites in the first and second sets of vignettes (k = 0.66 and k = 0.54, respectively), without significant improvement from training. A quantitative definition of lithium response showed an improvement between the two stages (ICC1=0.71 and ICC2=0.75, respectively). Mixture modeling of score distribution indicated three subpopulations (full responders, partial responders, non responders). Conclusions Accurate phenotypic delineation appears to be crucial in pharmacogenomics of lithium. The impact of lithium response phenotyping on GWAS findings will be discussed.

PD03

NEUROIMAGING CORRELATES OF TREATMENT RESPONSE IN ANXIETY DISORDERS

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Background: Social anxiety disorder (SAD) is a frequent anxiety disorder with a high heritability and a typical begin in early adolescence. Functional neurobiological characteristics of SAD are hyper(re)active limbic, frontal and parietal brain regions (meta-analysis: Brühl, et al. 2014 Neuroscience Biobehavioral Reviews, 47, 260-280), involved in emotional
and attentional processes. At the structural level, some studies that compare healthy subject with SAD patients found increased cortical thickness in frontal, parietal and other brain areas in SAD patients (e.g. Brühl, et al., 2014, Human Brain Mapping, 35, 2966-77). Cognitive-behavioural therapy (CBT) is the gold-standard psychotherapeutic treatment for SAD. At the neurofunctional level, parieto-occipital and amygdala hyperactivations typically normalize after CBT in SAD. At the structural level, pharmacotherapy with escitalopram decreased/normalized cortical thickness in SAD in bilateral dorsal temporal cortex (Cassimjee, et al., 2010, Metabolic Brain Disorders, 25, 369-374). In spider phobia, successful CBT normalized brain volume in cortical midline and amygdala (Schienle, et al., 2014, Journal of Anxiety Disorders, 28, 276-279). But until now information about structural changes in SAD associated with psychotherapy and treatment response is scarce. Therefore, we investigated the change in cortical volume in SAD after 10 weeks of CBT in a group setting (CBGT). Methods: Twenty-four patients suffering from SAD underwent structural T1 MRI before and after CBGT. Structural brain changes were investigated using surface based morphometry implemented in FreeSurfer (http://surfer.nmr.mgh.harvard.edu/). Morphometry was compared between pre and post therapy (Reuter, et al., 2012, NeuroImage, 61, 1402-1418). Furthermore, correlations between the change in morphometry and the change in SAD symptoms (Liebowitz Social Anxiety Scale (LSAS)) were computed.

Results: Clinically, CBGT resulted in a significant reduction of SAD symptoms. Structurally, the cortical volume was reduced after therapy in the left inferior parietal cortex. Treatment success as reflected in the reduction of LSAS was correlated with cortical volume reduction in bilateral superior dorsomedial prefrontal cortex (dmPFC). Furthermore, structural changes predicting treatment outcome will be discussed. Conclusion: In conclusion, we found a normalizing effect of CBGT on parietal cortex volume, whereas symptom improvement was correlated with a normalization of frontal cortex volume. The dissociation between neurobiological effects of treatment and individual treatment success could point to different processes: Treatment affecting primarily parietal, attention-related regions whereas treatment success, i.e. symptom improvement is associated with changes in prefrontal regions, typically involved in emotion regulation.

PD04

EFFECTS OF ERYTHROPOIETIN ON WORKING MEMORY RELATED BRAIN ACTIVITY IN MOOD DISORDERS

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Introduction: Cognitive dysfunction in depression and bipolar disorder (BD) is insufficiently targeted by available treatments. Erythropoietin (EPO) increases neuroplasticity and improves cognitive function in mood disorders, but the neuronal mechanisms of these effects are unknown. This functional magnetic resonance imaging (fMRI) study assessed the neuronal underpinnings of the EPO-associated improvement of executive function. Methods: Patients with treatment-resistant major depression, who were moderately depressed, or with BD in partial remission, were randomized to 8 weekly infusions of EPO (40,000 IU) (N=30) or saline (N=26) in a double-blind, parallel–group design. Patients underwent fMRI, mood ratings and blood tests at baseline and week 14. During fMRI patients performed an n-back working memory (WM) task. Imaging data was acquired on a 3T Siemens scanner and analyzed with FEAT-FSL software. Associations between changes in neural response and WM performance were examined in Statistical Package for Social Sciences. Results: EPO improved WM accuracy compared with saline (P=0.043). EPO-treated patients also showed increased WM-related response in right dorsolateral prefrontal cortex (dLPFC) (P=0.036) and greater deactivation of the left hippocampus (P=0.018) at follow-up. Exploratory whole-brain analyses revealed that EPO increased WM-associated activity in the superior frontal gyrus (SFG) compared with saline (P=0.012). Across the entire sample, WM improvement correlated with increase in WM-related dLPFC and SFG activity and hippocampal deactivation (r=0.28-0.30, P<0.05). The effects of EPO were independent of changes in mood or red blood cells (P>0.08). Conclusions: This highlights changes in WM-associated activity in dLPFC, SFG and hippocampus as key neurobiological effects associated with improved executive function in EPO-treated patients. Clinical trial registration: clinicaltrials.gov: NCT00916552.

PW1

HABITS AND COMPULSIVITY – OCD AND BEYOND

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Obsessive-compulsive disorder (OCD) is a psychiatric condition that typically manifests in compulsive urges to perform irrational or excessive avoidance behaviors. For some time, researchers have proposed that the need to perform these senseless compulsions might arise from an imbalance between automatic habits and more purposeful, goal-directed control over action. In three separate case-control laboratory studies, we found convergent support for this hypothesis, demonstrating that OCD patients have a bias toward forming habits, likely driven by deficits in goal-directed control over behavior. A fourth study replicated this effect, and using functional magnetic resonance imaging (fMRI), delineated the neural correlates of this imbalance. Specifically, we revealed an association between habit-forming in OCD and
abnormal patterns of hyper-activation in regions associated with goal-directed control over action, the caudate and medial orbitofrontal cortex. These data provide convergent support for the habit hypothesis of OCD, such that it exhibits excellent neurobiological convergence with the known pathophysiology of the disorder. More recently, using large-scale online data collection and computational modeling, we found that these deficits in goal-directed control were not unique to OCD, but rather constitute a dimensional marker of compulsivity across many psychiatric disorders, including addiction and eating disorders. Moreover, ‘compulsivity’, as a trans-diagnostic trait, explained deficits in goal-directed control better than any existing DSM diagnostic category included in this investigation.

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**PW2**

**REWARD AND AVERSION AS BRAIN-BASED BIOMARKERS OF DEPRESSION**

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To assess the neural mechanisms of reward and aversion we have developed a novel reward paradigm involving the sight and taste of chocolate and an unpleasant sight and taste condition. Using this we have shown that those at high “risk” of MDD, recovered depressed patients have reduced brain activity to reward and increased activity to aversive stimuli (McCabe C, Cowen PJ, Harmer CJ. Neural representation of reward in recovered depressed patients. Psychopharmacology (Berl). Sep 2009;205(4):667-677). To assess if these results were trait markers and not just scars of illness or medication history we also examined young people with a family history of MDD. We found that there were indeed decreased reward and enhanced aversive processing even before the onset of MDD in this group (McCabe C, Woffindale C, Harmer CJ, Cowen PJ. Neural Processing of Reward and Punishment in Young People at Increased Familial Risk of Depression. Biol Psychiatry. Jun 14 2012). Following on from this I will discuss our recent data examining the neural response to reward and aversion in adolescents with high depression scores. Our preliminary results reveal reduced response to reward as might be expected but interestingly also reduced responses to the aversive stimuli.


I will discuss how the promotion of reward-seeking and punisher-avoidant behaviours could over time improve low mood. Finally I will discuss our recent work using multivariate pattern recognition as a more sensitive measure of investigating the whole brain networks involved in the processing of positive and negative information in the human brain. I will discuss how this methodology could be used in the brain-based diagnosis of MDD and for enhanced neural biomarker detection and prediction of antidepressant treatment response.
PW3

PSYCHEDELIC DRUGS IN SCIENCE AND MEDICINE

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My research career in psychopharmacology began in 2005 when I embarked on a PhD at the University of Bristol under the tutelage of Sue Wilson within David Nutt's Psychopharmacology Unit. My thesis focused on sleep as an index of serotonergic function in MDMA users and incorporated tryptophan depletion and polysomnography. While completing my PhD, I began initiating a feasibility study to investigate the acute brain effects of psilocybin (a compound in “magic mushrooms”). Conducted in the Bristol Royal Infirmary, this would become the first controlled study of a psychedelic in the UK since the 1960s. After completing this, I moved to Imperial College London in 2009 to continue my research with psychedelics under the mentorship of Prof Nutt. I subsequently conducted a series of brain imaging studies, carried out at Cardiff University, involving psilocybin. These included the first ASL, fMRI and MEG studies of the acute action of a psychedelic and a number of articles have followed from this work, including papers in PNAS, Journal of Neuroscience and Schizophrenia Bulletin.

In 2012, I conducted an fMRI study with MDMA that would be the focus of a two-part television programme on Channel 4, entitled “drugs live – the ecstasy trial”. The data from this study is published in Biological Psychiatry, the International Journal of Neuropsychopharmacology and Frontiers in Human Neuroscience. Most recently, I have completed a combined fMRI and MEG with LSD, the first modern brain imaging study of this compound, and the results have been submitted for review. My research with psychedelics has taken place within a broader context of renewed interest in their therapeutic potential, has helped to highlight mechanisms by which they may be clinically useful and lay the foundations for the translation of these insights into further clinical trials. In line with this, I am currently running a small-scale feasibility study designed to assess the safety and efficacy of psilocybin in treatment-resistant depression. Initial results are extremely promising.

PW4

PSYCHOSIS, WHAT HAS STRESS GOT TO DO WITH IT? A JOURNEY THROUGH THE HPA AXIS AND THE IMMUNE SYSTEM

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Stress has been widely recognized to play a role in precipitating the onset and relapse of psychosis. Over the last decade, I have dedicated my research work in investigating the biological mechanisms underlying the link between stress and psychosis. I have previously shown how the activity of biological systems involved in the stress response, such as the hypothalamic-pituitary-adrenal (HPA) axis and the immune system, is abnormal at the onset of psychosis. In particular, patients with first episode psychosis show high cortisol levels during the day, but a blunted cortisol awakening response (Mondelli et al., 2010), and increased levels of inflammatory markers (Di Nicola et al., 2013). I later showed how increased diurnal cortisol levels and increased inflammation accounted for reduced hippocampal volume at the onset of psychosis (Mondelli et al., 2011).

During this presentation, I will focus on the possible causes and clinical consequences of the abnormal biological stress response in patients with psychosis. In particular, I will show some of our recently published data showing that childhood trauma contribute to increased inflammation in adulthood (Baumeister et al., 2015), as well as some of our unpublished data showing that childhood sexual abuse is associated with an increased cortisol awakening response in healthy controls (controls with abuse vs controls without abuse: 727.1±112.4 vs 477.2±50.7 nmol min/l), but with a blunted cortisol awakening response in first episode psychosis (patients with abuse vs patients without abuse: 356.3±57.1 vs 486.2±48.0 nmol min/l; interaction p=0.007). Finally, I will show some of our recently published data showing that blunted cortisol awakening response and increased inflammatory markers predict poor treatment response at the onset of psychosis (Mondelli et al., 2015).

In conclusion, psychosocial stress appears to partially contribute to the increased inflammation and HPA axis abnormalities present at the onset of psychosis. Increased inflammation and blunted cortisol awakening response appear to predict patients with worse clinical outcome at the onset of psychosis. Biological markers of stress response should be considered for stratification of future therapeutic strategies in first episode psychosis.
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