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S01

THE IMPORTANCE OF USING CLINICALLY RELEVANT DOSES OF MDMA AND CATHINONES IN RODENT AND PRIMATES WHEN INVESTIGATING THEIR NEUROPHARMACOLOGICAL EFFECTS

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The ability of MDMA to induce both acute adverse effects and long term serotonergic neurotoxicity in laboratory animals is well documented. However most of these studies have used doses of the drug that have paid scant regard to the pharmacokinetics of the drug in either humans or animals. The recreational use of MDMA and, importantly, the current clinical investigations of the drug for therapeutic purposes demand better translational pharmacology to allow an accurate risk assessment of the drug's ability to induce adverse events. Recently several animal and human studies have been conducted on the pharmacokinetics of MDMA and these investigations indicate that the risks of MDMA ingestion suggested by many of the earlier animal studies should be re-evaluated. MDMA-induced acute behavioural and body temperature changes result from the rapid release of monoamines by MDMA (primarily serotonin and dopamine), while long-term neurotoxicity is induced by metabolites of the drug (Esteban et al., Psychopharmacology 154: 251-60, 2001). Therefore acute physiological changes in humans can be fairly accurately mimicked in animals by appropriate dosing, although allometric dosing calculations have limited value. Long term changes however require the drug to be metabolized in a similar manner in experimental animals to that occurring in humans. This is problematic because the actual neurotoxic metabolites have not been finally identified and crucially because the rate of metabolism of MDMA and its major metabolites is very different in humans and rats or monkeys. Humans metabolize MDMA slowly in comparison to rats and squirrel monkeys. Consequently acute adverse events such as hyperthermia in humans probably limit the chance of recreational users ingesting sufficient MDMA to produce neurotoxicity, in contrast to experimental animals. Since MDMA inhibits the major enzyme responsible for its metabolism in humans this also assists in preventing neurotoxicity, particularly during binge dosing. These observations allow questions as to whether MDMA alone produces neurotoxicity in the human brain, although its combination with other recreational drugs may induce neurotoxicity. Translation of experimental animal data from studies on cathinones such as methylmethcathinone (mephedrone) to humans is even more problematical as little data exist on plasma concentrations in recreational users. Although mephedrone has a similar chemical structure and molecular weight to MDMA our studies suggest that it has a different neurochemical and behavioural profile to MDMA (King et al., this meeting; Shortall et al., this meeting). It is currently unclear whether this is due to a different pharmacodynamic or pharmacokinetic profile.

S02

PRECLININCAL AND CLINICAL STUDIES ON THE INTERACTION OF MDMA WITH OTHER RECREATIONAL DRUGS

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3,4-Methylenedioxymethamphetamine (MDMA , 'ecstasy') is a recreational drug commonly consumed with other drugs of abuse in particular among younger sections of the population. Recent trend assessment by the European Drug Monitoring Agency (EMCDDA) indicate an increase in the simultaneous consumption of MDMA with other drugs of abuse, the most common being ethanol and cannabis. Studies reveal several interactions between MDMA and ethanol exposure. Preclinical studies show that prexposure to ethanol potentiates the neurotoxic effects of MDMA in rats and may cause memory impairment. Repeated MDMA given during ethanol deprivation affects subsequent reinstatement in rats with a history of ethanol consumption in addition to increasing ethanol-induced dopamine release in the nucleus accumbens. Furthermore, the combination of ethanol and MDMA facilitated conditioned place preference and motor stimulant effects. In mice, MDMA-induced dopaminergic lesion increases consumption of and preference for ethanol while decreasing sensitivity to ethanol. In addition, in adolescent mice preexposure to ethanol prolongs the conditioned rewarding effects of MDMA. In humans, coadministration studies reveal varying psychomotor effects which may involve pharmacokinetic alterations. With regard to interactions between cannabis and MDMA, cannabinoid agonists enhance the rewarding effects of MDMA: when combined with low dose MDMA, low dose THC produces CPP, lowers the self-administration threshold dose of MDMA and attenuates the THC withdrawal syndrome. On the other hand, THC may decrease the neurotoxicity of MDMA. In humans, combined intake of MDMA and THC may impair task performance and may synergize to decrease cognitive performance. However, THC may increase the desired subjective effects of MDMA. Overall, these studies suggest that the cannabinoid system plays an important role in the rewarding effects of MDMA and that the combinations of the drugs might impair psychomotor and cognitive performance. Preclinical and clinical reports on polydrug consumption and in particular the combination of MDMA and other drugs of abuse such as ethanol and cannabis suggest that important interactions between these drugs may occur.

S03

EVALUATING THE MECHANISMS, RISKS AND POSSIBLE BENEFITS OF MDMA (ECSTASY)

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Introduction: In view of MDMA's popularity as a recreational drug, animal studies demonstrating serotonergic neurotoxicity after MDMA administration at doses that overlap with those used by humans, and the role serotonin (5-HT) plays in several essential functions such as emotion, memory, sleep, pain, and higher order cognitive processes, it is important to determine what the risks and possible benefits of MDMA on the human brain are. Particularly also because some authors have begun to (re)advocate the use of MDMA as a therapeutic tool (e.g., anxiety and posttraumatic stress disorders).
Methods: Previously, there were no methods available for directly evaluating the effects of MDMA in the living human brain. However, development of in vivo neuroimaging tools have begun to provide insights into the effects of ecstasy in human brain. These are: single photon emission computed tomography (SPECT), positron emission computed tomography (PET), proton magnetic resonance spectroscopy (1H-MRS), pharmacological magnetic resonance imaging (phMRI), in addition to structural and functional magnetic resonance imaging (fMRI and sMRI).
Results: There seem to be dose-dependent and transient reductions in serotonin transporter (SERT) densities in which females may be more vulnerable than males. In addition, age (of first MDMA exposure) and use of other drugs of abuse are important confounding factors. New imaging techniques such as phMRI, fMRI and sMRI provide new insights into the effects of this popular recreational drug on the human brain. For instance, we observed a significant reduction in hippocampal volume (-10.5%) in a small sample of MDMA users using sMRI.
Conclusion: The few studies conducted so far provide suggestive evidence that people who heavily use ecstasy are at risk of developing 5-HT neurotoxicity. However, because most studies have had a retrospective design, in which evidence is indirect and differs in the degree to which any causal links can be implied, longitudinal studies in human ecstasy users are needed in order to draw definite conclusions. In this presentation the mechanisms, risks and possible benefits of MDMA will be reviewed, focusing on neuroimaging work and our longitidunal study (the NeXT study).

S04

EVALUATING THE HUMAN HARMS AND POSSIBLE THERAPEUTIC USES OF ECSTASY

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Ecstasy or more correctly MDMA was developed in the 1950s as a potential antidepressant but though never licensed soon gained acceptance as an aid to psychotherapy especially couples therapy in the USA. Its utility was widely accepted and the drug went under the colloquial name "empathy". In the 1970s its use begain to spread from treatment to the party and then to the rave scene. Its ability to promote wellbeing and empathy as well as giving energy to dance for long periods was welcomed by nocturnal clubbers. However due to the cynical denial of water to clubbers several deaths occurred from dehydration and hyperthermia. These events coupled with its being renamed to a more controversial "ecstasy" lead to demands for its banning which ensued in 1981 and for no obvious reason it was made a Class A drug alongside heroin and crack cocaine [Nutt DJ et al (2009) MDMA (ecstasy): A review of its harms and classification under Misuse of Drugs Act 1971 http://drugs.homeoffice.gov.uk/publication-search/acmd/acmd-MDMA-report-2009]. Since then use has continued but the quality of MDMA tabs has fallen and many now contain none of this drug which has been replaced by other stimulants such as bzp and caffeine. Deaths from ecstasy though few in number and rarely just due to the drug alone are widely reported so exaggerating its harms in the public mind [Forsyth A International Journal of Drug Policy 12 (2001) 435–453]. The other health harms purported to be due to the drug e.g. brain damage and cognitive impairment have on occasions been greatly exaggerated and are mostly either due excessive dosing [see Fantegrossi WE, et al. (2004) Neuropsychopharmacology 29(7): 1270–81] or worse to other drugs e.g. methylamphetamine given by mistake [Ricaurteet al (2002) Science (2003) 301: 1479] or to excessive exercise rather than simply MDMA itself. The comparative harms of MDMA have been found to be low in comparison with other Class A drugs [Nutt DJ et al (2010) Lancet 376: 155866] which challenges its legal status but resistance to changing its class has been peculiarly vocal and illogical. This legal status has severely impeded research on the potential therapeutic utility of MDMA in psychotherapy and other psychiatric disorders such as autism and depression. Thankfully due to the efforts of a small committed group this situation is slowly improving and trials of MDMA as an adjunct to psychotherapy in resistant PTSD are looking promising [Mithoefer et al (2010) J Psychopharmacology. July 2010]. Recent research suggests that it may also have utility in improving outcome from head injury [Edut S et al (2011)Psychopharmacology 214, Number 4877-889, DOI: 10.1007/s00213-010-2098-y]

S05

THE ROLE OF GLUTAMATE IN CORTICAL GAMMA OSCILLATORY BEHAVIOUR: TRANSLATIONAL APPROACHES IN VITRO

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The ability of the oscillatory activity of groups of neuron to synchronise represents a means by which various regions of the brain communicate with one another. It is becoming clear that in psychiatric disease states, such as schizophrenia, disruption of synchrony for particular frequency bands may underlie aspects of cognitive dysfunction associated with this disorder. In particular, disturbances in gamma (30-80Hz) frequency oscillations have emerged as a candidate to explain cognitive dysfunction observed in schizophrenia patients. What are the mechanistic features underlying a deficit in gamma frequency oscillations? Two inter-related lines of evidence are attractive. Firstly, NMDA receptor hypofunction in animal models and humans reproduces core symptomatic features of the disorder. Secondly, in animal models and post-mortem human brain tissue, reductions in biomarkers for distinct interneuron populations are observed. Using a combination of electrophysiology, pharmacology and anatomy the implications of NMDA receptor function on cortical interneurons for synchronous gamma frequency oscillations in the rodent and human neocortex will be presented.

S06

ENTRAINING ERRANT ENSEMBLES: HIPPOCAMPAL-PREFRONTAL OSCILLATIONS IN COGNITION, SLEEP AND DISEASE

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Coordinated, rhythmic activity spanning anatomically distributed neuronal networks underpins cognition and mediates limbic-cortical interactions during learning, memory and decision-making. Accordingly, disruption of this coordinated activity is likely to generate cognitive impairments in a range of neuro-psychiatric disorders. Electrophysiological metrics of network activity provided by electroencephalography (EEG), local field potential (LFP) and multi-unit recordings therefore constitute sensitive, translational biomarkers of cognitive function and dysfunction. For example, multi-site electrophysiological recordings have been used to define the cellular and neuronal network bases of hippocampal-prefrontal interactions during wakefulness and sleep in both humans and rodents, showing that coherent rhythmic activity in a 5-10 Hz 'theta' frequency band reflects functional connectivity between the two structures (Anderson et al., 2009, Cerebral Cortex 20: 1604-12; Jones & Wilson, 2005, PLoS Biology 3: 2187-2199). Meanwhile, higher-frequency 'gamma' oscillations at > 40 Hz reflect state-dependent, coordinated activity in local hippocampal and prefrontal networks. We have recently combined chronically implanted recording electrode arrays and systemic pharmacology in rats to quantify the neurophysiological bases of psychomimetic drug action in ketamine- and phencyclidine-based models of cognitive dysfunction in schizophrenia, with particular focus on theta and gamma rhythmicity. I will review data showing that ketamine and phencyclidine elicit aberrant hippocampal and prefrontal activity in theta, gamma and high-frequency (140-180 Hz) ranges in behaving animals across acute and chronic timescales. This aberrant activity manifests at both cellular and network levels and can be dissociated from overt behavioural changes such as hyperlocomotion; in addition to modelling abnormal oscillatory activity evident in EEG recordings from neuro-psychiatric patients, it may also provide insight into the mechanisms of ketamine's antidepressant properties. Furthermore, hippocampal-prefrontal interactions during sleep are also disrupted in rodent models of cognitive impairment, potentially reflecting the sleep disturbances that are core features of many brain diseases. Electrophysiology in behaving animals should therefore remain a central approach to understanding psychomimetic drug action and neuro-psychiatric disease mechanisms.

S07

A REVIEW OF THE EVIDENCE OF GLUTAMATE ABNORMALITIES IN DEPRESSION

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There is growing interest in the application of glutamatergic treatments in patients with mood disorders. A natural corollary of this interest is investigation of glutamate activity in depressed patients. Early studies investigated plasma and CSF levels of glutamate; findings were inconsistent but a tendency to increased glutamate levels can be discerned in patients with acute depression. More recent investigations have utilised proton magnetic resonance spectroscopy (MRS) to provide a non-invasive means of measuring glutamate and its metabolites in cortical and limbic regions in depressed patients. In these studies glutamate is usually measured as Glx which includes both glutamate and glutamine as well as a small contribution from GABA. Glutamine, which is present mainly in astrocytes, is both a metabolite and precursor of glutamate. Studies in anterior brain regions have generally shown decreased Glx levels in acutely depressed patients and normal levels following recovery. In contrast, two studies in occipital cortex have reported increased levels of Glx in depression. We also found elevated glutamate levels in this brain region in young people at risk of depression through a positive parental history. More recent investigations have used technical developments to produce a clearer separation of glutamate and glutamine in the MRS spectrum. This has led to the proposal that the key abnormality in depression is a decrease of glutamine relative to glutamate, suggestive of impaired glutamate-glutamine cycling and consistent with the reported presence of glial abnormalities in neuropathological studies of patients with mood disorder (Yuksel and Ongur, Biological Psychiatry, 68-785-794, 2010). MRS measures of glutamate hold promise as means of understanding glutamate changes in depression and perhaps for identifying patients who might respond to treatments modifying glutamatergic activity. Several challenges remain including resolving the relationship between MRS visible Glx, glutamate neurotransmission and glutamate-glutamine cycling, controlling for the effects of antidepressant drug treatment in depressed patients and clarifying possible regional brain differences in glutamate levels in depression. Technical advances and the wider available of magnets of higher field strength should aid the resolution of these important issues.

S08

MODULATING THE GLUTAMATERGIC SYSTEM: A PROMISING AVENUE FOR DEVELOPING NEW TREATMENTS FOR MOOD DISORDERS

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Introduction: Current pharmacotherapy is generally ineffective for a number of patients with severe and recurrent mood disorders. A major constraint of existing therapeutics is that they are associated with a significant lag of onset of action. This delayed onset of antidepressant effects can result in considerable morbidity, including increased risk for suicidal behaviors. Pharmacological strategies that rapidly reverse depressive symptoms including suicidal ideation would have an enormous impact on public health. Several converging lines of evidence suggest that dysfunction of the glutamatergic system—particularly the N-methyl-D-aspartate (NMDA) and AMPA receptors and their respective subunits—may play important roles in the pathophysiology of major depressive disorder (MDD) and bipolar depression (BPD). Therefore, testing the efficacy of glutamatergic modulators could yield an improved knowledge of the neurobiological processes involved in these complex illnesses, and lead to the development of radically improved treatments.
Methods: Six trials with glutamatergic modulators have been conducted to date at NIH in treatment-resistant depression (2 open-label studies with riluzole, 1 double-blind placebo-controlled study with memantine, and 3 controlled studies with the NMDA antagonist ketamine). In addition, we have obtained biomarker data using electrophysiological recordings (polysomnography [PSG], magnetoencephalography [MEG]), neuroimaging (positron emission tomography [PET], magnetic resonance spectroscopy [MRS]) as neural correlates of antidepressant response to ketamine.
Results: We found that the inhibitor of glutamate release riluzole appears to have antidepressant effects in treatment-resistant depression (MDD, BPD). In the two controlled studies with ketamine, a rapid antidepressant response was found. In the first study in MDD, we found an onset of antidepressant action within 110 minutes. The effect size for the drug difference was very large (d=1.46) after 24 hours and large (d=0.68) after 1 week. In the BPD study, we found an antidepressant response within 40 minutes (d=0.52); this improvement remained significant through Day 3. With regards to biomarkers predicting antidepressant response, we found that increases in slow wave activity (SWA, a putative marker of synaptic plasticity) and gamma power cortical activity correlated with decreases in depressive symptoms following ketamine infusion. Furthermore, pregenual anterior cingulate cortical activity in response to an emotional and cognitive task predicted antidepressant improvement to ketamine.
Conclusions: Modulating the glutamatergic system appears to be important to the mechanism of immediate antidepressant response. Electrophysiological and neuroimaging studies are yielding important insights into the neural correlates of rapid antidepressant action.

S09

40 YEARS OF PSYCHOPHARMACOLOGY: HOW FAR HAVE WE REALLY COME?

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Since the initial development, during the mid 1950s, of the original drugs useful in the treatment of mental disorders followed by the elucidation of their basic mechanisms of action involving amine and amino acid neurotransmission, through the 60s, no new drugs working by entirely new mechanisms have reached the clinic. After years of intesnse and intellectually productive pre-clinical psychopharmacological research recently there has been a sharp reduction in such activities funded by the major pharmaceutical companies. This decline has been associated with the closure of pharmaceutical neuroscience research facilities based in the UK and elsewhere. Why have we reached this situation when drug treatment of pschiatric disorders remains far from perfect? Antidepressants act pharmacologically through inhibition of noradrenaline and/or serotonin reuptake while antipsychotics utilise the dopaminergic system, in particular the dopamine D2 receptor. Over the past four decades our knowledge of the receptors and signalling systems associated with amine neurotransmission has greatly increased but understanding of the neurobiology of the mental disorders we aim to treat has progressed far more slowly. Taking the SSRIs as an example it is interesting to note that these drugs, with their broad effect on serotonin function, have been clinically (though this view has been challenged by meta-analysis studies) (Kirsch et al 2008 PLoS Med. 5 e45) and commercially far more successful in the treatment of depression and anxiety than any selective agonist or antagonist of one of the 14 5-HT receptors available as potential targets. This leads to the following conclusions – serotonin has a role in depression but we do not have sufficient knowledge of the disorder to fully understand what this role is. Secondly while we have a mass of information on the pharmacology of serotonin we know far less about its detailed functional importance in specific behaviours, including the inter-relationships between serotonin and other systems important in the expression of behaviour. In future we need to put the two together by adopting experimental approaches, which include more relevant animal models, and new technology, such as functional neuroimaging techniques, that will allow meaningful translational research into mental disorders to take place. A key step in improving treatment of mental disorders may come from greater understanding of the interaction between genetic and environmental factors in determining human behaviour.

S10

MENTAL HEALTH IN THE RISK-AVERSE SOCIETY

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Introduction: The 21st century countries in the Western World are probably the safest and most secure societies that have ever existed. Even so people tend to feel more and more insecure. On a national or sometimes global level we panic in an alarmist way. There seem to have developed a governmental strategy to avoid all risks at any cost. This also has potential implications on the anxiety level in the population. People are seeking psychiatric help for matters that was considered normal crises two decades ago. This also has implications on legislation where you now can see laws that restrict normal human behavior. Methods: The governmental and societal approach is in many ways similar to the way a patient who suffers from panic disorder behaves. Hence I defined "The National Panic Syndrome" to have an alternative interpretation to why the safest countries in the world are prohibiting everything that is almost dangerous. To state my case I compare the objective risks in real life with, for example, the legislation regarding new pharmaceuticals, different chemicals and the alarms about different infectious diseases. Clearly the fear from inhabitants, media and governmental institutions are exaggerated. The agoraphobic part of the "National Panic Syndrome" is even more stigmatizing. By protecting the young generation from everything nearly dangerous or stressful we produce inhabitants that cannot cope with minor setbacks. We have an enormous increase in young people suffering from anxiety disorders, self harm behavior and suicidal intention after mild traumas. To explain this phenomenon I also defined a syndrome among the population which I call "The Safety Junkie Syndrome". The safer it gets, the more safety you seek.
Results: There are a lot of international comparing studies that suggests that the governmental strategy to use the principle of precaution makes people more afraid. This alarmist principle is not state of the art in a psychiatric setting and probably a counterproductive way to treat fear. Therefore I use a cognitive behavioral therapeutic approach on a societal level to give perspective with different examples of what is dangerous and not.
Discussion: We are living in a better and safer society than any generation before us. But even we get rid of many dangers we produce even more new ones. The population isn't feeling better and this is evident in the younger population. Can the Safety Junkie Syndrome be an alternative explanation to this phenomenon and if so, does this affect clinical practice and the pharmaceutical industry?

S11

EVOLUTIONARY BASED APPROACHES TOWARDS THE MODELLING OF DEPRESSION

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Depression is one of the most burdensome diseases in the world. The search for novel drug based therapies for this disorder has not however been a success. Indeed, the growing recognition that current antidepressants are inadequate and the lack of progress in improving on these drugs has led to several major pharmaceutical companies significantly downsizing their research investment or pulling out of this area altogether. This serious situation demands that new approaches are taken. The ethological approach invites analysis of the form, function, ontogeny and phylogeny of depression at all levels from molecular through to societal. In behavioural terms depression is a cluster that includes hunched posture, avoidance of eye contact, sleep disruption, and suppression of appetites for sex and food. The largely defensive nature of this behavioural syndrome indicates that it is an adaptation developed in response to situations where an individual has a need to stay within a social group that has become hostile to their presence. The social roots of depression mean that it cannot be assumed to be present throughout the phylogenetic scale, as it will have only developed in species with similar social needs to our own (Hendrie C.A. Pickles A.R. (2009) Depression as an evolutionary adaptation: implications for the development of preclinical models. Med Hypotheses 72: 342–347). The inclusion of sleep and appetite disruption in the behavioural cluster indicates that this response is organised around the third ventricle (Hendrie C.A., Pickles A.R (2010) Depression as an evolutionary adaptation: anatomical organisation around the third ventricle, Med Hypotheses 74: 735–740). The ethological approach therefore points towards new theories, the type of new animal models that are needed and the species that should be used in them.

S12

RECENT GENETIC FINDINGS IN SCHIZOPHRENIA AND THEIR IMPACT ON NOVEL THERAPIES

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The past few years have seen remarkable developments in schizophrenia genetics. This has come about from the application of new methods (e.g. genome wide association studies, GWAS) and the discovery of a new form of genetic variation (copy number variation, CNV). This talk will review the recent developments, present the key findings, and discuss the many remaining controversies, with particular reference to the therapeutic implications. Current controversies include: the number and nature of schizophrenia risk genes; how they interact with each other and with the environment; and how statistical genetics should (or should not) utilise psychopharmacology in the gene discovery process.

S13

THE NEURAL BASIS OF RESILIENCE IN RESPONSE TO STRESS

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Acute life stress is known to increases the risk of an individual developing depression, with some community-based studies suggesting that as many as 89% of depressed patients had experienced a stressful event prior to their episode. Resilience refers to an individual's ability to adapt in the face of acute life stress and to maintain wellbeing in spite of traumatic and stressful life events. Resilience can be conceptualized as a specific combination of protective factors. Historically, discussion of resilience focused on social and environmental factors, however recent reviews advocate a more integrated account, encompassing neurotransmitters, genes, and functional neural anatomy (Charney, DS (2004) Psychobiological Mechanisms of Resilience and Vulnerability: Implications for Successful Adaptation to Extreme Stress. Am J Psychiatry, 161, 195-216). Neuroendocrine studies suggest that the stress hormones cortisol and DHEA, and critically the ratio between them, may be important biological markers of resilience. Meanwhile roles for various genetic polymorphisms have also been established; for example, Caspi, A et al (2003). Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene. Science, 301(5631), 386-9, showed that individuals carrying two long alleles of the 5-HTT gene were relatively protected against depressogenic effects of life stress. Neurocognitive studies indicate that better problem solving strategies, presumably mediated by prefrontal cortex, are associated with greater resilience to life stress. Resilient individuals are also biased towards positive interpretation and optimism which may be reflected in positive biases on emotional memory and attention tasks, contrasting with the negative biases typically observed in depression. Neuroimaging research suggests that normal hippocampal structure and function in the face of acute stress may be a marker for resilience. fMRI studies of responses to aversive and anxiogenic stimuli also suggest critical roles for ventromedial prefrontal cortex, and amygdala in responses to stress. A study of subjects genetically at risk for depression (non-depressed twins of bipolar patients; Krüger S et al (2006) Risk and resilience markers in bipolar disorder: brain responses to emotional challenge in bipolar patients and their healthy siblings. Am J Psychiatry. 163(2):257-64) suggested that increased medial prefrontal response to negative mood induction may be a marker for resilience. A hypothesis of greater cognitive control (mediated by prefrontal regions) over negative emotional responses (mediated by limbic regions) is a plausible neurocognitive account of resilience. Systematic neurocognitive and neuroimaging investigation of individuals with different responses to life stress is required to provide a more detailed characterisation of key mechanisms. Understanding these mechanisms has implications for the development of interventions designed to promote wellbeing in the face of severe life stress.

S14

NOVEL TREATMENTS FOR STRESS- PRECLINICAL TARGETS

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Dysregulation of the brain emotional systems that mediate arousal and stress is a key component of the pathophysiology of anxiety disorders and affective disorders. Activation of brain stress systems is also hypothesized to be a key element of the negative emotional state produced by dependence that drives drug seeking through negative reinforcement mechanisms. A key brain arousal/stress system involving the neuropeptide corticotropin releasing factor has been identified that mediates hormonal responses to stressors via the hypothalamic pituitary adrenal axis but also sympathetic and behavioral responses to stressors via extrahypothalamic systems in the extended amygdala. A host of other peptide systems converge on the extended amygdala to contribute to stress responsivity and include dynorphin, vasopressin, orexin, substance P, neuropeptide Y and nociception. Compelling evidence argues that these brain stress systems mediate emotional homeostasis and play a key role in the allostatic states of anxiety and stress. Understanding the function of the brain stress and anti-stress systems provides insight into the neurobiology of basic brain emotional circuitry that guides motivated behavior and provides a rich substrate for novel treatments of stress disorders.

S15

TRANSLATIONAL MODELS OF ANXIETY: INDIVIDUAL DIFFERENCES IN GENOTYPE AND BEHAVIOURAL PHENOTYPE

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Introduction: Individual differences in both genotype and phenotype can affect the likelihood of developing mood and anxiety disorders. For example, polymorphisms in 5-HT system genes are implicated in anxiety disorders. So too is the behavioural trait of high anxiety. An understanding of the neurobiological and neurochemical basis of these individual differences will therefore provide important clues as to the aetiology and treatment of such disorders. Consequently, we have developed a programme of research to identify 5-HT related polymorphisms and high trait anxiety in a New World primate, the common marmoset.
Methods: Individuals with high trait anxiety and patients with anxiety disorders fail to discriminate safety from danger cues. Thus, we tested marmosets on their ability to develop discriminative conditioned responses in a pavlovian, aversive discrimination paradigm, in which one of two auditory cues predicted a 0.3s burst of aversive loud noise (120dB). Their performance was compared to that on a more traditional test of anxiety in primates, exposure to a rubber snake. In parallel, marmosets were genotyped by PCR for a novel 5-HT transporter (5-HTT) polymorphism we have recently found in the promoter repeat region of the gene (unpublished results).
Results: Seven out of 27 marmosets failed to show discriminatory behavioural and autonomic conditioning. Their failure was predicted by the enhanced heart rate and behaviour they exhibited to the safety cue, early on in training; potential indicators of enhanced anxiety. An additional indicator of enhanced anxiety was the increased distance the 'failed' animals maintained from a rubber snake, compared to those animals that had discriminated successfully. Increased distance from an anxiety-provoking stimulus was also associated with a novel dinucleotide polymorphism within the upstream regulatory region of the marmoset 5-HTT gene, a polymorphism that regulates gene expression, dose-dependently.
Conclusions: Individual differences in fear generalization and a polymorphism in the upstream regulatory region of the 5-HTT gene are associated with heightened anxiety in the common marmoset. Ongoing studies using structural MRI and microPET will provide critical guidance for future investigations that will manipulate activity within identified neural circuits to determine their contribution to anxiety and identify drugs with therapeutic potential. Support: AMS, James S McDonnell Foundation, YS, Ministry of Education, Culture, Sports, Science and Technology and Osaka University, Japan. Funding: Medical Research Council (MRC) Programme Grant (ACR). Resreach performed within the Behavioural and Clinical Neuroscience Institute, University of Cambridge, funded jointly by the Welcome Trust and MRC.

S16

EVIDENCE BASED OPPORTUNITIES TO IMPROVE PREDICTION OF TREATMENT RESPONSE IN DEPRESSED ADOLESCENTS

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Objectives: Attempts to predict treatment response from clinical phenotypes have achieved at best, modest success [Wilkinson P, Kelvin R, et al. Am J Psychiatry. 2011 168(5):495-501; Wilkinson, P., et al., Br J Psychiatry, 2009. 194(4): 334-41]. Therapeutic precision could be enhanced by i) establishing a quantitative trait of depressive symptoms ii) including selected measures of genetic, physiological and neurimaging variables.
Methods: Item response analysis was used to classify a sample (n=3,500) of individuals on the K-Sads depression section to illustrate the greater precision of a quantitative trait model compared to a DSM IV category approach [Cole DA, Cai L, et al. Psychol Assess. 2011 May 2. [Epub]. Genetic and endocrine assay procedures were used in a prospective design to validate gene x hormone prediction of depression onsets [Goodyer, I.M., et al Br J Psychiatry. 2010 197:365-71]. An association study was used to examine endocrine and adversity correlates with abnormalities of brain function during depression in adolescents [Treadway MT PLoS One. 2009;4(3):e4887]. Structural and functional neuroimaging before and after CBT treatment for unipolar depression were used in a prospective study of adult patients with DSM defined unipolar depression [Fu CH, Williams SC, et al., Biol Psychiatry. 2008 15;64(6):505-12].
Results: The longitudinal study using neuroimaging on depressed adults revealed that baseline dorsal anterior cingulate activity. The imaging association study suggests a key relationship between anterior cingulate morphology, a history of early adverse events and circulating cortisol. The gene and hormone findings show that the association between higher morning waking cortisol levels and subsequent depression is moderated by possessing genetic variants in 5-HTTLPR(s allele) or BDNF (Val66Val).
Conclusions: Taken together these findings suggest a pathophysiology that may involve corticoid mediated effects on the anterior cingulate structure and function in depressed individuals with a prior exposure to genetic and environmental moderators and mediators which may influence treatment response. Future studies using trials methodology could benefit from using an assessment protocol prior to randomization that stratified patients on one or more of the aforementioned variables to evaluate treatment response.

S17

USING ZEBRAFISH TO EXAMINE THE GENETICS OF DRUG SEEKING AND IMPULSIVITY

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Zebrafish have become a favoured system in which to perform forward genetic screens to identify genetic mechanisms underlying disease phenotypes. In order to use zebrafish to examine the genetics of drug addiction we have previously developed behavioural assays of compulsive drug seeking in adult zebrafish (Kily et al 2008). Here we extend these studies to the development of assays of impulsivity, a key predictor of propensity for compulsive drug seeking and behavioural disorders (Belin et al 2008). Individual fish were trained in a three-choice serial reaction time task, similar to the 5-choice task used with rodents.(Robbins, 2004). Following habituation, the fish were subjected to two, 20-minute initial training sessions during which they were oriented to a food magazine. Food availability was contingent on illumination of a light above the magazine. Subsequently, all training sessions commenced with illumination of the magazine light and following entry to the magazine the first trial was initiated. In a trial, there was an initial 20-second interval, after-which a barrier separating the fish from the choice zone was lifted. Fish were briefly exposed (5-sec) to three spatially distinct, but identical, stimuli (white LEDs in separate response apertures), presented in a random order after a 5 sec inter-trial interval (ITI). Entries to the correct response aperture either during the stimulus presentation, or within a 5-sec limited hold period following presentation, were reinforced with illumination of the magazine light and delivery of a food reward. Training sessions were carried out on consecutive days, and lasted for 20-minutes. Fourteen consecutive training sessions were performed under these parameters. Following training, all fish were screened for anxiety (using a novel environment challenge) and drug seeking behaviour (using conditioned place preference). The omission-error rates and premature response rates were comparable with rodent data, premature responses (i.e., entries to the response apertures during the ITI) constituted 26 ± 5% of trials, omission-errors 25 ± 5% of trials and correct responses constituted 55 ± 5% of trials. High levels of premature responding in the three-choice test were found to be a remarkably strong predictor for high stress responses in the fish, explaining 88% of the variance in our sample. In conclusion, we have established an assay of impulsivity in adult zebrafish. We are now in the position to screen lines of wildtype and mutant zebrafish to identify genetic factors contributing to impulsivity and drug seeking behaviour. Funding support: Medical Research Council UK G1000403. National Centre for the Replacement Refinement and Reduction of Animals in Research G1000053

S18

REAL-TIME BIOSENSING OF GLUTAMATERGIC AND CHOLINERGIC NEUROTRANSMISSION IN VIVO: IMPLICATIONS FOR PSYCHOPHARMACOLOGY

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Enzyme-coated microelectrodes for the amperometric measurement of several neurotransmitters in vivo, specifically acetylcholine (ACh) and glutamate, have begun to revolutionize our understanding of the regulation and function of these signaling molecules. This novel technology has been particularly fruitful for psychopharmacological research. We have been particularly interested in the cortical mechanisms that mediate the attentional enhancement produced by agonists at α4β2*, but not α7, nicotinic acetylcholine receptors (nAChR). In animals performing the Sustained Attention Task (SAT), α4β2* nAChR agonists specifically enhance the detection rate in signal trials that are preceded by factual or perceived non-signal trials (non-signal trials resulting in correct rejections or missed signal trials). Cholinergic transients are observed specifically during such incongruent trial sequences. α4β2* nAChR agonists augment the amplitude of these transients, thereby enhancing the switch from endogenous to exogenous attention and thus detection performance. Our research also revealed the reasons why the non-selective nAChR agonist nicotine is less effective in enhancing attentional performance than alpha4beta* agonists. Nicotine also stimulates the α7 nAChR and thereby dose-dependently increases the duration of the transient release event by several 10s of seconds. Such “noisy” release events are less likely to mediate the precisely timed, cholinergic mediation of a processing mode switch during incongruent trial sequences. This hypothesis was substantiated by evidence indicating that in the presence of an α7 nAChR antagonist, nicotine significantly enhanced SAT performance and evoked robustly “sharper” transients. Finally, our research has also revealed that in addition to cholinergic transients there is a more tonic component of cholinergic neurotransmission that is measured by microdialysis and does not merely indicate transient release events integrated over longer periods of (sampling) time. Indeed, our current circuitry model demands that the tonic and transient component of cholinergic neurotransmission originate from separate populations of cholinergic neurons (Hasselmo & Sarter, Neuropsychopharmacology, 2011, 36, 52-73) The tonic component of cholinergic neurotransmission influences detection-mediating cortical circuitry via stimulating α4β2* nAChR. This influence is particularly significant in situations requiring the cognitive control of attention, such as when prediction errors or distractors necessitate enhancement of detection as well as filtering mechanisms. Agonists at α4β2* nAChR are therefore expected to benefit specifically the deficits in the cognitive control of attention and thus are predicted to benefit the cognitive symptoms of patients with schizophrenia (e.g., Sarter et al., Neuropharmacology, 2011, in press). Supported by PHS grants MH080332 and MH086530.

S19

EEG ASSESSMENT OF PREATTENTIVE SENSORY GATING IN THE ALERT RAT, WITH TRANSLATABLE RELEVANCE TO SCHIZOPHRENIA

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The mismatch negativity (MMN), a mid-latency event-related potential (ERP) that is observed is when a sequence of repetitive sensory stimuli is broken by a dissimilar stimulus, is attenuated in schizophrenia. The MMN occurs without focused attention, so it is considered a manifestation of a preattentive filter that suppresses the processing of monotonous background sensory stimulation, thereby indirectly enhancing the processing of novel sensory events. Dysfunction in such a preattentive filter can inundate high-order sensory and executive systems with extraneous sensory input, possibly contributing to the cognitive impairments observed in schizophrenia. Thus, there is considerable interest in developing a preclinical model of MMN deficits in rodents for developing treatments for cognitive impairments in schizophrenia. The research reported here comprises the first step in this process: validating the correspondence between the putative rat MMN and the human MMN. We recorded the putative rat MMN epidurally while performing the parametric manipulations of sensory stimulation that are known to affect the amplitude of the human MMN. These manipulations include varying the degree of similarity between the standard and deviant stimuli, varying the number of standard stimuli preceding each deviant stimulus, and varying the inter-stimulus interval. Additionally, we determined the effect of NMDA antagonism, which is known to affect the magnitude of the human MMN, on the putative rat MMN. No single component in the rat putative MMN waveform has all of the characteristics of the human MMN. However, two mid-latency components in the rat share many common features with the human MMN. When considered as a group rather than singly, there is a moderately strong case that these components of the rat MMN correspond to the human MMN. If one considers this research as a case study of validating rodent models of impaired ERP's in humans, several principles emerge: First, it is necessary to determine the location and orientation of the predicted dipoles in rats given the dipole localisation in humans, for simply assuming that the rat and human ERP's will be equivalent at homotopic cranial positions is likely to be misleading. Second, in order to fully validate the correspondence between rodent and human ERP's, it is necessary in the rat to perform the parametric variations of sensory stimulation known to affect the human ERP. Third, the impact of psychopharmacological manipulations on rat ERP's can depend not only the acute dose of drugs, but also the stress caused by administration and the cumulative dose.

S20

DESIGN AND STATE OF THE ART PHENOTYPING OF A NOVEL MOUSE MODEL OF ALZHEIMER'S DISEASE

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Several genetically engineered rodent models exist that recapitulate pathological and cognitive hallmarks characteristic of Alzheimer's disease (AD). Heavy over-expression of human, mutated transgenes encoding for the amyloid precursor protein (APP), the microtubule associated protein tau and/or presenilin (PS1) enables easy quantification of end-stage protein accumulations corresponding with cognitive defects in young animals. A more promising research strategy, however, should capture the beginning pathology (prodromal AD) so as to better understand disease mechanisms and develop optimally effective therapeutics. This prodromal phase (termed preclinical AD, Sperling et al., (2011) Alzheimer's & Dementia 7: 280-292) encompasses a pathological phase, during which clinical symptoms of cognitive decline are absent, but other reliable biomarker may exist which map the disease trajectory. What is required in terms of experimental research is the development of models that mimic this protracted preclinical AD stage, and its application to these dynamic biomarkers, on which we report here. Experimental model: We have generated a mouse model by targeted knock-in of single-copy mutated APP and tau genes into the safe HPRT locus, controlled by the CaMKII-alpha regulatory element. Mice were crossed with an asymptomatic PS1 line to generate PLB1-Triple mice. Gene expression and tissue analyses confirmed stable, forebrain specific and gene-dose-dependent protein expression. Preclinical AD stage biomarkers: While Stage 1 preclinical AD is characterised by the absence of markers for neuronal injury and cognition, Stages 2 and 3 are by and large clinically asymptomatic, but first pathological alterations present as amyloidosis and neuronal impairments prior to the emergence of subtle cognitive change. In keeping with this disease trajectory, PLB1-Triple presented subtle amyloid and tau-related pathologies from ca 4-6 months with slow progression of primarily intracellular amyloid and phosphorylated tau. As early as 6 months, we observed evidence for neuronal impairments using 18F-FDG micro PET/CT metabolic imaging, with hypometabolism identified in parietal and temporal cortex. This phenotype was progressive as anomalies worsened following a sigmoidal trajectory. Consistent with metabolic failure, functional brain abnormality was revealed by wireless surface EEG recordings. Increased wakefulness alongside a slowing of EEG spectral power were early symptoms at 5-6 months and longitudinal re-testing confirmed progression to sleep fragmentation at 12-14 months. Yet, first cognitive phenotypes in episodic-like memory did not emerge before ~8 months of age and became more eminent at 12-14 months. These data compellingly suggest that preclinical AD can be modelled in animals and back-translated using human-relevant biomarkers with significant promise for research that enriches the mechanistic understanding of pathologies underlying asymptomatic stages of AD.

S21

ROLE OF HISTAMINE IN COGNITION: REVIEW OF RESULTS FROM ANIMAL STUDIES

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The role of brain histamine was initially acknowledged for the sedative and orexigenic side effects of commonly used antihistamine or psychoactive compounds such as neuroleptics. These undesired side-effects are essentially mediated by the blockade of H1 receptors (H1R) that are crucial for the regulation of the sleep/wake pattern, and diurnal rhythm of food intake. The interest in brain histamine as a therapeutic target for brain pathologies was revived in the past decades by the discovery of the H3R and the complex cytoarchitectonic of the histaminergic system, comparable to dopaminergic, serotonergic and noradrenergic systems. The source of brain histamine is neurons localized in the hypothalamic tuberomamillary nuclei that project axons to the whole brain, and are organized into functionally distinct circuits influencing different brain regions, and displaying selective control mechanisms. These widespread projections activate arousal circuits during wakefulness. Their activity is related to a high level of vigilance, where brain histamine is mainly responsible for the qualitative, cognitive aspects of vigilance. Histamine is also implicated in the coordination of goal-directed behaviours such as obtaining food, and the consolidation or weakening of memories. These functions can be implemented presumably by engaging independent populations of histaminergic neurons according to the brain regions required for a particular behavioural outcome. All four histamine receptors are expressed in the brain, with distinct distribution and density in the brain. However, only the H3R has become a drug target for the treatment of neurologic and psychiatric disorders, such as sleep disturbances and cognitive deficits associated with Alzheimer's and Parkinson's disease, schizophrenia and attention deficit hyperactivity disease. Blockade of H3Rs increases the release of several neurotransmitters, hence agents with multiple and complementary mode of action are more likely to show effects against core and comorbid symptoms. The implications of the histaminegic system in other pathologies are currently being adressed; preclinical studies from our laboratory indicate that histamine is required for the anorexiant effects of endogenous molecules, with mechanisms that challenge the assumption of histamine being a satiety signal in the CNS. Also, the integrity of the histaminergic system is necessary for SSRI to exert their acute effects in experimental animal models, thus suggesting the involvement of histamine in mood disorders. Several questions regarding the physiology of the brain histamine were answered in recent years, but the challenge of identifying new and better drug targets is not over yet.

S22

TRANSLATIONAL EFFICACY OF SELECTIVE H3 INVERSE AGONISTS; FROM PRECLINICAL TO CLINICAL EFFECTS ON WAKE PROMOTION

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Excessive daytime sleepiness (EDS) is a symptom associated with multiple disorders including narcolepsy, sleep apnea, shift work sleep disorder, and Parkinson's disease. A current mechanism of action under study for treating EDS is inhibition of the H3 receptor, a presynaptic negative regulator of histamine release in the central nervous system. Preclinical and clinical electroencephalographic (EEG) studies were undertaken to determine the efficacy of this mechanism in maintaining wakefulness across species from rodent to human. This presentation reviews data demonstrating that the statistically significant wake promoting effects of H3 inverse agonists translate across species and that use of EEG studies as a biomarker for efficacy in wakefulness is useful for demonstrating the translational wake promoting effects of H3 inverse agonists from preclinical to clinical studies.

S23

IMAGING THE BRAIN H3 RECEPTOR IN VIVO WITH POSITRON EMISSION TOMOGRAPHY

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The discovery that the histamine H3-receptor (H3R) is an inhibitory auto and hetero-receptor in the primate brain, has attracted attention to its potential as a therapeutic target in a variety of disorders of cognition, including Alzheimer's disease (AD) and Schizophrenia. Investigation of the physiological and pharmacological role of histaminergic neurotransmission in general, and H3R in particular, would greatly benefit from the ability to estimate the status of these receptors in the living brain. Hence the development of a practical positron emission tomography (PET) ligand designed to quantify H3R availability, is of great practical benefit for the pharmaceutical industry, as well as the academic researcher. In support of the GSK H3R inverse agonist development program, we evaluated the GSK compound library of H3R selective compounds, to define a compound with the potential to be developed as a PET ligand. GSK189254 was selected and labeled with carbon-11. [^{11}C]GSK189254 was evaluated in the porcine and non-human primate brain to evaluate its selectivity, specific binding and tissue kinetics. The pre-clinical evaluation has provided sufficient support to progress to human PET studies. Human brain studies with [^{11}C]GSK189254, provided data consistent with that acquired in pre-clinical species, and [^{11}C]GSK189254 was used to evaluate candidate therapeutic compounds in development by the GSK Neurosciences Centre for Excellence in Drug Discovery. Pre-clinical and clinical PET data were used to make Go-no-Go decisions in the development of H3R selective compounds, and in defining the clinical dose range. This presentation will describe the course of the H3R PET ligand development and the use of [^{11}C]GSK189254 PET to expedite drug development.

S24

EFFECTS OF HISTAMINE AUGMENTING AND DEPLETING MANIPULATIONS ON COGNITION, FMRI AND ERPS IN HUMANS

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The discovery that histamine H3-receptor antagonists/inverse agonists are able to improve cognition in experimental animals has attracted attention to the role of the histamine transmitter system in human cognition. The search for H3-antagonists/inverse agonists as potential treatments of cognitive impairments would benefit from more knowledge about the role of histamine in human cognition and a model of cognitive impairments in humans associated histaminergic dysfunction. We have attempted to establish a model of histamine related cognitive impairment characterised by the use of H1-antagonists. Several placebo and active drug controlled, cross-over studies in healthy volunteers show that oral doses of the H1-antagonist dexchlorpheniramine impair performance on tasks largely in cognitive domains of psychomotor performance and attention, but not memory. This pattern of results is confirmed by a review of studies that have investigated the effects of H1-antagonism on human cognition. The clear effects on sensori-motor speed were further investigated by studying the effects of H1-antagonism on psychomotor functioning using Event Related Potentials, which suggested that H1-antagonists mainly affect sensory processes, possibly responsible for the observed psychomotor impairment. In contrast, a subsequent functional Magnetic Resonance Imaging study with a similar aim suggested that H1-antagonists do not directly affect sensory processes, but indirectly affected other cognitive functions recruited when task demands increase. As there is a clear discrepancy between enhancing effects of H3-antagonists/inverse agonists on memory and the lack of impairing effects of H1-antagonists on memory, H1-antagonism seems unsuitable as a model used to test all potential cognition enhancing effects of H3-antagonists. An alternative model of low level histamine functioning is L-histidine depletion which was hypothesised to decrease histamine synthesis in the central nervous system and affect cognitive performance. As a proof of concept it was shown that L-histidine levels decreased in peripheral blood and affected electrophysiological measures of response preparation. However, the effects were small and further studies on improving this potential model of cognitive impairments associated with low level histamine need to be conducted. Additional future steps in modelling histaminergic dysfuction in healthy humans and obtaining knowledge about the role of histamine in human cognition are studying the role of histamine H2-receptors in cognition and memory in particular and unravelling the effects underlying effects of histaminergic manipulations on attention.

S25

ANTENATAL DEPRESSION AND CHILDREN'S OUTCOMES

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There is increasing attention to foetal programming of children's behaviour, particularly in terms of links between mothers' mental state in pregnancy and children's risk for aggression and other behavioural problems. I report data from three samples. In the first, a study of 799 families who underwent Assisted Reproductive Technologies, it is possible to test for prenatal influence whilst controlling for genetic relatedness between mother and child. Mothers' perceived stress In pregnancy predicted antisocial behaviour in offspring, even in unrelated mother-child pairs. In a 16 year follow-up of a study of perinatal illness, adolescents whose mothers were depressed in pregnancy were at a fourfold risk for violent crime and/or physically aggressive conduct disorder, even when controlling for sociodemographic risk, re-exposure to depression, smoking in pregnancy, and mothers' and fathers' antisocial behaviour. Finally, a new study of 310 infants, mothers' depression in pregnancy predicted anger and early signs of aggression by 6 months of age. I discuss what additional evidence is needed to prove antenatal depression exerts causal effects on infant development and what might be the underlying mechanisms.

S26

IMPACT OF IN UTERO EXPOSURE TO ANTIDEPRESSANTS ON THE FETUS

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There is a common concern over the use of antidepressant drugs during pregnancy. Exposure to the fetus has been linked to different adverse outcomes but, in most studies, first trimester exposure to any antidepressant has not been associated with an increased risk for congenital malformations. However, associations between cardiovascular defects and e.g. paroxetine, fluoxetine and clomipramine have been suggested in some, but not in all, studies. Further, most authors agree that women using antidepressants have a tendency to preterm delivery. On the other hand, similar effects have also been attributed to the depression itself. A large number of studies have described neonatal symptoms associated with antidepressant exposure, e.g. respiratory difficulties, low Apgar score, hypoglycaemia, cyanosis at feeding, and CNS-effects. An increased risk for persistent pulmonary hypertension of the newborn (PPHN) has also been described; primarily after late exposure to an SSRI. To elucidate some of the questions above we undertook a study based on the Swedish Medical Birth Register for the period July 1, 1995 – 2007. All women who reported the use of antidepressants in early pregnancy or were prescribed such drugs during pregnancy (14 821 women with 15 017 infants) were retrieved from the register. Maternal characteristics, maternal delivery diagnoses, infant neonatal diagnoses and presence of congenital malformations were compared with the population (1 062 190 women with 1 236 053 infants), using Mantel-Haenszel technique and with adjustments for critical characteristics. There was an association between antidepressant treatment and pre-existing diabetes and chronic hypertension but also with many pregnancy complications. Rates of induction of delivery and of caesarean section were also increased. The rate of preterm birth was increased but not of intrauterine growth retardation. Neonatal complications were common, notably after tricyclic drugs. The congenital malformation rate was increased after tricyclic drugs and associations between use of paroxetine and congenital heart defects and hypospadias were found. Finally, the increased risk of PPHN was verified. Our analysis, which is the largest data set available based on prospective exposure information, supports the idea that use of antidepressants during pregnancy increases the risk for a number of pregnancy, delivery, and neonatal complications. However, with this study design it is not possible to dissociate these effects from possible effects of an underlying psychiatric pathology.

S27

MATERNAL ANTIDEPRESSANT EXPOSURE AND CNS DEVELOPMENT IN THE RAT OFFSPRING

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As antidepressant use increases amongst women of childbearing age, there is an increasing concern about quantifying the risk that such antidepressant treatment has on the foetus, neonate and whether such treatment has any enduring effects in later life. Making such evaluations clinically creates a number of problems, not least being the ethical challenges posed by conducting controlled longitudinal studies. In addition, such studies would need to include all clinical scenarios by which antidepressant treatment is instituted, e.g. women who receive antidepressant treatment during pregnancy compared to that in postpartum depression. Alternatively, these different antidepressant exposures may be modelled in laboratory animals, particularly rodents, i.e. rats, rabbits and mice. Such models have become an important mandatory feature of preclinical safety evaluation in the wake of the thalidomide disaster of the early 1960s. However there are several limitations to these studies: they may often employ doses and routes of exposure which are not clinically relevant; they explore teratogenic endpoints with little behavioural sequelae evaluated; and testing of the offspring may not occur at intervals stretching into adulthood. Thus, there is a need to develop preclinical approaches that can address these limitations. Such approaches would employ a range of relevant tests for assessing CNS developmental consequences that would evaluate the effects of prenatal and neonatal exposure of antidepressants on general behaviour, anxiety, learning and memory. An appropriate test battery can be drawn from those found to be most relevant for examining chemicals that have a well-established impact on CNS development of the offspring, e.g. following heavy metal (e.g. lead) exposure. Such studies should be conducted at pharmacologically relevant doses using the oral route of exposure, and involve exposure periods that equate to pregnancy and lactation in humans. Using the SSRI antidepressant fluoxetine, we have found that prenatal exposure increased anxiety-like behaviours in the elevated plus maze at 2, 3, but not 4 months of age in the offspring. No effect was seen on locomotor activity, recognition memory or spatial learning and memory. When postnatal exposure of fluoxetine to the mothers was employed, it had no effect on any behaviours in the offspring. These results suggest that there are measureable behavioural changes following prenatal fluoxetine exposure, which, although seen in adulthood, are ultimately transient. Ideally, prospective, long-term human behavioural studies are necessary to determine if this animal model approach can be extrapolated back to the clinical scenario.

S28

WHAT ARE THE MECHANISMS UNDERLYING THE IMPACT OF MATERNAL DEPRESSION AND ANTIDEPRESSANT USE ON THE OFFSPRING?

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Introduction: Ultimately the destiny of an individual is the results of multiple inputs – some protective, some detrimental – that occur throughout the development, starting in utero and continuing in childhood and early adulthood. Some of these inputs have clinical relevance and have clear, documented effects on long-term biology and psychopathology: for example, maternal depression, both antenatal and postnatal, or childhood adversity. However, the combinations and interactions of these multiple inputs are infinite, and very difficult to model even in the largest cohorts. Of particular relevance for this talk, it is challenging to dissect the effects, during pregnancy, of depression vs. antidepressant treatment, and then to dissect both these effects vs. the effects of depression in the postnatal environment. Therefore, a variety of approaches are needed, ranging from the molecular to the epidemiological, to try to draw some meaningful conclusions. Methods: In this talk, I will review data from our three main lines of research addressing this issue: the South London Child Development Study, where mothers who were depressed in pregnancy (in 1986) and their offspring have been followed up into offspring's adolescence; the Psychiatry Research and Motherhood Study, where mothers depressed in pregnancy (and their babies) are currently assessed for neuroendocrine response to stress; and a molecular study where the mechanism by which maternal care affects the stress responsivity of the offspring is investigate in a human fetal hippocampal stem cell line. Results and Conclusions: Consistently, we demonstrate that stress affects clinical, biological and molecular outcomes, with relevance, within the perinatal context, for both physical and mental health.

S29

UNDERSTANDING NEUROTROPHIC FACTOR CHANGES IN MODELS OF DEPRESSION AND IN MAN

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Although classical neurotransmitter-based hypotheses propose that major depression is due to a dysfunction of monoaminergic systems, ample evidence suggests that mood disorders may originate from deficits in neuronal plasticity. On this basis, altered expression of key proteins, such as neurotrophic factors may play a relevant role in depressive disorders. One of these proteins is the neurotrophin BDNF that can be considered a valuable marker of neuronal plasticity. During the last few years we have shown that the expression of BDNF is significantly reduced in animal models of depression, including rodents exposed to early life stressors as well as animals with genetic alterations of susceptibility genes for depression. For example, using serotonin transporter (SERT) mutant rats, which show anxiety and depression related behavior, we found a significant reduction of BDNF in hippocampus and prefrontal cortex. These changes were due to a significant reduction of specific BDNF transcript that, within the prefrontal cortex, occurred through epigenetic changes. With respect to pharmacological treatments, we have shown that chronic treatment with the antidepressant duloxetine not only increases the expression of selected BDNF transcripts in rat hippocampus, but also modulates the intracellular trafficking of BDNF protein, with enhanced levels of mBDNF in the synaptosomal compartment. We also found that reduced levels of BDNF mRNA in SERT knockout rats are normalized by chronic duloxetine treatment through the modulation of selected transcripts that are not regulated in wild type animals. The potential clinical relevance of neurotrophin abnormalities in depression is sustained by the investigation of circulating levels of BDNF. Although it may be difficult to compare changes of serum neurotrophin with those found in selected brain structures, the available data strongly agree with the evidence from animal studies. Indeed serum BDNF levels are reduced in naïve-depressed patients and they are restored to control levels by antidepressant treatment. Furthermore, we recently found that, in agreement with our data in SERT knockout rats, the expression of BDNF is significantly reduced in lymphocytes of control subject carrying the short variant of the serotonin transporter gene, suggesting that such alteration may contribute to depression susceptibility. In summary these data support a role for the neurotrophin BDNF in depression and in antidepressant response. Understanding BDNF biology within this context might be crucial for developing effective pharmacological strategies aimed at regulating neurotrophin expression and function in selected brain structures in order to achieve better clinical outcomes.

S30

ARC AND TRKB EXPRESSION IN HUMAN CORTICAL POST-SYNAPTIC DENSITY EXTRACTS

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Both animal and human studies suggest that BDNF signalling via TrkB receptors is disrupted in both schizophrenia and mood disorder. BDNF-induced activation of TrkB is one of the mechanisms leading to increased synaptic Arc signalling during synaptic plasticity. We have previously shown that Arc mRNA is increased in three different animal models of depression. In order to assess both TrkB and Arc expression and a possible relationship between them, we have assessed protein levels of both TrkB and Arc in purified extracts of the post-synaptic density (PSD) from frontal cortex of post-mortem brain samples from the Stanley Consortium collection.

The PSD was purified using sucrose gradient centrifugation methods adapted for use with human brain as outlined by previous studies. Stanley Consortium human brain samples were obtained from 15 control, 15 major depressive disorder, 15 schizophrenia and 15 bipolar disorder cases. Antibodies for Arc and TrkB obtained from BD Biosciences and Cell Signalling respectively, and fluorescent secondary antibodies were used for Western blotting using 60 ug purified PSD extract per case. The Licor Odyssey near-infared image analyser was used to visualise and analyse immunoblots. Arc and TrkB vales were normalised to beta actin (Sigma-Aldrich) values for each case in duplicate. One-way ANOVA and Spearman's correlation tests were used to assess the effect of potentially confounding variables. Any significant ($p<0.05$) variables were included in Multivariate ANOVAs when assessing the effect of diagnosis.

For Arc protein expression in prefrontal cortical PSD fraction, a main effect of diagnosis was found ($p = 0.02$). An increase in major depressive disorder was found relative to the control group. Full-length TrkB was reduced in psychiatric illness relative to controls, however these findings did not reach statistical significance.

Protein levels of Arc appear to be increased in cortical PSD samples from patients with major depressive disorder relative to controls. This is consistent with findings from animal models of depression. From these preliminary findings we have been unable to find corresponding changes in TrkB, however further studies are underway to further assess neurochemical changes that accompany increased PSD Arc expression in major depressive disorder.

S31

THERAPEUTIC AGENT AND DRUG DESIGN TARGETS: BRAIN NGF RECEPTORS

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Alzheimer's disease is the most common cause of dementia, affecting around 500,000 people in the UK alone. The inability to form new memories is the most common early symptom, with subsequent cognitive dysfunction, behavioural disturbance and deficits in activities of daily living. Memory formation is associated with the interaction of the cholinergic basal forebrain neurons with hippocampal glutamate neurons. Current treatments for Alzheimer's disease are cholinesterase inhibitors, which act by slowing the breakdown of acetylcholine released from cholinergic cells by the enzyme acetylcholinesterase. However, presumably because the cholinergic cells continue to die, this treatment only lasts for a limited period. The cholinergic neurons are reliant on the neurotrophins for maintenance of synaptic connections in adulthood. In particular, nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) are thought to play important roles in onset of pathology, but also may be of therapeutic relevance (Allen and Dawbarn 2006, Clinical Science 110, 175-91). We aim to produce small molecules able to mimic NGF or BDNF which stimulate their respective tyrosine kinase receptors, TrkA and TrkB. We have used in silico techniques to select compounds for testing in vitro based on the crystal structure of the TrkAIg2 domain in complex with NGF. Using Unity4 from the Tripos suite of software we reduced eight million compounds to tens of thousands of in silico "hits" or potential binders. Using a combination of criteria, including maximising the chemical diversity of test compounds, drug-like attributes and synthetic accessibility, we selected a few hundred compounds for testing achieving a ~10% in vitro hit-rate. Our radioligand competition assay measures the ability of the compound to compete with 125I-labelled NGF binding to the full length human TrkA receptor expressed on HEK cells. Successful compounds are tested for their ability to activate the signalling system downstream of TrkA. The binding site is then verified using Nuclear Magnetic Resonance HSQC (heteronuclear single quantum coherence) with 15N-labelled TrkAIg2. Using these methods we have identified a number of chemical families which act as leads for rational design. Agonists at the TrkA receptor would work by specifically stimulating cholinergic basal forebrain cells this would keep them healthy and halt the disease progression. This programme is being repeated using TrkB to find small molecules able to mimic BDNF. Funding for this project was provided by The Medical Research Council and Severnside Alliance for Translational Research, Bristol Research into Alzheimer's disease and Care of the Elderly (BRACE), The Alzheimer's Society, and Alzheimer's Research UK. SJA is a Sigmund Gestetner Senior Research Fellow. Automated fluorescence microscopy analysis was made possible by a Wellcome Trust Equipment Grant (CA McArdle; WT078407).

S32

NOVEL MRI-BASED PLATFORM FOR EFFICIENT GENE DELIVERY TO THE BRAIN

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Gene transfer technology can correct genetic mutations in the brain. Neuro gene delivery via direct intrapranchymal injections of adeno-associated viral (AAV) vectors is a locally administered treatment that requires accurate delivery to maximize safety and efficacy. The large volume and convoluted architecture of the human brain is a considerable barrier to translating small animal findings into efficacious clinical procedures. Too little target coverage and the treatment risks being ineffective. Conversely, excessive distribution or off-target gene delivery increases the possibility for unexpected adverse effects. Optimal viral vector delivery into the brain is challenging and brain distribution of viral vectors is uncertain. To address this issue we developed viral vector delivery system that permits direct MRI monitoring of vector distribution within the brain in real-time. This significant advance allows for the first time to adjust parameters of vector infusion while delivering gene therapy, giving surgeon full control over gene transfer technology. To allow for precise intracerebral delivery of biologics for therapy of neurological disease we also developed a skull-mounted aiming device (SmartFrame) and integrated software platform (ClearPoint) for interventional MRI guided placement of deep brain stimulators. In anticipation of upcoming gene therapy clinical trials in brain disorders we adapted this device for real-time convection enhanced delivery (RCD) of therapeutics via a custom designed infusion cannula. Based on real-time MRI data, this system allows selection of brain targets, provides instructions for cannula insertion along a chosen trajectory, and permits visual monitoring of infusions. Subsequent to our discovery that AAV2 vectors undergo anterograde transport along thalamocortical projections resulting in transduction of cortical neurons, we analyzed properties of several AAV serotypes and evaluated their potential for correcting genetic deficit in the brain via axonal transport. Combination of RCD and axonal transport may allow for predictable gene transfer over large cortical and sub-cortical regions of a human brain. Our advanced gene delivery system is currently tested for delivery of therapeutic genes in Parkinson's (PD), Huntington's (HD) and Nieman-Pick, AADC deficiency in children and brain tumors. Data will be provided to demonstrate promises and challenges in successful clinical translation of gene transfer technology for CNS disorders.

S33

AETIOLOGICAL PATHWAYS INVOLVED IN THE PERSISTENCE AND REMISSION OF ADHD DURING ADOLESCENCE

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ADHD is a common neurodevelopmental disorder that starts in childhood and frequently persists into adult life. It is a major cause of psychiatric morbidity and psychosocial impairments in children and adults. While the precise causes of ADHD remain unknown, it is recognised that multiple causal factors are involved. To date, four main clues lead the way in generating testable hypotheses of the causal mechanisms. First, the high heritability of ADHD implicates genetic factors. Second the immediate and marked response of ADHD symptoms to stimulant medication implicates dysregulation of dopamine pathways. Third the association of ADHD with environmental factors, particularly those occurring during the prenatal period of development, suggests epigenetic processes initiated by environmental exposures. Fourth the association of ADHD with cognitive performance impairments, structural and function brain deficits and neurophysiological changes, implicates various potential neurobiological processes including cognitive control, state-regulation and reward pathway deficits; as a cause or consequence of the disorder. The neurobiological processes that mediate genetic influences on ADHD behaviours are not however well understood. To investigate the links between genes, brain and behaviour and delineate more precisely the causal processes involved, we recently completed a series of family and twin studies designed to identify the cognitive processes that mediate genetic effects on ADHD. The results suggest that reaction time (RT) variables (mean RT and standard deviation of RT) represent a unitary construct across a range of speeded reaction time tasks, that explain around 85% of the familial effects on ADHD. A further separate factor that explains most of the residual familial influences on ADHD is best described as an 'error factor', particularly reflecting commission errors that might implicate response inhibition processes. These two processes are reflected in recent cognitive models of ADHD including the the attention-arousal model and a developmental model described by Halperin. The Halperin hypothesis in particular proposes that the maturational processes on cognitive control during adolescence mahy suppress an earlyt onset and enduring arousal deficit that persists from early childhood; leading to remission of ADHD in some cases and and persistence of ADHD in others.

S34

MODELLING ADHD IN ANIMALS

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Attention-deficit hyperactive disorder (ADHD) is the most common adolescent psychiatric disorder affecting between 7-10% of the population. Although symptomology is heterogeneous, it is characterised by developmentally inappropriate hyperactive and inattentive/impulsive behaviours with a pervasive impact on life settings, such as home and school. The aetiology of ADHD is unclear and although polymorphisms in several genes linked to dopamine, noradrenaline and serotonin neurotransmission show association no single causal genetic alteration has been identified. Indirect evidence suggests that hypofunction of dopamine in cortical-striatal-thalamic brain circuits contributes to the neurobiology of ADHD. For instance, stimulants like methylphenidate used to treat ADHD are potent inhibitors of the dopamine transporter DAT. Animal models of ADHD are invaluable to improve our understanding of the cause of, and drugs used to treat, the disorder but few existing models adequately mimic the behavioural deficits or underlying neurobiology. The Spontaneous Hypertensive rat (the most popular preclinical model) is hyperactive and impulsive but these effects are not reversed by methylphenidate and animals develop hypertension with age which is not a feature of ADHD. Likewise, DAT knockout mice and 6-hydroxydopamine lesioned rats are hyperactive but have reduced rather than elevated striatal DAT thought to accompany ADHD. By treating young rats (PND24-27) with the irreversible DAT inhibitor, GBR 12909, we attempted to induce a rebound long-term up-regulation of DAT following drug withdrawal to mimic fronto-striatal hypodopaminergic function thought to occur in ADHD. Such rats show long-term hyperactivity, impaired novel object discrimination and an altered fMRI response to methylphenidate but the behavioural changes attenuate with age. This presentation also compares the temporal pattern of brain regional activity change produced by systemic administration of therapeutically relevant doses of amphetamine, atomoxetine, guanfacine and methylphenidate to anaesthetised normal adult rats using BOLD functional MRI. In general these drugs produce positive BOLD effects (thought to reflect neuronal activation) in very few brain areas; including the nucleus accumbens, substantia nigra, entorhinal cortex and medial orbital cortex. However all four drugs produce much more widespread and intense negative BOLD in the motor and somatosensory cortices, caudate putamen, lateral globus pallidus and bed nucleus of the stria terminalis. The overall pattern of BOLD changes produced by all four compounds, which operate through distinct pharmacological mechanisms, was surprisingly similar and may represent a 'fingerprint pattern' of activity change that may be useful to predict the therapeutic benefit of new drugs developed to treat ADHD.

S35

PHARMACOLOGICAL NEUROIMAGING OF ADHD DRUGS IN HUMANS

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Introduction Neuroimaging research has increased our understanding of neurobiological mechanisms underlying clinical symptoms of attention deficit hyperactivity disorder (ADHD) and their response to treatment with stimulants and other pharmacological interventions. This presentation summarises structural and functional MRI (fMRI) studies of reward circuits in adults with ADHD, PET/SPECT studies of the dopamine system in ADHD and pharmacological fMRI studies investigating the effect of single doses of ADHD drugs on task-related brain activity. Method This review is based on a systematic literature search and ongoing research of our group in Cambridge [Del Campo N, Tait RJ, Acosta-Cabronero J, et al. Neuroimage 2011; 55: 101-112; Chamberlain SR, Hampshire A, Müller U, et al. Biol Psychiatry 2009; 65: 550-555; Dodds CM, Müller U, Clark L, et al. J Neurosci 2008; 28: 5976-5982; Müller U, Suckling J, Zelaya F, et al. Psychopharmacology 1995; 180: 624-633]. Results Ventrostriatal hyporesponsiveness during reward processing is one of the best replicated fMRI findings in adults with ADHD. Group effects in PET and SPECT studies investigating D2 receptor and dopamine transporter (DAT) availability in ADHD patients as compared to healthy controls are inconsistent. D2 receptor availability in the striatum correlates with the severity of ADHD symptoms. Atomoxetine, guanfacine and methylphenidate modulate event-related brain activity in striatal and prefrontal regions during ADHD-specific cognitive tasks. Conclusion There is converging evidence from functional and pharmacological neuroimaging in ADHD supporting the model of neurodevelopmental deficits in fronto-striatal circuits modulated by dopamine, noradrenaline and ADHD medication.

S36

PHARMACOLOGICAL TREATMENT OF ADHD IN ADULTS

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Introduction: ADHD is a common disorder with a prevalence rate of 3-5% in children as well as adults. In psychiatry, addiction centers and forensic psychiatric services, the prevalence of ADHD in adults is estimated higher, at around 20%. Not recognising ADHD in adulthood may lead to chronicity of the comorbid conditions, as ADHD brings instability in all areas of functioning, including taking care of one's mental and physical health (Kooij, J.J.S. ADHD in adults. Diagnostic assessment and treatment. Pearson Assessment and Information, 2010. (Orders only at: bestelling-nl@pearson.com). After careful assessment of ADHD and comorbid disorders, ADHD in adulthood can be effectively treated with psycho-education, medication, coaching and cognitive behaviour therapy. Treatment is best provided by a multidisciplinary team that specialises in ADHD in adults.
Methods: Pharmacological treatment of ADHD usually comes after treatment of more acute or severe disorders like depressive or bipolar episodes, anxiety disorders and addiction. Because of the inattention problems of ADHD patients, antidepressant medication is usually preferred above cognitive behaviour therapy for anxiety or depression. Light therapy for seasonal affective disorder and melatonin treatment for the frequent delayed sleep phase syndrome are usually effective, though yet little studied. Available, but off-label medications used for ADHD in adults are stimulants (methylphenidate, dexamphetamine), atomoxetine, bupropion XL, modafinil and tricyclic antidepressants.
Results: Based on 16 years of clinical experience and on efficacy and safety data in the literature, first and other choices of medication will be discussed, as well as common dosing schedules in adults, side effects, contra-indications and combined treatment of stimulants with antidepressants, mood stabilisers and melatonin.
Conclusions: ADHD in adults is a common disorder in psychiatry, which can be diagnosed and differentiated from other, often comorbid conditions. All disorders must be addressed and treated in the right order, based on severity. Treatment of ADHD in adults is not just treatment of ADHD, but of a combination of disorders that cluster in our patients.

MA01

DIFFERENTIAL REGULATION OF HUMAN HIPPOCAMPAL NEUROGENESIS BY PRO-INFLAMMATORY CYTOKINES

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Neurogenesis and inflammatory processes are both considered as possible mechanisms having significant roles in the pathophysiology of major depression (MD). Animal and human studies have shown reduced neurogenesis in the adult hippocampus, with antidepressants being able to increase the number of newborn neurons. Additionally, levels of the pro-inflammatory cytokines IL-1β and IL-6 have been shown to be elevated in a subset of MD patients. While animal studies have indicated a detrimental effect of IL-1β on neurogenesis, observations are contradictory for IL-6, with studies suggesting both neuroprotective and neurodegenerative roles. This prompted us to investigate the effects of IL-1β and IL-6 on differentiation of human brain cells. We used a conditionally immortalized human hippocampal stem cell line (HPC03A/07, ReNeuron, UK) as a model. Cells were allowed to proliferate for 72 hours followed by 7 days of differentiation, in the presence of IL-1β (10 ng/ml) or IL-6 (50 ng/ml). To assess changes in neuronal differentiation, cells were subjected to immunocytochemistry. Levels of mRNA were measured by real-time quantitive polymerase chain reaction, and results were calculated using GAPDH and β-actin as housekeeping genes. While IL-6 increased both immature, doublecortin-positive neuroblasts (+38%, $p<0.05$), and mature, microtubulin-associated protein-2-positive neurons (+62% $p<0.01$), IL-1β was detrimental to neurogenesis (-42%, $p<0.05$; -35% $p<0.05$, respectively). IL-1β caused an up-regulation of all enzymes conducive to neurotoxic products within the kynurenine pathway (IDO, KMO and KYNU), while no significant changes were detected for the enzymes that catalyse formation of neuroprotective metabolites (KAT1, KAT2 and KAT3). This differential regulation of mRNA was detected after 24 hours under proliferation conditions, and it was maintained when cells were allowed to differentiate. In contrast, no significant changes in the levels of any of these enzymes were observed when cells were treated with IL-6. Neither the antidepressant amytriptiline (1microM) nor the IDO inhibitor 1-methyltryptophan (500microM) were able to reverse the damaging effects of IL-1β on neurogenesis. Treatment with the KMO inhibitor Ro 61-8048 (10microM) partially reversed this damage (doublecortin-positive neuroblasts -24%, $p<0.05$). Our findings provide further information on the pathways involved in the cytokine-induced changes in the human brain, and suggest that KMO inhibitors may be useful in controlling detrimental effects caused by IL-1β. This work was funded by NARSAD and the European Union Framework 7.

MA02

NEUROCHEMICAL CHANGES IN AN IMMUNOLOGICALLY-INDUCED HIGH RISK STATE FOR MOOD DISORDER: INTERFERON-ALPHA TREATMENT OF CHRONIC HEPATITIS C VIRAL INFECTION

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Introduction: Growing evidence links vulnerability to depression with activation of the inflammatory system. One model of inflammation-related depression is in the treatment of chronic hepatitis C virus (HCV) infection with the pro-inflammatory cytokine, interferon-alpha (IFN). This treatment is associated with induction of depression in 30-50% of cases. However, the mechanisms by which this occurs remain poorly understood. An improved understanding might suggest potential strategies to address this important clinical problem. Furthermore this also provides a rare opportunity to investigate dynamic changes in vulnerability to depression within individuals. Proton magnetic resonance spectroscopy (MRS) provides a safe non-invasive measure of local brain chemistry. Using MRS, we have previously observed elevated levels of total glutamate and glutamine (Glx) in cerebral cortex of people at high risk of future mood disorder, having recovered from unipolar depression or bipolar disorder. We hypothesised that similar elevations in Glx might be induced during treatment with IFN.
Methods: Patients with chronic hepatitis C viral infection without evidence of cirrhosis, scheduled to receive treatment with IFN as part of their routine clinical care, were scanned at baseline and again after 4-6 weeks of treatment with IFN. Those with current axis I disorders by DSM-IV were excluded. Healthy control volunteers, medically fit and without current or past axis I disorder by structured clinical interview, were similarly scanned on one occasion. MRS measurements were obtained using standard short echo-time PRESS (TE=30msec) of a 25x20x20mm cortical voxel. Spectra were analysed using LCModel. Results: At baseline, patients had similar levels of cortical Glx to that observed in healthy volunteers. With IFN treatment a significant elevation of cortical Glx levels was observed ($p<.05$).
Conclusions: Treatment of HCV infection with IFN is associated with the induction of a neurochemical picture (elevated cortical Glx) similar to that seen in other groups at elevated risk of mood disorder. This points to potential similarities in mechanism of vulnerability.

MA03

DECREASED SUBJECTIVE RESPONSE TO ALCOHOL AMONG INDIVIDUALS WITH THE BIPOLAR PHENOTYPE

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Elevated lifetime prevalence rates of alcohol use disorders (AUDs) have been reported in bipolar disorder (46% in BD I; 39% in BD II), and exceed those reported in schizophrenia or major depression (Regier, et al., 1990, JAMA, 264: 2511-2518). Diminished subjective responses to alcohol (low levels of response; LLRs) have been widely reported among individuals at-risk for AUDs. It has been hypothesized that LLRs might lead to greater consumption, increasing the risk of developing AUDs. Therefore, it is possible that the elevated prevalence rate of AUDs seen in the bipolar disorders may be partially explained by LLRs to alcohol. However, this possibility has not been tested in individuals with a history of developed bipolar illness or with the common bipolar phenotype seen in young people. Participants were selected based on their prior experience of mood elevation identified using the Mood Disorders Questionnaire (MDQ), a validated screening tool for bipolar disorder. Twenty male adult participants with the common bipolar phenotype (i.e., MDQ scores ≥ 7) and twenty male control participants (MDQ = 0), matched for age, IQ, body mass index (BMI) and weekly alcohol intake were assessed using a randomized, double-blind, cross-over, within-subjects design. Participants with a family history of AUDs were excluded. Subjective (Drug Effects Questionnaire; DEQ, Biphasic Alcohol Effects Scale; BAES) and pharmacokinetic (pulse, heart rate, breath alcohol content; BrAC) responses to acute alcohol (8mg/kg) versus placebo administration were taken at multiple time points (0, 30, 45, 60, 120, 180 minutes). Both groups of participants obtained similar peak BrAC levels following consumption of the alcoholic beverage. In order to control for expectation effects on subjective ratings (e.g., DEQ and BAES), placebo scores were subtracted from the alcohol scores for each time point. Following alcohol administration, participants with the bipolar phenotype provided significantly decreased ratings of the DEQ subscales 'high' ($p = 0.001$) and 'feel effects' ($p = .01$) across time points; and showed reduced amplitudes of response and quicker decline. Between-group differences on measurements of stimulant or sedative responses did not differ. There is a significantly decreased subjective response to alcohol among young people with the bipolar phenotype. It is not attributable to any difference in weekly alcohol intake, or to any physiological differences (e.g., absorption rates), or family history of alcohol misuse. These observations demonstrate a link between experience of mood elevation and LLRs in young people, perhaps mediating vulnerability for AUDs. Financial support for this research was provided by the Medical Research Council (MRC) and the Oxford University Clinical Academic School (OUCAGS).

MA04

DISRUPTED NEURAL ACTIVATION IN BIPOLAR PHENOTYPE DURING RISKY DECISION-MAKING

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Introduction: Risky behaviours are frequently observed in bipolar disorder and may both reflect underlying pathophysiology and influence clinical outcome. The anterior cingulate cortex, striatum and orbitofrontal cortex appear to play dissociable roles in the representation of values when making decisions between actions and processing outcomes (Rogers et al, 2004, Biological Psychiatry, vol. 55, 594-602). However, the functional correlates of risky decisions in bipolar disorder remain unclear.
Methods: Thirty six bipolar phenotype individuals (by virtue of scores ≥7 on the Mood Disorder Questionnaire (Hirschfeld, et al., 2000, The American Journal of Psychiatry, vol. 157(11), 1873-1875) and both with and without a diagnosis of bipolar disorder) (18 male, 18 female) and 40 healthy controls (21 male, 19 female) completed a risky decision-making task during event-related functional magnetic resonance imaging (fMRI) in a 3-Tesla scanner. Participants made a series of choices between binary-outcome gambles for monetary rewards. The gambles differed in their expected value: the magnitude of gains, magnitude of losses, and the probabilities with which these outcomes were delivered. fMRI data were analysed using FMRIB's Software Library (FSL; Smith, et al., 2004, Neuroimage, vol. 23, S208-S219), thresholded at $Z>2.3$ and whole-brain corrected at $p<0.05$. Signals associated with expected value of actions, the value of outcomes and differences between groups were examined a priori ($Z> 2.3$) and subject to small volume corrections.
Results: Expected values while deciding between actions were associated with enhanced BOLD amplitudes within the bilateral caudate and putamen, as were the values of anticipated and received outcomes. Relative to controls, bipolar phenotype individuals showed significantly reduced signals within visual areas while contemplating the expected values of candidate actions and the values of chosen actions prior to learning their outcomes. By contrast, bipolar phenotype individuals showed enhanced value within the amygdala when learning the value of decision outcomes.
Conclusions: Bipolar phenotype individuals showed altered representation of action and outcome values during decision-making. These effects may represent vulnerability markers for bipolar disorder and be associated with risky behaviour. Further studies are required to investigate the effects of pharmacological treatments for bipolar disorder on the neural correlates of risky decision-making.
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MA05

VISUO-SPATIAL MEMORY IN BIPOLAR DEPRESSION: NEUROPSYCHOLOGICAL AND HPA AXIS CORRELATES

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Animal and human models have highlighted the role of cortisol in the modulation of memory processes; attempting to understand this link is of critical importance. In a programme of research we have profiled neuropsychological and HPA axis function in individuals with a diagnosis of bipolar disorder, before examining if these functions can be altered through an intervention with an antiglucocorticoid drug (mifepristone; RU-486). Results indicated that in 20 patients with bipolar disorder (with depressive symptoms; BD), significant global deficits were observed in neuropsychological functioning as well as afternoon (1pm – 4pm) hypercortisolaemia. Following mifepristone treatment, significant improvements were observed in aspects of visuo-spatial memory, specifically spatial working memory (SWM). The magnitude of SWM improvement was significantly correlated with baseline hypercortisolaemia (Young AH et al. 2004. Neuropsychopharmacology 29:1538-45). To explore these findings in more detail, a second cohort of 53 patients with BD and 47 healthy controls was recruited. Specific aims were to i) to utilise the novel Object Location Memory (OLM) test (Kessels RPC et al. 1999. Behavior Research Methods, Instruments, & Computers 31:423-8) to examine separable independent processes within visuo-spatial memory in BD; ii) to examine the broader neuropsychological factor structure in order to explore the component processes underpinning visuo-spatial memory in BD; iii) to utilise the cortisol awakening response (CAR) and dexamethasone suppression test (DST) to explore the relationship between the HPA axis and visuo-spatial memory processes. Results indicated that i) BD patients exhibited significant impairments in fine-grain metric spatial memory ($p<0.0001$; $d=-1.02$) which, unlike other spatial processes in the OLM, could not be explained by other neuropsychological deficits. ii) The underlying neuropsychological component structure of BD and controls differed. Using hierarchal regression, a unique profile of processes underpinning aspects of visuospatial memory was observed in BD suggesting a form of cognitive 'scaffolding' to support performance on some measures. iii) Correlation between neuropsychological processes and peripheral HPA axis measures were not observed. Spatial memory processes in BD can be altered by direct HPA axis manipulation. A number of interesting avenues for future research have been identified that will further our knowledge of the integration between the biological mechanisms underlying neuropsychological impairment in mood disorders and should develop our understanding of integration between cognitive processes in general.
These studies were supported by the Stanley Medical Research Institute (SMRI) and the Medical Research Council (MRC).

MA06

COGNITIVE FUNCTION AND PLASMA LEVELS OF NEUROTROPHIC AND INFLAMMATORY PARAMETERS IN PATIENTS WITH BIPOLAR DISORDER

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Introduction: Bipolar disorder (BD) is a severe and disabling chronic disease. BD patients, even under treatment remain vulnerable for relapses and cognitive impairment. The neurobiology of bipolar disorder and the cognitive impairment in these patients remains unclear. There is evidence suggesting the role of brain-derived neurotrophic factor (BDNF) and increased levels of pro-inflammatory molecules in the pathophysiology of BD and the cognitive impairment in these patients. Objective: The present study investigated the cognitive performance, plasma levels of BDNF and pro-inflammatory molecule (TNF-α and its soluble receptors) in euthymic BD type I patients in comparison with healthy controls. The underlying hypothesis is that plasma levels of BDNF and TNF-α and its soluble receptors (sTNFR1 and sTNFR2) are associated with poorer cognitive performance in BD patients.
Methods: We have evaluated 25 BD type I patients in euthymia and 25 healthy controls. The cognitive examination included the Frontal Assessment Battery (FAB) and Mini-Mental State Examination (MMSE). Plasma levels of BDNF, TNF- α and its soluble receptors were measured by Enzyme-linked immunosorbent assay (ELISA).
Results: BD patients presented a poorer performance on the FAB scores in comparison to healthy controls (mean ± SD, BD patient: 12.80 ± 2.87, healthy control: 14.92 ± 1.91, $p = 0.006$) as well subtests related with sensitivity to interference ($p = 0.02$) and inhibitor control ($p = 0.02$). BD patients presented higher BDNF plasma levels than healthy controls (3991.54 ± 2358.26, 1752.19 ± 1358.96, respectively, $p = 0.001$). Regarding BD patients, TNF- α plasma levels were positively correlated to inhibitor control ($\rho = 0.50$, $p = 0.02$). Considering healthy controls, plasma levels of BDNF were positively correlated to MMSE ($\rho = 0.50$, $p = 0.02$) and motor programming was negatively correlated with sTNFR2 plasma levels ($\rho = - 0.47$, $p = 0.02$).
Conclusions: BD euthymic patients present impairment in executive function. Poorer executive performance is associated with lower MMSE, lower educational levels and increased plasma levels of BDNF.
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MA07

EFFECT OF LITHIUM ON GLUCOCORTICOID RECEPTOR FUNCTION IN EUTHYMIC BIPOLAR DISORDER PATIENTS

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Introduction: It has been suggested that hypothalamic-pituitary-adrenal (HPA) axis dysregulation and, as a consequence, increased cortisol levels, is not only a state phenomenon, but may also be a trait phenomenon in mood disorders. Cortisol exerts its effects mainly by binding to the glucocorticoid receptor (GR) and, of particular interest in certain brain regions, the mineralocorticoid receptor (MR). Indeed, Bipolar disorder (BD) has been characterized by hypothalamic pituitary adrenal (HPA) axis hyperactivity and glucocorticoid insensitivity which improve after effective treatment. Furthermore, we have previously shown that antidepressants modulate GR and MR function; whereas mood stabilizers like lithium and valproic acid also modulates GR and MR function is still not yet clear. In this study, we thus further investigate the effect of mood stabilizers on the GR and MR function in euthymic bipolar disorder patients and in healthy controls.
Methods: Blood samples was obtained in the morning (9:00-10:00AM) from twenty euthymic bipolar disorder patients and fifteen age-sex matched healthy volunteers. Whole blood was diluted tenfold with RPMI-0640 medium. All solutions were prepared in pyrogene-free sterile saline (NaCl 0.9%) in order to achieve final concentrations in the cultures of: 20 ng/mg for lypopolysaccharide (LPS); 10 μM for lithium and 10 μM valproic acid; 10nM and 100nM for dexamethasone and prednisolone. Cultures were kept at 37°C, 5% CO2. After 24h, plasma was obtained by centrifugation and stored at -20 for the measurement of interleukin-6 (IL-6) by ELISA. GR function was measured by glucocorticoid inhibition of LPS-stimulated IL-6 levels. IL-6
Results: ELISA assays have been carried out for 4 patients and 4 controls so far. Preliminary results suggest lithium also modulates GR function in bipolar disorder patients. Conclusions: Understanding the pathophysiology of bipolar disorder and the mechanism of action of lithium may improve treatment options of this devastating psychiatric disorder.
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MA08

ATTENTIONAL BIAS MODIFICATION REDUCES DEPRESSIVE SYMPTOMS AND WAKING CORTISOL RISE IN PREVIOUSLY DEPRESSED PATIENTS

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The majority of patients with depression will experience further episodes of the illness throughout their life. There is therefore a strong incentive to develop secondary preventative strategies for the illness. Recent work has described negative biases in the deployment of attention to emotional information in individuals who have previously been depressed [Joormann and Gotlib (2007), JAP, 116:80-5], which suggests that reducing these biases may reduce the recurrence of depression. In the current study we tested this hypothesis by examining the impact of an attentional bias training (ABT) regime on both measures of depressive symptoms and a biological marker of depressive susceptibility (waking cortisol rise) in previously depressed patients. In addition we assessed whether the effects of ABT depended on the emotional stimuli (faces vs. words) used in the training. 62 patients who had at least two previous episodes of depression and who were not currently depressed or receiving treatment were enrolled. Patients were randomised to receive either a positive or neutral version of the ABT task which was administered twice daily for two weeks. In addition randomisation determined whether the ABT task presented words or pictures of faces. Measures of attentional bias (dot-probe task), symptoms (BDI and trait-STAI) and HPA function (salivary cortisol measured every 15 minutes for the first hour after waking) were taken at baseline, immediately following the ABT task and then again a month later. Waking cortisol rise was calculated as the difference between the first and the peak cortisol samples. As expected, positive ABT (using either words or faces) led to an increase in positive attentional bias across the training period [$F(2,112)=3.1$, $p=0.05$]. The effect of training on both depressive (BDI) and anxious (trait-STAI) symptoms depended on whether words or faces were used in training [$F(2,112)=3.7$, $p=0.03$]. Whereas word ABT did not influence these measures, positive (compared to neutral) face ABT lead to a significant decrease in symptoms [$F(2,56)=3.7$, $p=0.03$]. This protective effect occurred across the follow-up period rather than during training. Face based ABT was also found to reduce waking salivary cortisol rise, again during the follow-up period [$F(2,54)=4$, $p=0.02$]. These results suggest that face based ABT may be effective in reducing the risk of recurrence in previously depressed patients. Interestingly, reminiscent of the effects of antidepressant medication, the effect of ABT on symptoms and HPA function appeared to lag behind its cognitive effects.
This study was supported by an Experimental Medicine Grant from the MRC

MA09

SHORT-TERM ANTIDEPRESSANT ADMINISTRATION REDUCES NEGATIVE BIASES IN EMOTION PROCESSING IN SUBJECTS WITH HIGH NEUROTICISM

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Introduction: A growing number of studies suggest that antidepressant drugs may act by modifying neuropsychological biases in emotional information processing early on in treatment (Pringle, A., et al, 2011, Progress in Neuro-Psychopharmacology and Biol Psychiatry, in press). Recently we have further supported this model by translating evidence of early antidepressant effects on neural responses to emotional stimuli in healthy volunteers to a population at risk with subclinical features of depressive and anxious cognitive-emotional biases (Di Simplicio, M., et al. 2011, Mol Psychiatry, epub) . The aim of the present study was to investigate the behavioural effects of short-term repeated antidepressant administration on subjects with high neuroticism who present biases in emotional processing related to increased vulnerability to psychopathology. We hypothesised that repeated SSRI administration would reduce the negative biases in facial expression processing and memory for self-descriptors previously reported in the same population (Chan, S.W., et al., 2007, Psychol Med. 37(9):1281-91).
Methods: Never-depressed highly neurotic subjects (n=39) were randomized to 20 mg/day citalopram versus placebo for 7 days, in a double-blind, between-groups design. On the last day of treatment participants completed a battery of psychological tests measuring emotional processing, including tasks of emotional facial expressions recognition, categorisation and memory of self-descriptors and emotion-potentiated startle. Data were analysed using between-groups repeated measures analyses of variance with treatment group as between-subjects factor and stimuli valence as within-subjects factor. Interpretation of significant interaction effects was aided by simple main effect analyses. Results: Volunteers receiving citalopram showed a higher threshold to recognise negative facial expressions and a lower threshold to recognise positive facial expressions (valence x group Anova: $F(1,37)=8.881$, $p=.005$) compared to subjects on placebo. Citalopram also produced a significantly higher number of correctly recognised positive compared to negative self-descriptors (valence x group Anova: $F(1,32)=4.229$, $p=.048$).
Conclusions: Our results extend data from non-selected healthy volunteers' studies and confirm that short term SSRI treatment can reduce negative biases in the processing of emotional facial expressions and produce a positive bias in memory for self-descriptors also in a population at risk for depression and anxiety. Further research could explore whether longer treatment would also induce changes in affect in this population sample presenting a tendency for low mood and high anxiety levels and whether this would be related to the observed early changes in emotional information processing.

MA10

SHORT-TERM SSRI TREATMENT REMEDIATES AMYGDALA HYPERACTIVITY IN DEPRESSED PATIENTS: A PLACEBO-CONTROLLED STUDY

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Introduction: studies in healthy volunteers have shown an early attenuation of negative emotional biases by antidepressant treatment in both behavioural and fMRI paradigms (Harmer CJ et al. 2006, Biol Psychiatry 59, 816-20); it has been proposed that this change in emotional processing could mediate the therapeutic effect of antidepressants (Pringle A et al. 2010 [Epub ahead of print]). Here we extend the findings into a depressed population using a placebo-controlled design.
Methods: The study included 42 depressed individuals randomized in a double-blind manner to either 10 mg/day escitalopram or placebo for 7 days, and 17 drug-free healthy volunteers. fMRI data (neural responses to implicit presentation of emotional faces – gender discrimination task) were acquired at 3T on the last day of the treatment and in untreated healthy volunteers. A priori regions of interest for bilateral amygdala were used.
Results: In the absence of clinically significant changes in mood, seven days escitalopram treatment was associated with decreased right amygdala activation to fearful faces, relative to placebo-treated individuals, whereas there was no difference in amygdala activation between escitalopram-treated patients and healthy controls.
Conclusions: Our data support a model of antidepressant action in which delayed improvement in subjective mood occurs after remediation of negative affective biases by antidepressants early in treatment. This could allow relearning of emotional associations in a more positive emotional environment. Previous studies in depressed patients have shown attenuated amygdala activation in response to emotionally salient stimuli after several weeks of antidepressant treatment. Our work indicates that this is an early effect of treatment which precedes clinical improvement in mood.
The study was funded by MRC.

MA11

FRONTAL WHITE MATTER ABNORMALITIES AND NEUROPSYCHOLOGICAL TESTING IN PATIENTS WITH SEVERE TREATMENT RESISTANT DEPRESSION UNDERGOING TWO SITE DEEP BRAIN STIMULATION

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Brain white matter abnormalities are an index of vascular disease and are associated with treatment refractoriness in major depressive disorder. We investigated the correlation between the total volume of such abnormalities in the frontal lobes as measured by high resolution T2 weighted MRI and specific neuropsychological tests. These were obtained pre-operatively and have been previously demonstrated to be abnormal in our patients with severe and chronic treatment resistant depression undergoing deep brain stimulation. White matter hyperintensities (WHM) were identified and manually traced using a free-hand tracing tool in MRIcroN and MANGO; each hyperintensity was filled which allowed the volume of WMHs in each slice to be recorded as well as the total volume of WMHs. The total amount of white matter for each patient in each slice was also obtained to calculate the percentage of WMHs. Spearman's nonparametric bivariate correlation (SPSS v 19) was carried out between volumes of WMHs with neuropsychological test scores (trails A and B, Stroop (expressed as t values) and Hayling). 8 patients (2 male) with major depressive disorder, 5 recurrent, age 49 ± 8.4 yrs, duration of illness 19 ± 14 yrs, and in the current episode for 11.5 ±10 yrs were recruited. At baseline they were severely depressed with (MADRS 39.5 ± 7.8, HAMD 17 26 ± 5.8, GAF 31 ± 10) and had failed to achieve sustained response with a number of treatments including an average of 22 psychotropics (excluding benzodiazepines) alone and in combination, 43 ECT treatments (4.5 courses) and VNS in two cases. Not all patients could complete all neuropsychological tests. Three patients had much higher volumes of WMHs that the others (average 6% of white matter volume v 1.5%). The results showed no correlation between clinical or neuropsychological test scores and WMHs: MADRS $r2=0.117$, $p>0.05$, HAM-D(17) $r2=0.069$, $p>0.05$, GAF $r2=-0.101$,$p>0.05$, SSAI $r2=0.516$,$p>0.05$, TMT part A $r2=0.108$,$p>0.05$, TMT part B $r2=0.036$,$p>0.05$, Stroop test, colour name condition $r2=0.119$,$p>0.05$, word reading condition $r2=0.071$,$p>0.05$ and inhibition $r2=0.145$,$p>0.05$, and finally the Hayling test scores $r=0.267$,$p>0.05$. The study has a small sample size, however it indicates that the cognitive deficits observed in individual patients do not seem to correlate with small vessel pathology as identified by WMHs and is therefore likely to be associated with functional impairment due to depression. In addition there is no correlation between WHMs and severity of depression or functional impairment in this chronic and severely treatment resistant group.

MA12

REDKITE: KETAMINE AS A TREATMENT FOR DEPRESSION

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ReDKITE is a phase 1 safety study looking at the effect of ketamine in treatment resistant depression (TRD) in a routine NHS setting. Studies show ketamine has a rapid antidepressant effect in TRD patients not taking antidepressants. Suicidal ideation is also reduced (Price et al, 2009, Biol Psychiatry, 66, 522-526).The longest effect reported so far is 3 months following 6 infusions, and 15 months with maintenance treatments. Thrice weekly repeated ketamine has not been shown to be associated with tolerance or memory impairment (Aan et Rot et al, 2010, Biol Psychiatry, 67, 139-145). We are exploring the efficacy of ketamine when used in the routine NHS setting of an ECT clinic, in which participants continue there current medication. The study is an open label, dose escalation, clinical trial and is split into two stages. In stage 1, 12 participants receive a low dose of intravenous ketamine weekly for 3 weeks. Descriptive statistics will be used as this is a safety trial with small numbers of participants. So far, the study has recruited 7 participants. Three participants experienced a fast mood improvement. Two of whom relapsed and went on to receive further ketamine infusions prescribed by their psychiatrist. Two other participants did not experience a change in mood and two were withdrawn from the study early due to adverse events. The longest mood improvement has lasted 7 months following 2 extra treatments. There has only been one incident when a side effect (panic attack) has not been tolerated. Study results so far support the notion that ketamine is effective as a fast acting antidepressant and is safe in a NHS patient setting. The challenge is to find out what methods can prevent relapse and to identify treatment responders. The study is funded by the National Institute for Health Research and sponsored by Oxford Health NHS Foundation Trust.

MA13

THE EFFICACY OF MIFEPRISTONE IN BIPOLAR DEPRESSION – EFFECT ON SPATIAL WORKING MEMORY

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HPA axis dysregulation is implicated in many mood disorders. Dysfunction in the negative feedback system of the HPA axis may be the cause of the abnormally high levels of cortisol seen in bipolar disorder. Hypercortisolaemia is associated with depression and impaired cognitive functioning. Therapeutic interventions targeting glucocorticoid receptors which regulate the negative feedback system could therefore be effective. A preliminary double-blind, placebo-controlled crossover study by our group found that administration of the corticosteroid receptor antagonist mifepristone resulted in selective improvement in neurocognitive functioning and improvements in mood compared to placebo. Improvements were apparent 14days after cessation of treatment (Young AH et al 2004 Neuropsychopharmacology 29; 1538-45). The present study aimed to replicate this using a parallel group design in order to assess whether these improvements were enduring. It was hypothesised that following treatment with mifepristone, there would be an improvement in neurocognitive performance, specifically in spatial working memory. In a randomised double blind, parallel group design, 58 patients (31 male) from the North East of England and Christchurch, New Zealand with bipolar depression, confirmed using the Structured Clinical Interview for DSM IV Disorders (SCID) were administered either 600mg of mifepristone or placebo for 7 days. Spatial working memory was assessed at baseline, 2 weeks after cessation of treatment and 6 weeks after cessation of treatment. Spatial working memory was assessed using a computerised test from the Cambridge Neuropsychological Test Automated Battery (CANTAB). Neurocognitive data were analysed using repeated measures analysis of covariance (ANCOVA). Data for the spatial working memory test was calculated as absolute change from baseline. For missing data, last observation was carried forward. Preliminary analysis of data showed no main effect of treatment but there was a significant interaction between treatment and visit ($F(1,53)=4.06$,$p<.05$) with significantly greater improvement in between search error rate by week +6 following mifepristone. The data suggest that mifepristone is effective in improving spatial working memory in patients with bipolar depression. Neurocognitive dysfunction in bipolar disorder may in part be due to HPA axis dysregulation. The improvement shown after administration of mifepristone lends support to the theory that GR antagonists may work by resetting the homeostatic set point of the HPA axis (Belanoff JK et al 2002 Biological Psychiatry 52;386-92) and which was supported by evidence from our cross-over study (Gallagher P et al 2008 Journal of Psychiatric Research 42:1037-1041.

MA14

A NATURALISTIC EVALUATION AND AUDIT DATABASE OF AGOMELATINE (NEVADA): CLINICAL OUTCOME AT EIGHTEEN MONTHS

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Agomelatine is a recently licensed antidepressant drug with a novel mode of action. Agomelatine exerts agonist activity at melatonergic MT1 and MT2 receptors and antagonist activity at 5HT2c receptors (Agomelatine Summary of Product Characteristics, accessed on-line, February 2009 http://www.medicines.org.uk/EMC/medicine/21830/SPC/Valdoxan/). Published data suggest a preferable side effect profile compared with other licensed antidepressants (Kennedy S H et al; A double-blind comparison of sexual functioning, antidepressant efficacy and tolerability between agomelatine and venlafaxine XR; Jnl of Clin. Psychopharmacology 2008; 28; 329-333); Kasper S et Lemoine P; Comparative efficacy of the antidepressants agomelatine, venlafaxine and sertraline; European Neuropsychopharmacology 2008; 18; S331-2)). Whilst trial data and local experience may provide guidance as to agomelatine's clinical value, naturalistic reports from a wider clinical environment may determine its ultimate place in treatment. The NEVADA programme is a naturalistic UK-wide evaluation designed to capture a national picture of the clinical value of agomelatine. A live database is used to collect demographic and outcome data from various centres across the UK. Here we report interim data collected at eighteen months. Secondary care centres from across the UK were approached to participate in the study. Following local approvals, staff were trained on the use of the database and provided with access to enter data. Following an independent prescribing decision, data were collected for all patients prescribed agomelatine at treatment initiation, weeks four, eight and twelve. After eighteen months of data collection, twelve centres were enrolled in the study, and 141 baseline reports were collected. The study cohort were between 19 and 77 years of age, 93% (n=131) had an ICD-10 diagnosis of a severe and/or recurrent depression and 59% of patients (n=83) had experienced three or more prior episodes of depression. At the time of agomelatine initiation, 94% (n=132) had received at least one antidepressant in the current depressive episode, and 57% (n=81) of patients were suffering an episode lasting over twelve months. At eighteen months, 93 patients had either completed twelve weeks of agomelatine treatment or discontinued their treatment prior to the twelve week study period. Of those with complete data sets 59% (n=55) continued treatment at twelve weeks. Of those who discontinued treatment (n=38), 55% (n=21) discontinued due to lack of efficacy, and 29% (n=11) due to an adverse event. A mean reduction of 0.94 points in the CGI-S (Clinical Global Impression-Severity) scale was observed. This patient cohort suggests that the prescribing of agomelatine is often limited to those patients who are among the most ill and possibly suffering a treatment-resistant depression. Despite such severity of illness, 59% (n=55) of patients remained on treatment at week twelve and a reduction in CGI score was observed. Data from a broader population are required to inform if the drug is efficacious in less severely ill populations. Funded by an unrestricted research grant from Servier Laboratories Ltd. Please note this report represents work in progress.

MA15

ERYTHROPOIETIN - A CANDIDATE TREATMENT FOR MOOD SYMPTOMS AND COGNITIVE DYSFUNCTION IN DEPRESSION

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Introduction: Current pharmacological treatments for clinical depression have a significant treatment-onset-response delay, insufficient efficacy for many patients and fail to reverse cognitive deficits. In particular, memory deficits often persist into periods of remission and show correlation with hippocampus volume reduction and illness chronicity. Erythropoietin (Epo) has important neuroprotective and neurotrophic actions and improves cognitive function in animal models and patients with cognitive decline.
Methods: We systematically reviewed the published findings from animal and human studies exploring the potential of Epo to treat memory dysfunction and mood symptoms in patients with depression. A systematic search on Pubmed was performed using the following search profile: ((Erythropoietin) AND ("Mood Disorders"[Mesh] OR "Depression"[Mesh] OR "antidepressive agents"[MeSH Terms] OR "antidepressive agents"[Pharmacological Action])) OR ((Erythropoietin) AND ("amygdala"[MeSH Terms] OR "hippocampus"[MeSH Terms] OR "memory"[MeSH Terms] OR "neuronal plasticity"[MeSH Terms])). Additional hand searches were carried out to ensure inclusion of all relevant articles. Selection criteria: original investigations with a double-blind placebo-controlled design of the effects of EPO on A) hippocampus-dependent memory function, and depression- and anxiety-relevant behaviour in animal models B) hippocampus-dependent memory and depression-relevant neurocognitive processes in healthy human volunteers and patients with depression.
Results: The systematic search identified 49 articles of which five animal studies and seven human studies met the criteria of this study. All reviewed animal studies but one and all human studies demonstrated that Epo had beneficial effects on hippocampus-dependent memory function and antidepressant-like effects on behavioural measures. These effects appear to be mediated through direct neurobiological actions of Epo rather than upregulation of red cell mass.
Conclusions: The present findings are consistent with neuroadaptive effects of Epo and highlight Epo as a candidate agent for future treatment of cognitive dysfunction and mood symptoms in depression. These results suggest that larger-scale clinical trials of Epo as a new antidepressant with beneficial effects on depression-relevant cognitive function are warranted.

MA16

DULOXETINE VS INDIVIDUAL GENERIC SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS) IN THE TREATMENT OF A SEVERE DEPRESSIVE EPISODE

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Introduction: There is an increasing evidence base suggesting serotonin noradrenaline reuptake inhibitors (SNRIs) may be more efficacious than SSRIs, particularly for more severely depressed patients. A study of duloxetine (HMFT) has been presented which demonstrated higher remission rates for duloxetine versus a pooled group of SSRIs when the secondary endpoint of remission as measured by the 17-item Hamilton Depression (HAM-D17) total score was assessed. This post hoc analysis presents results for the individual SSRIs versus duloxetine from HMFT. Methods: HMFT was a 12-week randomised, parallel-arm, open-label study of duloxetine vs various SSRIs. There were 3 study periods (Screening at Visit 1, treatment from Visit 2 for 12 weeks and 2 weeks' optional down-titration). For patients randomised to an SSRI, the choice of SSRI (citalopram, sertraline, fluoxetine or paroxetine) was at the investigator's discretion. During the active treatment phase, the starting dose of duloxetine was 30mg or 60mg but the dose could be increased at the investigators' discretion. SSRI dose was selected by the investigator consistent with the approved US label. Key inclusion criteria were: adults with non-psychotic Major Depressive Disorder, PHQ-9 score >15 at visit 1, QIDS16 self-rated score >19 at visits 1 and 2. Standard safety assessments were performed. The primary endpoint was remission defined as a patient-rated QIDS16 score <5. Secondary endpoints included remission as defined by HAM-D17 score <7 (total and subscale scores), Brief Pain Inventory and Sheehan Disability Scale. Results: 750 patients were randomised (duloxetine 372, SSRIs 378). 66% were female. Mean HAM-D17 total score at baseline was 25 for both groups. Overall, between treatment differences in remission rates based on QIDS were not statistically significant, although remission as defined by HAM-D17 total score was statistically significant (duloxetine 53% vs SSRIs 44%, $p<0.05$). The individual SSRI results for HAM-D remission rates at week 12 (MMRM) were: duloxetine (n=365) 53%, citalopram (n=153) 41%, $p<0.05$, fluoxetine (n=57) 46% remission, ns, paroxetine (n=44) 54% remission, ns and sertraline (n=117) 44% remission, ns. Conclusions: The trends observed for individual SSRI results, with the exception of paroxetine, for remission are similar to the overall pooled SSRI result. Duloxetine provided statistically significantly greater remission versus citalopram. Other comparisons versus SSRIs did not reach statistical significance, potentially because the study was not powered for comparisons of individual SSRIs versus duloxetine. Statistical comparisons between duloxetine and individual SSRIs should be interpreted with caution given selection of an individual SSRI was based on investigator discretion.
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MA17

EFFICACY OF TOPIRAMATE IN BORDERLINE PERSONALITY DISORDER: A SYSTEMATIC REVIEW

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Introduction: There is growing evidence suggesting some psychotropics ameliorate some symptoms associated with borderline personality disorder (Abraham et al. Journal of Affective Disorders, 2008, 111:21-30). Antiepileptic agents have been shown to have mood stabilising effects in patients with bipolar affective disorder. They have also been shown to have anti aggressive effects in a variety of disorders. Their use has been extended to a variety of disorders including borderline personality disorder. Topiramate, an anticonvulsant initially developed as a hypoglycaemic for diabetes has been investigated in a few studies for its efficacy in borderline personality disorder. We sought to evaluate the current evidence for the effectiveness of Topiramate in borderline personality disorder (BLPD). Methods: We conducted a literature search using the data bases, Medline, PsychInfo and Embase using the keywords Topiramate, borderline personality disorder and emotionally unstable personality disorder. Results: We found seven articles published in peer reviewed journals, of which three were double blind randomised controlled trials and four were case reports. Three articles reported significant reduction in anger for patients with BLPD treated with topiramate. Significant reductions in aggressive behaviour and hostility were noted in three of the studies. Notable reductions in interpersonal sensitivity and improved tolerance to rejection were reported in two studies. In three studies significant reductions in self-injurious behaviour and suicidality were noted. One report noted significant reductions in hospital admissions following use of Topiramate whilst in another there were significant reductions in affective instability. Marked reductions in quarrelsome behaviour and social avoidance were noted in one study. People with BLPD commonly present with somatisation and anxiety symptoms. These symptoms were reduced with the use of Topiramate in two of the studies. No improvements were reported for low mood associated with BLPD with Topiramate. Similarly no significant changes were noted for the following symptoms; paranoia, obsessive compulsive disorder and inability to stick to boundaries.
Conclusions: Few studies with robust methodology have been conducted exploring the benefits of Topiramate in BLPD. To our knowledge this is the first systematic review of the literature on the use of Topiramate in BLPD. Available literature suggests that Topiramate may have some positive impact on some symptoms associated with BLPD. Topiramate is generally well tolerated in BLPD. More randomised double blind studies need to be conducted to establish the efficacy of Topiramate in BLPD. This project was self-funded by the authors

MA18

RETROSPECTIVE INVESTIGATION OF PRIMARY CARE MONITORING OF ANTIDEPRESSANT DRUG TREATMENT (2006-2009)

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Since the early 1990s the volume of antidepressant prescribing in Scotland has increased substantially (ISD Scotland, 2008) as it has elsewhere in the UK (Hollinghurst et al, BMJ, 330, 999-1000). This is mainly explained by increasing duration of prescribed antidepressants (Moore et al., BMJ, 339, b3999) and may reflect improving practice; with more patients receiving prolonged treatment in line with current guidelines (NICE, CG90). However, it is unknown whether these longer durations of antidepressant prescribing in primary care are conducted with appropriate review. This study aimed to assess continuity of antidepressant therapy in a UK primary care setting at the individual patient level and to assess whether this is conducted with appropriate review. Data were recorded from medical records in two Aberdeen practices, of patients initiated on antidepressants in the year following April 1st 2006. The follow up period was three years. Data recorded included demographic information, details and dates of antidepressant prescriptions, dates of General Practice consultations for antidepressant review, and psychiatric history. Data were analysed using SPSS Version 17. All continuous data subject to univariate analysis was non-Normal (except for age), so was assessed for significance using the Mann-Whitney U test and Spearman's rank correlation. Variables associated with duration of treatment in the univariate analysis were entered into a stepwise multiple regression. Duration of treatment was log-transformed to allow normal distribution of residuals. The sample consisted of 191 patients. Median duration of treatment for the first episode was 180 (IQR=60, 429) days, with 29% patients receiving antidepressants for 60 days or less. Half of the sample discontinued medication within 180 days of commencement. Less than a third of patients at high risk of recurrent depression received at least 2 years of therapy, in line with current guidelines. Age and previous receipt of antidepressants contributed significantly to predicting treatment duration ($p<0.01$); effect size ($R2=0.1$). The median interval between antidepressant review consultations increased progressively with increasing treatment duration. There were no significant predictors of frequency of antidepressant review. Despite recent increases in the average duration of antidepressant prescribing, a high proportion of patients in our study discontinued treatment prematurely. There is also evidence that some patients are not reviewed adequately during the second year of chronic treatment. Depression management could thus be improved by assertive review (and better characterisation) of patients who discontinue early; and scheduled re-assessment of treatment in the second and subsequent years of continuation therapy.
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MA19

SYMPTOMATIC TREATMENT OF INTERFERON-ALPHA-INDUCED DEPRESSION: A SYSTEMATIC REVIEW

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Introduction: Current treatment of hepatitis C involves combination therapy with interferon-alpha (IFN-a) and ribavirin. Despite its efficacy, IFN-α induces neurotoxic effects such as depression, which compromises its tolerability. For that reason understanding and treating the potential psychiatric complications of IFN-α therapy is very important. The purpose of this systematic review is to give an overview of the available and effective therapies in treating IFN-α-induced depression. Moreover, recommendations for the use of specific antidepressants and other therapeutic methods are discussed.
Methods: We performed a systematic search using Pub Med, The Cochrane Library, Scopus, Embase, Ovid of Medline, Psychoinfo and ISI web of Knowledge. From a total of 1115 papers initially identified, we selected 69 papers concerning symptomatic treatment of interferon-α-induced depression in HCV patients, which included a total of 768 patients. Results: Selective Serotonin Reuptake Inhibitors (SSRIs) can be considered the first choice drugs for the treatment of IFN-α-induced depression, as demonstrated in open label studies, case reports and a randomized, double-blind, placebo-controlled trial. Also 5-hydroxytryptophan (5-HTP) has been suggested to be effective as monotherapy or as augmentation of SSRI. Clinical cases show positive effects of tricyclics, however, they do not provide sufficient evidence for the use of these drugs. Results of two cohort studies have reporteted the effectiveness of amisulpiride, but not of levosulpiride. Mirtazapine has been demonstrated to be a better choice of treatment in those cases where insomnia or anorexia are developed. Milnacipram can be particularly useful in cases of concomitant medications for other co-morbidities, because the occurence of drug-drug interactions are extremely unlikely with that drug. Psycho-stimulants represent an empirical treatment without controlled data to support their use, however, they may offer an alternative approach in treatment-resistant cases. Only two case reports have shown the favorable use of bupropione, in particular if sexual dysfunction or craving for illicit drugs are present. When depressive symptoms are severe and antidepressants are ineffective or poorly tolerated, ECT becomes a possible choice, but there was only a case report to confirm these findings. Conclusions: We have highlighted the risks and benefits of various antidepressants, assessing side-effect and drug-drug interactions. We have also evaluated the evidence for the efficacy of other alternative treatment options. Our observations may help clinicians with managing IFN-a-induced depression. Furthermore we have emphazised needs for new studies in both verify the existing findings and identifying new treatment options.

MA20

THE EFFICACY OF MIFEPRISTONE IN BIPOLAR DEPRESSION- EFFECT ON MOOD SYMPTOMS

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Hypothalamic-pituitary-adrenal axis dysregulation is implicated in the pathophysiology of mood disorders and the rationale for developing novel treatment strategies using antiglucocorticoid techniques is supported by a Cochrane review (Gallagher et al 2008 Cochrane Database Syst Rev). We have previously shown, in a random-order cross-over design placebo controlled pilot study, that 600mg daily of the glucocorticoid receptor antagonist, mifepristone taken for a week improved neuropsychological performance, including spatial working memory, verbal fluency and spatial recognition memory. We also measured mood using the MADRS a week after the end of treatment and showed an improvement from baseline which was not seen after placebo treatment (Young et al 2004 Neuropsychopharmacology 29; 1538-45). We now report on mood symptoms from a parallel group, placebo controlled study of mifepristone. 50 patients (27 male) from the North East of England or Christchurch, New Zealand who fulfilled SCID criteria for bipolar depression were randomised using a 6 block design to receive treatment with 600mg mifepristone daily or placebo. Outcome measures consisted of neuropsychological performance, neuroendocrine function and mood. Patients had 8 clinical assessment visits and the MADRS was completed at each. Visits were weekly for the first 6 weeks then fortnightly. Trial medication was commenced after visit 3. Preliminary LOCF ITT analysis of the MADRS score using a repeated measures ANOVA with time as the within subject variable revealed an effect of time ($F=14.2$; $df=7,336$; $P<0.0005$) but not an effect of treatment nor a time x treatment interaction. In this study there was an average improvement in depression scores which was independent of treatment allocation. This finding differs from our pilot study (Young et al, 1994) in which the improvement was seen only in those patients receiving active treatment. This difference may reflect the different designs of the two studies (crossover vs parallel) or differences in the population. The criteria for inclusion in the pilot study included bipolar disorder with treatment resistant depressive symptoms and in this study a DSM-IV diagnosis of bipolar depression. Consequently there were a greater proportion of patients recruited from tertiary care for the pilot study and the placebo response may have been minimised. The failure to separate patients from controls may also have been a pharmacokinetic/dosage effect. In unipolar psychotic depression, Schatzberg and colleagues have shown greater efficacy at 1200mg and shown that patients with higher plasma drug levels are more likely to respond (Blasey et al 2009 Contemp Clin Trials 30; 284-8). Gallagher P et al 2008 Cochrane Database Syst Rev Young AH et al 2004 Neuropsychopharmacology 29; 1538-45 Blasey CM et al 2009 Contemp Clin Trials 30; 284-8

MA21

LONG TERM SYMPTOMATIC AND FUNCTIONAL OUTCOME FOLLOWING MULTIMODAL TREATMENT FOR RESISTANT AFFECTIVE DISORDERS

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Introduction: Little research exists regarding the longer-term outcome of treating patients with previously treatment-resistant depression. We recently demonstrated significant benefits in the short-term after a period of individualised, multimodal treatment in a specialist inpatient unit (Wooderson et al. 2011, Journal of Affective Disorders, 131, 92-103). Here we report on the long-term outcome of this treatment. Methods: Patients were followed-up between 8-81 months (median 33 months) after discharge from a specialist Affective Disorders Unit. Clinical outcome was assessed prospectively using the Hamilton Rating Scale for Depression (HRSD) administered at admission, discharge and follow-up. Functional and quality of life data were also collected at follow-up. In this report we focus on 88 patients who had received a period of intensive, multimodal inpatient treatment of at least 6 weeks. Results: In the total group (n=88), HRSD scores progressively declined from admission (median 21, IQR 17-25) through discharge (median 12, IQR 7-16) to follow-up (median 9, IQR 4-18): admission v discharge and admission v follow-up both $p<0.001$. The change in HRSD was larger in those with bipolar disorder (n=22; 20, 7 and 8) than those with unipolar disorder (n=59; 21, 12, 11). At follow-up, a good outcome (very much or much improved on the Clinical Global Impression (CGI) scale) was maintained in 82% of bipolars and 63% of unipolars, whilst 14% and 22% respectively showed a poor outcome (no change or worse on CGI). The remainder showed an intermediate outcome (slightly improved on CGI). Scores on the Global Assessment of Functioning scale improved from a median of 65 (60-70) at discharge to 75 (60-80) in bipolar and 71 (60-80) in unipolar patients at follow-up ($p<0.05$). Conclusions: Treatment gains from specialist inpatient treatment are maintained in the medium to long term, and patients show some continued symptomatic and functional improvement after discharge. Sources of financial sponsorship: This research was supported by the NIHR Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust and the Institute of Psychiatry (King's College London); the NIHR had no further role in the study design; in the collection, analysis and interpretation of data or in the writing of the abstract.

MA22

A PROSPECTIVE STUDY OF THE EFFECT OF SOCIAL SUPPORT IN TREATMENT-RESISTANT DEPRESSION

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Introduction: Previous research suggests social support may have a strong influence on the clinical outcomes of those with depression. Good social support has been suggested to act as a buffer against depression (Krantz, S.E. & Moos, R.H., 1988, Journal of Consulting and Clinical Psychology, 56, 863-869) and also have a protective function against the recurrence of depression in both unipolar (Moos, R.H. 1990, Journal of Nervous and Mental Diseases, 78, 105-112) and bipolar patients (Weinstock, L.M. & Miller, I.W. 2010, Comprehensive psychiatry, 51, 497 – 503). Furthermore, lack of social support during depressive episodes has been reported to predict poor outcome of treatment (Paykel, E.S, 1994, Acta Psychiatrica Scandinavica Supplementum, 377, 50-58). Social support for patients with treatment-resistant depression has been little researched.
Methods: We aimed to study prospectively the relationship between social support at baseline with outcome of depressive symptoms at follow-up, in a sample of 49 subjects with a history of inpatient treatment for TRD. Depression symptoms and social support were measured at baseline and follow-up using the 21-item HAM-D and the self-rated Oslo-3 Support Scale respectively. The latter scale measures; number of close confidents, amount of concern shown by others and ease of gaining practical help from neighbours. Individual item scores were totalled, with higher scores representing greater social support. Group comparisons for demographic and clinical variables were conducted using t-tests and chi-square comparisons for ordinal and categorical variables, respectively.
Results: N = 34 subjects had previously received a diagnosis of unipolar depression, n = 11 bipolar depression and n = 4 depression secondary to other diagnoses. The median period of time between baseline and follow-up was 22 months (IQR = 20 – 24.5). At follow-up, n = 26 subjects had either remained the same or improved with regards to their HAM-D score ('good outcome'), whilst n = 23 subjects had declined ('poor outcome'). There were no significant differences in: the number of months between the two time points, baseline relationship status or chronicity of illness between the outcome groups. Baseline HAM-D scores were significantly higher in the good outcome group, compared to the poor outcome group (15.4 v 9.2, t = 2.6, p = 0.014). Multiple regression analysis showed that greater levels of social support at baseline significantly predicted good outcome, independently of baseline depression severity (OR 1.32, p = 0.039).
Conclusions: These findings suggest that greater levels of social support at baseline predict good outcome in depressive symptoms, for subjects with a history of TRD. Interventions to improve social support may therefore be helpful in improving prognosis for these patients. This research was supported by the NIHR Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust and the Institute of Psychiatry (King's College London); the NIHR had no further role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

MA23

REDUCED SALT AND SUGAR TASTE THRESHOLDS IN SEVERE TREATMENT RESISTANT DEPRESSION: PRELIMINARY FINDINGS- A POSSIBLE BIOMARKER?

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Reduced appetite is a recognised symptom of major depressive disorder and patients often report that food has no taste. This may arise from altered serotonin and noradrenaline levels, at the level of the taste receptor cell or in the brain taste transmission pathways. We investigated whether objective taste thresholds are significantly altered in patients with treatment resistant depression. We recruited 12 patients (6 female; average age: 51) attending a tertiary psychopharmacology clinic. Major depressive disorder was diagnosed using the MINI. Two were excluded due to incomplete data sets. Patients had MADRS and HAM-D scores in the moderate to severe range (MADRS 18-35; mean 28; HAM-D 12-20 mean 18) and were on many different antidepressant medications (SSRIs, SNRIs, MAOIs etc.). Taste recognition thresholds for sweet and salt were determined at the front of the tongue using standard protocols; solute concentrations of 0.3-100mM were applied in a pseudorandom order, in a single blind design. Positive responses at each concentration were recorded until five negative (low concentration) and five positive (high concentration) responses were obtained for each taste. Taste function curves were calculated. Intensity and pleasantness of concentrated (1M) solutions were also measured in each subject. The taste functions were pooled for analysis against our cohort of healthy volunteers (n=49). Compared with the healthy controls, depressed patients had significantly blunted sucrose and salt thresholds. Healthy vs. depressed: Sweet: 31mM (11-42 interquartile range) vs. 65mM (53-334) p=0.0003, Salt: 21mM (12-34) vs. 88mM (31-330) p=0.0011. Perceived intensity of 1M of salt was increased in depressed patients (41mm (21-73) vs. 73 (55-81) on a 150mm scale, p=0.02) but there was no difference in pleasantness nor any difference in intensity and pleasantness for 1M Sucrose. These data show that severely depressed patients, who have not recovered, have significant blunting of their taste thresholds. We believe this is due to illness rather than treatment - we have previously shown that antidepressants can differentially increase taste sensitivity in healthy volunteers – for example an SSRI and a NARI antidepressant significantly lower the threshold for bitter, sour and sweet tastes to different degrees but not salt (Health et al., 2006, J Neurosciences 26(49) 12664-71) and sweet taste threshold is lowered after light therapy (Srivastava et al., 2010, J Psychopharmacology 24(S3) A24). Thus taste thresholds may represent a biomarker for depression which is not altered by concomitant therapy and merits further investigation.

MA24

HYPOCORTISOLISM IN CARERS IS ASSOCIATED WITH POOR OUTCOME IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION

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Introduction: Carers of patients with psychiatric disorders show high levels of anxiety and depression, and physiological change involving the hypothalamo-pituitary-adrenal (HPA) axis, a proposed mechanism whereby environmental stress can lead to mental illness (Da Roza Davis, JM, Cowen, PJ (2001). Psychological Medicine 31, 1475-8). Amongst carers of patients with treatment-resistant depression (TRD), we set out to determine the psychological and physiological consequences of caring, and the association of these consequences with long-term outcome in patients.
Methods: 35 informal carers of patients with severe TRD requiring inpatient treatment were recruited and compared with 23 non-caring controls matched for socio-demographic factors. HPA-axis activity was assessed using the cortisol awakening response (CAR) by collecting repeat saliva samples on waking. Repeat cortisol levels were analysed using the trapezoidal method to give area under the curve with respect to ground (AUCg). The Involvement Evaluation Questionnaire and General Health Questionnaire were administered to measure carer burden and psychiatric caseness respectively. Independent t-tests were used to compare differences between carers and controls and a linear regression model was used to determine the association of CAR with carer status whilst controlling for confounding variables. Data on long-term patient outcome, measured using the Hamilton Depression Rating Scale, were also obtained and linear regression was used to determine the association between CAR in carers and remission status in patients. Results: 34% of carers met criteria for psychiatric caseness on the GHQ, compared with 4% of controls ($\chi 2$=7.2, p=0.009). Carers showed an impaired CAR as indicated by their lower AUCg (20.6 nmol/L.h, SD=7.8) than controls (26.0 nmol/L.h, SD=9.7, t=2.34, df=56, p=0.023). Caring was independently associated with AUCg after controlling for potential confounders (ß= -0.360, SE=2.4, p=0.010). Within the carer group, reduced AUCg was associated with non-remission of TRD in patients (ß= -0.354, SE=2.59, p=0.044). Conclusions: Caring for patients with TRD is associated with adverse psychological and physiological changes suggesting hypocortisolism (Fries, E, Hesse, J, Hellhammer, J, Hellhammer, DH (2005). 30, 1010-6). These changes are associated with poor patient outcome. Longitudinal studies are required in order to confirm the direction of this association, but if carer stress does indeed influence patient outcome, then interventions to reduce this could be important in the management of TRD. Such interventions may also benefit the carers themselves and should be the subject of future research.
The study was supported by the NIHR Biomedical Research Centre at South London and Maudsley NHS Trust & Institute of Psychiatry (King's College London) and the Institute of Social Psychiatry.

MA25

THE CAR (CORTISOL AWAKENING RESPONSE) IN TREATMENT RESISTANT UNIPOLAR AND BIPOLAR DEPRESSION

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Introduction: Hypothalamic-pituitary-adrenal (HPA) axis dysfunction is found in some patients with depression, with preliminary evidence that it is especially prevalent in patients with Treatment Resistant Unipolar Depression (TRUD). A naturalistic measure of HPA axis activity is the Cortisol Awakening Response (CAR); although found to be elevated in depression, it has yet to be studied specifically in TRUD. Furthermore the CAR has never been measured in Bipolar Depression. In this study the aim was to measure the CAR in saliva in patients with TRUD and Treatment Resistant Bipolar Depression (TRBD) in comparison to healthy controls.
Methods: The CAR was measured in saliva in 31 patients (23 females and 8 males) with a primary diagnosis of unipolar TRD, 14 patients (8 females and 6 males) with TRBD and 43 controls matched for age, gender, weight, body mass index and menstrual history over 2 consecutive days. The Hamilton 21 Item Rating Scale was used to rate the degree of depression; a cut off score of 17 was an essential criterion for inclusion in this study. Salivary cortisol was collected using the drooling method. Adherence to the protocol was closely monitored and subjects were asked to use forms and note their collection times. Non adherence to the time protocol by 15 mins or more resulted in exclusion from the sample.
Results: The CAR, as measured by the Area under the curve (AUCg) was higher in patients with TRUD compared to controls (mean±SD Day 1 23.2±9.3 vs 18.8±7.2 nmol/l.h, p=0.02; mean of 2 days 23.1±8.6 vs 18.3±6.5 nmol/l.h, p=0.01). On the contrary in subjects with TRBD the AUCg was lower compared to controls (mean±SD Day 1 14.2±5.4 vs 18.8±7.2 nmol/l.h, p=0.03; mean of 2 days 15.0±5.1 vs 18.3±6.5 nmol/l.h, p=0.07). Subjects with TRUD had a higher AUCg compared to subjects with TRBD (mean of 2 days 23.1±8.6 vs 15.0±5.1 nmol/l.h, p=0.002).
Conclusions: There is a heightened CAR in TRUD, a finding reported previously by ourselves. However in this study we also show that subjects with TRBD have the opposite pattern, i.e. a reduced secretion of cortisol following awakening. This attests to a fundamental biological distinction between Unipolar and Bipolar Depression, the former characterised by hypercortisolism and the latter by hypocortisolism. This previously unreported finding has potentially important implications in the understanding and treatment of Bipolar Depression and in differentiating the two types of depression.
This work was supported NIHR Biomedical Research Centre at South London and Maudsley NHS Trust & Institute of Psychiatry (King's College London)

MA26

A LONGITUDINAL STUDY OF TREATMENT-RESISTANT DEPRESSION: REMISSION, RECOVERY AND EPISODE PERSISTENCE

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Introduction: Systematic studies on the longitudinal outcome of treatment-resistant depression (TRD) are scarce. We aimed to assess the longitudinal outcome of TRD, and predictors of good and poor outcomes.
Methods: 118 participants with confirmed TRD (77 cases with unipolar, 27 with bipolar and 14 with secondary TRD) were followed up for a mean (SD) duration of 39 (20) months. Longitudinal outcomes were obtained for every month of follow-up using the Longitudinal Interval Follow-up Evaluation (LIFE) chart. Outcomes were operationalised into: sustained recovery; remission; subsyndromal depression; depressive episode, and (for bipolar patients) subsyndromal mania and manic/mixed episode. The association of potential risk factors with these outcomes was assessed, primarily for unipolar TRD.
Results: Most participants had achieved either sustained recovery (48%) or remission (12%), while a substantial minority suffered persistent subsyndromal depression (20%) or persistent depressive episode (20%). For unipolar TRD, achieving remission or recovery was predicted by strong social support (OR; 95% CI=1.90; 1.12, 3.22), particularly having multiple confidants (OR; 95% CI=3.79; 1.06, 13.47) and supportive neighbours (OR; 95% CI=4.05; 1.30, 12.65). Social support also predicted recovery in bipolar TRD. The main independent predictor for persistence of depressive episode was baseline symptom severity.
Conclusions: 1) A large proportion of cases with TRD continue to experience a significant level of persistent symptomatology; thus, more effort is required to improve the longer-term prospect of patients with TRD; 2) The study confirms the important role of social support in TRD and suggests that interventions designed to increase support should be part of the management of TRD; 3) Outcome predictors in TRD are similar to that of major depression in general. This supports the view that TRD forms part of the spectrum of general depressive disorder rather than representing a unique condition.

MA27

ACUTE EFFECTS OF HIGH DOSE HYDROCORTISONE ON SLEEP IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION: A DOUBLE BLIND PLACEBO CONTROLLED STUDY.

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Up to a third of people with major depressive disorders do not respond to concerted therapeutic efforts and there is a dearth of novel therapeutic interventions. Treatment resistance is associated with HPA axis dysregulation in depression and there is some evidence that a short course of high dose steroids may be sufficient to trigger a beneficial response in people who have treatment-resistant depression and who are on 'standard' antidepressant treatment (Goodwin et al 1992 J.Affect.Disord. 26: 73-83). Sleep disturbance in depression also may be related to HPA dysregulation; disrupted sleep continuity as well as decrease in both REM latency and slow wave sleep in the first cycle may reflect HPA abnormal function at central mineralocorticoid and glucocorticoid receptors. Ten patients (age 45-71 mean 54.3, 5F) with DSM-IV major depression took part in a double-blind randomized controlled study of the effects of 7mg/kg hydrocortisone (HCORT) IV or placebo given at approximately 15:00 on 3 consecutive days. They were not responding to their current treatment and had failed at least two treatments in the current episode. Mean MADRS at baseline was 28. Sleep was measured using home polysomnography and subjective questionnaires at baseline, on the third day, and at 4 weeks. Current drug treatment continued unchanged throughout the study. One person remitted on active treatment and none on placebo. There were no significant differences between baseline and day 3, or between groups on any of the sleep measures. However the baseline sleep measures showed a very wide variation, depending on whether the patients were taking a REM-suppressing antidepressant (eg SSRI, MAOI) or a drug that is known to increase slow wave sleep (eg trazodone, mirtazapine). In the 3 patients in the HCORT group not taking REM-suppressing drugs, REM sleep was reduced on the HCORT day (Pt A baseline 126, HCORT 50min, Pt B baseline 105, HCORT 49min, Pt C baseline 152, HCORT 90min, which is similar to our healthy volunteer study differences (mean baseline 116, HCORT 58). There were no changes in sleep latency, REM onset or slow wave sleep. This is a very small sample, as is typical of such complex studies in this group with resistant depression. Total REM sleep changes, observed in healthy volunteers, were only observed in patients who were not taking REM suppressing antidepressants. We are grateful to the James Tudor foundation for supporting this study.

MA28

MR AND GR FUNCTION, BUT NOT ONLY GR, PREDICTS OUTCOME IN TREATMENT RESISTANT DEPRESSION

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Introduction: It has been replicated that in the depressive episode hypothalamic-pituitary-adrenal (HPA) axis hyperactivity progressively normalizes alongside treatment and precedes the resolution of depressive psychopathology[1].Therefore, the improvement of altered HPA axis function during treatment could predict response or non-response to treatment. We propose a suppressive test using prednisolone, a synthetic glucocorticoid that is similar to cortisol in its pharmacodynamics and pharmacokinetics and compared two synthetic glucorticoids, dexamethasone and prednisolone, in their ability to suppress the HPA axis in depressed patients.Dexamethasone probes glucocorticoid receptor (GR) function, while prednisolone probes both GR and mineralocorticoid receptor (MR) function.[2]. The purpose of this study is to compare whether a Treatment Resistant Depression (TRD) patient's response to dexamethasone and prednisolone suppression test shortly after admission was predictive of the subsequent responsiveness of inpatient treatment of their depression[3]. Second, we wished to test whether the additional effect of prednisolone on the MR could lead to a different suppressive response compared with dexamethasone.
Methods: We recruited 2 groups: (a)TRD patients, (b) controls. We compared the effects of placebo (AUCPLACEBO), prednisolone (AUCPRED) and dexamethasone (AUCDEX) on salivary cortisol secretion on 9:00 to 17:00 h in TRD inpatients on admission, prior to intensive treatment. and controls. Responders and non-responders to treatment were defined by reduction of HAMD- 21 score of at least 50%. After treatment, before discharge, the patients were again assessed.
Results: There was a significant difference in the AUC PRED on admission between those who subsequently responded to treatment and those who did not [responders 21.1 (3.2) vs. nonresponders 47.3 (9.5) nmol X h/L: $p = 0.026$]. On the other hand,the comparison of AUC PLACEBO and AUCDEX did not show a significant difference between subsequent treatment responders vs.non-responders [54.5(13.5) vs. 76.3 (8.2) nmol X h/L: $p = 0.19$] and [19.2 (11.4) vs. 39.9 (11.8) nmol X h/L: $p = 0.22$], respectively. Conclusions: The prednisolone suppression test on admission predicts the clinical outcome on discharge and distinguishes between subsequent treatment responders and non-responders, with more abnormal responses (i.e. less suppression to prednisolone) predicting a poorer response to treatment.in TRD patients. Moreover, these data suggest that the prednisolone test is a sensitive state marker to monitor HPA axis dysregulation in depression, and normalization is associated with increased likelihood of a clinical response to treatment.

MA29

COMBINATION OF STRESS AND CENTRAL 5-HT DEPLETION PROMOTES A DEPRESSION RELATED PHENOTYPE IN A PUTATIVE MODEL OF TREATMENT RESISTANT DEPRESSION

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There is a need for new antidepressants on account of treatment resistance to conventional antidepressants in a proportion of depressed patients. In this regard animal models may be employed to determine new leads for antidepressant activity. In our laboratory we have combined a depression-inducing factor, immobilisation stress, with a vulnerability factor for treatment resistance, central 5-HT depletion, to develop an animal model resistant to conventional antidepressant treatment. Male Sprague Dawley rats (n=8-10 per group) were treated once daily for three consecutive days with DL-4-chlorophenylalanine (pCPA, 150 mg/kg, i.p.), a tryptophan hydroxylase inhibitor, in order to achieve central 5-HT depletion. 48 hours following the final treatment of pCPA, the animals were subjected to immobilisation stress for 2 hours per day for three consecutive days. 24 hours following the cessation of stress, the animals were exposed to the forced swimming test (FST) comprising a 15 minute acclimatization period on day 1 and a 5 minute test on day 2 when immobility behaviour, defined as the absence of escape oriented behaviour, was scored. Neither pCPA treatment nor immobilisation stress alone influenced immobility time in the FST. Combination of pCPA with immobilisation stress however provoked an increase in immobility time compared to either treatment alone and to vehicle and stress free control groups. The novel antidepressants ketamine (25 mg/kg, i.p.) or L-NA (10 mg/kg, i.p.) were subsequently tested by treating the animals 1 hour prior to the onset of each session of immobilisation stress. Doses of these agents were selected based on their ability to provoke an acute antidepressant-like action in the rat FST. Neither agent reduced the increase in immobility induced by pCPA in combination with immobilisation stress suggesting that both compounds are dependent on an intact 5-HTergic system to produce an antidepressant response. Typically pCPA treated animals showed a 60% depletion of cortical 5-HT concentrations. In addition both ketamine and L-NA increased cortical 5-HT concentrations in non pCPA treated animals consistent with a modulatory action of these agents on central 5-HT neuronal transmission. In conclusion, immobilisation stress coupled with central 5-HT depletion promotes a depression related phenotype. The novel antidepressants ketamine and L-NA fail to reverse this behaviour consistent with a role for 5-HT in their antidepressant activity. This proposed model of treatment resistant depression may prove useful in testing for new antidepressants effective against treatment non responsive depression.
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MB01

GENDER DIFFERENCES IN COMMONLY-USED BEHAVIOURAL PHARMACOLOGY TESTS

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Behavioural pharmacology relies on animal models which are primarily validated using the male laboratory rat. Despite growing evidence of sex differences, many researchers only employ male animals in studies; this is primarily due to females' oestrous cycle variations. The objective of the present study therefore was to examine whether gender has any effect in some commonly employed behavioural pharmacology tests. Male and female Sprague Dawley (SD) rats (n=48) were examined in the following behavioural pharmacology tests: Desipramine (DMI: 0, 2.5, 5, 10mg/kg i.p. 3 times over 24 h) on immobility time in the forced swim test (FST); Diazepam (DZP: 0, 0.625, 1.25, 2.5 mg/kg i.p. 30 min prior to test) on anxiolytic behaviour in the elevated plus maze (EPM); Amphetamine (AMP: 0, 0.2, 0.5, 1.0, 2.0, 5.0 mg/kg s.c. immediately prior to test) on locomotor activity in the homecage monitoring apparatus (HCMA). A counter-balanced design was employed, eliminating any effects of day or time on behaviours. In the case of female rats, testing over a number of days ought to resolve any variations in behaviours as a result of the oestrous cycle. Data was analysed using 2-way ANOVAs and appropriate post-hoc tests, using the significance level $p < 0.05$. Females were more active than males in all three tests. A significant reduction in immobility time with DMI was found for males in the FST at 5mg/kg ($p < 0.05$), with no effect observed in females. The control females' low baseline contributed to the lack of a DMI dose-response effect. Similarly DZP (1.25 mg) increased open arm time and open arm entries (both $p < 0.05$) for males but not for females. The absence of drug effect for females is again due to their higher baseline open arm time and entries. There was a significant effect of AMP dose on distance moved for both sexes ($p < 0.001$). The peak locomotor stimulating effects in males were seen at the 1-2 mg/kg AMP dose levels, whilst in females a dose of 0.5 mg/kg produced the greatest effect. Given the females' absence of drug responses in the EPM and FST due to altered baseline behaviours the suitability of including female rats in such tests must be re-evaluated. Thus behavioural tests must be designed to account for gender differences in baseline behaviours to allow for unambiguous extrapolation of the results.

MB02

USING VIRAL VECTOR-MEDIATED GENE TRANSFER TO TARGET SPECIFIC NEUROCHEMICAL PATHWAYS IN VIVO

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Viral vectors are modified viruses used as a tool to transfer genetic material into a target cell. The popularity of using viral vectors has increased due to their highly versatile nature in targeting specific brain regions and particular cell types within that region. Since the viral genome has no self-replicating abilities, the use of viral vectors represents a safe method to modify gene expression in the brain. Animal investigations into neurochemical pathways have traditionally employed lesion studies (i.e. loss of function), systemic drug delivery paradigms, and targeted drug infusions directly into the brain regions of interest. Using viral vectors, with cell-type specific promoters, it is possible to target neurones in vivo based on the neurotransmitters they synthesise, and to modulate their function without inducing cell loss. In the present study, we investigated the efficacy and selectivity of gene transfection targeted to the adult rat (Male, Wistar, 250g) medial prefrontal cortex (mPFC), using adeno- and lentiviral vectors (10^9 TU/ml). The viral vectors contained cell-type specific promoters to restrict the expression of green fluorescent protein (GFP) to neuronal cells (Supersynapsin); glutamatergic neurones (CamKII); and GABAergic neurones (GAD). Transfection efficiency and cell specificity were assessed using immunohistochemistry and fluorescence microscopy. Our results show that in the rodent mPFC, lentiviral vectors with either the Supersynapsin promoter or the CamKII promoter, produced stable GFP expressing neurones for up to 4 weeks in vivo. The neuronal specificity of the Supersynapsin and CamKII promoters was confirmed, with the CamKII promoter conferring further specificity to a glutamatergic phenotype. The adenoviral vector with a GAD promoter, was found to transduce very few neurones that could be visualised 4 weeks post viral injection, and were not specific to a GABAergic phenotype. These studies have shown that lentiviral vectors with either a Supersynapsin or CamKII promoter will specifically target neuronal cells in the adult rat mPFC, and the CamKII promoter can provide further selectivity through targeted expression in glutamatergic neurones. The adenoviral vector with a GAD promoter lacked both transfection efficiency and cell specificity in the adult rat prefrontal cortex.
This work was funded by the Wellcome Trust.

MB03

CONSEQUENCES OF IN UTERO EXPOSURE TO FLUOXETINE ON ADULT BEHAVIOUR IN THE RAT

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The prevalence of depression during pregnancy has been estimated at 10-18%. Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine are often used to treat depression in this clinical scenario, due to their perceived low side-effect profile. However, as fluoxetine can cross the placenta, effects on the offspring, which may manifest behaviourally later in life, cannot be ruled out. As controlled studies of such effects cannot be carried out in humans for logistical and ethical reasons, animal models may provide a useful alternative in this area of research. The present study investigates the effect of in utero fluoxetine exposure, through maternal administration during gestation, on adult behaviour of male and female offspring. Pregnant Sprague-Dawley female rats (n=6-8/group) received vehicle (distilled water) or fluoxetine (5mg/kg) by oral gavage from gestational days 7-21. Locomotor activity in the open field (OF) and anxiety-like behaviour in the elevated plus maze (EPM) of separate offspring groups (n=6/group) were examined at 8, 12 or 16 weeks of age. Recognition memory in the novel object recognition (NOR) test was measured at 14 weeks of age. Data were analysed using Two-Way ANOVAs with Student-Newman-Keuls Post-Hocs where appropriate with $p<0.05$ considered statistically significant. At 16 weeks, there were significant effects of sex in both the EPM and OF. In the EPM, females displayed higher percentage open arm time, an inverse measure of anxiety, as well as higher locomotor activity in the OF. There was a decrease in percentage open arm time in the EPM following in utero fluoxetine exposure in males only at 8 weeks and overall at 12 weeks, with no effects at 16 weeks. In the OF, locomotor activity was unaffected by drug exposure at any timepoint. There was also no effect of in utero fluoxetine exposure on novel discrimination ratio in the NOR. In conclusion, prenatal fluoxetine exposure led to a transient increase in anxiety-like behaviour, as measured by the EPM, in adulthood, without affecting locomotor activity, learning or memory. The anxiogenic effects observed are similar to those seen following neonatal clomipramine administration, a well-established rodent model of depression (Andersen et al., 2002, Developmental Psychobiology, 41(1):50-57). These results suggest that manipulation of the serotonergic system during a critical period of neuronal development, in rodent models, leads to transient effects on anxiety-like behaviours in adulthood. Post-mortem investigations are necessary to determine the mechanisms by which these effects may occur.
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MB04

THE NK1 RECEPTOR ANTAGONIST RP 67580 INDUCES IMPULSIVITY IN WILD TYPE MICE TESTED IN THE 5-CHOICE SERIAL REACTION TIME TASK

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The neurokinin-1 receptor knock-out (NK1R-/-) mouse is a model of Attention Deficit Hyperactivity Disorder (ADHD). We have reported that NK1R-/- mice show inattentiveness, impulsivity and perseveration in the 5-Choice Serial Reaction Time Task (5-CSRTT) (Yan et al., 2011, PLoS ONE, 6: e17586). Here we tested whether these behavioural deficits are replicated in wild-type mice treated with an NK1R antagonist (RP 67580 or L 733060). Male wild-type and NK1R-/- mice (129/SvXC57BL/6 crossed with an outbred MF1 strain, N=12) were trained to criterion in the 5-CSRTT, as described in Oliver et al. (2009, Psychopharmacology, 204, 679-692). They were then tested with a long, and a variable, inter-trial interval (LITI: 7s; VITI: 2, 5, 10 and 15s). All animals were given an i.p. injection of saline, RP 67580 or L 733060 (5 and 10mg/kg), or no injection (NI). The sequence of these six test conditions was randomised, with each being tested once in every mouse at weekly intervals. Data were analysed with a repeated-measures ANOVA. At the lower dose of RP 67580, wild-type mice showed an increase in premature responses in the VITI ($t(10) = 2.77$, $p<0.05$), but there were no effects on omissions or perseveration. Overall, the high dose of RP 67580 blunted responding in the test: in both genotypes there was an increase in omissions ($F(2,40) = 8.48$, $P < 0.001$) and a decrease in premature responses ($F(2, 40) = 7.56$, $P < 0.01$), as well as an increase in the latencies to respond and to collect the reward. However, perseveration remained consistently greater in NK1R-/- mice than wild-types ($F(1, 20) = 4.52$, $P < 0.05$). There was no effect of L 733060 on any of these behaviours. The lower dose of RP 67580 mimicked the increase in premature responses (an index of impulsivity) reported in NK1R-/- mice. The failure to replicate the increase in omissions (an index of inattention) and perseverative responses suggests i) early intervention with antagonist during training is required to replicate all deficits seen in NK1R-/- mice or ii) these behaviours are not directly mediated by NK1R. At high doses, RP 67580 blunted responses in both genotypes, suggesting drug effects unrelated to antagonism of NK1R. Finally, the absence of effect of L 733060 may reflect a lower affinity for NK1 receptors than RP 67580 in mice. These results show that a lack of NK1R function induces impulsive behaviour in wild-type mice.

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MB05

LOCAL APPLICATION OF A D-AMINO ACID OXIDASE (DAO) INHIBITOR IN THE VENTRAL TEGMENTAL AREA INCREASES EXTRACELLULAR DOPAMINE IN THE RAT PREFRONTAL CORTEX IN VIVO

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D-amino acid oxidase (DAO) is the metabolising enzyme of D-serine, a major endogenous co-agonist at the glycine site of the N-methyl D-aspartate (NMDA) receptor. Dopamine (DA) output from the ventral tegmental area (VTA) is modulated by NMDA receptors. DAO inhibition may therefore indirectly enhance NMDA receptor activation in the VTA and consequently alter mesocortical DA output. Such effects may be relevant to the development of DAO inhibitors, and D-serine, as potential treatments for schizophrenia and other neuropsychiatric disorders. We have previously shown that systemic DAO inhibition increases cortical dopamine release (Betts et al, in preparation), but the locus of effect was not known. First, double-labelling immunofluorescence was employed to investigate the potential expression of DAO in the VTA, using antibodies against DAO and tyrosine hydroxylase (TH; a marker of dopamine neurons). Second, a single injection of sodium benzoate (a DAO inhibitor; 200µg/µl) or vehicle was administered into the VTA of anaesthetised male Sprague-Dawley rats. In vivo microdialysis and high-performance liquid chromatography (HPLC) were used to measure levels of DA and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in the medial prefrontal cortex (mPFC). mPFC measurements continued for 2 hours post-injection. Data were analysed using a repeated measures ANOVA. Probe placements were confirmed histologically. DAO immunoreactivity was seen in many TH-positive neurons in the VTA, as well as in some other cell types. A significant increase in extracellular levels of DA was observed in the mPFC following intra-VTA SB injection (n=4), when compared with vehicle (n=5). Levels peaked 40 minutes after SB administration (59% increase) and remained elevated for a further 40 minutes ($p<0.05$). There were also sustained increases in levels of DOPAC and HVA (maximum increase 105% and 72%, respectively, $p<0.05$). These data support the hypothesis that inhibition of DAO in the VTA enhances activation of mesocortical DA neurons, presumably via increasing D-serine availability and thereby NMDA receptor-mediated signalling. Ongoing studies using intra-VTA administration of D-serine itself will further explore this hypothesis.

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MB06

REPEATED TESTING MODIFIES COGNITIVE PERFORMANCE OF NK1R+/+ AND NK1R-/- MICE IN THE 5-CHOICE SERIAL REACTION-TIME TASK

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Previously, we found that mice lacking functional substance P-preferring NK1 receptors (NK1R-/-) display impulsivity and inattentiveness in the 5-Choice Serial Reaction-Time Task (5-CSRTT) (Yan et al, 2011, PLoS ONE 6: e17586) and are thought to model attention deficit hyperactivity disorder (ADHD). Here, we investigated whether deficits in the cognitive performance of NK1R-/- mice were still evident when the 5-CSRTT was repeated. Male NK1R+/+ and NK1R-/- mice (129/SvXC57BL/6 crossed with an outbred MF1 strain; N=11-12/genotype) were trained in the 5-CSRTT (Oliver et al, 2009, Psychopharmacology, 204: 679-692). The treatment-naïve mice were then tested using both a variable inter-trial interval (VITI, ITI=2-15s) and a long ITI (LITI, ITI=7s) schedule (NI-1). Once-weekly, thereafter, the two tests were randomised and each repeated twice (NI-2 and NI-3). Statistical analyses were carried out using repeated-measures ANOVA. When the LITI test was repeated, both NK1R+/+ and NK1R-/- mice showed a reduction in %omissions ($F(2, 38) = 6.1$, $P < 0.01$) and latency to correct response ($F(2, 37) = 5.4$, $P < 0.05$). Perseveration was increased in both genotypes in the VITI tests ($F(2, 35) = 7.4$, $P < 0.01$) and the pattern of change was similar in the LITI tests although it failed to reach statistical significance. Nevertheless, the genotype differences in these elements of cognitive performance still remained. Further, when repeating the LITI tests, %accuracy improved in NK1R-/- mice, only ($F(2, 37) = 3.4$, $P = 0.05$). There was no change in %premature response or latency to collect reward, and the latter measure was greater in NK1R-/- mice during NI-3, as in NI-1 ($F(1, 21) = 5.9$, $P < 0.05$). The pattern of changes in cognitive performance was similar when the VITI test was repeated, except for %premature response. This measure of impulsivity in NK1R-/- mice was prominent in the first VITI test, but disappeared when the test was repeated, due to a reduction in %premature response in the knockouts, only ($F(1, 30) = 9.8$, $P = 0.001$). The performance of both NK1R+/+ and NK1R-/- mice improved when rehearsing the 5-CSRTT. This finding indicates that, when investigating the effects of drugs using this test, task learning could be a confounding factor. However, NK1R-/- mice still displayed inattentiveness and perseveration even after their third experience of the tests. These results confirm the robustness of these deficits and consolidate NK1R-/- mice as a model of ADHD.

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MB07

THE SUB-CHRONIC PCP INDUCED DEFICITS IN NOVEL OBJECT RECOGNITION ARE SELECTIVELY ATTENUATED BY COGNITIVE ENHANCERS

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Introduction: We have consistently shown that sub-chronic phencyclidine (PCP) treatment in female hooded-Lister rats produces robust cognitive impairment in the NOR test which can be successfully reversed by atypical, but not classical antipsychotics and novel targets (Grayson et al., 2007, Behav Brain Res 184 (1); 31-38; McLean et al., 2011, Eur Neuropsychopharmacol 21; 333-343).
Aim: The aim of this study was to further validate the PCP model by identifying whether cognitive enhancers with a diverse pharmacology show efficacy in the NOR paradigm. Methods: Two cohorts of adult female hooded-Lister rats, cohort A; n=60 and cohort B; n=40 received either PCP (2mg/kg, i.p; n=80) or saline (0.9% NaCl i.p; n=20) twice per day for 7-days, followed by 7-days washout. Testing consisted of a 3min acquisition phase whereby rats explored two novel objects followed by a 1min ITI. In the retention trial, rats explore a familiar and a novel object for 3min. Data are expressed as the mean ± S.E.M. (n=8-10 per group) and analysed by ANOVA followed by post-hoc Student's test or Dunnett's t-test.
Results: There was no difference in exploration time (s) of the two familiar objects in the acquisition trial in any group. In the retention trial, vehicle treated rats spent significantly ($P<0.01$) more time (s) exploring the novel compared with familiar object. This effect was abolished in sub-chronic PCP-treated rats who lost the ability to discriminate the two objects and to recognise the familiar object. Fluphenazine (0.2 mg/kg), fluoxetine (5 mg/kg) and memantine (5 mg/kg) failed to attenuate the sub-chronic PCP-induced deficit, whereas risperidone (0.1mg/kg; $P<0.01$), modafinil (50 mg/kg; $P<0.05$) and tacrine (2.5 mg/kg; $P<0.01$) significantly reversed the cognitive impairment.
Conclusion: The atypical antipsychotic risperidone, analeptic agent modafinil and the acetylcholinesterase inhibitor, tacrine attenuated the PCP-induced recognition memory deficit whereas the classical antipsychotic fluphenazine, the SSRI fluoxetine and the NMDA antagonist memantine all failed to ameliorate the cognitive deficit. These data further validate the model, showing lack of efficacy of antidepressant and classical antipsychotic agents. Efficacy of cognitive enhancers with diverse pharmacology can be detected using this model thus strengthening its utility in the detection of novel targets to enhance cognition impaired in a variety of disorders.

MB08

SELECTIVE BLOCKADE OF DOPAMINE D3 VS D2 RECEPTORS ENHANCES NOVEL OBJECT RECOGNITION IN RATS: ROLE OF THE PREFRONTAL CORTEX.

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The dopaminergic system is involved in a diverse array of physiological processes including endocrine function, motor behaviour, emotion and cognitive function. There is growing evidence that dopamine D3 receptor antagonists have procognitive effects. This present study examines the role of prefrontal cortex (PFC) dopamine D2 and D3 receptors in a rodent model of cognition using selective ligands. Novel object recognition (NOR), a visual recognition task reliant on rats natural preference for novelty, was parametrically manipulated so that amnesic properties of drugs were assessed following short inter trial interval (ITI) delays (2min) while procognitive effects were examined using a delay-induced impairment (4h ITI). The systemic and local bilateral PFC application of the selective dopamine D2 antagonist, L741,626, the selective dopamine D3 antagonist, S33084, and the selective dopamine D3 agonist, PD128,907 were assessed on NOR. Male Lister Hooded rats received (n=12) received each dose or combination of drugs in a pseudorandom order over the course of 4 weeks. Object exploration data from the choice trial was analysed using repeated-measures ANOVA, while discrimination indices and total object exploration was analysed using ANOVA and appropriate post hoc tests. Acute treatment with both the selective D2 receptor antagonist, L741,626 (0.16-2.5mg/kg), and the dopamine D3 agonist, PD128,907 (0.63-10.0µg/kg), dose-dependently impaired performance in the NOR task following short ITI delays. Acute administration of the D3 antagonist, S33084 (0.04-0.16mg/kg), dose-dependently reversed delay-dependent impairment of performance in NOR. The reversal of the delay-induced impairment of NOR by S33084 (0.16mg/kg) was prevented by L741,626 (0.63mg/kg), while S33084 (0.16mg/kg) blocked the PD128,907 (2.5µg/kg) induced impairment of NOR with a short ITI. Bilateral PFC microinjection of S33084 dose–dependently (0.63-2.5µg/side) improved NOR. In contrast, bilateral PFC microinjection of L741,626 dose-dependently (0.63-5.0µg/side) impaired performance in NOR. These results provide further evidence that blockade of dopamine D3 receptors enhances cognitive function, while activation of the dopamine D3 receptor with agonists and blockade at the dopamine D2 receptor impair cognition. Furthermore, the microinjection studies suggest that dopamine D2 and D3 receptors located in the PFC have a role in modulating performance of NOR.
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MB09

TACRINE IMPROVES COMPOUND DISCRIMINATION REVERSAL LEARNING IN AGED RATS

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Age-related cognitive decline affects more than one psychological domain, reflecting changes in production and binding sites of neurotransmitters such as dopamine and serotonin. There is also an increased risk of developing neurodegenerative disorders such as Alzheimer's disease. Aged rats exhibit decline in cholinergic function and, like in humans and monkeys, they have age-related impairments in set-shifting and reversal learning. Elevation of frontal acetylcholine (ACh) via cholinesterase inhibitors has been used to treat attentional impairments in Alzheimer's disease patients, but there have been no reported attempts to investigate the effects of such treatments on age-related attentional set-shifting impairments. Aged male Lister hooded rats (n = 12; 16-19 months at start; 18-21 months at completion) were tested six times on the rodent ID/ED attentional set-shifting task (Birrell and Brown, 2000, J. Neurosci., 20(11), 4320-4324). The initial two tests recorded a baseline level of performance and investigated the validity of repeated testing in aged rats. For the remaining four tests each rat was administered (ip) either vehicle (saline) or one of three doses (0.1, 1 or 3mg/kg) of the cholinesterase inhibitor, tacrine. Each rat was tested once at each dose, with dose administration counterbalanced in a pseudo-latin square design. Trials to criterion data were analysed by repeated measures ANOVA. Performance did not differ between the first two tests, with rats repeatedly showing attentional set-shifting costs at the ED shift stage, demonstrating that aged rats can produce consistent data over multiple tests. Although there was no young control group, performance at reversal stages appeared worse than in previously observed normal young rats. Acute administration of tacrine at 3mg/kg improved performance at all reversal stages without effect on any other stage of the task. However, rats did not show formation of attentional set during tests three to six. Increasing central ACh improves compound discrimination reversal learning in aged rats. Given the uncertain role of cortical ACh in performance on the attentional set-shifting task (Chen et al, 2004, Eur. J. Neurosci., 20, 1081-1088; Tait and Brown, 2008, Behav. Brain Res., 187, 100-108), this may reflect changes in non-cortical function. ACh in the dorsomedial striatum mediates reversal learning (Ragozzino et al, 2002, Brain Res., 953, 205-214), and striatal cholinergic function changes in normal aged rats (Kurotani et al, 2003, Exp. Gerontol., 38, 1009-1013). We therefore suggest that increased availability of ACh in the dorsomedial striatum mediates improved reversal learning in aged rats.
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MB10

EFFICACY OF MODAFINIL AND NICOTINE, BUT NOT RISPERIDONE, TO IMPROVE OBJECT RECOGNITION MEMORY DEFICITS INDUCED BY A 6 HOUR INTER-TRIAL INTERVAL IN FEMALE RATS

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Introduction: Alzheimer's disease is a neurodegenerative disorder and the leading cause of dementia in the elderly. Acetylcholinesterase (AChE) inhibitors can improve symptoms in mild to moderate Alzheimer's disease and alleviate certain cognitive deficits in patients with schizophrenia when given as an adjunct to atypical antipsychotic treatment [Racchi et al., 2004, Pharmacological Research, 50: 441-451; Ribeiz et al., 2010, CNS Drugs, 24: 303-317]. We have recently shown that the AChE inhibitor, donepezil, attenuates a delay-induced deficit in object recognition memory in female rats (McLean et al., data to be presented at ECNP, 2011). The aim of this study was to compare the efficacy of the atypical antipsychotic, risperidone, the wake-promoting agent/analeptic, modafinil, and nicotine, to reverse the delay-induced cognitive deficit in object recognition memory.
Methods: Adult female hooded-Lister rats received risperidone (0.16 mg/kg; i.p.), modafinil (50 mg/kg, p.o.), nicotine (0.2 mg/kg, s.c.) or vehicle and were tested in the novel object recognition (NOR) task with a 6 hour inter-trial interval (ITI). One week later, rats received the same doses of risperidone, modafinil, nicotine or vehicle and were tested in the NOR task with a 24 hour ITI. All drugs were administered 30 min prior to the acquisition trial. Results: In all treatment groups and in both experiments there was no preference for the left or right identical objects in the acquisition trial. In the retention trial vehicle and risperidone treated rats were unable to distinguish between the novel and familiar objects following a 6 hour ITI. Modafinil and nicotine treated rats spent significantly more time exploring the novel object compared to the familiar object following a 6 hour ITI ($P<0.01$ and $P<0.05$ respectively). Following a 24 hour ITI all treatment groups spent more time exploring the novel compared to the familiar object however this effect failed to reach statistical significance, although in the modafinil treated group this effect closely approached significance ($P=0.07$).
Conclusions: Modafinil and nicotine improved a delay-induced cognitive impairment following a 6 hour ITI in a test of visual recognition memory, of relevance to schizophrenia and Alzheimer's disease. We have previously shown that risperidone attenuates sub-chronic PCP-induced deficits in NOR; however, in this study this atypical antipsychotic had no efficacy to reverse the delay-induced deficit. Following a 24 hour ITI none of the compounds tested were effective. These data suggest that the 6 hour ITI NOR task may be useful to detect novel cognitive enhancers.

MB11

DEVELOPMENT OF A TOUCHSCREEN-BASED VISUAL DISCRIMINATION TASK IN THE MOUSE: A STRAIN COMPARISON OF ACQUISITION AND REVERSAL LEARNING

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Introduction: Neurological disorders such as Alzheimer's disease and schizophrenia are associated with a range of cognitive impairments including working memory deficits and impaired cognitive flexibility (Keeler and Robbins, 2011, Biochem Pharmacol, doi:10.1016/j.bcp.2010.12.028). Recent years have seen a surge in the use of touchscreen technology which could potentially enable the assessment of different cognitive abilities in a fully translatable manner across species (Bussey et al., 2001. Behavioural Neuroscience, 115(4):957-60). Herein, four commonly used mouse strains were characterised in a touchscreen-based visual discrimination paradigm, with the view to establishing a functional assay that can be used to characterise animal models and cognitive enhancers relevant to these disorders preclinically.
Methods: The study was performed in male mice from 4 different strains (n = 12 per strain; all 26 – 28 g) C57BL/6J, DBA/2J, 129S2/SvHsd and CD1 (Swiss SPF Crl: CD1) using 8 Med-Associates mouse operant chambers where one wall had been replaced by a touchscreen, under the control of K-Limbic software (Conclusive Solutions). Habituation to the chamber and autoshaping phases preceded the visual discrimination task. In the task, mice were presented with two different images (spider and plane; counterbalanced across groups) displayed in two of 3 locations. A nose-poke at one image was rewarded by a food pellet, whilst nose-poking the other resulted in a negative 10 sec 'time-out' and a repeat of that same trial under a correction procedure. A session was completed after 30 correct trials or 45 minutes, separated by an inter-trial interval of 10 sec. Once a stable performance criterion (≥75% trials correct for 3 consecutive days) was reached, rewarded images were reversed. Data are presented as mean sessions required to reach criteria ± sem.
Results: Strain differences in autoshaping performance were seen with the 129S2 mice requiring more sessions ($p\leq0.0001$ one-way ANOVA) and completed fewer trials per session ($p\leq0.0001$). The rate of task acquisition differed significantly between strains ($p\leq0.0001$ one-way ANOVA). 129S2 mice required fewer sessions to reach criterion (6 ± 0.4 sessions) when compared with C57BL/6J and DBA/2J mice (10 ± 0.7 and 12 ± 0.7 sessions respectively), whereas CD1 mice failed to reach criteria (>20 sessions, not included in statistical analysis). Of note, significant image biases were detected in each strain during task acquisition with 129S2 ($p = 0.0025$), C57BL/6J ($p = 0.0518$) and DBA/2J ($p = 0.0339$) mice all showing a preference for the spider image. Reversal performance also differed significantly between strains ($p\leq0.0001$ one-way ANOVA) as 129S2 mice required fewer sessions to reach criterion (9 ± 0.5 sessions) when compared with C57BL/6J and DBA/2J mice (13 ± 0.8 and 14 ± 0.4 sessions).
Conclusions: The present study showed substantial strain differences in performance during autoshaping, acquisition and reversal phases of a touchscreen-based visual discrimination task which should be considered when choosing background strains for future pharmacological and transgenic studies. Future studies will continue to focus on task development and pharmacological validation.
This work was performed at and funded by Janssen Pharmaceutica under the Innovative Medicines Initiative.

MB12

ENDOCANNABINOID LEVELS AND EXTINCTION DEFICITS IN THE APPSWE/PS1ΔE9 MOUSE MODEL OF ALZHEIMER'S DISEASE

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Introduction: The endocannabinoid signalling system (ECS) has been implicated in a number of neurodegenerative disorders including Alzheimer's disease (AD). The ECS comprises 2 principal endocannabinoids (ECs) anandamide (AEA), 2-arachidonoylglycerol (2AG) and a number of EC-like molecules including oleoylethanolamide (OEA) and palmitoylethanolamide (PEA). Levels of 2AG were found to be raised following exposure of rat hippocampal neurons to β-amyloid peptide. The present study used the APPswedish presenelin 1 deleted exon 9 (APPswePS1ΔE9) mouse model of AD in order to investigate the impact of advanced disease progression on in-vivo levels of ECs.
Methods: Behavioural characterisation of the mouse model comprising a locomotor activity task and a contextual fear memory (CF) paradigm were conducted using male wildtype and APPswePS1ΔE9 mice at the ages of 4, 6 and 8 months (n=18-20). Following behavioural testing, animals were sacrificed and hippocampal and frontal cortical levels of ECs were quantified using liquid chromatography mass spectrometry (LCMS). Statistical testing comprised repeated measures ANOVA, two-way ANOVA and one-sample t-tests.
Results: APPswePS1ΔE9 mice were hyperactive compared to their wildtype littermates independent of age ($p<0.001$). APPswePS1ΔE9 were able to learn, and 24 hours later, recall CF at a better rate than their wildtype counterparts. However, 48 hours after acquisition of CF, unlike wildtype animals, APPswePS1ΔE9 of all ages were unable to extinguish CF ($p<0.01$). LC-MS analysis showed a significant age-related increase in AEA, OEA and PEA in the frontal cortex and hippocampus of both wildtype and APPswePS1ΔE9 mice ($p<0.001$). APPswePS1ΔE9 showed significantly higher hippocampal AEA levels than wildtype animals ($p<0.05$). No significant differences relating to genotype or age were seen for 2AG.
Conclusion: APPsweΔE9PS1 were found to be hyperactive relative to wildtype mice and were able to learn and recall CF as well as their wildtype littermates. However, their inability to extinguish the contextual fear memory at 4, 6 or 8 months of age indicates defective cognitive flexibility. Although raised hippocampal AEA levels might be expected to facilitate extinction of fear memory, this does not appear to be the case in this instance. On-going studies will address this issue.
Keywords: APPsweΔE9PS1, contextual fear memory, endocannabinoids.
Financial Sponsorship: Medical Research Council, Alzheimer's Research UK

MB13

HOW DOES A MINOR HEAD INJURY RESULT IN ENDURING SYMPTOMS? A PROSPECTIVE INVESTIGATION OF POSTCONCUSSIONAL SYNDROME AFTER MILD TRAUMATIC BRAIN INJURY

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Introduction: Traumatic brain injury is one of the most common neurological conditions. Each year in the UK at least 1 million cases present to hospital, of which 90% are actually mild traumatic brain injury (MTBI). A significant proportion (about 15-30%) of MTBI patients is at risk of developing postconcussional syndrome (PCS) (King,2003,Br J Psychiatry 183:276-8; Williams et al., 2010,J Neurol Neurosurg Psychiatry 74:1116-22). The aim of this study was to investigate the contributions of cognitive, emotional and behavioural factors to the development of PCS and to identify early predictors.
Methods: A prospective cohort design was employed. 126 patients met the diagnosis of MTBI (mean age 38.32 years; male 63%) completed baseline questionnaire assessments within 2 weeks after injury, and 108 patients completed follow-up questionnaire assessments at both 3 and 6 months after injury. A series of self-report measures were used to assess baseline somatic, cognitive, behavioural and emotional responses. The primary outcome measures were the ICD-10 Diagnosis for PCS and the Rivermead Postconcussion Symptoms Questionnaire. Data from 107 patients were entered into final analysis. Demographic and clinical characteristic variables were compared between the PCS cases and non-cases using independent-sample t tests and χ^2 tests. Significant variables from the individual regression analysis were subjected to multiple logistic regression modelling with PCS outcome entered as the dependent variable. A stepwise backward logistic regression procedure was used to derive the model. The Likelihood Ratio Test was used to select predictor variables in the logistic regression model. Fit of the model was assessed by the Hosmer-Lemeshow ''goodness of fit statistic'' for significance.
Results: Of 107 participants, 24 (23%) patients met the criteria for PCS at 3 months, and 23 (22%) at 6 months. Significant predictors indicated by individual logistic regression analysis including illness perceptions, stress, HADS anxiety and depression, and all-or-nothing behaviour, were then entered into two separate multiple regression analysis. All-or-nothing behaviour was found to be an independent predictor for PCS at 3 months (Odds Ratio 1.141, $p = 0.002$), while negative illness perceptions was an independent predictor at 6 months after injury (Odds Ratio 1.053, $p = 0.021$).
Conclusions: The study provides good support for the proposed cognitive behavioural model for PCS. Patients' negative illness beliefs and certain behavioural response play important roles in the development of PCS, indicating that they may be important early intervention targets.
This study is funded by the School of Medicine Research Management Committee at the University of Southampton.

MB14

THIS ABSTRACT HAS BEEN WITHDRAWN.

MB15

EFFECTS OF ESMIRTAZAPINE ON DRIVING PERFORMANCE AND THE ROLE OF CYP2D6 PHENOTYPE

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Esmirtazapine at low doses is evaluated as a novel drug for the treatment of insomnia. Esmirtazapine's elimination half life is long (i.e. >20 hrs) which raises the question whether it is free from residual daytime drowsiness and safe for driving the next morning. Furthermore, esmirtazapine is metabolized through CYP2D6 and its clearance is twice as low in poor metabolizers as compared to extensive metabolizers. Thirty-two healthy subjects (16 females) participated in a randomized, double-blind, placebo-controlled study in order to assess effects of single and repeated doses of esmirtazapine 1.5 mg and 4.5 mg on driving performance. Zopiclone 7.5 mg was included as active control. All subjects were subjected to P450 2D6 (CYP2D6) phenotyping in order to distinguish poor metabolizers from extensive metabolizers of esmirtazapine. Performance was assessed using the standardized on-the-road driving test. The primary study parameter was standard deviation of lateral position (SDLP), which is an index of "weaving". Treatment conditions were defined as follows: nocturnal doses of 1.5 mg esmirtazapine on Day 1-7; : nocturnal doses of 4.5 mg esmirtazapine on Day 1-7; nocturnal doses of placebo on Day 1-7; and, nocturnal doses of placebo on Day 1-6 and zopiclone 7.5 mg on Day 7. Overall, low doses of esmirtazapine (1.5 mg) did not produce any clinically relevant change in SDLP after single and repeated dosing compared to placebo. Driving impairment, i.e. a significant rise in SDLP, did occur after a single-dose administration of the higher esmirtazapine dose (4.5 mg), but was resolved after repeated doses. Acute driving impairment was more pronounced after both doses of esmirtazapine in a select group of poor metabolizers (N=7). A single dose zopiclone 7.5 mg also increased SDLP as expected. It is concluded that single and repeated evening administration of esmirtazapine 1.5 mg is generally not associated with impaired driving the next morning. A single-dose of esmirtazapine 4.5 mg significantly impaired driving, but generally resolved after repeated administration. Exploratory analysis in a small group of poor CYP2D6 metabolizers suggested that these subjects are more sensitive to the impairing effects of esmirtazapine on car driving. These results emphasize the need to take factors into account which cause inter-individual variability in either treatment response or drug metabolism when investigating the drug effects on driving performance.
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MB16

THE EFFECT OF ATOMOXETINE ON IMPULSIVITY IN PARKINSON'S DISEASE

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Introduction: Parkinson's Disease (PD) is associated with degeneration of dopaminergic pathways. However, PD also causes deterioration of the locus coerulus, which is the main cortical source of noradrenaline (NA). It has been posited that abnormal NA neurotransmission in PD may play a central role in some of the cognitive deficits associated with the disease. One cognitive function associated with NA is impulsivity, and indeed PD patients experience difficulties with response inhibition to varying degrees. Of particular concern is the fact that a significant minority of PD patients develop pathological behaviours, which are impulsive and/or compulsive in nature, such as pathological gambling and binge eating. These behaviours have been shown to be associated with elevated impulsivity (Housden et al, 2010, Neuropsychopharmacology, 35, 2155-64). Enhancing NA transmission using Atomoxetine, a NA reuptake inhibitor, reduces impulsivity in humans with attention-deficit hyperactivity disorder, healthy humans and rats. Moreover, a recent study reported that atomoxetine reduced questionnaire-rated impulsivity in PD patients (Marsh et al. 2009, Movement Disorders, 24, 277-282). Therefore, we aimed to investigate the effect of a single dose of atomoxetine on a variety of cognitive measures which index impulsivity. Method: 25 PD patients took part in a double blind placebo controlled crossover study. 40 mg of atomoxetine or placebo were administered to each participant on two separate occasions which were at least a week apart. 1.5 hours after drug administration, cognitive tests were administered. Blood samples were taken pre- and post-cognitive testing in order to confirm the presence of atomoxetine. Subjective ratings were also taken from participants throughout the session. Results: Data were analysed using repeated-measures ANOVA. Differences between placebo and atomoxetine conditions were found in relation to measures of impulsivity on the cognitive tests administered. These measures are: delay aversion, from the Cambridge Gamble Task; Stop signal reaction time from the Stop Signal Task; Reflection impulsivity, from the information sampling task; errors of commission from a Go/No-Go task. Conclusions: These results have implications for the treatment of cognitive symptoms related to PD, particularly impulsivity. This is especially important due to the pathological impulsive behaviours that some PD patients develop. Currently, dopamine treatments are reduced in order to ameliorate these symptoms; however this can mean that motor symptoms are not adequately treated. It may be that combining NA and dopaminergic treatments could be the optimal way to address the full spectrum of symptoms in PD.

MB17

HUMAN EEG CORRELATES OF LEARNED IRRELEVANCE: EFFECTS OF THE MUSCARINIC M1 ANTAGONIST BIPERIDEN

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Learned irrelevance (LIrr) refers to a reduction in associative learning after pre-exposure of the conditioned (CS) and unconditioned stimulus (US) in a non-contingent fashion. It reflects the ability of normal individuals to filter out inconsequential stimuli. In acute schizophrenia this ability is compromised, resulting in sensory overload and disrupted LIrr. Besides changes in dopaminergic and glutamatergic signaling, the muscarinic system also plays a role in the underlying pathofysiology of schizophrenia. Yet the role of muscarinic neurotransmission in human LIrr is unclear. Furthermore, there is a great lack of electrophysiological data on human LIrr. The goal of the current study was to investigate EEG correlates of a within-subject LIrr paradigm in 17 normal healthy individuals. Furthermore, the effects of the muscarinic M1 antagonist biperiden (2 mg biperiden hydrochloride, Akineton®) versus placebo on LIrr were assessed. The study was conducted according to a double blind, placebo-controlled crossover design and was approved by the Medical Ethics Committee of Maastricht University. The LIrr task was presented as a visual detection task using letter sequences; participants were instructed to give a response to the target letter X. The letter preceding the X (i.e., the predictor letter) could be predictive of its occurrence according to three conditions: random (RAN; no prediction), preexposed (PE; partial prediction) and non-preexposed (NPE; full prediction). The most important dependent variables were reaction time (RT, in ms) to the target and a LIrr-index which was calculated as follows: (RTPE/RTRAN) - (RTNPE/RTRAN). For the EEG recording, separate ERP averages for the N1 and P3 peaks were calculated for the different stimulus types (i.e., predictors and targets), as well as for the NPE, PE, and RAN stimuli. All data were analyzed by repeated measures ANOVAs. As expected, LIrr was found to be intact in young healthy volunteers after placebo, reflected by shorter RTs to NPE-cued than to PE-cued targets (289 vs. 376 ms, respectively; ($F(2,28) = 21.73$, $P < 0.001$). Furthermore, in the placebo condition the P3b latency was relatively shorter for target stimuli which were partially (PE condition; 355 ms post-stimulus) or fully predicted (NPE condition; 316 ms post-stimulus) compared to targets which seemed to occur in a random fashion (RAN condition; 387 ms post-stimulus; $F(2,26) = 11.99$, $P < 0.001$). This suggests that the predictability of the occurrence of a target stimulus is mainly reflected by these EEG components. Biperiden had no effect on the LIrr-index ($F(1,14) = 0.06$, n.s.), although prolonged reaction times were evident (362 ms after placebo vs. 402 ms after biperiden; $F(1,14) = 12.43$, $P < 0.01$). Biperiden increased the N1 amplitude of PE predictor letters at the Fz and FCz electrode channels (Fz placebo: -3.57 vs. Fz biperiden: -6.20; FCz placebo: -4.30 vs, FCz biperiden: -6.43; $Fs > 5.77$, $P < 0.05$), suggesting an effect of this drug on early perceptual processing. In conclusion, the within-subject paradigm used in the current study in combination with EEG can reveal brain mechanisms involved in LIrr. M1 antagonism did not affect LIrr performance but seemed to influence early information processing.
No external financial sponsorship was used for the current study.

MB18

DOPAMINERGIC MODULATION OF COGNITIVE FUNCTION. THE INFLUENCE OF METHYLPHENIDATE ON COGNITIVE PERFORMANCE IN HEALTHY VOLUNTEERS

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Dopamine is known to be involved in (spatial) working memory and other cognitive functions. This has raised interest in the effects of dopaminergic drugs such as methylphenidate, which is thought to act mainly via dopamine reuptake inhibition, on cognition in healthy volunteers. Methylphenidate is prescribed for Attention Deficit Hyperactivity Disorder (ADHD) and Narcolepsy but is increasingly used by healthy individuals in attempts to enhance their normal cognitive performance (Sahakian et al., 2007, Nature, 450: 1157-9). In the current study the effects of 3 doses of methylphenidate on episodic- and working memory, cognitive flexibility, impulsivity and planning were investigated in healthy volunteers. In a double blind placebo-controlled crossover study, 19 healthy male volunteers (mean age=23.4, SD=5.4) were tested after a single dose of placebo or 10, 20, or 40 mg of methylphenidate. Cognitive testing included a word learning test, a spatial working memory test, a set-shifting test, a stop signal test and a computerized version of the Tower of London planning test. Episodic memory consolidation was significantly improved relative to placebo after 20 ($F(1,14)=4.937$, $p<.05$) and 40 mg ($F(1,14)=6.084$, $p<.03$) of methylphenidate. Methylphenidate also improved set shifting and stop signal task performance but did not affect spatial working memory or planning. To the best of our knowledge, this is the first study reporting enhanced episodic memory consolidation after methylphenidate in a dose-related fashion over a dose range that is presumed to reflect a wide range of dopamine reuptake inhibition.
This study was sponsored by F. Hoffmann La-Roche Ltd, Basel, Switzerland.

MB19

BEHAVIOURAL WITHDRAWAL DURING PAVLOVIAN CONDITIONING IN HUMANS

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Stimuli that are reliable predictors of primary reinforcers can exert an influence over the vigour of responses made in instrumental contexts (e.g. Pavlovian-Instrumental Transfer), a finding well established in the animal literature (Dickinson A & Balleine B, 1994, Anim Learn Behav 22:1–18). The motivational characteristics of a predictor can influence action vigour even in situations where the outcome is completely independent of that action, for example in Pavlovian approach and withdrawal behaviour. While the influence of appetitive Pavlovian influences has received some attention in recent years in humans (Talmi D. et al, 2008, J Neurosci 28:360–368), human Pavlovian withdrawal has not yet been demonstrated. Here, twenty participants (10 male, 10 female, mean age 26.7 (sd 8.03)) underwent passive Pavlovian conditioning to abstract images that were predictive of: (i) monetary gains; (ii) monetary loss; (iii) painful electric shocks. In order to ensure attention to the stimuli, participants were required to respond to occasional flickers of a fixation cross, presented in the centre of the conditioned stimulus (CS). We provide the first demonstration of behavioural withdrawal in humans, as indexed by reaction times (RTs) to this flicker detection task, which was completely independent of conditioning. Participants were significantly slower to respond to fixation flickers that appeared during presentation of CSs predictive of negative outcomes than those appearing during CSs predictive of positive ($p<.014$) or neutral outcomes ($p<.002$). This Pavlovian withdrawal behaviour occurred even though participants were explicitly instructed that their ability to detect the fixation flickers bore no relation to the outcomes. Hence, Pavlovian withdrawal appears to be automatic and reflexive, mirroring findings in animals; this verification is vital in extrapolating animal models of learning and behaviour to humans.
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MB20

MOTIVATIONAL MECHANISMS UNDERLYING THE EFFECT OF NEGATIVE MOOD ON PAVLOVIAN-TO-INSTRUMENTAL TRANSFER.

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Pavlovian-to-instrumental (PIT) transfer has been extensively studied in animals and has, more recently, been adapted for use in humans. It has been demonstrated that humans are able to transfer predictive Pavlovian stimulus-outcome relationships to independently learned instrumental responding for that same outcome (Hogarth et al, 2006, Addiction, 101(8), 1153-1166; Balleine and O'Doherty, 2009, Neuropsychopharmacology, 35(1), 48-69). It is believed that such a transfer effect is modulated by the predictive strength of the stimulus, which, in turn, exerts a motivational influence driving the instrumental responding (Everitt and Robbins, 2005, Nat Neurosci, 8(11), 1481-1489). The effect of negative mood on the likelihood and vigour of this instrumental response, in humans, is examined in two general PIT studies in the presence of positive or aversive outcomes. A Pavlovian training schedule was used in which three compound stimuli AX, BX, CX predicted an outcome of 10p or an aversive noise on 90%, 50% and 10% of presentations respectively. This was followed by a mood induction procedure, a short phase of instrumental training and finally, transfer performed under nominal extinction. Data from a total of 32 participants was analysed (16 Females, 16 Males) for each study, split equally between the neutral and negative induced mood groups. Data was analysed using a 2 (mood) by 3 (stimuli) mixed ANOVA. Pavlovian learning prior to mood induction did not differ between the groups and all participants successfully acquired the instrumental response. During transfer, contingency awareness was unaffected by the mood induction procedure. However, Pavlovian to instrumental responding was reduced in the negative mood condition, in particular when the outcome was aversive ($F(2,60)=5.694$; $p=0.005$). These findings suggest that the motivation to perform an instrumental response to obtain reward, or to avoid punishment, in the presence of stimuli predicting reward or punishment is reduced under conditions of negative mood. Furthermore these data highlight a role that negative mood may have on addictive processes.
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MB21

MOBILE COGNITIVE ASSESSMENT: VALIDATION OF NEUROPSYCHOLOGICAL ASSESSMENT ADMINISTERED ON AN ANDROID TABLET

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Tests of neuropsychological function, including memory, attention and processing speed, are widely used to assess the impact of illness, physiological state or treatment on cognitive function. Portable devices such as mobile phones, handhelds and tablet PCs are useful platforms as they allow assessments to be made in a wider range of settings than with conventional computers. Assessments may be made in an everyday life setting, or practitioners may carry out tests when visiting patients. The use of smartphones and small tablets, with input made using a touchscreen, is rapidly increasing. It important to assess the validity of assessments made on these devices, as the interface differs from that of conventional computer-based tests. A three level approach to validation is proposed: (1) Device-level, evaluating the accuracy of internal timing and correct software implementation; (2) Intrinsic, evaluating the ability of a test to discriminate between stimulus types of differing difficulty within a test; (3) Extrinsic, evaluating the ability of a test to discriminate between states affecting cognition within or between individuals. A test battery has been developed using Java on the Android operating system. Device-level validation confirmed correct operation in terms of presentation algorithms and error scoring. Internally-recorded timing was compared to externally measured response times, and showed high agreement ($r > 0.995$). Intrinsic validation used a memory scanning task in which responses to stimuli not in the memory set were expected to be longer than those in the set. This was confirmed, with differences of about 100 msec observed between the two conditions. Extrinsic validation will use the effects of alcohol, and compare changes in performance to those seen both with conventional computers, and with mobile phones (Tiplady et al., 2009, Alcoholism: Clinical and Experimental Research 33: 2094-2102) The validation model presented here provides a broadly based framework for assessing different aspects of system validity. A wide range of assessments can be set up on touchscreen tablets to evaluate relevant domains of cognition. These tests can be effectively used in a variety of environments, increasing ecological validity, and making tests available that could otherwise only be administered in a specialized setting. Financial sponsorship: None.

MB22

MOTOR-, TEMPORAL- AND REFLECTION- IMPULSIVITY: WHICH RELIES MORE ON EXECUTIVE FUNCTIONS?

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Research suggests that impulsivity can be conceived of as consisting of a number of subtypes. Three proposed subtypes are Reflection Impulsivity (the tendency to make quick decisions under conditions of uncertainty), Temporal Impulsivity (the tendency to delay gratification), and Motor Impulsivity (the ability to inhibit a pre-potent response). The current study investigated whether challenging central executive processes with a task that is thought to rely on executive function, will increase impulsivity in each of the subtypes. Tasks used were the Information Sampling Task (IST; Clark et al. (2006). Biological Psychiatry, 60(5), pp. 515-522) measuring Reflection Impulsivity, The Single Key Impulsivity Paradigm (SKIP; Dougherty et al. (2005). Behaviour Research Methods, 37(1), pp. 82-90) measuring Temporal Impulsivity and the Stop Signal Task, from which the Stop Signal Reaction Time is the key outcome variable (SST; Logan (1994). Inhibitory Processes in Attention, Memory and Language, pp. 189–239) measuring Motor Impulsivity. Participants ($n = 33$) were assigned to either the executive function challenging condition (experimental condition), or a control condition, running in parallel to the performance in the impulsivity tasks. The experimental condition involved a random letter generation task, during which participants were required to generate random letters in response to a tone repeated every second; the control condition involved a task in which participants were asked to produce one syllable (ba) every second. SST was affected by challenging executive function; an interaction was found between time (pre-post) and condition, $F(1,27)=6.404, p=.018$, indicating an increase in stop signal reaction time (SSRT) when executive function was challenged. High SSRTs indicate elevated impulsivity. No other effects were found. Thus the present study demonstrated motor impulsivity, but not on reflection- or temporal impulsivity to be affected by challenging executive function. These data suggest that the motor subtype of impulsivity is dissociable from the temporal and reflection subtypes and that motor impulsivity is partly reliant on the executive functions that mediate random letter generation.

MB23

INCREASED NEURAL PROCESSING OF REWARDING AND AVERSIVE FOOD STIMULI IN RECOVERED ANOREXIA NERVOSA

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Introduction: Recent evidence has shown that individuals with acute anorexia nervosa and those recovered have aberrant physiological responses to rewarding stimuli. We hypothesized that people recovered from anorexia nervosa would show impaired neural responses to both rewarding and aversive disorder-relevant stimuli.
Methods: Using functional magnetic resonance imaging (fMRI), the neural response to the sight and flavour of chocolate, and their combination, in 15 women recovered from restricting-type anorexia nervosa and 16 healthy controls matched for age and BMI was investigated. The neural response to a control aversive condition, consisting of the sight of mouldy strawberries and a corresponding unpleasant taste, was also measured. Participants simultaneously recorded subjective ratings of "pleasantness," "intensity," and "wanting".
Results: Despite no differences between the groups in subjective ratings, individuals recovered from anorexia nervosa showed increased neural response to the pleasant chocolate taste in the ventral striatum ($p<0.001$) and pleasant chocolate sight in the occipital cortex ($p=0.001$). The recovered participants also showed increased neural response to the aversive strawberry taste in the insula and putamen (both $p<0.001$), and to the aversive strawberry sight in the anterior cingulate cortex and caudate (both $p<0.001$).
Conclusions: Individuals recovered from anorexia nervosa have increased neural responses to both rewarding and aversive food stimuli. These findings suggest that even after recovery, women with anorexia nervosa have increased salience attribution to food stimuli which in turn might constitute a neural biomarker. These results aid our neurobiological understanding and support the view that the neural response to reward may be a potential target for prevention and intervention strategies in anorexia nervosa.
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MB24

RESTITUTION OF BRAIN RESPONSES TO FOOD STIMULI AND FEEDING IN TYPE 2 DIABETES BY GLP1 AGONIST EXENATIDE

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Introduction: Appetite control and satiety are dysregulated in insulin resistance and type 2 (T2) diabetes. We investigated the impact of a GLP1 agonist, Exenatide, on regional brain responses to food stimuli and feeding in people with T2 diabetes.
Methods: Six subjects with lifestyle ± metformin treated diabetes (age 56.2±6.4 yrs, BMI 30.06±3.03) were studied in random order, fed (400kcal mixed meal) or fasted (50mls water) with and without GLP1 agonist (Byetta, 10 mcg sc). They viewed food and non-food images presented in a block design paradigm during blood oxygen level dependant (BOLD) brain imaging.
Results: The BOLD response evoked by food image viewing was markedly affected by satiety state in a large contiguous cluster spanning thalamus, striatum and insular cortex. Data were extracted from this group cluster for each participant under each condition. The differential evoked response (fed vs fasted) was diminished by the GLP1 agonist Exenatide, (Figure, $p < 0.02$). Figure: Interaction of Exenatide, Satiety State and Evoked Response to Food Images.
Conclusions: This preliminary analysis indicates that T2 diabetes influences the neural networks activated in the fed and fasted state in man and that the GLP-1 agonist may render these responses more similar to non-diabetic controls. These data provide a neural substrate for the known satiety effects of GLP1 therapy and provide a protocol for investigating modulators of disordered appetite control in diabetes.
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MB25

IS THE INCREASED CONSUMPTION OF PALATABLE FOOD PRESENTED BY NEONATAL HANDLED MALE ADULT RATS IN RELATION TO NON-HANDLED ONES RELATED TO THE OPIOID SYSTEM?

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Early life experiences influence neuroendocrine systems and behaviour in adult life. Rats subjected to repeated brief maternal separation (handling) show reduced stress response and increased consumption of palatable food when adults, what can be related to the food's hedonic properties and reward systems. Opioid neurotransmission in the shell of the nucleus accumbens is thought to participate in generating hedonic impact for natural sensory pleasures and also contribute to eating behaviour. The aim of this study is to evaluate the influence of opioid system in the increased consumption of palatable food showed by neonatal handled male rats in adult life. Twenty-five litters of Wistar rats were divided into non-handled and handled (placed in an incubator 10min/day, days 1-10 after birth). When adults, 39 male animals were used (between behavioral and biochemical analyses). To evaluate the involvement of opioid system on palatable food consumption on these animals, naloxone and beta-endorphin were administrated in the accumbens shell of the rats, after their habituation to a new environment with sweet food (Silveira PP et al. 2005; Int. J. Devl Neuroscience 23:93-99); food consumption was measured. The immunocontent of mu opioid receptors in the nucleus accumbens was evaluated by western blotting. Results were analyzed by repeated measures ANOVA or Student's t test. All animal proceedings were approved by the Institutional Ethical Committee and followed the recommendations of the International Council for Laboratory Animal Science, and of the Federation of Brazilian Societies for Experimental Biology. During the habituation to the new environment with sweet food, neonatal handled animals showed a decreased latency to reach palatable food in relation to non-handled ones (interaction between days of habituation and group [$F(1,27)=9.19$, $P=0.005$)] and an increased consumption of palatable food [$F(1,27) = 8.18$, $P<0.01$]. Under drug administration, no differences were seen between groups in the consumption of palatable food neither with naloxone nor with beta-endorphine [$F(1,42)=0.636$, $P>0.05$ for group and $F(2,42)=0.96$, $P>0.05$ for drug]. In addition, no differences between groups were observed in the immunocontent of mu opioid receptor in the nucleus accumbens [$t(8)=1.85$, $P>0.05$]. In conclusion, from the results we have until now, opioid system does not seem to drive the increased consumption of palatable food showed by neonatal handled animals in relation to non-handled ones in adult life. However, more experiments need to be done to confirm that; additionally, we cannot eliminate the possibility of an interaction between opioid system and others reward systems.
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MC01

AUDIT ON BASELINE BLOOD TESTS IN ADULTS IN A PSYCHIATRIC INPATIENT UNIT

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Introduction: Clinical guidelines at the South Essex partnership trust as well as NICE guidelines, strongly emphasize that patients who are admitted to psychiatric inpatient units should have baseline blood tests performed on admission and soon after any medication change, including fasting blood glucose, lipids, liver functions, urea and electrolytes, full blood counts and thyroid function tests. To establish whether patients admitted to Keats Ward, Weller Wing (SEPT) which is a psychiatric inpatient unit for adults, have had baseline blood tests on admission accordance with guidelines.
Method: Audit sample included patients, admitted to Keats Ward. Initial audit (Audit1) included patients admitted between 1st November 2009 and 30th April 2010. A reaudit was completed in December 2010. This included patients who were admitted between 1st August 2010 and 31st October 2010 (Audit2). Inclusion criteria: A retrospective collection of data for 25 service users admitted to Keats ward. Age group of the patients was between 18-65 years. The sample included patients who were naive to antipsychotic medication, and patients with an established diagnosis and prescribed antipsychotics. Exclusion criteria: Patients who were admitted to Mental health Assessment Unit, old age psychiatric inpatient unit and patients who were admitted for detoxification of alcohol and illicit drugs. Patients whose inpatient records could not be accessed were also excluded. Data Analysis:1. Baseline blood tests performed on patients were categorised as following: Baseline blood tests taken on days 0-4, 5-7, 8-13 and more than 14 days after admission. 2.Baseline blood tests not performed in patients and the reason given; 3. Average stay in hospital.
Results: Audit1 showed that 64% patients had baseline bloods taken during their current admission. 28% of patients (n=7) had blood tests taken between 0-4 days, 20% (n=5) had blood taken between 5-7 days; Audit2 showed an improvement in that 92% patients had their blood tests taken during their current admission. 52% of patients (n=13) had blood tests taken between 0-4 days, 24% (n=6) had blood taken between 5-7 days; In Audit1, 36% of the patients (n=9) had no blood tests performed during the current admission. One patient refused blood tests and this was documented in the notes. In Audit2, 8% patients (n=2) had no blood tests performed during the current admission and no reason was documented on the medical notes. The average length of stay was 36 days in Audit1 and 18 days in Audit2.
Conclusion: The audit has highlighted the uncertainty of how soon after the admission should the baseline blood tests be performed. The results of the audit1 revealed that baseline blood tests taken in Keats ward, Weller Wing were well below what has been recommended by the guidelines. However the results improved in the reaudit. We suggest that baseline blood tests should be performed within 0-4 days after admission. Additionally if the blood tests are not performed then a reason for this should be documented in the medical notes. We recommend a formal timescale should be introduced into the guidleines as to when the baseline blood tests should be performed, as this would optimise patient care.
Financial Sponsorship: No funding received to conduct this audit.

MC02

PRESCRIPTION OF LICENSED MEDICATIONS FOR UNLICENSED APPLICATIONS IN PSYCHIATRIC INPATIENTS: PREVALENCE, ADHERENCE TO RECOMMENDATIONS, AND INFLUENCES ON PRESCRIBING

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Drugs are often prescribed outside the narrow terms of their market authorisation ('product licence'). Despite the availability of a broad range of classes of psychotropic drugs, many patients remain troubled by persistent and disabling symptoms following a series of interventions, and in this situation many doctors will prescribe outside the terms of the licence ('off-label prescribing'), hoping to offer their patients an improved chance of recovery. College Report CR142 'Use of Licensed Medications for Unlicensed Applications in Psychiatric Practice' offers guidance and recommendations regarding this important aspect of current psychiatric practice. We wished to determine the extent of prescribing for unlicensed applications among psychiatric inpatients, to ascertain whether prescribing followed these recommendations, and to examine the influences on prescribing reported by doctors. All prescriptions for all patients who received inpatient care within a two-month period in three wards (two acute wards and one psychiatric intensive care unit) were analysed: when needed, handwritten medical notes were examined, and doctors were asked about the reasons for particular treatment decisions. During the study period, 59 male patients received a total of 287 prescriptions, and 57 female patients received a total of 327 prescriptions. Among male patients, 23 (39%) were prescribed a drug for an unlicensed application: 33 prescriptions (12% of the total) were outside the terms of the licence, due to different indication (21 prescriptions), duration of treatment (9), or recommended daily dosage (3). Among female patients, 34 (60%) received a drug for an unlicensed application: 64 prescriptions (20% of the total) were outside the terms of the licence, due to different indication (47 prescriptions), length of treatment (14), or daily dosage (3). When asked about prescribing decisions, there was much uncertainty about what was licensed and what was not; and medical notes revealed scant record of adherence to current recommendations. 'Off-label' prescribing was a feature of overall management in approximately 50% of patients, and 16% of prescriptions were not for licensed applications. Documentation of decisions regarding unlicensed prescribing is poor, and educational initiatives are needed to better inform this aspect of current psychiatric practice.
Funded by a grant to Rebecca Henry through the Flexibility and Sustainability scheme run by Hampshire Partnership NHS Foundation Trust Research and Development Unit.

MC03

SURVEY OF THE RECORD KEEPING OF CONTRACEPTIVE METHODS AND COUNSELLING IN WOMEN OF CHILD BEARING AGE TAKING PSYCHOTROPIC MEDICATION

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Introduction: It is important for women with child bearing potential to use effective contraception to avoid unplanned pregnancy whilst taking psychotropic medication because of the risk of congenital abnormalities in the unborn baby. Contraceptive methods may have an effect on the mental health of women. Hormones used in contraceptive preparations may interact with psychotropic medications resulting in reduced bioavailability of the contraceptive formulation or the psychotropic medication. Aim: To assess the record keeping of the contraceptive method used and of counselling regarding the need to avoid unplanned pregnancy given to women of child bearing age. Method: The documentation in 100 randomly selected case notes relating to women up to age of 50 seen in the out-patient clinics of 4 Community Mental Health Teams and by the doctors in the Crisis Resolution and Home Treatment Team within the months of July and August 2010 was checked. Results: • Of the 100 women in the sample there was no documentation of the contraceptive method used by women of child bearing age in more than 90% of cases. • In 90% of women there was no documentation regarding counselling the women about the risks of psychotropic medication to the unborn child. • 13 patients were prescribed Depakote although there was no documentation of Folic Acid prescription for any of them. • 1 of the 4 pregnant women in the study was on Carbamazepine for epilepsy. • Of the 15 women who had contraceptive method documented in the notes, 1 patient used a combined contraceptive pill, 5 patients used progestogen only preparations, no patient used intrauterine contraceptive device. Recommendations: 1. In all women of child bearing age, the need for effective contraception should be assessed before psychotropic medication is prescribed, discussed and documented. 2. The doctor prescribing psychotropic medication is responsible for informing the woman regarding the possible teratogenic effects of the medication prescribed, and the need to plan any pregnancy. This information should be documented in the records and communicated to the General Practitioner. 3. The woman may have to seek specialist help regarding the need to tailor the contraceptive depending on the psychotropic medication prescribed. The dose of emergency contraception may have to be increased. The dose as well as the choice of contraceptive should be reviewed whenever there is a change in psychotropic medication. Financial Sponsorship: No funding received to conduct this survey.

MC04

PRACTICES OF CHILD AND ADOLESCENT PSYCHIATRISTS IN MONITORING OF PATIENTS ON ANTIPSYCHOTIC MEDICATION

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Introduction: Antipsychotic medication is increasingly being prescribed to children and adolescents for a wide range of disorders. Children and adolescents show a greater sensitivity to side effects than adults and these include extra pyramidal side effects, weight gain, obesity and the metabolic syndrome (Correll 2008).
Method: A questionnaire looking at child and adolescent psychiatrists and their monitoring practices of antipsychotic medication was designed. Issues investigated included attitudes, investigations at baseline and follow up reasons for not monitoring as well as any correlations between MRCPsych status, gender and age. We included consultants and other training grades within three trusts within the East of England. Links to the questionnaires were distributed to the relevant clinicians and the survey was completed anonymously online. Results: There were 37 responses.32 (86.5%) clinicians agreed that monitoring was important for children and adolescents on antipsychotic medication.32 (86.5%)clinicians performed baseline physical monitoring (weight and BMI) on their patients and the same number repeated these baseline measurements. Liver function tests was the most common investigation at baseline reported to be carried out by 34(91.9%)clinicians.17(45.9%)clinicians reported to have repeated both blood glucose and lipid profiles at least once in almost all of their patients(>80% of encounters).3 clinicians (8.1%) were reportedly not carrying out any investigations at baseline. The commonest reasons provided for not monitoring included children being unable to tolerate investigations or this being done by another clinician (GP, Paediatrician). There was no significant difference in practices of psychiatrists in terms of membership, grade, and gender or whether they had children under 18.A chi-square analysis showed that there was a statistical difference in the understanding of the importance of monitoring for children and adolescents on antipsychotic medication. Older clinicians (>40 years old) believed it was more important ($\chi 2 = 4.73$) than their younger counterparts (<40 years old).In terms of actual monitoring, the measurement of lipid profiles ($\chi 2 = 4.08$), repeating lipid profiles ($\chi 2 = 7.45$) and repeating LFTs ($\chi 2 = 6.22$), it is the younger (<40 years old) clinicians who actually perform these test more to a statistically significant extent, with a critical value of 3.84 (p=0,05) Conclusion: The results of this survey indicate that there is overall modest monitoring of adverse effects in children and adolescents. Routine monitoring of adverse effects is inconsistent among prescribers. The survey highlights the need for training and more guidance on prescribing and monitoring of antipsychotic use in children and adolescents. Funding: No Financial Sponsorship.

MC05

ACUTE DYSTONIC REACTIONS WITH ARIPIPRAZOLE TREATMENT: THREE CASE REPORTS

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Aripiprazole is an atypical antipsychotic useful in the treatment of treatment resistant schizophrenia and other psychoses. Extrapyramidal side effects including acute dystonia are thought to be rare with aripiprazole. The reduced propensity to cause extrapyramidal side effects is thought to be associated with its postulated mechanism of action. It is believed to have partial D2 receptor agonistic action in mesocortical pathways, antagonism at D2 receptors in the mesolimbic system, partial agonism at 5-HT1α receptors, low affinity antagonistic action at H1 and α1 receptors and negligible anticholinergic effects. We present three cases of acute dystonia during treatment with Aripiprazole in first episode psychosis. To our knowledge, four case reports have been previously published reporting acute dystonia with Aripiprazole treatment. In the first report, a 22 year old lady with schizophrenia experienced repeated occulogyric crises eleven months into Aripiprazole treatment. Reduction in the dose of aripiprazole and Procyclidine treatment reduced the frequency of attacks. In the second report, a 24 year of man recovered from a first psychotic episode on Aripiprazole. He developed tongue dystonia with fasciculations and dysarthria a year into treatment. Since commencement of Procyclidine, dystonia has not recurred. In the third report, a 27 year old lady with acute psychotic illness developed acute generalised body dystonia two weeks into treatment with Aripiprazole. Withdrawal of Aripiprazole along with Procyclidine use successfully ended the dystonia. Acute dystonia occurs as an idiosyncratic reaction with Aripiprazole treatment. It appears that it can occur at any stage of treatment even though it seems to be more common in the early phases of treatment. A previous history of dystonia with other antipsychotics may well be another risk factor. Co-prescription with other psychotropics may also be a risk factor to consider as noted in two previous case reports (Shanghadia et al, 2007, 19:89-90, Desarker et al, 2006, American Journal of Psychiatry 163:1112-1113). Dystonia with Aripiprazole may also be a dose dependent phenomenon since a reduction in dose was associated with cessation or reduction in frequency of acute dystonia our cases. Use of anticholinergic medication was associated with reduction or cessation of acute dystonia. We found no data on the incidence of dystonia with Aripiprazole, however from our population of patients with first episode psychosis on Aripiprazole the incidence would be around 0.05% as compared to 10% with typical antipsychotics. More data is needed to get a more accurate figure of the incidence.
This project was self funded by the authors

MC06

BEHAVIOURAL SCIENTISTS APPEAR NOT TO HAVE SPECIALIST KNOWLEDGE OF LABORATORY ANIMAL BEHAVIOUR

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A detailed knowledge of the species used in behavioural studies is essential if a full understanding of drug action is to be gained. This is also important because even simple manipulations such as individual housing have profoundly different effects in territorial species such as mice and colonial species such as rats. Therefore, whilst it should be the case that psychopharmacology takes a full account of the natural histories of the species it uses, including their social organisations, it does not. A meta-analysis of 100 psychopharmacology-related papers published in 2010/11 revealed that 99% of these mention the animals' physical housing conditions only. This raises questions as to whether the effects of social factors on experimental findings are ignored because they are not considered to be important, or because their importance has not been considered. In order to investigate this, a short on-line questionnaire was prepared that asked a series of simple questions (to do with nomenclature/physical characteristics, habitats, reproductive behaviour, social behaviour etc) about Rats (Rattus norvegicus), Mice (Mus musculus) and two other well known species (Fox, Vulpes vulpes; Elephant, Loxodonta africana). Potential participants were identified using the ISI Web of Knowledge and by opportunistic sampling. Replies from 147 behavioural scientists and 93 others were eventually forthcoming (from approximately 10 x that number of emails sent out). Frequency counts of correct answers were obtained and analysed using Chi squared. Data revealed that behavioural scientists had no more knowledge of rats than non-behavioural scientists and on several items knew more about Elephants. Similarly, whilst they had more knowledge of some aspects of the mouse (name, Latin name, physical characteristics, activity patterns and characteristics of newborns) than the other two animals, scores were not impressive (only about 40% of behavioural scientists getting these correct at best) and they knew more about the social organisation of Elephants than they did about the social organisation of mice. It is concluded that since behavioural scientists are largely unaware of the social organisations of the animals they commonly work with, they are also unaware of the major impact this can have on their data. At least this increases variance; at worst it can render results meaningless. It is revealing that several behavioural scientists indicated that they had declined to complete the questionnaire because they had no need of such information (and hence did not have it). Current findings indicate that there is a major educational task ahead.

MD01

EFFECTS OF PLAIN PACKAGING ON EYE MOVEMENTS TOWARDS HEALTH WARNINGS AND BRAND INFORMATION IN NON-SMOKERS, WEEKLY SMOKERS AND DAILY SMOKERS

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Introduction: There is considerable current interest in the potential of plain packaging, whereby cigarettes are sold in generic packs with minimal brand information, as a tobacco control strategy. This may take the form of uncoloured packs containing a health warning and the brand name only, in a standard format and without imagery or colouring. However, there has been little research into the behavioural effects of plain packaging.
Method: We investigated eye movements towards brand and health warning information, on plain and branded packs, in non-smokers (n = 15), weekly smokers (n = 14) and daily smokers (n = 14). Participants were presented with pack images, half comprising common branded packs, and half plain packs, which included a pictorial health warning in the bottom half, and brand information in the top half.
Results: A 3 (smoking status) × 2 (pack type) × 2 (location) ANOVA of number of saccades (eye movements) indicated a main effect of pack type ($F [1, 39] = 5.51$, $p = 0.024$), with more eye movements when branded packs were presented compared with plain packs. However, this was qualified by a pack type × location interaction ($F [1, 39] = 30.98$, $p < 0.001$), indicating equal eye movements towards brand and health warning locations for the branded packs ($p = 0.49$), but more eye movements towards the health warning location than the brand information for plain packs ($p = 0.023$). This was further qualified by a smoking status × pack type × location interaction ($F [2, 39] = 3.52$, $p = 0.039$), indicating that this effect was present in non-smokers and weekly smokers, but not in daily smokers.
Conclusions: These findings indicate that eye movements to health warnings are greater than to brand information when presented on plain packs, but not on branded packs, and that this effect is present only among non-smokers and weekly smokers. This latter finding argues against the tobacco industry assertion that plain packaging will prevent existing customers from identifying brand information. Plain packaging may therefore serve to selectively highlight the salience of health warnings in non-smokers and weekly smokers, and therefore be particularly effective as a tobacco control strategy to reduce uptake.
This project received no external funding.

MD02

DRUG-CUE INDUCED OVERSHADOWING: SELECTIVE DISRUPTION OF NATURAL REWARD PROCESSING BY CIGARETTE CUES AMONGST ABSTINENT BUT NOT SATIATED SMOKERS

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Addiction is characterized by an increased salience of cues that predict drug reward (drug cues) and a hyposensitivity to 'natural' rewards, and both of these effects can be exacerbated by drug (e.g. tobacco) abstinence. No study to date has found an interaction between these processes. We investigated this by incorporating drug cues into associative learning processes that are highly dependent on salience (overshadowing, blocking) with a reward outcome. We predicted that in abstaining smokers, drug cues would overshadow neutral cues, exacerbate blocking of neutral cues, and be resistant blocking themselves by neutral cues predicting a financial reward outcome. Satiated smokers (n=24), smokers asked to abstain for 12 hours (n=24) and non smoking controls (n=24) were compared on a novel instrumental learning task, requiring them to learn contingencies between pictorial cues (neutral or smoking related images) and outcomes. After two training phases in which correct responses were financially rewarded, a testing phase was used to assess whether drug cues affected levels of overshadowing and blocking. Additional measures included a dot probe task to index attentional bias, exhaled carbon monoxide, and subjective tobacco craving. Abstaining smokers showed drug-cue induced overshadowing, attributing higher reward value to drug cues than to neutral cues that were equally predictive of reward, whilst satiated smokers and controls rated both cues equally. Overshadowing was positively correlated with expired CO levels, which in turn were correlated with craving in abstainers. However, blocking did not differ between the groups and drug cues did not interact with the degree of blocking in either group. Abstaining smokers also showed an attentional bias towards probes following cigarette images shown for a short duration but not a long duration. These results provide the first evidence that drug cues can interact with reward processing in addicted individuals. This effect was accompanied by an attentional bias to drug cues, and was positively related to a biological assay of recent smoking behaviour. Further, this effect was not shown amongst satiated smokers, in agreement with previous findings that tobacco deprivation can exacerbate attentional bias and can induce behavioural reward insensitivity. Degree of blocking was not affected by the use of drug cues in any of the three groups. The results of this study suggest that treatment strategies should acknowledge interactions between drug cue salience and reward hyposensitivity rather than addressing them in isolation.

MD03

DRINKING STATUS BUT NOT ACUTE ALCOHOL CONSUMPTION INFLUENCES IMPULSIVE DECISION MAKING

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Delay discounting is a measure of impulsive decision making. Several studies have shown that heavier drinkers value smaller immediate monetary rewards over larger delayed rewards compared with lighter drinkers. However, findings on alcohol's acute effects on delayed discounting are inconsistent. One explanation is that delay discounting may vary with the type of reward offered, where heavier drinkers tend to discount the value of alcohol rewards more steeply than monetary rewards. The aim of the present study was therefore to investigate: 1) the effects of alcohol on delay discounting, 2) the effects of drinking status on delayed discounting, and 3) whether these effects differ according to reward type. Healthy, heavy and light social alcohol users (n = 96) were examined in a double-blind placebo-controlled design. Participants received either an acute dose of alcohol at 0.40 g/kg or 0.60 g/kg or placebo in a between-subjects design. Delay discounting of alcohol and monetary rewards was measured using hyperbolic and Area Under the Curve (AUC) models of delay discounting. Mixed-model ANOVAs of discount data were conducted with a within-subjects factor of reward type (alcohol, monetary) and two between-subjects factors of challenge condition and drinking status. For the hyperbolic model higher discount scores indicate greater delay discounting (reverse for AUC model). A mixed-model ANOVA of transformed hyperbolic discount scores indicated a main effect of reward type ($F [1, 90] = 23.63$, $p < 0.001$, $\eta 2 = 0.21$), where all participants had higher discount scores for alcohol rewards compared with money rewards. A further main effect of drinking status was significant ($F [1, 90] = 3.83$, $p = 0.031$, $\eta 2 = 0.05$), where heavier drinkers had higher discount scores compared with lighter drinkers. A mixed-model ANOVA of transformed AUC discount scores also indicated a main effect of reward type was significant ($F [1, 90] = 16.13$, $p < 0.001$, $\eta 2 = 0.15$), where all participants had lower discount scores for alcohol rewards compared with money rewards. Our data indicate that all drinkers in the range examined, showed greater impulsive decision making towards alcohol rewards. Additionally, we observed that heavier drinkers discount the value of all delayed rewards more steeply than lighter drinkers. These findings suggest that impulsive decision making is influenced by individual differences in alcohol use that is irrespective of state changes in alcohol intoxication. Further research is required to determine the casual relationship between drinking status and impulsive choice.
Funding: University of Bristol Studentship.

MD04

THE ACUTE EFFECTS OF ALCOHOL ON VIEWPOINT DEPENDENCE IN SPATIAL MEMORY AND CONTEXTUAL FEAR MEMORY

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Introduction: Despite alcohols frequent involvement in real-life traumatic events, our understanding of the way in which it might affect trauma-related symptoms remains unclear. Following a traumatic event, individuals may show persistent elevated fear responses to trauma-related cues. A contextual fear memory paradigm offers a valuable method to assess alcohol-induced impairments in memory of an aversive event. The present study aimed to examine the effects of a low dose of alcohol on the acquisition and extinction of fear utilising a contextual fear memory paradigm and, concurrently, assess same- and shifted-view object location recognition to assess egocentric and allocentric memory, respectively. Methods: Utilising a double-blind independent group design participants were administered alcohol (0.4 g/kg) or placebo. A virtual environment was used to present objects and test recognition memory from the same viewpoint as presentation (tapping egocentric memory) or a shifted viewpoint (tapping allocentric memory). Within the same virtual environment, participants then underwent a conditioning and extinction protocol. Conditioned stimuli were paired with an aversive electric shock from one viewpoint of the virtual environment and extinguished from a second viewpoint. Participants returned the following day for a test of extinction memory recall and its relationship to context. Skin conductance response (SCR) was recorded throughout as an index of conditioned responses. Results; There was a selective impairment of shifted-view recognition following alcohol compared to placebo ($p = 0.01$), whereas same-view recognition was spared. Fear acquisition was unaffected by alcohol with both groups demonstrating intact learning of the association between the conditioned stimulus and unconditioned response. The alcohol group showed impaired extinction learning with persistent conditioned responses throughout the extinction block, whilst the placebo group showed a clear reduction in conditioned responses ($p < 0.001$). Alcohol-induced reductions in extinction learning were highly correlated with decreases in shifted-view recognition ($r(11) = -0.81$). Conclusions; Our findings suggest that, at low doses, alcohol may selective impair the encoding of contextual information that would normally modulate extinction learning. These findings have clear clinical implications not only for individuals who have consumed alcohol prior to experiencing a traumatic event but also for individuals with Posttraumatic stress disorder who may alcohol to try and alleviate trauma-related symptoms. This study was funded by the Alcohol Education Research Council.

MD05

EFFECTS OF ACUTE NICOTINE AND ALCOHOL ON THE RATING OF ATTRACTIVENESS IN SOCIAL SMOKERS AND ALCOHOL DRINKERS

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Alcohol consumption has long been associated with increased risky sexual behaviours, yet the mechanism that underlies this effect is poorly understood. Anecdotally, acute alcohol consumption is believed to increase the perceived attractiveness of others, an effect that has received some experimental support. Furthermore, nicotine has been shown to non-contingently increase the reward value of natural reinforcers in animals and to increase the perceived attractiveness of faces in human research. As nicotine and alcohol are often consumed together, we examined the combined effects of nicotine and alcohol on attractiveness ratings of facial and non-facial stimuli. Ninety-five (49% male) light smokers and social alcohol drinkers attended one experimental session, at which they consumed either an alcoholic or non-alcoholic drink and smoked a nicotinized or denicotinized cigarette. Whilst smoking, they completed a computer-based task, during which they rated the attractiveness of male faces, female faces and landscapes on a 7-point scale. A 2 (picture: face, landscape) × 4 (group: double placebo; placebo nicotine, alcohol; nicotine, placebo alcohol; nicotine, alcohol) ANOVA of ratings of attractiveness indicated significant main effects of target ($F [1, 91] = 135.94$, $p < 0.001$) and group ($F [3, 91] = 2.94$, $p = 0.037$). Participants gave higher attractiveness ratings to landscapes ($M = 4.46$, $SD = 0.66$) compared to faces ($M = 3.64$, $SD = 0.60$). The main effect of group was examined further using independent t-tests which revealed significantly higher ratings in the nicotine and alcohol ($M = 4.29$, $SD = 0.50$) group compared to the double placebo group ($M = 3.86$, $SD = 0.64$). Furthermore, no significant group effects were observed on subjective outcomes ($ps > .05$) suggesting that these effects were not mediated by mood or craving. These findings indicate that co-administration of alcohol and nicotine (via smoking) significantly increases ratings of attractiveness compared to placebo. Ratings of attractiveness were also higher for nicotine/placebo alcohol and placebo nicotine/alcohol groups compared to placebo but this difference did not reach statistical significance, suggesting the effects of nicotine and alcohol worked additively to increase ratings of attractiveness. The lack of a significant target by group interaction indicates that these effects were not restricted to facial stimuli. These data suggest that co-commitant administration of nicotine via smoking and alcohol increase the affective valence of stimuli, which in turn may play a role in their continued use. This project received no external funding.

MD06

EFFECTS OF ACUTE INHALATION OF VAPORIZED CANNABIS OR PLACEBO ON CARDIOVASCULAR AND SACCADIC EYE MOVEMENT MEASURES: A PILOT STUDY

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Cannabis is the most commonly used illicit drug worldwide and its long-term effects are poorly understood. Much of the recent research that has been done has used pure Δ9-tetrahydrocannabinol (THC) the main psychoactive constituent of cannabis. However, THC is not the only constituent of cannabis and therefore reports of its effects are not a good model of 'street' cannabis use. Presented here are data from a pilot study to determine the feasibility of reliably measuring the effects of an acute inhalation of a low and a high dose of vaporized cannabis, in raw botanical form or placebo on subjective, cardiovascular and saccadic eye movement (SEM) measures. This was a double-blind, placebo controlled crossover study in five healthy male, non-dependent, experienced cannabis users. Exclusion criteria included history of a major psychiatric disorder (especially psychosis), or meeting DSM-IV criteria for substance misuse (alcohol or drugs). The botanical cannabis material (~19% w/w THC) or placebo (0% w/w THC) was weighed to give a dose of ~7mg and ~20mg of THC, or a comparable mass of placebo material. This was administered using a "Volcano Classic" vaporiser (Storz & Bickel GmbH & Co. KG) on three separate days at least a week apart. Subjective, Cardiovascular and SEM data were collected over a period of 60min. Data were analysed as a change from baseline on each separate occasion using a two-way ANOVA with Bonferroni post-test, with a significance of $P<0.05$. There was a significant dose dependent increase in heart rate following cannabis. This effect was significantly different for the high dose compared with placebo at: 5, 15, 20 and 40min. However, there was no significant effect on the systolic or diastolic blood pressure. Two of the five measures of SEM recorded showed a significant effect; a dose dependent increase in the magnitude of errors made that was significantly different for the high dose compared with placebo at: 5, 20 and 40min. A significant effect of time on peak velocity was also seen. The volunteers reported the effects of the inhalations were similar to their normal experience of smoking cannabis. These data show that the use of inhalation using a vaporiser is a viable method of cannabis administration. This provides a naturalistic way to investigate the effects of botanical cannabis in healthy volunteers.
This work was supported by an educational grant from the Beckley Foundation.

MD07

DEPENDENCY, PSYCHOSIS AND FREQUENCY OF USE IN HIGH VS. LOW POTENCY CANNABIS PREFERENCE

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Introduction: High potency cannabis such as 'skunk', which contains high levels of psychoactive 'Delta-9-tetrahydrocannabinol (Δ9-THC)' and low levels of Cannabidiol (CBD), has increasingly dominated the street-market. Concurrently, the number of people diagnosed as cannabis dependent has increased in recent years. Previous research has also linked psychosis and frequency of use with cannabis preference in schizophrenic populations. This study examined whether participants preferring high potency cannabis are more likely than those preferring low potency varieties to be cannabis dependent, use more frequently, and have higher schizotypy scores.
Method: 416 cannabis users aged 16-24 years old were tested twice; once when intoxicated and once when drug-free. Both subjective (participant expressed) and objective (Δ9-THC and CBD levels in cannabis and hair samples) measures of cannabis preference were collected.
Results: High potency preference was significantly associated with increased cannabis dependency, increased cannabis cravings when drug-free and more frequent cannabis use. No relationship between psychosis and cannabis preference was found.
Conclusions: This study is the first to demonstrate that preference for higher potency cannabis and dependence are linked, as well as to provide detailed information about patterns of cannabis preference. These findings have important public health implications in terms of educating people about which types of cannabis may be more addictive, thus leading to increased dependence.

MD08

CANNABIDIOL POTENTIATES THE CONSOLIDATION OF CONDITIONED FEAR MEMORY IN HUMANS

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Introduction: Cannabidiol (CBD), a non-psychoactive constituent of the cannabis plant, has been found to potentiate consolidation of conditioned fear memory in laboratory animals. CBD also attenuates the memory deficits resulting from Δ9-THC administration in cannabis smokers. The present study used a fear conditioning and recall paradigm to examine whether these pro-mnemonic effects of CBD are present in healthy human volunteers. Methods: 48 healthy volunteers were randomised to receive either 24ml CBD (n = 17) or placebo (n = 16) via inhalation post learning of contextual fear memory in a contextual fear conditioning/extinction paradigm. Participants underwent acquisition in context A, where a CS+ was paired with a 4mA shock (UCS) and were subsequently extinguished in context B, where the UCS was never presented. At recall 24 hours later, participants were presented with conditioned stimuli in acquisition and extinction contexts. Skin conductance and UCS expectancy data were collected during acquisition, extinction and recall. Demographic and psychometric data were collected for all participants.
Results: A significant effect of CBD on memory consolidation was found, evidenced by greater differential skin conductance response (CS+ > CS-) and expectancy ratings at recall in participants in the CBD group compared to the placebo group. Groups were well matched on demographic and psychometric variables.
Conclusions: This is the first study to show enhancement of both explicit and autonomic fear memory by CBD in healthy volunteers. This enhancement of consolidation may explain the attenuation of memory deficits in smoked cannabis with a high CBD:THC ratio. The observed pro-mnemonic effects of CBD suggest it may be a promising candidate for improving the efficacy of exposure-based therapies.

MD09

IMPACT OF CANNABINOIDS ON COGNITION, PSYCHOTIC-LIKE SYMPTOMS AND PSYCHOLOGICAL WELL BEING

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Introduction: Cannabis varies considerably in the level of its two major constituent canabinoids – delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Recently it was found that those who smoked cannabis containing traceable levels of CBD exhibited fewer psychotic-like symptoms than those whose cannabis had no CBD present (Morgan & Curran, 2008). The present study aimed to replicate those findings and to also determine whether the protective effects of CBD may extend to the harmful effects of cannabis including memory impairment and reduced psychological wellbeing.
Method: 120 current cannabis smokers (66 daily and 54 recreational users) were classified into groups according to the presence or absence of CBD and high versus low levels of THC, derived from hair analysis. Participants were assessed on measures of psychosis-like symptoms, memory (prose recall; source memory) and depression/anxiety.
Results: The previous findings were replicated, with lower psychosis-like symptoms present in those whose hair had CBD compared with those without. However, this was seen only in recreational users who had higher levels of THC in their hair. Daily users indicated a preference for high THC/low CBD cannabis ('skunk') to other strains, but there was no preference difference between CBD or THC groups. Higher THC levels in hair were associated with increased depression and anxiety. Prose recall and source memory were poorer in daily users with high THC levels in hair whilst recognition memory was better in individuals with CBD present in hair.
Conclusion: Recreational users of cannabis whose hair contains high levels of THC and no CBD show more psychotic-like symptoms than those with high THC and detectable CBD. Thus CBD attenuates the psychotic-like effects of cannabis over time. In terms of memory, CBD attenuates the effects of THC on familiarity but not the THC-induced impairment of recollection. These findings raise concerns for the harms stemming from use of varieties like 'skunk' which lack any CBD, yet are currently dominating the supply of cannabis in many countries.
The research is funded by the Medical Research Council.

MD10

THE NEURAL CORRELATES OF ATTENTIONAL BIAS IN OPIATE ADDICTION AND THEIR MODULATION BY CUE-ELICITED CRAVING

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Attentional bias towards heroin related stimuli is frequently demonstrated in opiate addiction and is associated with relapse risk (Marissen et al 2006, Addiction, 101, 1306-1312). However, the brain areas underlying this effect are currently unknown. In addition to poor drug related attentional control, drug craving is also thought to be important for the maintenance of addiction. Considering the importance of both attentional control and craving in addiction, an investigation into the interaction between these factors is warranted. We aimed to identify the brain areas involved in attentional bias in opiate addiction, and examine the effect of craving on attentional bias. 12 newly detoxified male opiate addicts were scanned twice whilst carrying out an emotional Stroop task containing heroin, negative and neutral words using a 3 Tesla MRI Scanner. On one occasion participants viewed a "craving" video containing scenes of heroin preparation before the task, and on another occasion, a "neutral" video. Participants were asked to identify the colour of the text as quickly as possible, with reaction time used as an index of attentional bias. Behavioural and fMRI data were analysed using repeated measures ANOVAs using SPSS and SPM8 respectively. There was a clear attentional bias towards heroin words with participants taking longer to identify the colour of heroin words compared to neutral and negative words ($p=0.004$) after both the craving and neutral video. However, no significant effect of craving on reaction times was seen. There was a non-significant trend for incorrect colour identification for all word conditions after the craving video. The attentional bias towards heroin related words was associated with enhanced activation of the bilateral insula, entire cingulate gyrus, precuneus, and bilateral dorsolateral prefrontal cortex when compared with neutral and negative words. Furthermore, this attentional bias was associated with reduced activation in the primary motor cotex, supplementary motor area, somatosensory cortex and the caudate ($p<0.001$ unc). Craving resulted in a reduced activation of the right inferior frontal gyrus and anterior cingulate cortex across all word conditions ($p<0.001$ unc) and an increased activation in the thalamus and reduced suppression of the ventral anterior cingulate specifically towards heroin words ($p<0.001$ unc). Attentional bias was associated with a distinct pattern of brain responses involved in cognitive control. Craving modulated brain responses involved in cognitive control with the anterior cingulate being a key site of interaction. This study is funded by the Medical Research Council (MRC)

MD11

REDUCTION IN ILLICIT OPIATE USAGE DURING A SUPERVISED METHADONE TREATMENT PROGRAMME

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Introduction: The Cardiff Drug Intervention Program (DIP) is part of government strategy to help opiate users into appropriate treatment. The aim of this study was to examine patient outcomes during supervised methadone treatment at DIP using a range of outcome measures.
Methods: Data were collected retrospectively from patient records. Outcomes were measured using the Christo Inventory for Substance-misuse Services (CISS) score at 0, 3 and 6 months, money spent on heroin per day, change in injecting behaviour and drug urine screen.
Results: At the time of the study, 40 patients were treated at DIP of whom 28 agreed to be included. The mean age was 30.6 ± 5.1 years, 21 patients were male and the mean time in treatment at DIP was 133.7 ± 67.2 days (range 31 - 267). Patients' drug usage histories showed that all 28 previously used heroin and alcohol, whilst 96% previously used crack cocaine, 89% cannabis and 89% benzodiazepines. 16 of the 28 patients were injecting prior to treatment at DIP, which was reduced to 8 during treatment. Mean CISS scores at 0, 3 and 6 months were 11.75 ± 2.86, 7.76 ± 2.82*, and 5.4 ± 3.43* respectively (*$p<0.01$ vs month 0, Kruskal Wallis test with Dunn's post hoc analysis). Analysis of drug screen urines revealed that of 257 samples taken over the study period, 79% were positive for opiates (other than methadone), 43% for cocaine, 38% for benzodiazepines and 42% for cannabis. The proportion of positive opiate screens was 94% at the start of treatment and 50% at six months ($p<0.01$, Fisher's Exact Test, n=93). The mean self-reported reduction in heroin spending was £24.36 ± £14.03 with patients in months 6-8 of treatment at DIP showing the largest reduction.
Conclusions: Treatment at DIP appeared to be associated with positive outcomes as assessed by the measures employed in this study. CISS scores were significantly lower at three and six months compared with the start of treatment. Money spent on heroin per day, and the number of clients reporting injecting behaviour were also reduced, although it must be noted that these were self-reported measures. Drug urine screen analysis indicated that usage of opiates (excluding methadone) decreased as methadone treatment continued, with a significantly smaller proportion of positive results at six months than at treatment initiation. The percentage of urines positive for cannabis increased with time, although the change did not attain statistical significance.
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MD12

DECREASED CEREBRAL BLOOD FLOW AFTER INTRAVENOUS PSILOCYBIN

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Introduction: This study sought to identify the functional brain correlates of the psychedelic state using arterial spin labelling and the classic psychedelic drug psilocybin (magic mushrooms). Psilocybin has been used for centuries in 'healing' ceremonies and it has a more recent history of use in psychotherapy. Psilocybin produces an unusual state of consciousness, characterised by perceptual distortions and vivid imagination, and it is not uncommon for users to describe their experiences as 'meaningful' and 'beneficial'. Understanding how the brain changes during such states may reveal how the brain maintains its usual state of consciousness during normal waking and have implications for therapeutic applications of psychedelics.
Methods: Fifteen healthy, hallucinogen-experienced subjects (5 females and 10 males), mean age 34.1 (SD 8.2) participated in this study. Subjects underwent an anatomical scan followed by two task-free functional scans, each lasting 18 minutes. Pulsed arterial spin labelling was used to measure dynamic changes in cerebral blood flow (CBF) following the saline/drug infusions. Solutions (10ml) were infused manually over 60 seconds beginning 6 minutes after the start of each functional scan. In every case, subjects received placebo (saline) in the first scan and psilocybin (2mg) in the second. Within-session changes in CBF following infusion were taken to the group level to reveal regions where CBF was significantly different after psilocybin versus after placebo.
Results: Only decreased CBF was observed after psilocybin (mixed effects analysis, cluster threshold = 2.3, p = .05 FWE) and this was significant in a number of subcortical and cortical regions. The decreases were remarkably well localized to key connector hubs in the brain, such as the thalamus, medial prefrontal cortex (mPFC) and posterior cingulate cortex, and ratings of the intensity of the drug effects correlated positively with the magnitude of the CBF decreases in the mPFC.
Conclusions: This was the first psychedelic drug fMRI study of its kind and the first modern neuroimaging study of psilocybin. The observed decreases in CBF were in brain regions that are known to have higher than average activity and connectivity. Decreased activity in these hub regions may compromise the brain's ability to integrate and constrain information processing, explaining the unconstrained quality of cognition in the psychedelic state. Moreover, the observed decreases were in regions that are typically hyperactive in depression (e.g. the mPFC), suggesting that psilocybin may be useful in this condition – perhaps by destabilising a pathologically attracting brain state. Funders: Beckley foundation, Neuropsychoanalysis Foundation, MAPS & Heffter Research Institute.

MD13

BEHAVIOURAL AND NEUROCHEMICAL RESPONSES TO CHRONIC INTERMITTENT MEPHEDRONE ADMINISTRATION IN THE RAT

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4-Methylmethcathinone (mephedrone) was classified as a class B drug under the Misuse of Drugs Act, 1971 in the UK on 16th of April, 2010. Before this, mephedrone was the most popular of the cathinone derivatives to be used recreationally. It has been implicated in a number of deaths in the UK (Schifano et al., 2010, Psychopharmacology: 214, 55). Users of mephedrone have compared its effects to 3,4-methylenedioxymethamphetamine (MDMA) and its rise in popularity was probably due to its initial legal status and the perceived decline in purity of other illicit drugs (Brunt et al., 2011, J Psychopharmacol In Press). However, there is little information available on the behavioural and neurochemical effects of mephedrone in laboratory animals. This study examined the effect of repeated mephedrone injection on behaviour and brain neurotransmitter levels in rats. Adult male Lister Hooded rats (n=24, 215-405g, CRUK) received mephedrone HCl (1mg/kg or 4mg/kg, i.p.) or saline (1mg/kg, i.p.) twice a week on consecutive days, over three weeks, to mimic bingeing in humans. The mephedrone dose schedule used is comparable to that required in rats to produce a clinically relevant dose of MDMA (Green et al., 2009, Psychopharmacology 204; 375). Following each injection, locomotor activity (LMA), novel object recognition (NOR) (week one), conditioned emotional response (CER) (week two), prepulse inhibition of the acoustic startle (PPI) and LMA again (week three) were measured. One week after the final dose, striatum, frontal cortex and hippocampus were collected for quantification of dopamine, serotonin and their metabolites using High Performance Liquid Chromatography with electrochemical detection. Mephedrone (4mg/kg) caused a significant but transient increase in LMA, 10 minutes after the first dose ($p<0.01$, Two-way ANOVA, repeated measures) and 5 minutes after the sixth dose ($p<0.05$, Two-way ANOVA, repeated measures) both lasting less than 20 minutes. Neither dose of mephedrone had any significant effect on NOR (but total object exploration in trial one was reduced), CER or PPI. No alterations in dopamine or serotonin content were detected in any brain regions examined. In conclusion, repeated doses of mephedrone at 1mg/kg or 4mg/kg produced few significant effects on behaviour and no alterations in dopamine or serotonin levels in the rat brain regions examined. These preliminary data suggest that mephedrone has a different pharmacological profile to that seen following MDMA.
This work was funded by the School of Biomedical Sciences, University of Nottingham.

MD14

DIFFERENTIAL EFFECT OF CATHINONES AND MDMA ON BODY TEMPERATURE AND BRAIN NEUROCHEMISTRY IN THE RAT

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Recreational users of cathinones, especially 4-methylmethcathinone (mephedrone; currently implicated in 48 deaths in the UK; Schifano et al 2011 Psychopharmacology 214 593) have compared their effects to 3,4-methylenedioxymethamphetamine (MDMA, ecstasy). Recreational MDMA use can cause potentially fatal hyperthermia and in rodents (which exhibit hyper- or hypothermia depending on dose and housing conditions) this has been attributed to complex monoaminergic effects on central thermoregulation, peripheral blood flow and thermogenesis (Docherty & Green 2010 Brit J Pharmacol 160 1029). It remains unknown as to whether cathinones cause similar effects, and the present study examined the acute effect of cathinone, 2-(methylamino)propiophenone (methcathinone) and mephedrone on core body temperature and brain neurochemistry in the rat, with MDMA included for comparison. Adult male Lister hooded rats (400-500g; University of Nottingham BSMU cathinone study or 220-260g; CRUK, remaining compounds) were habituated to individual test arenas for 40min (room temperature ~19.5°C). Rectal temperature was measured and animals (n=5-6/group) received a single i.p. injection of (-)-cathinone, mephedrone, methcathinone, (±)-MDMA (4mg/kg HCl salt) or saline vehicle (1ml/kg i.p.). Rectal temperature was measured at 20min intervals for the next 2h, when rats were killed and frontal cortex, hippocampus and striatum collected for quantification of monoamine neurotransmitters and metabolites using HPLC with electrochemical detection. Cathinone caused a sustained elevation in core body temperature which reached statistical significance 40min after injection ($P<0.001$ versus vehicle, two-way repeated measures ANOVA) and remained elevated until 120min post-injection. Peak temperatures (40min post-cathinone) were 1.0±0.2°C higher than baseline. In contrast, the same dose of MDMA caused a sustained decrease in core body temperature which was statistically significant throughout the experiment; again the maximal effect was 40min post-injection (1.6±0.1°C below baseline; $P<0.001$ versus vehicle, two-way repeated measures ANOVA). Mephedrone produced a transient hypothermia which was significant only at 20min post-injection (0.7±0.1°C below baseline; $P<0.001$ versus vehicle, two-way repeated measures ANOVA), while methcathinone had no effect. Cathinone significantly increased striatal dopamine levels (64.0±3.3 versus 53.8±2.5pmol/mg for control; $P<0.05$, unpaired t-test) whereas MDMA significantly decreased hippocampal 5-HT levels (2.7±0.3 versus 4.2±0.3pmol/mg for control; $P<0.05$, one-way ANOVA). The cathinones clearly have differential effects to each other and to MDMA on both thermoregulation and brain neurochemistry. These differences do not correlate with variations in molar dose (21.5, 20.0, 18.7 and 17.4mmol/kg respectively for cathinone, methcathinone, mephedrone and MDMA). Contributing factors may include the balance of central versus peripheral effects, as only cathinone is metabolised to the sympathomimetic amines ephedrine and norpseudoephedrine.

MD15

EFFECTS OF MEPHEDRONE ON MONOAMINE RELEASE IN THE BRAIN: COMPARISON WITH D-AMPHETAMINE

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The amphetamine analogue mephedrone is a recreational drug banned by the Home Office in 2010. Although the neurochemical effects of mephedrone are unknown, it is established that other amphetamine analogues release DA and/or 5-HT. Here we compared the effects of mephedrone and d-amphetamine on brain DA and 5-HT release. Male Lister-hooded rats, anaesthetised with urethane, were implanted with microdialysis probe(s) in the prefrontal cortex (PFC) and/or caudate putamen (CP). Probes were perfused with standard artificial CSF or calcium-free aCSF with or without mephedrone, amphetamine, or the DA reuptake inhibitor GBR 12909. Dialysates were assayed for 5-HT (PFC) or DA (CP) by HPLC-ED. Mephedrone (10, 30, 100 µM, 60 min each) induced concentration-dependent increases in dialysate DA (Area under the curve (AUC): 539 ± 354 (3), 894 ± 341 (4), 1825 ± 729 (4) fmol) but failed to alter dialysate 5-HT levels (AUC: -17 ± 16 (4), 17 ± 20 (5), 33 ± 26 (5) fmol). Amphetamine (10, 30, 100 µM 60 min each) induced concentration-dependent increases in DA which were much larger than those induced by mephedrone. (AUC: 2966 ± 669 (8), 4801 ± 983 (8), 6089 ± 1323 (6) fmol). Amphetamine also induced modest concentration-dependent increases in 5-HT (AUC: 47 ± 16 (6), 99 ± 31 (6), 98 ±37 (4)fmol). Perfusion with calcium-free aCSF (100 min) decreased basal dialysate DA levels by more than half (86 ± 20 vs 37 ± 7 (10) fmol: basal vs calcium-free) and almost completely blocked the increase in DA following perfusion of GBR 12909 (30 µM, 80 min) (AUC 892 ± 126 (3) vs 85 ± 8 (3) fmol: standard aCSF vs calcium-free aCSF). In contrast, perfusion with calcium-free aCSF only partly blocked the DA response to mephedrone (100 µM, 80 min) (AUC: 4167 ± 1093 (5) vs 1715 ± 758 (4) fmol standard aCSF vs calcium-free). Similarly perfusion with calcium-free aCSF only partially inhibited the DA response to amphetamine (10 µM, 60 min) (AUC: 2966 ±669 (8) versus 696 ± 140 (3) fmol). Our data indicate that mephedrone causes the release of DA but not 5-HT in the brain but that it is less efficacious than d-amphetamine. The mephedrone-induced release of DA is at least partly calcium-independent and, in that respect, more closely resembles the response to d-amphetamine (a known releasing agent) rather than GBR 12909 (a DA reuptake inhibitor). We thank Prof Simon Gibbons (London School of Pharmacy) for the generous gift of mephedrone.

MD16

PARADOXICAL NEGATIVE MOOD CHANGES FOLLOWING 100MG. ACUTE MDMA IN A LABORATORY STUDY

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Introduction: to investigate the mood effects of acute oral doses of MDMA and methamphetamine, in a double-blind placebo controlled laboratory study.
Methods: 52 healthy volunteers comprised abstinent recreational users of stimulant drugs. They were administered acute oral doses of 100mg 3.4-methylendioxymethamphetamine (MDMA), 0.42mg/kg oral methamphetamine (METH), and matching placebo, in a counterbalanced double-blind procedure. Car driving performance on a laboratory simulator was also undertaken (findings presented elsewhere). This report covers the PANAS (positive and negative affect scale), at baseline, 3.0 hours, 4.5 hours, and 24 hours post-drug.
Results: under placebo, group mean positive and negative moods were reduced at the 3 hour session compared to baseline, then remained broadly stable over subsequent sessions. The PANAS positive mood scale showed far greater variance than the negative mood scale. In terms of drug effects, METH led to a comparative increase in positive moods at 3 hours which was significant (+4.6, $p<0.001$). Under MDMA there was a smaller increase in positive moods at 3 hours which did not approach significance (+1.8, ns). PANAS negative moods at three hours were significantly higher under METH than placebo (+2.5, $p<0.001$), and significantly higher after MDMA than placebo (+2.2, $p<0.001$). The absence of significantly positive mood gains with MDMA here, contrasts with the elated moods and euphoric feelings noted by Ecstasy-using dance clubbers. However they are consistent with some previous laboratory findings. In experiential-entactogenic types of laboratory study, significant positive mood gains are generally reported. Whereas in studies which involve cognitively demanding tasks (such as car driving, or other assessments), neutral-negative moods have been noted (Bedi & De Wit, 2010). The environmental situation is also important for other serotonergic agents such as LSD, with good and bad 'trips' related to the ongoing psychosocial situation. In this study the parent compound methamphetamine led to significant increases in both positive moods and negative moods. This may reflect its primary dopaminergic profile, and hence relative independence from situational factors. Other explanatory factors, such as dosage and neurohormonal influences, will also be discussed.
Conclusions: MDMA did not generate a significant increase in positive moods, which was rather unexpected in a psychoactive drug termed 'ecstasy'.
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MD17

METHYLPHENIDATE USE IN PREGNANCY AND LACTATION, A SYSTEMATIC REVIEW OF EVIDENCE

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As ADHD awareness increases more adults are being treated with stimulant medications (eg. methyphenidate, amfetamine, modafinil) (Van den Ban et al, 2010). New situations not frequently encountered when treating ADHD in children are now appearing, including the treatment of ADHD during pregnancy and lactation. We present a systematic review of the literature of use of methylphenidate during pregnancy and lactation and a case in which treatment was successfully continued during pregnancy. A 21 year old woman was diagnosed with ADHD in childhood and treated with Methylphenidate 72 mg/day slow release. Previous attempts to withdraw medication had ended in rapid deterioration of symptoms, including increased irritability, anxiety, mood instability, hyperactivity, impulsive behavior (two traffic accidents) and episodes of severe self harm. On becoming pregnant, it was decided to continue medication after discussing the risks in detail. After delivery, medication was interrupted to permit breastfeeding, however, within 4 weeks the patient deteriorated. Concerns were raised about her ability to raise the baby and social services became involved. In view of this, medication was reintroduced with great improvement. The baby was subsequently healthy and thrived, social services having no further concerns about his welfare. Six medical databases were searched (Pubmed, Psychinfo, Web of Science, Embase, Biosis, Medline) using appropriate search terms. Two case reports and a case series were identified. All the articles, reported combinations of methylphenidate with either known teratogenic drugs (phenytoin) or drugs of abuse (pentazocine, cocaine, alcohol and nicotine). Malformations reported included: congenital heart defects (n=2), polydactyly (n=1), and limb malformations(n=1). Other problems reported included premature birth, asphyxia and growth retardation. It is difficult to ascertain the effect of methylphenidate as a teratogenic agent in these cases since it was taken in conjunction with illicit drugs. In the one case where methylphenidate was prescribed by medical staff it was given in conjunction with a known teratogenic drug. Three case reports were identified regarding exposure to Methylphenidate through breast feeding. In all cases, children developed normally and no adverse effects were reported. Our systematic review revealed little existing evidence about the use of methylphenidate in pregnancy in mothers with ADHD. Identified cases were not representative of the general adult ADHD population having methylphenidate as monotherapy. Although the default medical position is to interrupt any non-essential pharmacological treatment during pregnancy and lactation, in ADHD this may present a significant risk. Doctors need to evaluate each case carefully before interrupting treatment.

MD18

EFFECTS OF CAFFEINE ON DRIVING PERFORMANCE

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Introduction: Coffee is often consumed to counteract driver sleepiness. The aim of this study was to examine the effects of coffee (80 mg caffeine) on simulated driving performance.
Methods: Non-sleep deprived healthy volunteers (N=24) participated in a double-blind placebo-controlled crossover study. After 2 hours of monotonous highway driving, subjects receive caffeinated or decaffeinated coffee during a 15-minute break, before continuing driving for another 2 hours. The primary outcome measure was the standard deviation of lateral position (SDLP), reflecting the weaving of the car. Secondary outcome measures were speed variability, subjective sleepiness, and subjective driving performance.Data was analyzed using SPSS, analysis of variance for repeated measures.
Results: Caffeinated coffee significantly reduced SDLP as compared to decaffeinated coffee, both in the first ($p=0.024$) and second hour ($p=0.019$) after the break. Similarly, the standard deviation of speed ($p=0.024$; $p=0.001$), mental effort ($p=0.003$; $p=0.023$), and subjective sleepiness ($p=0.001$; $p=0.002$) were reduced in both the first and second hour after consuming caffeinated coffee. Subjective driving quality was significantly improved in the first hour after consuming caffeinated coffee ($p=0.004$).
Conclusion: Caffeinated coffee (80 mg) significantly improves driving performance and reduces subjective sleepiness during monotonous simulated highway driving. Acknowledgment: the study was funded by Utrecht University. The authors have no conflicts of interest to disclose.

MD19

MODAFINIL INCREASES THE WITHIN-SESSION RISK-PREFERENCE OF MICE IN THE IOWA GAMBLING TASK

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Introduction: Poor decision-making is observed in neuropsychiatric patients. For example, patients with Bipolar disorder exhibit increased risk-taking behavior during manic episodes and during periods of euthymia. Such risky decisions can negatively impact daily and future living. Risk preference can be measured using the Iowa Gambling Task (IGT), wherein cards are chosen with differing levels of rewards and punishments. In the IGT, healthy subjects shift from risk-prone choices to low-reward but best-outcome options with increasing trial exposure, while Bipolar disorder patients take longer to shift. Understanding the genetics and neurobiology underlying these behaviors may assist in developing novel treatments for disorders. A within-session learning mouse version of the IGT has yet to be established and validated. Methods: C57BL/6N mice were trained in a mouse version of the IGT in 5-choice chambers. Mice could respond in 1 of 4 lit holes, each with varying reward levels and punishment (time-outs). Each session lasted 60 min or 250 trials. Performance was analyzed over 3 trial bins. One-week later mice were administered modafinil (32 mg/kg) or vehicle in a cross-over design. Results: Consistent with rats, three separate groups were identified with a group by trial period interaction ($F(3,776)=8.3$, $p<0.001$). One group selected the safer options with increasing trials, one group demonstrated little preference, while one third selected the riskier options over time. Importantly, performance did not differ between the three groups in the first third of the session. Moreover, upon retest there was a very strong test-retest reliability for risk preference ($r=0.946$). Finally, modafinil tended to increase risk preference in the safe-prone group ($F(1,6)=4.0$, $p=0.091$). Conclusions: Mice demonstrate within-session learning in the mouse IGT. Consistent with rat studies, three groups of safe-prone, intermediate, and risk-prone mice could be identified based on preference in the final third of trials. In contrast with rats however, safe-prone mice selected safer options based on minimizing punishment instead of maximizing reward. Consistent with an IGT study in human pathological gamblers, modafinil increased risk preference in safe-prone subjects. Finally, the test-retest reliability of this task supports its use in repeated testing in mice. The mouse IGT permits a rapid assessment of decision-making in mice, with some cross-species translational predictive validity for the human IGT. Thus, the mouse IGT may prove useful for understanding 1) the neurobiology & genetics underlying decision making, and 2) developing animal models of diseases as well as putative therapeutics.

MD20

INTERNAL RELIABILITY OF MEASURES OF SUBSTANCE-RELATED COGNITIVE BIAS

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There is growing interest in cognitive biases related to substance use, the presence of which is predicted by incentive-sensitization and other models of addiction (Franken, I. H. A. (2003), Progress in Neuro-Psychopharmacology & Biological Psychiatry 27(4): 563-579.; Field, M. and W. M. Cox (2008), Drug and Alcohol Dependence 97(1-2): 1-20). Evidence from the anxiety literature suggests that tasks commonly used to assess these may suffer from poor psychometric properties, such as low internal reliability (Schmukle, S. C. (2005), European Journal of Personality 19(7): 595-605).To date, no published study has examined the internal reliability of comparable tasks designed to assay substance-related cognitive bias. Here we examine estimates of internal reliability from seven studies investigating the salience of substance-related cues in alcohol and tobacco users using the visual probe and modified Stroop tasks. Studies 1 and 2 examined cognitive bias to alcohol cues in social drinkers, who received either placebo or an alcohol challenge. Studies 3 and 4 also examined cognitive bias in social drinkers, but with no challenge condition. Studies 5, 6 and 7 examined cognitive biases to tobacco cues in cigarette smokers, the first following either placebo or an nicotine challenge and the second following either placebo or an alcohol challenge, while the third did not use a challenge condition. Studies 1, 2, 5, 6, and 7 used a visual probe task and a modified Stroop task, while study 3 used two versions of the visual probe task (one using picture stimuli and one using word stimuli) and study 4 used two versions of the modified Stroop task (again one using picture stimuli and one using word stimuli). In all cases, different tasks and task formats were presented in counterbalanced order. Cronbach's α was calculated as an index of internal reliability. Bias scores were calculated for stimulus pairs in each task. Cronbach's α coefficients were calculated for each challenge condition (e.g. alcohol vs. placebo) separately where appropriate, and in these cases averaged across conditions. For the visual probe task, α coefficients ranged from 0.00 - 0.50, with no studies achieving the acceptable 0.70 level. For the modified Stroop task, α coefficients were somewhat higher, and ranged from 0.53 - 0.98, although in only two studies was the average α coefficient across conditions above the 0.70 level. There was no clear pattern of drug challenge being associated with α coefficient. The modified Stroop task is preferable to the visual probe task as a measure of substance-related cognitive bias, on the basis of its psychometric properties. Studies using cognitive bias tasks should not assume they are reliable, and should routinely report reliability estimates where possible.
Funding: University of Bristol studentship.

ME01

INVESTIGATING EMOTION PERCEPTION AND MOOD IN UNDERGRADUATE POPULATIONS

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Individuals with major depression have a negatively biased perception of their surroundings. Biases in emotion perception may play an important role in maintaining and causing negative mood states, creating a vicious cycle whereby the world is perceived negatively, in turn increasing negative affect. However, the causal relationship between emotion perception and affect has not yet been established. If this relationship exists, the experimental manipulation of emotion perception may have a therapeutic effect in those suffering from depression. The current study investigated whether the experimental manipulation of the perception of ambiguous emotional expressions, designed to induce a bias towards interpreting these as expressing positive emotion, influenced mood among individuals selected as having high levels of depressed mood. Seventy-seven participants were recruited on the basis of reporting high levels of depressed mood. Participants completed a computer-based task, repeated on four occasions over the course of one week, where they were required to judge ambiguous emotional expressions as happy or sad, from a computer-generated sequence of faces morphed from unambiguously happy to unambiguously sad. Those in the experimental condition received feedback designed to induce a shift in perception, so that faces initially perceived as sad where perceived as happy. Those in the control condition received feedback designed to induce no shift in perception. All participants completed measures of depressed mood, positive affect and negative affect BDI-ii and PANAS questionnaires at baseline, post-training and weekly for the two weeks following the training week. Emotion perception threshold did not differ between groups at baseline ($p = .868$), but was significantly different at the end of training ($p < .001$). Regression analysis indicated an improvement in positive affect in the training group compared to the control group ($R^2 = 0.249$, $b = 3.145$, 95% CI 0.049 to 6.242, $p = .047$). Although effects on depressed mood ($R^2 = 0.119$, $b = -1.500$, 95% CI -6.152 to 3.153, $p = .522$) and negative affect ($R^2 = 0.200$, $b = -1.801$, 95% CI -5.055 to 1.453, $p = .273$) did not achieve statistical significance, these were in the predicted direction. All analyses were adjusted for age, sex, ethnicity, socioeconomic position and baseline mood on the relevant measure. Our data indicate that it is possible to modify biases in the perception of ambiguous emotional expressions, and that this results in a corresponding improvement in positive affect. Future studies should investigate whether this can be achieved in clinical samples.

ME02

DOES PRESYNAPTIC STRIATAL DOPAMINE SYNTHESIS CAPACITY PREDICT SOCIALLY DESIRABLE RESPONDING?

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Introduction: Socially desirable responding (SDR), the tendency to present oneself in an overly positive manner, has been shown in [11C]-raclopride PET studies to be negatively correlated to human postsynaptic striatal D2/3 receptor availability (Reeves et al, 2007, Neuroimage34(4): 1782-1789; Egerton et al, 2010, Neuroimage53(2): 777-781). SDR is a complex personality construct which reflects both social conformity (Impression management, IM) and the degree to which individual's behaviour is viewed in a positive light (Self-deceptive enhancement, SDE). Egerton et al (2010) found that sensorimotor striatal D2/3 receptor availability predicts IM, but not SDE, at trend level. Although the interaction between SDR and measures of postsynaptic striatal dopamine function has been widely studied, none have so far investigated whether these relationships also occur with presynaptic dopamine function. In this [18F]-DOPA study we investigated whether human presynaptic striatal dopamine synthesis capacity predicts SDR.
Methods: 20 healthy volunteers (11 males, 9 females, age 37 ± 14 yrs) previously underwent [18F]-DOPA PET imaging to determine presynaptic striatal dopamine synthesis capacity. Volunteers were imaged using a high resolution ECAT EXACT3D PET scanner. All scans were corrected for head movement using frame by frame realignment. Normalised striatal functional subdivision maps, comprised of limbic, associative and sensorimotor regions, were used to sample individual dynamic [18F]-DOPA PET images. Ki values for each region were estimated by a Patlak analysis using the cerebellum as a reference region. To assess SDR, volunteers completed the Balanced Inventory of Desirable Responding (BIDR), which measures both IM and SDE, and the Lie scale of the revised version of the Eysenck Personality Questionnaire (EPQ-R) which provides a measure of global SDR. Statistical analysis was performed using SPSS 19.
Results: We found no significant relationship between overall striatal Ki values and IM ($r=-0.21$, $p=0.4$), SDE ($r=0.26$, $p=0.3$) or the Lie scale of the EPQ-R ($r=-0.34$, $p=0.1$). IM, SDE or the Lie scale also did not correlate to any of the functional striatal subdivisions (p values for all correlations were >0.05).
Conclusion: We found that presynaptic striatal dopaminergic synthesis capacity does not predict SDR and additionally does not correlate to either IM or SDE. These findings indicate that although SDR may be sensitive to striatal dopamine D2/D3 receptor availability, this relationship is not reflected in correlations to presynaptic dopamine synthesis capacity.
This study was funded by the Medical Research Council, UK and PET imaging was provided in collaboration with GE Healthcare.

ME03

D2 RECEPTOR OCCUPANCY BY ANTIPSYCHOTIC DRUGS: A META-ANALYSIS OF PET AND SPECT STUDIES

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All presently available antipsychotic drugs count action at dopamine D2/D3 receptors (D2R) among their pharmacodynamic properties. Indeed, optimally clinically effective doses are well correlated with those at which each drug induces near-maximal D2R occupancy (Stone, J.M. et al., 2009, Schizophrenia Bull, 35(4):789-797), and it is hypothesized that optimal antipsychotic effect requires a minimum level of D2R occupancy – the consensus being between 65 and 70 percent (Pani, L., et al. 2007, Eur Psychiat, 22(5):267-275). However, it is not known whether effectiveness is determined by this factor alone: if this is the case, then optimal doses of equally effective antipsychotics should produce similar D2R occupancies. Definitive comparison of different drugs is hindered by the relatively small size of receptor imaging study samples. We therefore conducted a patient-level meta-analysis in order to evaluate this hypothesis. We selected studies estimating antipsychotic striatal and/or temporal D2R occupancy using positron emission tomography (PET) or single photon emission computed tomography (SPECT). Dose-occupancy curves fitted to the pooled data for each drug were used to calculate D2R occupancy at optimal doses, as determined by randomised double-blind fixed-dose trials (Davis, J.M. & Chen, N. 2004, J Clin Psychopharmacol, 24(2):192-208). Cochran Q and I2 statistics were calculated to assess the presence and extent of heterogeneity. Subgroup analysis was conducted for atypical D2R antagonists. Striatal dose-occupancy curves were fitted to 742 data points for 14 antipsychotic drugs (2 typical; 12 atypical). Fitted D2R occupancies at therapeutically effective doses ranged from 42% (quetiapine; SE=2.6, n=60) to 91% (loxapine; SE=5.4, n=10). Significant heterogeneity was detected for all drugs ($Q=379$, $df=13$, $p<0.0001$; $I2=97\%$) and for the atypical D2R antagonists ($Q=238$, $df=10$, $p<0.0001$; $I2=96\%$). Temporal D2R occupancy ranged from 46% (quetiapine; SE=3.5, n=34) to 85% (haloperidol; SE=12.3, n=8). These results suggest that occupancy of a threshold level of striatal D2R cannot be the sole factor determining optimal clinical effect across all antipsychotic drugs; 65% striatal D2R receptor does not appear to be a necessary condition for antipsychotic effect. While the range of temporal D2R occupancies is somewhat smaller, it nevertheless seems hard to escape the conclusion that variation in optimally effective antipsychotic dosing cannot be explained solely in terms of either striatal or temporal D2R occupancy. This study did receive funding from any source.

ME04

GLUTAMATERGIC MECHANISM IS INVOLVED ON THE SUPRESSION OF LPS-INDUCED FEVER BY PARACETAMOL IN RATS

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Introduction: Glutamatergic neurotransmission in several brain areas is involved on the febrile response. Specifically in hypothalamus the concentration of glutamate and the core temperatures were simultaneously increased following systemic administration of LPS in rabbits (Eur. J. Pharmacol., 2008, 593:105). The aim of this study was to investigate the involvement of glutamate AMPA receptors on the brain mechanisms activated by pretreatment with the antipyretic paracetamol in rats after i.p. injection of LPS. Methods: Male Wistar rats (200g; n=3-6) received vehicle (ethanol 10% in saline plus 20µl tween 80) or paracetamol (200mg kg-1) i.p. 30 min before (0.5 ml) of LPS (50µg kg-1) or saline (control group). The rectal temperature (oC) was measured every 30 minutes for up 3h by telethermometry. The fever induced by LPS (3 h: 1.4 ± 0.06 oC) was reduced by treatment with paracetamol (3 h: 0.3 ± 0.08 oC). Saline injection did not alter the basal temperature of the animals (3 h: 0.1 ± 0.08 oC). After 3 hours the animals were deeply anaesthetized (50ml/kg of urethane 25%), perfused with paraformaldehyde 4% and their brains removed. 40-µm sections were used for immunohistochemistry. The immunopositive cells (IC) were counted by 2-3 examiners independently, bilaterally, in 3 sections/rat, in lateral hypothalamus (LH), anteroventral thalamic nucleus (AV) and ependymal and subendymal layer/olfactory ventricle (E/OV). Data were compared by one-way ANOVA followed by Duncan test ($p<0.05$).
Results: Pre-treatment with paracetamol induced a significant increase in GluR1-IC in LH of animals that received LPS when compared to saline (76%) or LPS alone (138%; $p=0.02$). A non-significant reduction (26%) was observed in LPS group when compared to saline. The number of GluR2-IC in LH was higher than GluR1, however no change was induced by either LPS or pretreatment with paracetamol. No change was also found in GluR1- or GluR2-IC in AV or E/OV when saline/LPS or paracetamol/LPS groups were compared to saline group ($p>0.05$). A reduction of 29% was induced by LPS only in GluR1 expression in E/OV, but it was not significant when compared to saline ($p>0.05$).
Conclusions: Glutamatergic mechanism in LH through GluR1 AMPA receptors is involved on the antipyretic effect of the paracetamol during LPS induced fever. However, this mechanism in AV or E/OV is not involved on the paracetamol antipyretic effect.
Support: FAPESP and FPA.

ME05

PHOSPHODIESTERASE 9 INHIBITORS INCREASE LEVELS OF CYCLIC GUANOSINE MONOPHOSPHATE IN RAT HIPPOCAMPUS

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Alzheimer's disease (AD) is a debilitating neurodegenerative disorder, presenting with symptoms including memory loss. Current therapy is in the form of cholinesterase inhibitors and NMDA receptor antagonists, though these have only been moderately successful, and have not substantially improved symptoms associated with AD. This investigation aimed to validate in vivo microdialysis as a measure of hippocampal cGMP levels, in response to phosphodiesterase (PDE) inhibitor administration. PDE inhibitors regulate basal levels of second messengers. PDE9A is the predominant PDE in the hippocampus (Marte et al. 2008, Journal of Neuroscience Research, 86: 3338-3347) and specifically metabolises cGMP, a cyclic nucleotide that regulates synaptic plasticity, including long term potentiation (LTP). Previous experiments illustrate that elevating hippocampal cGMP improves performance in preclinical cognitive tests (Blokland et al. 2006, Current Pharmaceutical Design, 12 2511-2523). If increasing cGMP can enhance LTP, and ultimately learning and memory this could reduce memory loss in sufferers of AD. Bilateral hippocampal probe implantation surgery was performed on 72 male Lister Hooded rats. After 48 hours, animals were subjected to microdialysis experiments, where known PDE inhibitors EHNA and IBMX, and other PDE9 specific inhibitors PF-04447943 and PF-4181366 were administered. Levels of cGMP were analysed using an ELISA. Samples were acetylated, and the appropriate reagents added so levels could be measured and compared to standard solutions using light spectrophotometry at 450nm. Data are the mean values, and statistically analysed using repeated measures ANOVA (RM Fit). Differences were considered significant where $P<0.05$. Local administration of EHNA (1 mM) and IBMX (100 uM) via the dialysis probe increased cGMP levels to a similar extent (230% of basal levels – 550 pM and 200% - 450 pM, respectively), comparable to literature values. Systemic PF-4181366 or PF-04447943 administration (0-30 mg/kg s.c.) evoked dose-dependent increases in hippocampal cGMP, although results were only significant at 30 mg/kg. When comparing the two drugs directly, comparable increases in cGMP were obtained at 30 mg/kg s.c. PF-4181366 reached 519 pM, 275% of basal levels, whereas PF-04447943 rose to 446 pM, 350% of basal levels. PDE9A inhibitor administration significantly increases hippocampal cGMP levels. Theoretically, an increase in this cyclic nucleotide may facilitate hippocampal long term potentiation and improve cognitive processing in patients with AD (Van der Staay et al. 2008, Neuropharmacology, 55: 908-918.). Further experiments are required to tests the effects of these PDE9A inhibitors when administered before cognitive tests, to determine whether they can in fact, improve the memory of subjects.
This project was performed at Eli Lilly & Co.

ME06

THE OBSERVING RESPONSE TEST FOR RATS AS A MODEL OF THE CHECKING SYMPTOMS OF OBSESSIVE-COMPULSIVE DISORDER: CHRONIC QUINPIROLE TREATMENT INCREASES CHECKING-RELATED BEHAVIOURS

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Obsessive-compulsive disorder (OCD) is a debilitating condition (prevalence 1-3%), with compulsive checking the most commonly-reported symptom. Compulsive checking routines relate to security/order/accuracy (e.g., checking doors are locked), often for many hours per day at the expense of normal function. Although existing animal models of compulsive checking help us understand the neuropharmacology underpinning OCD symptoms (e.g., home-base checking in an open field arena1), they tell us little about how such behaviours evolve, or to what extent they interfere with normal function. We developed a novel test of compulsive checking that permits investigation of repetitive, compulsive-like behavior in detail, to assess how compulsive checking might develop from a more 'normal' behavioural repertoire. In operant-conditioning chambers, rats were presented with two levers: 'active' lever presses gave food reward whereas 'inactive' lever presses had no consequence. Active lever position switched within-session. A third (observing) lever press, gave information about the position of the active lever by illuminating a light above the active lever for 15s. Perseverative observing lever presses (POLP; OLP with the light already on) gave no further information. We validated the compulsive-checking model using an established pharmacological model of OCD1: 10 consecutive days of quinpirole (dopamine D2-receptor agonist, 0.5 mg/kg i.p. n=12) or saline vehicle (0.9% w/v 1 ml/kg i.p. n=12), to determine if quinpirole would increase 'compulsive' responding. We predicted that 'checking' behaviour might be directed at the observing lever if it related to information-gathering and uncertainty-reduction. All experiments were conducted in accordance with the United Kingdom Animals (Scientific Procedures) Act, 1986. During the quinpirole-treatment phase, OLP and POLP increased compared with pre-treatment baseline performance (baseline vs quinpirole days 6-10 OLP $F(1,20)=25.88$, $p<0.001$; POLP $F(1,20)=6.70$, $p\leq0.018$), despite quinpirole suppressing other responding on ALP/ILP (ALP $F(1,23)=14.63$, $p\leq0.001$; ILP $F(1,23)=4.88$, $p<0.05$) Increased OLP and POLP was maintained for many weeks in the absence of any further drug treatment, during the post-quinpirole phase (e.g., post-quinpirole days 6-10 OLP $F(1,23)=4.48$, $p<0.05$; POLP $F(1,23)=15.63$, $p\leq0.001$), although responding on ALP/ILP returned to normal levels in the absence of quinpirole (ALP $F(1,20)=0.37$, n.s.; ILP $F(1,20)=0.00$, n.s.). Quinpirole robustly increased behaviours that were predicted to represent checking behaviour, and these behaviours were maintained for an extended post-drug period. This novel task has considerable potential for further study of how checking behaviour might develop and subsequently become excessive/inappropriate in disorders such as OCD. (1)Szechtman H. et al. (1998) Behavioral Neuroscience 112:1475-1485 Supported by a Wellcome Trust Programme Grant (089589/z/09/z) awarded to TWR, B.J. Everitt, B.J. Sahakian, A.C. Roberts and J.W. Dalley and completed within the University of Cambridge Behavioral and Clinical Neuroscience Institute, supported by a joint award from the Medical Research Council and the Wellcome Trust. Cd'A was funded by an Amgen scholarship and an in-vivo Training Initiative award from the British Association for Psychopharmacology.

ME07

ESTABLISHING PAVLOVIAN TO INSTRUMENTAL TRANSFER (PIT) WITH INTRAVENOUS NICOTINE AND SUCROSE IN RATS

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Introduction: Tobacco smoking associated environmental stimuli are known to induce relapse even after long periods of abstinence. Therefore it is essential to understand the underlying mechanisms that govern cue-induced relapse of nicotine seeking behaviour and decision making upon encountering drug-related cues. Pavlovian to instrumental transfer (PIT) was used to assess the effects of cues paired with nicotine or sucrose on instrumental responding for these same outcomes.
Methods: 16 male hooded Lister rats underwent sessions of Pavlovian training during which two reinforcers, intravenous nicotine infusion (0.03mg/kg) and sucrose pellet (45mg pellets), were paired with distinct cues. Instrumental training then established a lever press response for each outcome. Finally, responding on these two levers was assessed in the presence of each stimulus.
Results: When a single lever was available at test, the sucrose but not nicotine stimulus produced a general excitatory effect on both levers (general transfer). By contrast, when both levers were concurrently available at test, the sucrose but not the nicotine stimulus selectively enhanced responding for the sucrose over the nicotine lever (specific transfer). Conclusions:The finding of a general versus specific transfer effect under the single versus concurrent instrumental test accords with the view that offering animals a choice favours the retrieval of the identity of the instrumental outcomes guiding action selection. Additional parameters may be required to demonstrate drug PIT in this model, which more closely match sucrose training.

ME08

EFFECT OF CATHINONE ON LOCOMOTOR ACTIVITY, FEEDING BEHAVIOUR, BODY TEMPERATURE AND C-FOS IMMUNOHISTOCHEMISTRY IN THE SIBERIAN HAMSTER.

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Cathinone is a recreational drug originating from khat (Catha edulis Forsk) leaves which are regularly chewed in parts of the Middle East and Africa. Cathinone and its derivatives, however, have experienced increasing popularity as illicit drugs in the UK resulting in their recent classification as Class B drugs. Despite this there has been limited research into the acute effects of cathinone on behaviour in animals. Therefore this study investigated the acute effects of cathinone on locomotor and feeding behaviour, core body temperature, and neuronal activity in the Siberian Hamster. Twelve adult male Siberian hamsters previously implanted with radiotelemetry devices under fluothane anaesthesia were treated with vehicle, low (2mg/kg) or high doses (5mg/kg and 10mg/kg) of cathinone i.p. (volume: 1ml/kg) over 3 weekly experimentation days, rotating treatments in a Latin square design. Following each drug injection the behavioural profile was scored, and core body temperature and locomotor activity recorded from telemetry implants. Food intake and body weight were also measured. Hamster brains were collected after treatment with vehicle or 5mg/kg cathinone for immunohistochemical evaluation of c-fos expression as a marker of neuronal activation. Cathinone induced significant ($p<0.0001$, two-way ANOVA) dose-dependent increases in both temperature and locomotor activity lasting 60-90 minutes post administration. The low dose of cathinone increased rearing ($p=0.02$, t-test), and high doses increased rearing ($p=0.001$) and lateral head twitches ($p=0.02$); both cathinone doses decreased the time spent at rest (low dose: $p=0.0009$; high dose: $p<0.0001$). The number of c-fos immunopositive cells were significantly increased in the striatum ($p<0.0001$) and suprachiasmatic nucleus ($p<0.05$) following administration of a high dose of cathinone implying increased neuronal activity occurred in those areas. There was no significant effect of acute administration of cathinone on food intake or body weight. These results suggest that systemic administration of cathinone induces central effects including hyperthermia and hyperlocomotion and the sites of induction of these effects and the relevance to effects reported with the recreational use of cathinones in man is worthy of further investigation.

ME09

THE EFFECTS OF ALCOHOL ON DECEPTION RATE, SUCCESS AND MOOD

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Introduction: Deception research has focused on cognitive neuropsychology and psychopharmacological studies have been limited. Previous research suggests the effects of alcohol on the cerebral error detector facilitate deception. Research also suggests that cognitive abilities involved in deception are impaired following alcohol consumption. No studies have investigated the effects of alcohol on deception rate and success in an ecologically valid situation - an aim of the current study. Mood and deception have not been directly analysed but anecdotal evidence suggests that mood decreases with deception relative to truth, and therefore mood was assessed. Methods: A novel face-to-face, free-choice (truth/lies) group experiment was undertaken in order to analyse deception. 19 Participants (mean age 25.6 years) were given tokens representing money and played a game where they quizzed each other on token values. The game's aim was to make the interrogator believe the figure they were told was the token's true figure. Token rewards were given for successful lies, and punishments for unsuccessful lies. Participants (interrogators and interviewees) played the game in three conditions, alcohol (6 units vodka 37.5% with peppermint flavour, mean 0.064% BrAC), placebo (peppermint flavoured drink), and water control. Treatment order was randomised between groups. Mood, measured with Bond and Lader visual analogue scales (VAS), was tested at baseline and post-lie/truth. Results: Chi-squared analysis revealed no significant results for condition and deception rate, or for condition and deception success implying that alcohol did not affect how often, and how well a person lied. Results in mood, analysed via paired t-tests, measured pre-lie/truth and post-lie/truth differences for each condition separately. VAS adjectives were grouped into functional integrity, mood, and sociability factors in line with previous research (Farquhar et al. 2002 JPsychopharm 16, 379-384). 'Mood' increased after successful deception but decreased after truthful responses (P=0.05 or better). Comparisons between truth and deception using one-way ANOVA revealed that 'sociability' decreased with lies compared to truth telling (P=0.02). Conclusion: It is possible alcohol did not affect deception rate because of the complexity of deception as a cognitive process. Success rates may not have shown significance because both interviewees and interrogators were under the influence of alcohol together affecting cognitive functioning in both groups. Mood scores suggest that deception follows naturalistic reward/reinforcement processes, similar to other behaviours. Since successful deception offers the greatest reward the greatest positive mood was observed. Truth may increase sociability over deception due to the appraisal of a deceptive act and the stigma surrounding deception. No financial sponsorship was received for this study

ME10

TEMPORAL STABILITY AND ASSOCIATIONS OF 'DYSFUNCTIONAL ATTITUDES AND BELIEFS ABOUT SLEEP' IN PATIENTS WITH MOOD OR ANXIETY DISORDERS

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Depressive symptoms are common in patients with sleep disorders, and disturbed sleep is a symptom of most mental disorders. Depressed patients report poorer perceptions of sleep depth and quality than do matched controls, with similar overall sleep timing: and distortions of sleep perceptions are also seen in their non-depressed first-degree relatives. The aims of this study were to determine the temporal stability of 'dysfunctional attitudes and beliefs about sleep', and to examine whether individuals with lesser or greater severity of dysfunctional beliefs differed in performance in a series of computerised tasks. Individuals who previously reported scores in the highest or lowest quartiles on the 16-item Dysfunctional Attitudes and Beliefs about Sleep (DBAS-16) scale in earlier cross-sectional studies in patients with mood or anxiety disorders and their first-degree relatives, were invited to participate in an investigation of the temporal stability of measures of anxiety and depression (HADS-A and HADS-D) and disturbed sleep (DBAS-16, MOSS Index II), and the associations of dysfunctional beliefs with performance on the anti-saccade task, the attention network task, a stop-signal task and a visual probe task. The potential sample comprised 41 individuals (12 men, 29 women). Twelve did not respond to the invitation, 10 declined to participate, and 3 were unable to identify a convenient time to take part: leaving 11 women (mean age 53.1 yrs, range 39-66) and 5 men (mean age 51.0 yrs, range 41-75 years) who completed study questionnaires and computerised tasks. The interval between baseline and follow-up assessments was two years. DBAS-16 scores changed only slightly from baseline (mean, 3.94; SD, 2.54) to follow-up (mean, 4.14; SD, 2.02): and were highly correlated ($r=0.77$, $p<0.01$), indicating considerable temporal stability. Mean scores on the MOSS Index II scale decreased slightly, from 44.4 (SD, 21.85) at baseline to 36.9 (SD, 19.71) at follow-up, but were again highly correlated ($r=0.772$, $p<0.01$). By contrast, there was limited correlation between baseline and follow-up measures of anxiety and depressive symptoms. HADS-A scores were 11.13 (SD, 6.72) at baseline and 8.31 (SD, 6.03) at endpoint ($r=0.381$, $p=0.147$): HADS-D scores were 10.5 (SD, 6.66) at baseline and 7.56 (SD, 6.70) at endpoint ($r=0.423$, $p=0.102$). In patients with mood or anxiety disorders, measures of disturbed sleep and dysfunctional beliefs and attitudes about sleep appear to be stable over time, in contrast to measures of anxiety and depressive symptoms. LREC Reference Number: 08/H0505/164. No funding was sought or granted for this project.

ME11

CATHINONE: THE BEHAVIOURAL AND NEUROTOXIC EFFECTS ON LISTER HOOD RODENTS.

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The amphetamine-like alkaloid, cathinone, is the active constituent of khat leaves, which have been chewed recreationally in east Africa and southern Arabia for centuries. Recent global increases in cathinone use and several misuse related deaths has led to the UKs re-classification of all cathinone derivatives as class B substances. However, knowledge of its behavioural and neurotoxic effects remains limited. This study determined whether cathinone affected locomotor activity (LMA), novel object discrimination (NOD), conditioned emotional response (CER), pre-pulse inhibition (PPI), Ki-67+ve cell-count and neurotoxicity in Male Lister Hooded rodents (~8 weeks old). Rodents (n=24) were dosed (i.p) either 4mg/kg or 1mg/kg cathinone hydrochloride, or saline (0.9%) twice weekly for 3 weeks. Both acute and chronic (day 3,18) effects on LMA were monitored for 2-hours in a familiar arena. NOD was assessed during a 2-hour inter-trial interval. A modified CER paradigm was conducted, additionally measuring freeze-time in the light arena with a light-tone cue. PPI deficit was assessed measuring startle responses to pulses preceded by pseudo-random pre-pulses. Brain tissue was collected (day,35) and immunohistochemistry performed to count Ki-67+ve cells in the sub-granular zone of the dentate gyrus. High performance liquid chromatography permitted quantification of dopamine, serotonin, 5-hydroxyindoleaceticacid, dihydroxyphenylacetic acid and homovanillic acid. Results showed dose-dependent elevations in LMA (day 3,18) ($p<0.001$). NOD demonstrated an acute impairment of declarative memory function. Conversely, there was no effect on context or cue-dependent memory as determined by CER, despite a dose-dependent trend of reducing freeze-time in the light arena. Significant correlations of NOD-LMA ($r=-0.6013$), LMA-Ki-67 ($r=0.5267$), NOD-Ki-67 ($r=-0.5593$) were calculated. Cathinone had a dose-dependent effect on cumulative weight gain ($p<0.001$). An acute effect on weight was found from day 3-5, with the 4mg/kg and 1mg/kg groups weighing less than the controls ($p<0.01$,$p<0.05$). Cathinone increased Ki-67+ve cell-counts ($p<0.05$), although neurotransmitters levels, PPI and body temperature were unaffected. Cathinone caused dose-dependent hyperactivity possibly reflecting purposeless, stereotyped behaviour. Chronic increases in Ki-67 expression indicate enhanced dentate gyral cell proliferation; further research using BRDU could confirm this as neurogenesis. The significant correlations indicate that hyperactivity, not cathinone, led to increased Ki-67 expression and NOD deficit. Although cathinone did not impair context-dependent memory, a trend of reducing freeze-time in the light arena as cathinone dose increased suggests a selective effect on cue-dependant memory. Future study using telemetry devices to measure LMA and temperature and micro-dialysis to measure monoamines may supplement this research, whilst monitoring food intake to establish potential anorexigenic effects.

ME12

DEPRESSION AND IMMUNE RESPONSES: VALIDATION OF LPS-INDUCED ANHEDONIA IN SUCROSE PREFERENCE TEST IN MALE RATS

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Recently, evidence suggesting a link between depression and immune system activation is increasing. Depressed patients, for example, show elevation of inflammatory cytokines (for review: Dantzer et al., 2011, Psychoneuroendocrinology, 36, p426). Here, an attempt is made to combine a depression-related model with an immune challenge in rats. The sucrose preference test was used as a model to determine depression-like effects like anhedonia, i.e. lack of ability to feel pleasure or reward. Rats and humans show an innate preference for sweet solutions, which is altered when depressed. The immune challenge used is a bacteria-derived endotoxin, lipopolysaccharide (LPS). However, the LPS challenge elicits a biphasic response in which initial sickness behavior is followed by a depression-like phenotype. In a series of experiments, effects of various key parameters were determined: sucrose familiarisation (once/twice), deprivation (yes/no), drinking time (1-hr/overnight) and response duration (up to 9-days post LPS). Overall, data were analysed using repeated measures analysis of variance and where appropriate, post-hoc comparisons. Sprague-Dawley rats (n=11-12 per treatment group) demonstrated across all studies highly stable baseline fluid consumption of about 30 ml/day for water and 50-55 ml/day when given a choice between water and sucrose (1%), along with a consistent >85% sucrose preference (innate hedonia). After familiarization to sucrose, rats were injected with LPS (0-0.31-0.63-1.25 mg/kg i.p.) and total fluid consumption, sucrose preference (%) and body weight were measured at different intervals (1-6-24-48 hr up to 9 days). Without deprivation, volume of intake in the light phase was low in vehicle rats and further reduced by LPS resulting in unreliable preference ratios. Overnight deprivation resulted in increased intake volumes during 1-hr periods. However, preference in all groups including vehicle treatment dropped and variability increased likely due to thirstiness resulting in continued drinking from the bottle approached first. Across studies, LPS caused a clear reduction in fluid intake between 6-24 hr with some indications of reduced sucrose preference at 24-48 hr, but not beyond. LPS caused a consistent loss of body weight beyond 24-hr. Finally, when LPS was given just before dark-phase onset in non-deprived rats, overnight intake instead of 1-hr exposures at different intervals led to more consistent/high sucrose preference in vehicle rats. This generates a larger window for LPS-induced anhedonia. In summary, thorough investigation of various parameters indicates that the most reliable way to measure LPS-induced anhedonia in rats is proper familiarisation to sucrose prior to LPS administration, followed by overnight intake without deprivation. However, separating LPS-induced acute sickness- from delayed depression-like effects appears to be rather challenging.

ME13

ESTABLISHING CONCURRENT CHOICE PROCEDURES WITH INTRAVENOUS NICOTINE AND SUCROSE IN RATS

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The aim of the current study was to investigate rats' preference to choose intravenous nicotine compared to sucrose pellets, and the impact of outcome devaluation on this choice. 16 hooded Lister male rats were initially trained to self-administer intravenous nicotine or sucrose pellets via different levers on separate days. Once a reliable acquisition was established under a random ratio 4 (RR4) reinforcement schedule, the rats' preference for either nicotine or sucrose was assessed under a concurrent schedule, where both levers were available. Initial results revealed a wide distribution of preferences across the levers; the majority of rats expressing an increased preference towards the sucrose lever (80%). This trend continued over the course of the study, whereby on the fourth day, preference for sucrose increased further (90%). Tests were conducted to devalue the reinforcers on separate occasions either by an experimenter administered priming dose of nicotine (0.4 mg/kg SC) 10 minutes before the concurrent session, or by presenting unlimited access to rat chow. Nicotine devaluation resulted in a significant attenuation of nicotine infusions, whereas chow satiety produced a smaller reduction in sucrose preference. The current study highlights a number of key findings; primarily it illustrates the ability of non-drug alternatives to shift preference away from nicotine over time, a finding that is consistent with previous research regarding the reinforcing properties of cocaine compared with a non-drug reward. In addition, the devaluation procedure supports the role of value based decision making in drug addiction, consistent with current human research using concurrent choice procedure.. Furthermore, the variance of rats' preference towards nicotine or sucrose highlights the role of individual variability towards drug dependence, and such findings could be used to further assess the variety of endophenotypic characteristics indicative of vulnerability towards nicotine dependence. Finally, future research could utilise such a concurrent schedule design to investigate the role of clinically effective cessation agents, such as varenicline to gain a greater understanding of how these compounds work at a neurobiological level to attenuate nicotine-seeking behaviours.

ME14

SUDOKU PROBLEM SOLVING IMPAIRMENTS AFTER WEEKEND ECSTASY/MDMA USE

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Introduction: Previous research has shown impairments in memory, thinking and reasoning, in abstinent Ecstasy/MDMA polydrug users. The aim of this study was to assess if Sudoku problem solving would show similar drug-related impairments, since it requires all these higher cognitive/strategic skills. The contributory roles of other factors such as thermal stress and gender, were also investigated.
Methods: 20 recreational Ecstasy users (10 male and 10 female, mean age = 21.9), and twenty non-user controls (primarily alcohol drinkers, 10 male and 10 female; mean age = 22.1) were assessed 48 hours after weekend dance-clubbing. They completed the UeL questionnaire on lifetime drug usage, and a battery of self-rated questionnaires on thermal comfort, physical activity, and psychoactive drug use while clubbing. They then undertook three cognitive tasks: trail-making B, verbal anagrams, and a novel Sudoku problem solving task. Performance scores comprised the number of correct completions in a restricted time period.
Results: Ecstasy polydrug users were significantly impaired on all three cognitive tasks. Sudoku mean completions: controls 78.9, Ecstasy users 35.3 ($p<0.001$). Trail making completions: controls 84.4, Ecstasy users 69.7 ($p<0.01$). Anagram completions: controls 33.0, Ecstasy users 24.8 ($p<0.05$). The Ecstasy group was then split into two subgroups based on lifetime use. The lighter Ecstasy users showed non-significant trends towards impairments on all three tasks. Heavy Ecstasy users showed significant impairments every task, with Sudoku problem solving being particularly impaired (mean: 21.1 completions). Self-rated thermal overheating was positively correlated with the amount of Ecstasy taken (range 1-7 tablets: $r=0.78$, $p<001$). However these variables were also associated with lifetime Ecstasy use, making them difficult to separate as potential factors. Gender effects were investigated but were not generally significant. Task errors showed several significant group differences. Many Ecstasy users had a polydrug history, and the contributions of these other drugs will be debated. Qualitative findings, describing the unfocused and inconsistent strategies followed by some Ecstasy users, will also be described. Conclusions: Performance on three higher cognitive tasks was significantly impaired during the post-Ecstasy recovery period. Sudoku involves both memory updating and strategic planning, and seems particularly sensitive to the adverse neurocognitive effects of Ecstasy/MDMA.

TA01

EFFICIENT DECISION-MAKING IS DEPENDENT ON THE EFFICIENT PRUNING OF DECISION TREES

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How does one make a decision when faced with numerous alternatives? Here we demonstrate that efficient decision-making is dependent upon a reflexive process of 'pruning' away, or excising from consideration, less favourable options from a decision tree. 22 participants (18 males, 4 females) performed a decision-making task which was developed from Tanaka et al (Tanaka, S, et al (2006). Brain mechanism of reward prediction under predictable and unpredictable environmental dynamics. Neural Networks, 19(8), 133-1241) and was designed to reveal their pruning strategies. Subjects had to navigate between 6 environmental states, each of which led to two other states; every transition was associated with reward or punishment (win 140p or 20p, lose 140p or 20p). On each trial, participants were told how many moves were available (1-8), and had to devise a sequence of moves of that length in order to maximise their total winnings. A set of increasingly sophisticated computational models was fit to the data: (i) an 'optimal' model that assumed evaluation of all possible sequences of moves; (ii) a 'discounting' model, which assumed that subjects progressively failed to plan ahead fully when faced with larger numbers of moves; and (iii) a 'pruning' model with an additional discount factor, allowing for the possibility that the prospect of a large punishment exaggerated failures to plan ahead. Bayesian model comparison, in which more complex models are penalised, revealed that the 'pruning' model provided the best fit. Consistent with prior work using this task, participants demonstrated a selective pruning strategy: when they encountered a large loss they automatically pruned away that branch of the decision tree. Examination of the two pruning parameters derived from this model revealed that search curtailment specifically related to encountering a large loss (pruning) was substantially stronger than a general tendency not to plan. This work therefore demonstrates that efficient decision-making is dependent upon a reflexive pruning of less favourable options from a decision tree. Future studies should aim to test the hypothesis that this process is modulated by serotonin transmission and thus compromised in neuropsychiatric disorders (Dayan P & Huys J. M. Q. (2008). Serotonin, Inhibition and Negative Mood. PLoS Computational Biology, 4(2): e4; Soubrié P (1986). Reconciling the role of central serotonin neurons in human and animal behaviour. Behavioural Brain Science, 9, 319-364). Funding for this project was provided by the Medical Research Council.

TA02

TRAINING TO ENHANCE RECOGNITION OF HAPPINESS IN AMBIGUOUS FACIAL EXPRESSIONS REDUCES AGGRESSIVE BEHAVIOUR

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Introduction The ability to accurately identify emotion in others is critical to social functioning. For example, a tendency to interpret ambiguous emotional expressions as negative rather than positive (i.e., a negativity bias) may result in inappropriate behavioural actions. We explored the relationship between induced biases in the processing of emotional expressions and aggressive behaviour.
Method In experiment 1, healthy adults were trained to interpret ambiguous emotional expressions as representing happiness rather than anger (N = 38). This involved using morphed happy/angry faces in a 2AFC presentation. An initial training block calculated individual balance point, then a number of biased feedback blocks were presented (or control feedback) where participants were informed whether their response (happy/angry) was correct or incorrect. A final block without feedback at the end showed whether individual balance point had shifted or not. In experiment 2, a group of adolescents identified as being at high-risk of criminal offending completed a similar procedure, repeated four times over the course of a week (N =46).
Results In experiment 1, the manipulation successfully modified the perception of ambiguous facial expressions ($b = +1.41$, $SE = 0.35$, $t = 4.02$, $P < 0.001$), and this resulted in lower self-reported levels of state anger compared with a control group ($b = -0.90$, $SE = 0.35$, $t = 2.61$, $P = 0.014$). In experiment 2, perceptual bias was again successfully modified in the training group ($b = +4.22$, $SE = 1.23$, $t = 3.33$, $P = 0.003$), and these participants reported lower levels of aggressive behaviour up to two weeks after the completion of training ($b = -4.74$, $SE = 1.26$, $t = 3.61$, $P = 0.001$). In addition, aggressive behaviour rated independently by staff blind to experimental condition was also reduced ($b = -2.40$, $SE = 0.67$, $t = 3.77$, $P = 0.001$).
Conclusion The results of these two experiments provide strong evidence that emotion processing plays a causal role in the maintenance of aggressive behaviour, and may form the basis of a novel, simple, and effective behaviour modification treatment in aggressive individuals. This study received no funding.

TA03

INCREASED ANTERIOR CINGULATE ACTIVATION IN YOUNG PEOPLE AT INCREASED RISK OF DEPRESSION PERFORMING A NOVELTY DETECTION MEMORY ENCODING TASK

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Introduction: The anterior cingulate cortex (ACC) has been implicated in the pathophysiology of major depression because of its role in emotional and cognitive processes (Mayberg(1997).J Neuropsychiatry Clin Neurosci;9:482-497; Whalen et al(1998). Biol Psychiatry;44:1219-1228). Increasing evidence suggests that ACC dysfunction may also be implicated in vulnerability to depression. In this study we explored ACC involvement in novelty detection in those at increased risk of depression compared to those at low risk. Methods: 21 healthy people (aged 16-20 years) with a biological parent with a history of major depression (FH), and 32 age and gender-matched controls with no parental depression performed a block designed "novel vs. familiar", "animal/no animal" memory encoding paradigm at 3T (with familiar stimuli presented 4 times prior to scanning), followed by a post-scanning recognition memory test. In the recognition phase participants indicated which images were presented inside the scanner. The BOLD signal, accuracy and reaction times were obtained. Imaging data was analysed with FSLv4.1.7 at the whole brain level (cluster-based thresholding at $z=2.3$, corrected $p<0.05$).
Results: Reaction time and accuracy were similar in both groups in the encoding and recognition phases. The activation of the right dorsal ACC (BA24),$t(51) = 2.52$, $p = 0.015$; and the left insular, $t(51) = 2.45$, $p = 0.018$; was significantly higher during the novel versus familiar encoding in the high risk group compared to control group, presumably reflecting hypersensitivity in salience detection, particularly in the context of a later expectation of memory retrieval.
Conclusions: Hyperactivation of brain regions involved in salience detection (so called 'salience network'; Seeley et al(2007). J. Neurosci;27(9):2349 –2356) by the FH group reflects a need for greater resource allocation required to enhance performance to levels comparable with the controls. Seemingly, the pattern of ACC activation is task dependent as shown by hypoactivation in a memory encoding task in depressed people(Bremner et al(2004),Am J Psychiatry;161:637–645)and both hyper- and hypo-activation to different components of reward processing in high risk girls (Gotlib et al(2010).Arch Gen Psychiatry; 67(4):380-387). This evidence places this structure at the core of not only the pathophysiology of depression but potential biomarkers of depression. This work was supported by the Medical Research Council

TA04

HOW DO SUBJECTIVE AND OBJECTIVE MEASURES OF COGNITIVE FUNCTION RELATE IN PATIENTS WITH AFFECTIVE DISORDERS?

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Background: Patients with affective disorders experience cognitive dysfunction in addition to their affective symptoms. The relationship between subjectively experienced and objectively measured cognitive function is controversial with several studies of non-affective disorder patients reporting no correlation between subjective and objective deficits. The present study therefore aimed to investigate whether there is a direct correlation between subjectively reported and objectively measured cognitive function in patients with affective disorders, and whether subjective complaints predict objectively measured dysfunction.
Methods: The study included 45 participants; 15 with bipolar disorder (BD), 15 with unipolar disorder (UD) and 15 healthy individuals. Participants' subjective experience of cognitive function was assessed with the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) and their objective cognitive function was assessed with the Screen for Cognitive Impairment in Psychiatry (SCIP). Patients were also rated for affective symptoms with Hamilton Depression Rating Scale (HDRS) and Young Mania Rating Scale (YMRS).
Results: Patients with BD or UD, all in remission or partly remission, (mean+SD HDRS-score for BD: 11±6; UD 13±6) demonstrated both subjective and objective cognitive dysfunction relative to controls (all p-values < 0.01). There was no correlation between subjectively experienced and objectively measured cognitive dysfunction in BD (Kendall's tau = 0.08, $p = 0.7$). There was a non-significant trend towards a correlation in UD (UD: Kendall's tau = - 0.37, $p = 0.06$), which disappeared when we controlled for gender ($p = 0.1$). Multiple regression analysis demonstrated that patients' subjectively experienced cognitive function failed to predict objective cognitive function when controlling for gender, age, verbal intelligence and depression severity (all p-values > 0.05).
Conclusion: Clinicians should not solely rely on patients' subjective cognitive complaints to diagnose cognitive dysfunction in patients with affective disorder. If confirmed in a larger patient sample, our findings suggest that brief neuropsychological assessment is warranted for patients with affective disorder. This would help clarify whether patients have objective cognitive impairments and thereby inform treatment strategies targeting these cognitive deficits.

TA05

POOR DISCRIMINATORY PERFORMANCE OF THE PHQ-9, HADS AND BDI-II IN MEASURING SEVERITY OF DEPRESSIVE SYMPTOMS IN A UK SAMPLE OF PRIMARY CARE PATIENTS WITH A DIAGNOSIS OF DEPRESSION

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Guidelines advocate different treatment options for depression, dependent upon the severity of symptoms with antidepressant treatment being endorsed for more severe symptoms (NICE, CG90). To facilitate appropriate treatment instigation, general practitioners (GPs) in the UK are rewarded through the Quality Outcomes Framework (QOF) for assessing severity of depressive symptoms using one of the following tools: the Patient Health Questionnaire (PHQ-9)(Kroenke et al, JGIM, 2001; 16: 606-13); the Hospital Anxiety and Depression Scale (HADS) Depression subscale (HAD-D)(Zigmond et al, Acta Psych Scand, 1983; 67: 361-70); or the Beck Depression Inventory, Second Edition (BDI-II) (Beck et al, J Personality Assess 1996; 67: 588-97). However, the evidence base that relates to severity of symptoms is founded on studies using the clinician-rated, seventeen-item version of the Hamilton Rating Scale for Depression (HRSD-17)(Hamilton, 1960; J Neurol Neurosurg Psychiatry 23: 56-62) - not the scales recommended by the QOF. The aim of this study was to assess the discriminatory performance of each of the QOF-endorsed measures in categorising the severity of depressive symptoms against the HRSD-17 in primary care patients with a GP-generated diagnosis of depression. Adults with GP diagnosed depression from nine Scottish general practices participated. Questionnaire scores on the HAD-D, PHQ-9 and BDI-II were assessed against the HRSD-17 interview. The discriminatory performance of the measures was determined relative to the HRSD-17 cut-offs for symptoms of at least moderate severity, by both American Psychiatric Association (APA) and National Institute of Clinical Excellence (NICE) criteria. Receiver Operating Characteristic (ROC) curves were plotted. Area under the curve (AUC), sensitivity, specificity and likelihood ratios (LRs) were calculated. 267 patients took part: mean age=49.8 years (sd=14.1), 70% female, mean HRSD-17=12.6 (sd=7.62, range=0-34). In categorising depression severity by either APA or NICE criteria, all measures differed significantly from these standards (Wilcoxon Signed Rank Test, $p<0.01$). For APA criteria, AUCs were: HAD-D=0.84; PHQ-9=0.90; and BDI-II=0.86. Optimal sensitivity and specificity were reached where HAD-D≥9 (74%, 76%); PHQ-9≥12 (77%, 79%) and BDI-II≥23 (74%, 75%). For NICE criteria: HAD-D AUC=0.89; PHQ-9 AUC=0.93; and BDI-II AUC=0.90. Optimal sensitivity and specificity were reached where HAD-D≥10 (82%, 75%), PHQ-9≥15 (89%, 83%) and BDI-II≥28 (83%, 80%). LRs did not, however, provide evidence of sufficient accuracy for clinical use. None of the self-complete measures aligned adequately with HRSD-17. These scales are therefore invalid for the selection of treatment determined by depression severity, given this strategy is informed principally by an evidence base derived from trials using HRSD-17. This research was funded by NHS Quality Improvement Scotland.

TA06

SUPERIOR FACE RECOGNITION IN BODY DYSMORPHIC DISORDER

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Introduction. Individuals with body dysmorphic disorder (BDD) may have a propensity for viewing faces differently from healthy controls. In an attempt to explore these processing changes in more detail, we investigate face processing in BDD using two facial recognition tasks; one testing the recognition of facial characteristics, the other testing the recognition of facial expressions of emotion.
Methods. Participants with BDD (n=12) and healthy controls (n=16) were tested for inverted face recognition using the Inverted Famous Faces Task and the Facial Expression of Emotions Stimulus and Test emotion recognition task (FEEST). The groups were matched for Age, IQ and education.
Results. Participants with BDD showed a significant ability to correctly recognise inverted famous faces compared to well-matched controls. In contrast, participants with BDD showed a specific deficit in recognising fearful facial emotions.
Conclusions. BDD participants excel over controls at performing the inverted famous faces task. This is an unusual finding and may represent a neurocognitive marker for BDD. The specific deficit within the BDD group for recognising fearful expressions may be another feature of the disorder and, taking account of previous studies that suggest a deficit in recognising angry expressions, implicates the abnormal processing of negatively valenced emotional material that may represent a causal factor or a consequence of BDD. The specificity of these findings for BDD merit further investigation using other clinical groups and a larger sample size.
No funding was received for the implementation of this study. No conflict of interest.

TA07

ANTIOXIDANT DEFENSE SYSTEM IN PATIENTS WITH CORONARY HEART DISEASE WITH OR WITHOUT DEPRESSION.

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Introduction: Coronary heart disease (CHD) can predispose a patient to depression. Depression and heart disease have an intricate association and seem to have some biological vulnerabilities in common. Since both diseases are associated with oxidative stress, we aimed to analyze markers of oxidative stress in patients with CHD with and without depression.
Methods: Blood was collected from 66 patients with CHD amongst which 23 had comorbid depression. Oxidative stress parameters were investigated by measuring the activities of glutathione peroxidase (GPx-1), glutathione reductase (GR), Cu-Zn superoxide dismutase (CuZn SOD, SOD-1), glucose-6-phosphate dehydrogenase (G-6PD) and the levels of methemoglobin (metHb) and malondialdehyde (MDA) in erythrocytes.
Results: The activity of SOD-1 was significantly increased in depressed CHD patients when compared with 839.224 U/g Hb,±1216.013 U/g Hb and 2503.80±non-depressed CHD patients, (3169.52 p=0.02, respectively). The differences in GR, GPx-1, G-6PD activies as well as GSH, MDA and metHb concentrations were not significant.
Conclusions: Upregulations of SOD-1 in depressed patients might be seen as an adaptive response to the increased superoxide generation. Since a dismutation of the latter yields hydrogen peroxide, a concerted action of antioxidants, able to neutralize the byproduct of SOD-1 activity, is required. Thus no alterations in G-6PD, GR and GPx-1 activities may suggest redox imbalance in depressed patients.
This study was supported by the grant for PhD student Joanna Rybka cofinanced by European Union from the European Social Fund. This project is funded in part by the NARSAD Young Investigator Award to LA Carvalho. LA Carvalho also received funds by the British Council-Partek Partnership Award to Livia Carvalho, and the European Union Framework 7 project grant # n°22963 (Mood Inflame). The authors have no potential conflict of interest to declare.

TA08

INFLAME-BEAT: UNDERSTANDING THE ROLE OF INFLAMMATION IN PREDICTING DEPRESSION IN PATIENTS WITH HEART DISEASE

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Introduction: Cardiovascular disease and depression are two common and often co-existing disorders affecting the population worldwide. The prevalence of depression among patients with established coronary heart disease (CHD) is considerably higher as compared to the general population. Approximately 17%-20% of outpatients and 35-70% of inpatients with CHD meet criteria for major depression compared to 2-9% in the general population. In addition to psychological and social morbidity, depression exacerbates adverse cardiac outcomes in CHD patients. Indeed, depression is recognized as an independent factor greatly increasing the risk of cardiovascular morbidity and mortality. However, the physiological mechanisms underlying the increased incidence of depression in patients with CHD are yet to be understood. The aim of this work is to access the effect of depression on inflammatory and metabolic syndrome parameters and to subsequently investigate the possible implications this may have in CHD patients.
Methods: The INFLAME-BEAT project is a 2-year-prospective cohort study. The primary goal is to test the hypothesis that activated inflammatory response in patients with CHD is associated with future development of depressive symptom. CHD patients with depression (n=31) and without (n=74) were recruited (Ethics REC REF 09/H1103/19), and assessed for depressive symptoms by means of Beck depression inventory (BECK) and Patients Health Questionnaire (PHQ). Heart rate, full blood count and plasma cortisol, C Reactive Protein (CRP, inflammatory biomarker), cholesterol, LDL, HDL were measured.
Results: The higher score of Beck and PHQ among CHD depressed patients ($p<0.001$) was confirmed. CHD depressed patients showed elevated levels of CRP as compared with CHD patients without depression (mean ± SD, CHD: 4.74±7.16, CHD/depressed: 6.77±10.99, $p<0.05$). Heart rate was higher in depressed CHD patients (CHD: 60.85±12.36, CHD/depressed: 68.48±17.47, $p<0.05$). Furthermore, patients with depression had increased red blood cell distribution width (RDW) (CHD: 13.52±0.82, CHD/depressed: 14.16±1.50, $p<0.05$) and higher numbers of basophiles (CHD: 0.46±0.35, CHD/depressed: 0.69±0.62, $p<0.05$). No differences were found in plasma cortisol, cholesterol, LDL and HDL levels between the two groups. Conclusions: The presence of depressive symptoms seems to be associated with increased inflammation as evidenced by elevated plasma CRP levels. Higher numbers of basophiles and faster heart rate in depressed CHD patients further contribute to inflammation and higher risk of cardiovascular events. This project is funded by the NARSAD and ECNP Young Investigator Award to Livia Carvalho, and the European Union Framework 7.

TA09

SUBCHRONIC FLATTENING OF THE GLUCOCORTICOID RHYTHM INDUCES PERFORMANCE DEFICITS IN THE ATTENTIONAL SET SHIFTING TASK

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Bipolar disorder is characterised cognitively by executive dysfunction-including cognitive inflexibility-and biochemically by flattening of the glucocorticoid rhythm with elevation of the diurnal trough. Here we investigated the potential causal relationship between glucocorticoids and executive function using the attentional set shifting task (a rat analogue of the human ID/ED test of attentional flexibility). Groups of male Lister hooded rats (n=10 per treatment group) were treated for 15 days with corticosterone (50 µg/ml) or vehicle (ethanol 0.5%) in their drinking water to flatten the diurnal glucocorticoid rhythm. Rats then underwent the attentional set shifting task in which they perform a series of discriminations (simple (SD), compound (CD), reversal (Rev1), intradimensional (ID), reversal (Rev2), extradimensional (ED), reversal (Rev3)) to obtain food rewards. Data (trials to criterion) were analysed by ANOVA with post hoc t tests where appropriate. On completion of behavioural testing, the adrenals were removed post mortem and weighed in order to verify the effect of the treatment on circulating glucocorticoids. Corticosterone treatment successfully elevated trough glucocorticoid levels as evidenced by a significant decrease in adrenal: body weight ratio (8.2x10-5±3.3 x10-6 vs 5.6x10-5±4.6 x10-6; $p<0.001$). Corticosterone treatment caused a small but significant impairment in CD (7.2±0.3 vs 8.8±0.5 trials; $p<0.001$) as well as more pronounced significant deficits in ID (7.7±0.3 vs 11.9±0.6; $p<0.002$), Rev1 (13.1±0.4 vs 21±0.4; $p<0.001$), Rev 2 (13.1±0.4 vs 21.0±0.4; $p<0.001$) and Rev3 (12.2±0.6 vs 20.3±1.2; $p<0.001$). Furthermore, in contrast to vehicle treated animals, the corticosterone group showed no significant ID:ED difference; vehicle treated animals (7.7±0.3 vs 14.0±0.7 ; $p<0.001$), corticosterone treated animals (11.9±0.6 vs 12.6±0.5; p=NS). This is indicative of a failure to form an attentional set. Our data show that corticosterone treatment induces a general learning deficit (CD and ID deficits) as well as a consistent deficit in reversal learning (REV1, 2 and 3). The deficits observed in ID and reversal learning in particular suggest that corticosterone treated animals have difficulty in modifying their behaviour when presented with new information, as well as in adapting previously learnt rules and knowledge to a new discrimination; both of which are indicative of cognitive inflexibility. Further analyses of the pattern of responding and the possible differential nature of these deficits are underway. Joanne Wallace is the recipient of an MRC CASE studentship award jointly funded funded by the MRC and MSD.

TA10

CENTRAL TYROSINE HYDROXYLASE: A NEUROCHEMICAL MARKER IN THE OB RAT MODEL OF DEPRESSION?

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Introduction: Alterations in catecholaminergic neurotransmission has been a foundation stone of hypotheses relating to clinical depression and the mechanism of action of antidepressants (Schildkraut J.J. (1965). Am. J. Psychiatry. 122: 509-22). The olfactory bulbectomized (OB) rat is a well characterized model of depression (Kelly, J.P., et al., 1997. Pharmacol. Ther. 74: 299-316). The purpose of the present study was to measure central distribution of tyrosine hydroxylase (TH), the rate-limiting step in catecholamine biosynthesis in the (OB) model and to examine the consequences of chronic antidepressant (desipramine) treatment on any changes. Methods: Male Sprague-Dawley rats (225-250g on arrival) underwent olfactory bulbectomy or sham operation, and their brains were perfusion fixed five weeks later. Coronal slices (30µM) were made from a range of brain regions (frontal cortex, striatum, substania nigra and the ventral tegmental area). Immunohistochemical staining was performed to visualise TH and the volume proportion of TH fibres was quantified using the Cavalieri method (Mayhew, T.M and Olsen D.R., (1991). J. Anat. 178: 133-44). In a subsequent study, rats received either desipramine (10mg/kg) or vehicle once daily for 14 days via oral gavage, and on the following morning their distance moved (cm) in the open field test was assessed using EthoVision® video tracking technology. Animals received a further 7 days of treatment and 24 h after the last dose, the TH fibres were evaluated in the frontal cortex. Results were analysed using a Student's t-test or Two-Way ANOVA, followed where appropriate by a post hoc Student-Neuman-Keuls test. Results: Olfactory bulbectomy produced a significant regional-specific decrease in TH fibres in the frontal cortex ($p<0.05$ vs. sham-operated animals). In the subsequent study, a typical significant increase in locomotor activity was observed in the OB control group ($p<0.05$ vs sham-operated control) which was significantly attenuated by chronic desipramine treatment ($p<0.05$ vs OB control). The significant reduction in TH fibres in the frontal cortex was confirmed in the OB control group, but this effect was not significantly altered by chronic desipramine treatment. Conclusions: Olfactory bulbectomy in the rat is associated with a regionally specific reduction in TH in the frontal cortex, supporting an alteration in catecholminergic neurotransmission in this model. The lack of effect with desipramine treatment suggests that TH changes may be a "trait" marker of depression, which is not amenable to alteration by chronic antidepressant treatment. This work was supported by the Physiology Department, NUIG.

TA11

INVESTIGATING AFFECTIVE STATE AND MEMORY USING A NOVEL RODENT ASSAY: IMPLICATIONS FOR THE CAUSE AND TREATMENT OF DEPRESSION

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Recent studies in depressed patients have shown that negative memory bias (a tendency to recall negative information) is a key feature of the disorder. It has been hypothesised that negatively valenced emotional processing and its effects on memory may underlie the development and persistence of mood disorders and may be an important target for antidepressant therapy. We have developed a novel assay for rats to facilitate basic research into how affective state influences the reward value of a specific memory. The assay uses a bowl-digging task where rats form two independent memories for a substrate-reward association. Treatment or control is administered prior to memory encoding and reconsolidation sessions, where rats learn to discriminate the reward-paired substrate (A or B) from a different substrate (C) which does not contain reward. The reward value is kept consistent across sessions and, under control conditions, animals show no bias during a recall test. To assess the impact of negative affective state on memory, we pre-treated rats with the anxiogenic benzodiazepine inverse agonist, FG7142. To determine whether antidepressant drugs act by increasing the appetitive value of a particular memory, we also tested the antidepressant, fluoxetine. 16 Lister Hooded rats completed a within-subject fully randomised study for each drug. Subjects were treated with drug or vehicle prior to the memory encoding and reconsolidation sessions. 24hrs after the last pairing session, animals were presented with both reward-paired substrates (A and B) and %choice for the drug-paired substrate was recorded over 30 trials using random reinforcement (1 in 3) to prevent new learning. During pairing sessions, response latency and trials to criteria were recorded to assess any non-specific effects of treatment. FG7142 (1.0-5.0mg/kg, i.p.) induced a significant dose-dependent bias away from the drug-paired substrate ($F_{3,45}=5.2$, $p=0.004$, maximum effect -12.5%). In contrast, fluoxetine (0.3-3.0mg/kg, i.p) induced a significant dose-dependent bias towards the drug-paired substrate ($F_{3,45}=6.1$, $p=0.001$, maximum effect +8.5%). No effects were observed for either treatment during pairing sessions. These data suggest that memories formed during negative affective states have reduced reward value, which biases responding away from the associated cue. In contrast, fluoxetine induces a bias towards the associated cue suggesting acute antidepressant treatment enhances the reward value of the memory. We hypothesise that memories formed during negative affective states have reduced positive affective valence which leads to the anhedonia and negative mood observed in affective disorders, an effect which can be reversed by antidepressant treatment. This work was funded by the BBSRC and Pfizer UK.

TA12

CHRONIC PSYCHOSOCIAL STRESS IN TREE SHREWS INDUCES LATERALIZED CYTOSKELETAL AND SYNAPTIC CHANGES IN HIPPOCAMPUS AND PREFRONTAL CORTEX

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Psychosocial stress in tree shrews (Tupaia belangeri) is an established animal model of depressive disorders inducing neuronal and glial structural changes in specific brain regions. (Fuchs et al., 2005, Physiol Behav. 73:285-291). Recent data indicate that depression is associated to brain structural changes which have been reported of different magnitude between the right and left hemisphere. Growing evidence in animal models suggest that cytoskeletal microtubule dynamics may play a role on such structural alterations (Bianchi et al., 2009, Eur. Neuropsychopharmacol. 19:778-90). Here, we investigated the effects of psychosocial stress in tree shrews on the expression of microtubule dynamics markers and synaptic markers, in the right and left hippocampus and prefrontal cortex (PFC). Adult male tree shrews (n=6) were submitted to four weeks of psychosocial stress or non-stressed (n=6), as previously described (Fuchs et al., 2005, Physiol Behav. 73:285-291). Urinary cortisol was monitored using commercially available kits. At the end of the study, the hippocampus and PFC were dissected and processed for Western blot analysis of microtubule dynamics markers (Tyr/Glu-Tub, Acet-Tub and Delta2-Tub), pre-synaptic (synaptophysin) and post-synaptic (PSD-95) markers. Total alpha-tubulin was used as house-keeping protein. The ANOVA or t-test was used as statistical analysis. Results are expressed as mean±SEM in % of non-stressed animals. Tree shrews exposed to psychosocial stress showed decrease of body weight (93±2%, $p<0.05$), and increase in urinary cortisol (207±17%, $p<0.01$), confirming the stressful conditions of the animals. In the right hippocampus Tyr/Glu-Tub ratio decreased to 73±7% ($P<0.05$) and PSD-95 increased to 153±16% ($P<0.05$), suggesting decreased microtubule dynamics and post-synaptic remodelling. In contrast, the left hippocampus showed no changes. Moreover, in the right PFC Tyr/Glu-Tub ratio (156±9%; $P<0.05$), the neuron-specific Delta2-Tub (125±3%; $P<0.05$) and PSD-95 (120±5%; $P<0.01$) increased indicative of enhanced neuronal microtubule dynamics and post-synaptic remodelling. In contrast, the left PFC showed a decrease ($p<0.05$) in Tyr/Glu-Tub ratio (79±5%) and Delta2-Tub (82±3%), suggesting reduced microtubule dynamics; this effect was accompanied by decreased synaptophysin (83±2%; $P<0.05$) consistent with pre-synaptic alterations. The main results of the study show cytoskeletal and synaptic changes in the hippocampus and PFC with differences between the right and left hemisphere in response to psychosocial stress in tree shrews. In particular, the right hippocampus appears to be more vulnerable than the left one. Opposite responses were detected in the right and left PFC. These findings further support the possible involvement of neuronal microtubules in depressive disorders. Supported by the Eureka's Eurostars grant DEPSTER

TA13

DIAZEPAM ATTENUATES THE INSTRUMENTAL SUCCESSIVE NEGATIVE CONTRAST EFFECT IN A PROGRESSIVE RATIO OPERANT MODEL

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Evaluation of behavioural changes in response to reward gain or loss has been hypothesised to reflect underlying affective bias in animals (Paul et al. 2005). Previous studies have shown that successive negative contrast (SNC) is seen in animals where reward value is reduced relative to the expected outcome (Flaherty et al., 1999). In a progressive ratio lever task the benzodiazepine chlordiazepoxide significantly protected animals from the effects of unexpected devalue (Nikiforuk et al, 2009). In this study we have tested the effects of reward loss on performance variables using a progressive ratio operant task modified from our previous fixed ratio task (Mitchell et al, 2009). Having established instrumental (iSNC) we have tested the ability of diazepam to attenuate the effects of devalue on performance variables. Male Sprague Dawley rats were trained and tested using standard Med Associates 5-hole boxes and KLimbic software (Conclusive solutions Ltd). One group of animals were trained using a one pellet reward and the other group received a four pellet reward. At the end of training, a series of devalue sessions were introduced where the four pellet group received only a single pellet outcome for each correct response. Following baseline testing, the groups were merged to form a single 4 pellet group. Animals were then tested using a 30 min pre-treatment with diazepam (0.0, 0.3, 1.0 mg/kg i.p.) on a baseline day or devalue day using a fully randomised within-subject study design. Results from the devalue sessions (twice per week for 3 weeks) revealed a significant and reproducible main effect of SESSION for correct trials ($F(11.9, 190.1) = 4.11$; $P<0.0001$), premature responding ($F(12.76, 204.08) = 3.03$; $P < 0.0001$) and omissions ($F(12.59, 201.41) = 1.95$; $P < 0.03$) but not collection latency ($F(4.16, 62.34) = 1.08$; $P = 0.52$). Acute treatment with diazepam (0.3 and 1.0 mg/kg i.p.) selectively reduced the devalue effect on correct trials with a significant SESSION*DOSE interaction ($F(2, 32) = 4.27$; $P = 0.02$). Diazepam did not affect the devalue response for collection latency or premature responses. These data suggest that anxiolytic treatment can attenuate the contrast effect on correct trials.

TA14

DELETION OF THE PROTEINASE ACTIVATED RECEPTOR 2 HAS LIMITED EFFECTS ON ANXIETY BEHAVIOURS AND SPARES REFERENCE AND WORKING MEMORY

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Proteinase-activated receptors (PARs) are a family of novel G-protein coupled receptors. We have recently shown that PAR2 activation indirectly modulates hippocampal neuronal excitability and synaptic transmission in vitro (Gan et al., Brit J Pharmacol, in press,) and treatment with the PAR2 agonist SLIGRL induced deficits in tests of memory and anxiety in rats (Lohman et al., 2009, Neurobiol Learn Mem, 92, 301-309). Hence, in the present study we have investigated whether PAR2 deletion affects mouse behaviour in tests of learning and emotional behaviours. Locomotor activity (open field; OF), anxiety behavior (elevated plus-maze; EPM), spatial reference memory (Morris water maze; MWM), and non-spatial reference memory (T-maze continuous alternation; T-CAT) were investigated in mice (8-12 weeks) of both genders and all three genotypes (wildtype (WT), PAR2 heterozygous (HT) and PAR2 knockout (KO)) bred on a C57BL/6 background. An ANOVA was used for statistical analysis (general linear model for OF, EPM and T-CAT; repeated measures for MWM) with $P<0.05$ taken as significant. In the OF, no differences were observed in total locomotor activity between genotypes in either gender. HT males spent an increased time in the centre square compared to WT and KO males (WT: 40.2±6.0s, HT: 68.1±7.4s; $p<0.01$ compared to WT; KO: 35.3±3.4s, n=16). In contrast, no differences were observed between genotypes in females in centre square time. In the EPM, no differences were observed between genotypes in males. However, KO females exhibited decreased open arm entries (WT: 16.8±3.4%; HT: 17.1±3.0%; KO: 6.5±1.4%, $p<0.05$ compared to WT; n=8-16) and reduced open arm time (WT: 12.3±3.2%; HT: 10.4±2.7%; KO: 2.6±0.9%, $p<0.05$ compared to WT; n=8-16). PAR2 deletion had no effect on either spatial reference or non-spatial working memory. In the MWM, latency and path length progressively and significantly reduced within testing days (latency: male $F(4,42)=35.5$, $p<0.01$, female $F(4,41)=37.7$, $p<0.01$; path length: male $F(4,42)=40.3$, $p<0.01$, female $F(4,41)=56.3$, $p<0.01$), indicating that all mice learnt and remembered the platform position. However, there were no significant differences between genotypes. Furthermore, in T-CAT, there were no significant effects of genotype or gender on mean percent alternation (male: WT=58.3±3.4, HT=65.8±3.9, KO=61.2±4.9; female: WT=60.0±2.6; HT=59.5±4.8; KO=48.2±5.6; genotype: p=0.44, gender: p=0.43; n=8-16). These data indicate that PAR2 may play a gender specific role in anxiety whereas PAR2 deletion is without effect on memory. Further investigation is now underway to examine whether PAR2 activation by small molecule ligands leads to alterations in performance in locomotor, anxiety and memory tests.
The financial sponsorship for this study came from Iraqi government and University of Strathclyde.

TA15

PRENATAL CHRONIC MILD STRESS INDUCES ALTERATION IN OPEN FIELD BEHAVIOR, COGNITION AND SEROTONIN NEUROTRANSMISSION IN JUVENILE AND ADULT MICE. EFFECT OF TREATMENT WITH AMITRIPTYLLINE

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In humans, exposure to prenatal stress can adversely affect short- and long-term central nervous system (CNS) development. Here, we investigated the effects of prenatal stress on juvenile and adult mouse behaviour and hippocampal serotonergic neurotransmission, and whether an antidepressant, amitriptylline, could reverse the adverse effects of prenatal stress in adult female offspring. We also measured corticosterone levels in amniotic fluid as prenatal exposure to elevated levels of maternal stress hormone is thought to mediate adverse effects on CNS development. Stressed B6D2F1 dams were subjected to chronic mild stressors (e.g. overnight illumination, paired housing and 30o cage tilting) after mating until parturition, while the non-stressed dams were left undisturbed. A number of dams (non-stressed, N=6; stressed, N=7) were culled one day before predicted parturition to collect their amniotic fluid for determination of corticosterone levels. Post-weaning, the offspring (N=10-13/group/gender) were subjected to open field test, novel object recognition and contextual fear conditioning at two time points: 3 (juvenile) and 7-week-old (adulthood), for cognitive and anxiety-related behaviours assessment. Another 7-week-old prenatally-stressed female offspring (N=8) received amitriptylline (20mg/kg/day) through their drinking water for 10 days from the day before until behavioral tasks ended. Assessment of serotonergic activity by HPLC assay of 5HT and its major metabolite 5HIAA was made on hippocampi collected 48 hours after the behavioural testing ended. In the open-field test, adult prenatally-stressed females were hyperactive, but prenatally-stressed males were hypoactive compared to their non-stressed controls (stress x gender, $p=0.05$). There were no differences in anxiety-related behaviours at either age. Prenatal stress improved novel object-recognition in juvenile offspring ($p<0.05$), but impaired it in adult females (stress x gender, $p<0.05$), and this effect was reversed by amitriptylline treatment ($p<0.05$). Acquisition of contextual fear conditioning was enhanced in adult prenatally-stressed males but impaired in adult prenatally-stressed females. Juvenile and adult offspring showed no differences in serotonergic neurotransmission. Higher levels of 5HT and a lower ratio of 5HIAA/5HT levels in hippocampus were observed in amitriptylline-treated females versus non-prenatally-stressed and prenatally stressed females ($p<0.05$). There was a trend towards higher corticosterone levels in the amniotic fluid of prenatally-stressed dams but it did not reach significance. Exposure to stress in-utero thus affects the behavior of the offspring in an age- and gender-dependent manner, and adult females are more prone to exhibit adverse cognitive effects of prenatal stress. Administration of antidepressants in adulthood may reverse these adverse developmental effects.
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TA16

CHRONIC TRYPTOPHAN DEPLETION AN ANIMAL MODEL FOR DEPRESSION: HOW IMPORTANT ARE NEUROENDOCRINE AND GLUTAMATERGIC MEDIATIONS

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Background: Dietary induced-tryptophan (TRP) deficiency has been proposed as an animal model for depression. Studies have mostly tested acute TRP deficiency (ATD) with inconsistent results. Sub-chronic TRP deficiency (SCTD) may prove more reliable and sensitive. The aim was to test the hypothesis and to optimise the time of SCTD-induced depression-related behaviour with biochemical change.
Methods: Sprague Dawley (SD) rats were treated with a low TRP-containing diet for 0, 7 or 14 days. Peripheral and central neurochemical markers were measured. SCTD-induced depression-related behaviour was assessed by the forced swim test (FST). Sensitivity to antidepressants was tested by concomitant paroxetine treatment (10mg/kg/day via drinking water). One-way ANOVA with Tukey Test post-hoc analysis was used for statistical analysis of biochemical parameters. Behavioural data were tested for parametric assumptions with the Levene Test for homogeneity of variances and Shapiro Wilks for normal distribution and then differences were tested with two-way ANOVA with Duncan post hoc analysis.
Results: SCTD induced significant reductions in weight gain ($p<0.001$) and measures of peripheral and central TRP change. Corticosterone, aldosterone, and kynurenine (K), which has NMDA-ergic activity, increased, whilst kynurenic acid (KA), an NMDA receptor antagonist decreased. Corticosterone and aldosterone were significantly negatively correlated to weight gain (corticosterone: $r=-0.78$; $p<0.001$; $n=21$; aldosterone $r=-0.56$; $p<0.001$; $n=21$). 5-HT2 receptor binding Bmax was up-regulated ($p<0.001$). SCTD increased floating time and reduced swimming time in the FST which were reversed by paroxetine. Aldosterone was significantly and similarly increased at 7 ($p<0.05$) and 14 days ($p<0.001$), whereas other changes including corticosterone, maximised at 14 days SCTD.
Conclusion: Findings indicate that 14 days SCTD was optimal in this proposed model which resembles human depression in terms of behavioural and neurochemical attributes. Aldosterone may be an early marker or causal link for depression development, whereas increased cortisol and hippocampus 5-HT-receptor density could be correlates of depressive behaviour. Consequential increases in NMDA signalling through increased K/KA ratios suggests the model may be useful for testing novel antidepressants which transcend the monoamine theory of depression.
Acknowledgement The new work was supported by a grant from Bristol-Myers Squibb (Princeton, New Jersey, USA)

TA17

ASSESSING THE EFFECTS OF PSYCHOSOCIAL STRESS ON CORE BODY TEMPERATURE IN TREE SHREWS: A NEW STATISTICAL APPROACH

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The daily rhythm in core body temperature (CBT) is characterized by a temperature decline at the beginning of the resting period; such decline is delayed in depressed patients. In contrast to laboratory rodents, tree shrews are strictly day active and show a monophasic night sleep. The present study investigates the daily rhythm in CBT using an established model of depression, the psychosocial stress in tree shrews (Fuchs, 2001, CNS Spectr., 10, 182-190). To assess the effect of stress on CBT, a new statistical analysis approach has been established. Male tree shews (n=6) were measured during two control weeks followed by two weeks of psychosocial stress, as previously described (Fuchs, 2001, CNS Spectr., 10, 182-190). Non-stressed females (n=6) were also assessed for a gender comparison. For registration of CBT animals received radiotelemetric implants allowing continuous measurements every minute of every day, generating a time course for each animal on each day. Average weekly profiles were calculated for each animal. Different aspects of the CBT time course profile were summarized using non-linear regression techniques. The CBT in the morning was characterized by a linear decrease and in the afternoon by a linear increase. In contrast, the CBT from evening to midnight showed an exponential decrease followed by an exponential increase in the early morning hours. For each of these distinct periods a separate curve (or straight line) was fitted for each animal in each week (InVivoStat, Dose-Response module) and the parameters of the fitted curve/line recorded. The effect of stress or gender on these parameters was then assessed within-animal using a mixed-model repeated measures approach (InVivoStat, Repeated Measures module). The analysis revealed that the rate of exponential decrease during the evening was significantly different in stressed weeks compared to the control weeks ($P<0.001$). In particular, psychosocial stress induced a delay in the evening decline of CBT of approximately 40 minutes. Additionally, psychosocial stress induced a slight but significant ($P<0.01$) increase in Nadir temperature of $0.2\pm0.06°C$. No differences between males and females were detected. The present data shows a clear effect of psychosocial stress on CBT circadian rhythms. These findings confirm the reliability of our new statistical approach to assess the changes in CBT over time and prove that psychosocial stress in tree shrews is a suitable model to validate the effect of stress followed by treatment with potential antidepressant drugs.
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TA18

REPEAT COURSES OF ELECTROCONVULSIVE THERAPY: CHARACTERISTICS AND OUTCOMES

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Introduction: The use of repeat courses of ECT has not been studied to date despite Scottish national statistics demonstrating that a significant proportion of patients receive multiple treatment episodes. We sought to determine the characteristics of depressed patients who received several courses of ECT; the outcomes of treatment; and the use of prophylactic medication.
Methods: Analysis of local (Royal Cornhill Hospital, Aberdeen) ECT audit database (312 patients between 2002 and 2008).
Results: Repeat courses were common, with the more than half of all patients receiving more than one episode of treatment (range 2-16). The only factor predicting further treatment was outcome (reduction in MADRS score) at first course. This was significantly greater (-23.8+/-1.0 sem) in those receiving additional courses of ECT than those who did not (-19.2+/-1.5sem), in accordance with NICE guidance that only those showing a good response should be considered for further courses of treatment. Importantly, response magnitude was maintained throughout further treatment episodes. Although most patients received prophylactic antidepressant therapy, lithium use was limited, with an estimated 40% of patients receiving multiple treatments never having been exposed to this strategy. Conclusions: Repeat courses are common and effective, but maintenance medication may be under-used.
Source of Funding: University of Aberdeen

TA19

A COMPARISON OF METHODS OF MEASURING COGNITIVE FUNCTION FOLLOWING ECT

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Introduction: ECT is a safe and effective treatment for depression yet its use is limited by cognitive side effects. This study compares one commonly used standard method of measuring cognitive function (the Mini Mental State Examination, MMSE) with a computerised task (spatial recognition memory task, SRM) from the Cambridge Automated Neuropsychological Testing Battery (CANTAB). We examined the acute changes and correlate these with mood ratings. These are preliminary results from a prospective longitudinal study (with testing up to six months post-treatment). Each of the 7 cognitive domains contributing to the MMSE composite score was analysed separately to examine which domains change over time.
Methods: Patients receiving ECT in Aberdeen are tested using a standard battery prior to ECT, after four treatments, post treatment and at 1,3 and 6 months post treatment. The tests include the MMSE, MADRS (Montgomery Asberg Depression Rating Scale) and spatial recognition memory task (SRM) on the CANTAB. We present preliminary results limited to data obtained from the first three time points (Pre-, during and post-treatment) where we correlate cognitive measures with MADRS score.
Results: Both SRM Correct and MADRS scores decreased from pre- to post-treatment, no changes were found for MMSE scores. MMSE scores did decrease during treatment, but recovered to baseline post-treatment. Analyses of the 7 cognitive domains that create the composite score revealed this change was driven by the Orientation to Time component and, to a lesser extent, the Orientation to Place and Delayed Recall components. Pre-treatment, MADRS scores negatively correlated with SRM Correct, r = -.32, while MMSE scores did not. This was despite these cognitive measures correlating highly, r = .63. This correlation existed after 4 ECTs, r = .55; but neither cognitive measure was related to MADRS score. Post ECT, SRM Correct was negatively correlated with MADRS score, r = -.36 and positively correlated with MMSE scores, r = .31. However, there was no relationship between MMSE and MADRS scores.
Conclusions: Cognitive performance, assessed by the MMSE and SRM were found to be related pre- and post-treatment, but not during ECT. ECT affected MMSE scores during treatment but cognitive impairment was not apparent post-treatment, possibly due to ceiling effects. Both MADRS scores and the SRM Correct score declined. These data suggest that the composite MMSE score may not be sensitive to changes in memory that are successfully measured using a specific computerised task which shows that memory is affected by ECT but recovers over time.
No funding was required for the project.

TA20

A COMPARATIVE STUDY OF METHOHEXITONE AND PROPOFOL AS ANAESTHETIC AGENTS FOR ELECTROCONVULSIVE THERAPY (ECT): IMPACT ON SEIZURE THRESHOLD, SEIZURE DURATION AND OTHER TREATMENT PARAMETERS

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Introduction: Previous studies have suggested reductions in seizure duration and an increase of seizure threshold with the use of propofol as an anaesthetic agent for electroconvulsive therapy (ECT), Walder et al., Journal of Neurosurgical Anaesthesilogy.2001; 13:93-98.We set out to investigate the effects of the induction agents, methohexitone and propofol on seizure threshold, seizure duration, mean treatment dose per course and total number of treatments per course to recovery.
Methods: We conducted a retrospective comparative study using available records for patients who completed a course of ECT with methohexitone and later completed a course with propofol in our ECT suite. We compared seizure threshold, mean seizure duration, mean treatment dose per course and total number of treatments per course to remission. The Mann-Whitney (U) test and simple percentages were used for statistical analysis. Results: Six patients were identified and included in the study. All suffered from recurrent depressive disorder. Although seizure threshold showed a 23% increase with propofol when compared with methohexitone the difference was not statistically significant (U=0.5000). Mean seizure duration decreased by 59.7% with the use of propofol, being statistically significant as shown on EEG tracings (U=0.0313). A 27% increase in the total number of administered treatments was observed with propofol but was not statistically significant (U= 0.0625). Mean treatment dose increased by 25% with the use of propofol but this was not a statistically significant increase.
Conclusions: We conclude that both methohexitone and propofol have their place as anaesthetic induction agents in ECT. Differences in seizure duration, seizure threshold and other treatment parameters may not be important for therapeutic outcome. Other considerations have to be made in coming up with the choice of induction agent.
This project was not funded. All costs incurred by authors.

TA21

A COMPARISON OF ECT STIMULUS DOSING METHODS USING A CLINICAL SAMPLE

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Introduction: One facet of ECT practice which has changed significantly in recent years is the method of deciding upon dose. In early ECT practice, dose was often determined by giving a fixed dose to patients and noting whether or not a seizure occurred. A number of studies demonstrated that this led to adverse cognitive side effects which were hypothesised to arise from giving a dose which far exceeded the patient's seizure threshold. As a result, incrementally increasing dosing schedules were used to establish seizure threshold. In 2005 the Royal College of Psychiatrists, UK, recommended this stimulus dosing approach generally. Thus a number of methods can be used to calculate ECT dosage based on formulae, protocols or fixed dosing. It is unclear which should be considered superior. This study compares these various methods using a retrospective clinical sample.
Methods: A consecutive sample of patients receiving ECT in Aberdeen, between 2000 and 2008 was analysed. The empirically determined seizure threshold was used to calculate the proportion of patients who would have had a seizure if the half age or a fixed dosing method was used.
Results: 365 patients were included, the mean seizure threshold was 172mC (50-500mC). Males had a higher seizure threshold than females 197mC vs 159mC (p=.005). Patients treated using our local protocol had a significantly shorter mean seizure duration and cumulative seizure duration compared with other protocol methods. There was no difference in clinical efficacy. Seizure threshold was significantly higher in older (>65) adults F(1,211) 13.544, p <.001. Using the half age method 44.1% of patients would have had a seizure on their first stimulation, compared with 25.1% using a fixed dosing schedule of 175mC. An age based fixed schedule (200mC if <65 and 250mC if >65) would have resulted in 73.5% of patients having a seizure at between 1.5 and 2.5 times seizure threshold at first stimulation.
Conclusions: A fixed dosing schedule based on age would be superior to both the stimulus dosing method and half age method of dose calculation in terms of number of patients having a therapeutic seizure on first stimulation. This simplifies the ECT process and fewer restimulations and anaesthetics would be necessary.
No funding was required for the project.

TA22

A MRI INVESTIGATION OF ELECTROCONVULSIVE THERAPY (ECT) FOR THE TREATMENT OF DEPRESSION

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Introduction: According to the World Health Organization, depression is amongst the leading causes of disability worldwide. The most severe forms of depression, or those illnesses that fail to respond to pharmaceutical treatment, may be treated with electroconvulsive therapy (ECT). While ECT has been used in medical practice since the 1930s, little is still known about mechanism of action. A recent study by Nordanskog and colleagues (2010), in humans reported an increase in hippocampal volume after ECT treatment. The aim of this study was to test the hypothesis of both regional and gross changes in grey matter (GM) change after ECT treatment.
Methods: Twelve patients diagnosed with severe depression and about to undergo ECT treatment were recruited to the study. T1 weighted brain images were obtained using a Phillips 3 T MRI scanner immediately prior to the first ECT treatment and again after the course of ECT was finished. Clinical ratings of depressive symptoms were also assessed using the Montgomery Asberg Depression Scale (MADRS) prior to treatment, after four ECT treatments and again on completion of their ECT course. Finally, we also assessed memory performance using the spatial recognition task from the Cambridge Automated Neuropsychological Testing Battery (CANTAB). T1 weighted MRI images were analyzed using the program FreeSurfer (Athinoula A. Martinos Centre for Biomedical Imaging), which includes a set of automated tools for subcortical segmentation. First the images undergo an affine registration with Talairach space and then an initial anatomical labeling is performed. Finally, the images undergo a high dimensional nonlinear volumetric alignment to the Talairach atlas. We used the results of these segmentations to examine for changes in both in total GM volume as well as the GM volume of the hippocampus.
Results: The results of the hippocampal analysis revealed a significant increase in volume in the right hippocampus after ECT treatment ($p= 0.029$) and a trend towards a significant increase in total hippocampal volume ($p=.135$). These increases however, were found to be greater in males than in females. An increase in overall GM volume was also observed after ECT treatment ($p=0.012$). There were however, no significant correlations between these increases in GM and either change in depressive symptoms or memory performance. Conclusions: The results of this study illustrate that there is an increase in GM induced by ECT, however, this increase may not be the same in both sexes, highlighting the need for further research into potential sex differences in ECT treatment.

TA23

MATERNAL CHILDHOOD TRAUMA: EFFECT ON MATERNAL PSYCHOPATHOLOGY IN PREGNANCY AND OFFSPRING OUTCOME AT 11 YEARS

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Experience of childhood abuse and neglect elevates risk for mood disorders in later life. Maternal psychopathology during pregnancy has been identified as a key risk factor for offspring childhood maltreatment and adolescent depression. Previous psychiatric history, marital conflict, insufficient social support and lower age at first birth have been identified as key risk factors for antepartum depression. It has been proposed that prenatal experiences associated with maternal mental state influence foetal stress-regulation systems, with potential consequences on offspring adjustment in later life. The purpose of this study was to investigate the role of maternal history of childhood trauma on antepartum depression and offspring maltreatment and psychopathology. Information on maternal history of childhood trauma, maternal antepartum depression, offspring maltreatment and offspring childhood emotional problems was collected from a South London community-sample of 207 mother-infant dyads, who were followed prospectively from gestation to 11 years. Maternal history of childhood trauma significantly predicted maternal antepartum depression ($p < 0.0001$), offspring childhood maltreatment ($p = .0.003$) and childhood emotional problems ($p = 0.001$). Antepartum depression moderated the effects of maternal childhood trauma on offspring maltreatment and offspring psychopathology, whereby children whose mothers had a history of childhood trauma and who experienced antepartum depression, had significantly more reports of childhood maltreatment ($p = 0.001$) and significantly more emotional problems ($p = 0.001$), compared to children whose mothers did not have a history of childhood trauma and did not have antepartum depression. A history of maternal childhood trauma represents a significant risk factor for maternal depression during pregnancy, offspring childhood maltreatment and offspring childhood psychopathology. Children exposed to both maternal risk factors are at the greatest risk. Clinicians should endeavour to screen for a history of childhood trauma in early pregnancy in order to identify and support those women who may be at an elevated risk for mood disorders.
This research was funded by the Medical Research Council UK, the Psychiatry Research Trust and the South West GP Trust.

TA24

CHILDHOOD MALTREATMENT MODERATES THE EFFECT OF EXPOSURE TO MATERNAL ANTENATAL DEPRESSION ON PSYCHOPATHOLOGY IN OFFSPRING

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Introduction: Exposure to antenatal maternal depression and exposure to childhood maltreatment have each been associated with later offspring psychiatric problems in separate studies but have not examined in the same study. Aim To determine prospectively from a community-based study whether the association, already shown, between antenatal depression and adolescent offspring psychopathology is accounted for by childhood maltreatment.
Method: Diagnoses of maternal depression were made in pregnancy and during the child's lifetime, and of offspring psychopathology at age 11 and 16. Information on offspring maltreatment was obtained at 11 years. Complete data was available for 120 mother-child dyads (80% of original sample).
Results: 21% of offspring had been exposed to antenatal depression. 21% had been maltreated by 11 years. 30% of offspring were given a diagnosis of a depressive disorder or of a conduct disorder by 16 years. The risk of psychopathology for the offspring exposed to both maternal antenatal depression and to childhood maltreatment was 12 times greater than for offspring not so exposed. Childhood maltreatment moderated the effect of maternal antenatal depression on offspring psychopathology.
Conclusions: Research investigating the association between exposure to maternal stress in utero and later outcome for the offspring must take into account events in the child's postnatal environment.
Acknowledgements: The study was supported by the Medical Research Council UK Project Grant Nos G89292999N and G9539876N, the Psychiatry Research Trust and the South West GP Trust.

TA25

IS MATERNAL MIND-MINDEDNESS AT TWO MONTHS POST-PARTUM ASSOCIATED WITH DIAGNOSIS OF DEPRESSION AND PERSONALITY DISORDER?

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Introduction: Previous studies have found deficits in mother-interaction to be associated with maternal depression and also with maternal personality disorder. However, the capacity to read the baby's mental state has not been investigated in a sample of mothers with both depression and personality disorder. We aimed to examine the effects of the two diagnoses on maternal mind-mindedness at two months post-partum. A secondary aim was to examine the relationship between mind-mindedness and later infant attachment security. Method: The study includes a sub-sample (n=60) from a larger longitudinal study (Conroy et al, 2010, Soc Psychiat Epidemiol, 45:285–292). The sub-sample includes 30 women with a diagnosis of borderline personality disorder (BPD) and 30 women without BPD and their infants. Assessments at two months postpartum included video-recordings of mother-infant interaction. Assessments were made of infant attachment security at 18 months of age. The video-recordings were coded using the mind-mindedness coding scheme developed by Meins et al., 2006, Child Dev, 74, 1194-1211).
Results: Compared with healthy women, mothers with BPD were less likely to use mind related comments (mean: 9.83 (9.30) vs. 12.68 (7.40)) and less likely to use attuned mind related comments (mean: 7.39 (7.05) vs. 8.30 (7.52)) when interacting with their two month old babies, although the difference was not statistically significant. Compared with non-depressed women, women with depression were significantly less likely to use mind related comments (mean: 7.85 (6.95) vs. 3.09 (8.70) p=0.04) and to use attuned mind related comments (mean: 5.52 (5.21) vs. 9.10 (7.91) p=0.02). One-way ANOVA showed a trend for women with both depression and BPD to be the least likely to use mind related comments (p=0.06) and to use attuned mind related comments (p=0.08), compared with healthy women and with women with BPD only. Mothers of children who were rated as having disorganised attachment at 18 months used significantly fewer attuned mind related comments in interactions with their babies at eight weeks postpartum (p=0.02). Conclusions: Women with a diagnosis of both BPD and post-partum depression use the lowest proportions of mind related and attuned mind-related comments suggesting that it is the combination of depression and borderline personality that is the most important factor in limiting maternal mind-mindedness. The findings also support the widely-held view that disorganized attachment is more likely when children send out attachment signals which are not responded to appropriately by the caregiver.

TA26

MAJOR DEPRESSIVE DISORDER IN PREGNANCY IS ASSOCIATED WITH HYPOTHALAMIC-PITUITARY-ADRENAL AXIS OVERACTIVITY

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Antenatal depression is common, occurring in 10-15% of pregnancies, and is associated with an increased risk of preterm birth. Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis in Major Depressive Disorder (MDD) is one of the most consistent biological findings in psychiatry. Furthermore, normal pregnancy involves profound changes in the HPA axis, and the HPA axis is involved in the timing of delivery. Since both antenatal depression and HPA axis hyperactivity are associated with preterm birth, our objective was to address the hypothesis that antenatal depression will be associated with hyperactivity of the HPA axis and shortened gestational length. We compared cortisol levels and length of gestation in depressed and non-depressed pregnant women. We undertook a prospective study of women aged 20-40 years with a singleton pregnancy. Cases with a structured clinical interview (SCID) diagnosis of MDD of at least moderate severity (n=11) were compared with healthy controls free from lifetime psychiatric disorder (n=32). Those with obstetric complications, chronic medical conditions or taking medication were excluded. Assessment of maternal mood was undertaken after 25 weeks gestation. Cortisol was measured in saliva samples obtained at awakening and in the evening on two consecutive days at 32 weeks gestation. Gestational length was recorded. Groups were compared for average morning and evening cortisol and gestational length (Mann-Whitney U). Compared with healthy women, the MDD group had statistically significant higher average evening salivary cortisol levels at 32 weeks gestation (control (n=30) mean rank, 17.47; depressed (n=8) mean rank, 27.13; p = 0.029). There was no statistically significant group difference in morning cortisol or gestational length. Compared with women who were free from psychiatric disorder during pregnancy, those with MDD had raised evening salivary cortisol levels in the 3rd trimester of pregnancy. This mirrors the pattern of cortisol secretion frequently found in MDD outside of pregnancy and replicates recently published findings (O'Keane et al doi:10.1016/j.jad.2010.10.004). Although there was no difference in gestational length between the two groups in our study, the sample size was small. The results demonstrate a link between depression and altered pregnancy biology which may connect depression and shortened gestational length. This warrants further investigation, as improved understanding of the links between depression in pregnancy and abnormal biological factors will facilitate clinical decision-making aimed at reducing harm to both mother and baby, and will be an important consideration in the on-going debate on the risks and benefits of using antidepressant medication during pregnancy.
The research was supported by a grant from the Central Research Fund, University of London.

TA27

ASSOCIATION OF PRIMIPARITY WITH PERINATAL MOOD DISORDERS

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Introduction: Studies have demonstrated a strong association of episodes of postpartum psychosis and first pregnancies. This points to an interesting overlap with other pregnancy related disorders such as pre-eclampsia and is a potential clue to the aetiology of puerperal triggering. The aim of the present study was to investigate the effect of primiparity on a broader spectrum of perinatal mood disorders and in women with major depression in addition to bipolar disorder.
Methods: The sample was recruited as part of our ongoing research on genetic and non-genetic determinants of major affective disorders. Participants were interviewed using a semi-structured interview and psychiatric/general practice case notes were reviewed. An association between primiparity and perinatal episodes (PNE) might be biased by the fact that women who suffer PNE might be less likely to plan further pregnancies. Thus, for the current study we selected a sub-sample of 492 multiparous women with bipolar disorder type I, bipolar disorder type 2 or recurrent major depression, who had experienced at least one delivery affected by major psychiatric episodes (mania, depression or psychosis) and one delivery, which was unaffected. Contingency tables and Chi-Square test were used to test the hypotheses that primiparity was associated with PNE. Sub analyses were conducted separately for recurrent major depression, mania or psychosis and bipolar depression. Results: there was a significant association between first pregnancy and broadly defined perinatal episodes (p=0.0050). The statistically significant association between primiparity and PNE was replicated for recurrent major depression (p = 0.0077). In the bipolar group episodes of mania or psychosis, (p=0.0115), but not depressive episodes (p=0.9436), were associated with first pregnancies. Conclusion: The results of our study indicate that primiparity is associated not only with postpartum episodes in bipolar disorder, but also in recurrent major depression. It was of interest, however, that in bipolar women the association was only for episodes of mania or psychosis. Both biological and psychosocial factors might underpin this association. First pregnancies may be a greater psychosocial stressor than subsequent deliveries but there are significant biological differences that may also play a role and which are candidates for examination in further studies. Funding: ADF is funded by a Welsh Assembly Government Health Studentship. This work was supported by grants from the Wellcome Trust and The Stanley Foundation.

TA28

SEROTONIN INCREASES GLUCOCORTICOID RECEPTOR GENE EXPRESSION IN HUMAN FETAL HIPPOCAMPAL STEM CELLS

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Early life experiences influence an individual's stress reactivity and susceptibility to stress-related mood disorders, such as depression. It has been shown in animal models that variations in maternal care influence behavioural response to stress in the offspring. Moreover, maternal care affects the hypothalamo-pituitary-adrenal (HPA) axis responsivity of the offspring by modulating the expression of the glucocorticoid receptor (GR) in the hippocampus, where it plays a key role in HPA axis regulation through negative feedback inhibition (Weaver et al 2004 Nat Neurosci 7(8):847-854.) Accordingly, adverse early life experiences, such as maternal depression or childhood trauma, have been shown to decrease GR expression in several human studies (McGowan et al 2009 Nat Neurosci 12(3):342-348; Oberlander et al 2008 Epigenetics 3(2):97-106). In vivo and in vitro animal studies have proposed the molecular mechanism, which underlies the effect of positive early life experiences, such as good maternal care, on HPA axis regulation. This mechanism involves an increase in serotonergic signalling, which causes a subsequent increase in GR expression in hippocampal neurons due to changes in epigenetic regulation of the GR gene (Laplante et al 2002 Developmental Brain Research 139(2):199-203). However, it has not been shown that serotonin signalling is involved in this mechanism in humans. To investigate the effect of serotonin on human hippocampal GR expression, we used a human fetal hippocampal stem cell line (HPC03A/07, ReNeuron, UK) as an in vitro model. Cells were treated for 1 hour with 10nM, 100nM and 1μM serotonin hydrochloride. The levels of GR and its transcriptionally active splice variant GRα were assessed by real-time quantitive polymerase chain reaction. We observed a dose-dependent increase of the total GR mRNA levels upon serotonin treatment, with results reaching significance with 100nM concentration of serotonin (12.4% increase, $N=4$, $p<0.05$). In conclusion, we demonstrate that serotonin increases GR expression levels in the hippocampus during the early stages of brain development. Increased serotonin signalling is suggested to be a molecular correlate of positive early life experiences, such as good maternal care. Hence the demonstrated effect of serotonin on GR expression is hypothesised to be a mechanism through which good maternal care ensures normal HPA axis regulation in the offspring by increasing the GR expression in the hippocampus.

TB01

ASSOCIATIONS BETWEEN DISTURBED SLEEP, EMOTION REGULATION, ATTENTION TO THREAT AND COGNITIVE CONTROL IN HEALTHY VOLUNTEERS.

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Anecdotal and clinical observations suggest that poor sleep promotes negative affect and increases risk for mood and anxiety disorder. We recently demonstrated that poor sleep in healthy individuals is associated with increased negative affect and poorer cognitive control; assessed using subjective self-report questionnaires and experimental measures of executive attention and response inhibition (Baker et al, 2010, Journal of Psychopharmacology, 2010, 24, A26). Here we examined in a new cohort whether poor sleep is further associated with biases in emotion processing typically observed in anxiety and depression (e.g. selective processing of negative information) and a failure to inhibit negative intrusive thoughts. 94 undergraduates (88% females, mean age = 21.5 years) completed self-report measures of sleep quality (Pittsburgh Sleep Quality Index, PSQI), general sleep characteristics, trait anxiety and depression (Spielberger State-Trait Anxiety Index, STAI-T, STAI-D), worry (Penn State Worry Questionnaire, PSWQ), perceived control over anxiety (Anxiety Control Questionnaire, ACQ) and attentional control (Attentional Control Scale, ACS). Participants subsequently attended a single test session in which they completed a computerized modified visual probe measure of attentional bias to threat stimuli (presented subconsciously), and a five minute 'focus on your breathing task' throughout which thoughts were sampled at 12 time-points. Participants with poorer sleep (PSQI global) reported greater negative affect (depression, anxiety, worry) and a lesser ability to effectively control emotional reactions and perceived external threat (ACQ). Participants with poorer sleep also showed greater processing of threat relative to neutral stimuli presented outside of conscious awareness. Reported daytime dysfunction due to poor sleep was associated with poorer attention control (ACS). Poor sleep (in particular sleep disturbances and daytime dysfunction) was further associated with reduced attentional focus during the breathing task, while sleep quality (in particular increased sleep latency and reduced duration) was associated with increased negative thought intrusions during the same task. We observed significant relationships between poor sleep, negative affect, unconscious processing of threat, reduced ability to focus attention and susceptibility to negative thought intrusions. Our findings are consistent with suggestions that poor sleep may dysregulate key emotion processing networks (e.g. amygdala-prefrontal cortex) implicated in attentional bias to threat stimuli (particularly when presented outside of awareness) and converge with recent evidence that sleep deprivation dysregulates activity in this network when processing negative information (Yoo et al, 2007, Current Biology, 17, R877-R878).

TB02

DOSE RELATED SLEEP CHANGES IN HEALTHY VOLUNTEERS AFTER TWO DOSES OF HYDROCORTISONE: A DOUBLE BLIND PLACEBO CONTROLLED STUDY.

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Recent evidence suggests that short courses of high dose corticosteroids may allow patients with treatment resistant depression to respond to standard antidepressant treatments. This raises the question of the biological effects of acute administration of high dose steroids. The current study was designed to investigate the effects of hydrocortisone, given as a bolus during the biological corticosteroid nadir, on sleep in healthy volunteers, to help interpret a sleep study of patients with resistant depression. Volunteers in our MRI study of brain effects of high dose corticosteroids reported feeling more alert in the evening, increasing our interest in formal sleep analysis. 14 healthy male volunteers took part in a double blind, randomised 3-way crossover study, receiving placebo (P) (saline), 0.7 mg/Kg hydrocortisone (Low-L) and 7mg/kg hydrocortisone (High-H) at approximately 3pm on each study day, with an interval of at least 72 hours between study days. Subjects were prepared for home polysomnography and returned home to sleep at their normal bedtime. Recordings were analysed according to standard criteria by experienced raters who were blind to drug condition. Subjective sleep ratings were also collected. Total REM sleep was significantly reduced after hydrocortisone in a dose related manner (REM amount P 116min, L 93min, H 58min) and REM onset latency significantly increased (P 75 min, L 108 min, H 132 min). Slow wave sleep was increased significantly after the high dose (P 111 min, H 131 min) and latency to persistent sleep increased by the lower dose (P 15 min, L 26 min). Subjective quality of sleep was significantly worsened after the low dose. Suppression of REM sleep and increased slow wave sleep have been described in many studies using a cortisol challenge so these results are consistent with previous findings; we have shown a dose-related effect. Effects on slow wave sleep may be secondary to effects on CRH, but may also reflect direct effects of cortisol on sleep pathways. The mechanism of REM suppression is unclear. It is interesting that these effects were seen despite the time interval (8-12 h) between the hydrocortisone injection and the start of the sleep recordings. This suggests that in addition to the rapid non-genomic arousal effects of cortisol, longer term genomic effects also influence sleep. Our finding that the lower dose produced longer sleep onset time and reduced sleep quality is interesting and fits with the U shaped dose response effect of glucocorticoids reported in electrophysiological studies.

TB03

MODAFINIL IMPROVES PROBLEM SOLVING, COGNITIVE FLEXIBILITY AND CONTROL IN SLEEP DEPRIVED DOCTORS
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Introduction: Surgeons may on occasion have to perform operations under sleep deprived conditions when their cognitive and psychomotor abilities could be compromised. This study aimed to investigate the effect of a wake promoting drug, modafinil, on the executive functions and surgical skill of doctors after 24 hours of wakefulness.
Method: Thirty-nine male training grade doctors were recruited to take part in a double-blind placebo controlled study. The doctors were kept awake throughout the night after a day's work. At 3am twenty participants received 200mg of modafinil and nineteen of them received a lactose placebo. At 6am cognitive and psychomotor tests were administered.
Results: Modafinil improved performance on tests of higher cognitive function; participants in the modafinil group made fewer errors on the CANTAB reverse spatial span test ($F(1,38)=5.24$, $p=0.028$) and did not take as long to solve difficult planning problems on the CANTAB One Touch Stockings of Cambridge ($F(1,38)=4.34$, $p=0.04$), were less impulsive decision-makers on the CANTAB Cambridge Gamble Task ($F(1, 37) = 6.76$, $p=0.01$), and were more likely to pass the extra-dimensional shift stage on the CANTAB Intra-Extra Dimensional Set Shift task ($F(1,38) = 4.64$, $p=0.038$). In contrast, no improvement was seen in tests of clinical psychomotor performance. The modafinil group reported feelings of heightened alertness, corresponding with the point of estimated peak plasma concentration. However, these were transient and few side effects were reported.
Conclusions: The results of this study show that modafinil improved performance on complex cognitive tasks under sleep deprived conditions. These executive functions are clearly important for conducting surgical operations under stress and time pressure. However, these results await confirmation in a larger sample and extension using chronic dosing.

TB04

THE EFFECTS OF CAFFEINE TREATMENT AND BELIEF ON DAYTIME PERFORMANCE AFTER NORMAL AND RESTRICTED SLEEP
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Introduction: Previous research has investigated the effects of caffeine consumption, and belief of consumption on both waking performance and on sleep disruption. Our own research has compared caffeine treatment (caffeinated Vs decaffeinated coffee) and belief (caffeinated Vs decaffeinated) using 2x2 designs. We found greater improvements in performance and increased sleep disruption with belief of caffeine treatment compared to actual caffeine treatment. The present study investigated the effects of caffeine treatment and belief on waking performance next day under conditions of normal and restricted sleep. Methods: Ten male and 10 female healthy young adults (mean 20.75 years) who were moderate caffeine consumers (4.08 cups/day) all received both caf (approx. 170mg) and decaf coffee (approx. 2-3mg) treatment, as well as belief of treatment (told caf or decaf) after overnight caffeine withdrawal, making 4 treatment combinations with a minimum 1 day washout and treatment order based on latin squares. Half the participants underwent sleep restriction (4-8am sleep period verified by actiwatch, CNT(R)) whilst the others were allowed their normal sleep. Participants were tested at baseline and 40 minutes after coffee consumption with Bond & Lader visual analogue mood scales. Objective performance was similarly tested using the Penscreen Test Battery (Penscreen.com) including choice reaction time, number pairs, Sternberg memory and trail making. Multitasking was assessed with the Purple Framework – (purple-research.co.uk).
Results: Data were analysed blind using a 2x2x2 ANOVA (caf treatment, caf belief, sleep) assessing significant ($P<0.05$ or better) pre-post treatment differences. Participants were significantly more attentive after caffeine treatment, belief of treatment, and showed greatest post treatment improvements after restricted sleep. With objective assessments significant results included Choice reaction time and number pairs showing improved number correct and speed of correct responses for treatment belief, with greatest improvements seen after sleep restriction. Speed of choice reaction time response was improved for caffeine treatment. With multitasking concurrent performance was improved with belief of caffeine treatment on all 4 measures, though not caffeine treatment. Conclusions: Belief of caffeine treatment had a greater objective effect than actual caffeine treatment supporting earlier findings. Interestingly, this pattern of response was repeated under conditions of sleep restriction and with the novel investigation of increased task demands through multitasking. Under these conditions the adenosine inhibition provided by caffeine would be predicted to have greater effects in reversing performance deficits than mere belief of consumption. These findings suggest that the expectancy effects of caffeine outweigh pharmacological effects.
No financial sponsorship was received for this study

TB05

CNS IMPAIRING EFFECTS OF H1 BLOCKADE AS A FUNCTION OF HISTAMINE AVAILABILITY
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Research suggests that variations in histamine release throughout the sleep-wake cycle may explain variations in performance impairments observed after evening and daytime doses of histamine-1 (H1) antagonists. The mechanism responsible for the reversal of sedative effects might be mediated by restoring the balance between histamine release and synthesis. If histamine is only released during waking state, but histamine synthesis continues during sleep, then histamine availability will be largest shortly after awakening. Therefore, it could be expected that H1 antagonists are less likely to bind to H1 receptors (H1Rs) in times when histamine availability is highest, due to extensive competition between histamine and antihistamine for binding at the H1R. Hence, the aim of this study was to compare the effects of evening and morning doses of the first generation antihistamine hydroxyzine. It was expected that the sedative effect of hydroxyzine would be apparent in the evening after an evening dose, but would be smaller in the morning after a morning dose due to the greater release of histamine shortly after awakening. Eighteen participants (9 females) participated in a placebo-controlled, randomized, double blind, 3-way cross-over design. Cognitive performance was assessed using the divided attention task (DAT) and the attention network test (ANT). In combination with task performance-measures during the DAT and the ANT, event-related potentials were measured. Treatment periods consisted of (i) hydroxyzine in the evening and placebo in the morning, (ii) placebo in the evening and hydroxyzine in the morning, and (iii) placebo in the evening and placebo in the morning. Tests were performed one hour following drug or placebo intake in the evening, and 1 hour following drug or placebo intake in the morning. In the evening, the sedative effects were only apparent in some variables of the attention tasks, whereas in the morning hydroxyzine impairment was prevalent in most of the performance outcomes. Moreover, performance impairments observed after a morning dose were significantly larger than those observed after an evening dose of hydroxyzine for several tasks. The ERP-components of interest were P1, N1, N2 and P3. The ERP results were comparable with the behavioral data, showing that ERPs were more affected following morning administration of hydroxyzine than evening administration in the DAT. It is concluded that hydroxyzine-induced impairment is more prominent after morning doses as compared to evening doses, and that the present study could not completely establish direct evidence to confirm the hypothesis that histamine availability inversely affects the magnitude of antihistamine impairment.
No external sponsorship was used for the current study.

TC01

SEROTONIN RELATED CHANGES TO CEREBRAL BLOOD FLOW AND CEREBRAL BLOOD VOLUME DETERMINED BY BOLUS-TRACKING ARTERIAL SPIN LABELLING MAGNETIC RESONANCE IMAGING

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Advances in magnetic resonance imaging (MRI) have enabled measurement of cerebral blood flow (CBF) and cerebral blood volume (CBV) using contrast agent free approaches such as bolus-tracking arterial spin labelling (btASL) (1Kelly et al., 2010, Journal of Cerebral Blood Flow and Metabolism, 30(5):913-922). The aim of the study was to assess regional CBF and CBV changes induced by a range of manipulations to serotonergic (5-HT) neuronal transmission using btASL MRI. Male Wistar rats (n=7-8) received challenge injections of the 5-HT releasing agents d-fenfluramine (10mg/kg) or 3,4 methylenedioxymethamphetamine (MDMA) (20mg/kg), the serotonin transporter (SERT) inhibitor citalopram (30mg/kg) or the non selective 5-HT receptor antagonist metergoline (4mg/kg) at various times prior to btASL. In addition the effect of central 5-HT depletion induced by the tryptophan hydroxylase inhibitor p-chlorophenylalanine (p-CPA; 150mg/kg daily for 3 days, 72 hours prior to btASL) was assessed. Drugs were administered intraperitoneally and drug effects were compared to vehicle (saline) treated controls. Prior to placement in a 7-Tesla MRI scanner (Bruker BioSpec 70/30 magnet system), animals were anaesthetised with 0.1ml ketamine (10%) and 0.1ml xylazine (2%). A high resolution MR anatomical scan was conducted followed by a continuous ASL sequence that consisted of the preparation interval which contained the inversion pulse followed by snapshot Fast Low Angle Shot (FLASH) acquisition. Perfusion-weighted images were generated and analysed by the subtraction of labelled from control images as previously described1. Mean transit time (MTT), a measure that represents the time for labelled spins to traverse the vasculature, capillary transit time (CTT), a measure of the dispersion of the labelled bolus at the region of interest, and CBV values were generated. MDMA and d-fenfluramine induced a reduction in MTT and CTT and an increase in CBV values in primary motor, secondary motor and somatosensory cortices in comparison to vehicle treated controls ($p<0.05$; Student's T-test). Striatum, thalamus and hippocampus were unchanged. No change in CBF and CBV was evident following inhibition of SERT, 5-HT depletion, or non-selective blockade of the 5-HT receptors. In conclusion, enhancement of 5-HT release increases CBF and CBV. By contrast reduced 5-HT availability or blockade of 5-HT receptors fails to provoke a change. The results are consistent with a role for 5-HT in the regulation of perfusion and confirm that btASL is amenable for determination of CBF and CBV changes in response to 5-HT pharmacological challenges in a rodent model.
This study was funded by Trinity College Institute of Neuroscience.

TC02

OPTIMISED DESIGN MATRIX FOR KETAMINE PHMRI IN HUMANS: RELIABILITY, EFFECT SIZE AND THE INFLUENCE OF MOTION

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Introduction: Pharmacological MRI (phMRI) is an imaging technique used to investigate central pharmacological effects (Schwarz et al. 2004, Synapse 54: 1-10). Ketamine can induce a phMRI response that may serve as a CNS biomarker for the modulatory effect of other drugs relevant to the glutamatergic model of schizophrenia (Gozzi et al. 2008, Neuropsychopharm. 33: 1690-1703). phMRI often requires extended scan times and is thus more susceptible to artefacts such as scanner drift and head motion. Resolving these issues may depend on how head motion and variance in the response profile are modelled. These will impact upon the reliability and effect size of the response, which define the utility of the phMRI approach.
Methods: BOLD data were acquired from 10 healthy male participants, at rest, on two separate occasions. I.V. ketamine infusion began 5 minutes into the 15-minute scan. The phMRI response was modelled using a gamma variate (GV) regressor based on the results of a previous study (Deakin et al. 2008, Arch.Gen.Psychiatry 65: 154-164). Head motion was modelled in four ways: (1) all 6 head motion traces, (2) 1st component of Singular Value Decomposition (SVD) on motion traces, (3) 1st and 2nd components of SVD on motion traces, (4) no motion regressors. The effect of adding 1 or 2 additional regressors, designed to model differences in the temporal profile of the ketamine response, were also evaluated. A linear drift term was included in all models. Reliability was determined using the intra-class correlation coefficient [ICC(3,1)] (Shrout. & Fleiss, 1979, Psychol. Bull. 86: 420-428). Effect size and reliability were mapped voxel-wise and also evaluated on pre-specified regions of interest (ROI), both atlas- and coordinate-based.
Results: Robust responses to ketamine were observed in brain regions including the anterior cingulate cortex, dorsolateral prefrontal cortex and thalamus for all models, although magnitude and anatomical distribution of both effect size and ICC were model dependent. Overall, including the 1st SVD of the motion traces provided the most reliable responses at both the voxel and ROI level (ICCs > 0.6) and retained an excellent effect size (mean/SD at ROI level ~ 2.5 – 3). Performance was poor when shape-variant and motion regressors were combined. Conclusions: Modelling head motion effects with the use of the 1st SVD component of the motion traces yielded the most stable phMRI response and excellent effect sizes. Larger design matrices worked less well, possibly reflecting an over-fitting of the data. Funded by Eli Lilly.

TC03

MULTIVARIATE PATTERN RECOGNITION APPLIED TO PHMRI: MODULATION OF THE KETAMINE RESPONSE

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Introduction: Pharmacological MRI (phMRI) is an imaging technique used to investigate direct pharmacological effects on resting brain haemodynamics. NMDAR antagonists, such as ketamine, induce a phMRI response that may represent a pharmacological model to investigate the role of glutamatergic hypofunction in relation to schizophrenia. This may also serve as a CNS biomarker for the modulatory effect of other drugs. Methods: 16 healthy male participants underwent BOLD phMRI scan on four occasions. I.V. ketamine infusion (target plasma level 75ng/ml) began 5 minutes into the 15-minute scan on three occasions. Prior to the ketamine scans, participants were predosed with placebo, lamotrigine (300mg) or risperidone (2mg). A separate visit was included with oral placebo predosing and saline infusion. The order of visits was randomised. The phMRI response to ketamine was modelled in SPM5 using a single gamma variate regressor based on the results of a previous study [Deakin et al. (2008) Arch.Gen.Psychiatry 65 154]. Whole brain beta maps were passed to a Gaussian Process Classifier (GPC). This classifier is a supervised learning approach that produces probabilistic predictions on unseen test cases. Here, the GPC was trained on the beta maps from 15 participants with placebo-saline betas representing class one and placebo–ketamine representing class two. The placebo-saline, placebo-ketamine, lamotrigine-ketamine, risperidone-ketamine beta maps from 16th participant were then used as the test cases. This process was repeated until each subject's beta maps had acted as the test case. Results: The classification accuracies for the drug conditions against placebo-saline were: placebo-ketamine – 100%, lamotrigine-ketamine – 88% and risperidone-ketamine – 75%. The reductions in classification accuracy for the latter two align with the prediction that lamotrigine and risperidone attenuate the effects of ketamine. A similar trend was observed in the mean posterior probabilities of belonging to the placebo-ketamine group: placebo-saline – 0.12, placebo-ketamine – 0.88, lamotrigine-ketamine – 0.58, risperidone-ketamine – 0.49, with a statistically significant separation between ketamine vs lamotrigine and vs risperidone. Conclusions: The classification accuracy for ketamine alone showed an excellent separation from placebo. The classification accuracies for the lamotrigine-ketamine and risperidone-ketamine sessions evaluated on the placebo vs ketamine models provides good evidence that both drugs attenuate the ketamine phMRI response and indicate that risperidone attenuated the ketamine response more strongly than lamotrigine. This work indicates the potential of applying pattern recognition approaches to phMRI data and the sensitivity of the ketamine phMRI model to modulation by different pharmacological mechanisms.
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TC04

EFFECT OF KETAMINE ON BRAIN GLUTAMATE AND GABA IN HEALTHY VOLUNTEERS

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Ketamine, an uncompetitive NMDA receptor antagonist, induces perceptual and behavioual changes that have been likened to the positive, negative and cognitive symptoms of schizophrenia (Krystal, JH et al 1994, Arch Gen Psychiatry, 51:199-214). In rodents, systemic ketamine administration increases cortical glutamate levels (Moghaddam, B et al 1997, J Neurosci, 17:2921-7). In humans, increases in glutamine levels in anterior cingulate, measured using Proton Magnetic Resonance Spectroscopy (1H-MRS), have been reported following ketamine administration (Rowland, LM et al 2005, Am J Psychiatry, 162:394-6). It has been suggested NMDA receptors expressed on thalamic GABAergic interneurons are sensitive to ketamine antagonism, leading to loss of inhibitory tone and disinhibition of glutamatergic projection neurons (Olney, J.W. & Farber, N.B. 1995, Arch Gen Psychiatry, 52:998-1007). In this study we tested the hypothesis that ketamine administration in humans modulates thalamic GABA and cortical glutamate levels. Nine healthy volunteers underwent 1H-MRS imaging on a 3T GE MRI scanner. MEGAPRESS-IVS MRS data (to estimate GABA levels) were acquired from a 12cc midline subcortical voxel centred on the thalamus followed by an acquisition of short echo (30ms) PRESS data (to estimate glutamate levels) from a 8cc midline anterior cingulate voxel . A dynamically modeled intravenous infusion of ketamine was commenced (target plasma level150ng/mL), and the GABA and glutamate 1H-MRS acqusitions were repeated at 15 and 25 minutes after the start of the infusion respectively. After completing the scan, ketamine-induced effects were measured using the PANSS, concurrent PSI, BPRS and 5D-ASC. Ketamine led to a significant increase in schizophrenia-like symptoms and other psychological effects, as measured using all rating scales ($p<0.05$). It was not possible to measure glutamine reliably at 3T, but cortical glutamate levels were significantly higher following ketamine administration ($p<0.05$). There was no effect of ketamine on subcortical GABA or on any other brain metabolite as measured using 1H-MRS. 1H-MRS cannot distinguish between stored and released glutamate. Although the present findings indicate that ketamine modulates glutamate in anterior cingulate, it is not possible to say whether there is increased glutamate release. We found no evidence that ketamine leads to changes in GABA metabolism in the subcortical region. This does not exclude the possibility that ketamine acts via GABAergic mechanisms, however. PET or SPECT ligands sensitive to synaptic glutamate or GABA levels are needed to clarify the mechanism of action of ketamine in humans.

TC05

INVOLVEMENT OF THE ENDOCANNABINOID SYSTEM IN EMOTIONAL PROCESSING: A PHARMACOLOGICAL FMRI STUDY WITH Δ9-TETRAHYDROCANNABINOL (THC)

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Introduction: Processing of facial expressions of emotion is affected in psychiatric disorders such as major depression and schizophrenia. Evidence is accumulating for involvement of the endocannabinoid (eCB) system in emotional processing (Hill et al., 2009, Trends Pharmacol Sci, 30, 484-493). Both animal and human studies have shown that administration of eCB agonists such as Δ9-tetrahydrocannabinol (THC) can induce anxiolytic and prosocial effects. The purpose of the present study was to investigate the neurophysiological mechanisms underlying these effects in a double-blind, randomized, placebo-controlled, crossover pharmacological fMRI study.
Methods: Eleven right-handed healthy males underwent two functional MRI sessions receiving THC (6 mg) or placebo using a Volcano vaporizer. Emotional processing was assessed with an emotional faces task consisting of two conditions involving processing of facial expressions of emotion (fearful ('FF') and happy faces ('HF'), respectively) and a sensorimotor control condition ('CT'). In SPM5, effects of THC on brain activity were assessed in regions of interest, which were defined based on pooled placebo and THC group activity maps for FF and HF minus CT (thresholded at $t=4.1$, $p<0.001$, uncorrected, clusters ≥ 10 voxels).
Results: The effect of THC administration on performance accuracy was different between task conditions (drug*condition effect, $p<0.05$), with a THC-induced decrease in the mean percentage of correctly identified emotions for FF only ($p<0.05$). Pooled group activity maps yielded a network of activated brain regions, including bilateral prefrontal cortex, hippocampus and occipital gyrus, and right amygdala, inferior orbital frontal cortex, supplementary motor area and superior parietal gyrus. Activity in this network showed an interaction effect between drug and condition ($p<0.05$), indicating that THC administration had a different effect on the processing of FF and HF. This effect reflected a THC-induced decrease in FF activity and an increase in HF activity.
Conclusion: THC induced different effects on the processing of FF and HF, both in performance and brain activity. These effects suggest that THC administration altered emotional bias from increased reactivity towards negative stimuli to increased reactivity towards positive stimuli, thereby supporting the notion that eCB agonists such as THC may have anxiolytic and prosocial effects. This is consistent with clinical trials testing the eCB antagonist rimonabant for treatment of obesity, which showed depressed mood and anxiety as the most common adverse events (Christensen et al., 2007, Lancet, 370, 1706-1713). The present findings suggest that the eCB system may be a promising candidate for novel therapies to target symptoms of depression.
This study is performed within the framework of Top Institute Pharma, project number T5-107.

TC06

OPIOID RELEASE IN HUMAN BRAIN REWARD SYSTEM INDUCED BY AN ACUTE AMPHETAMINE CHALLENGE: A [11C]CARFENTANIL PET STUDY

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Amphetamine administration produces β-endorphin release of in the rodent striatum, as measured by microdialysis (Olive et al,2001, J Neurosci, 21, RC184). However, a direct demonstration that psychostimulants induce endogenous opioid (EO) release in the living human brain has not been available. Changes in the binding of the μ-opioid selective PET radioligand [11C]carfentanil to μ-OR, following physiological and psychological interventions, have been interpreted as evidence of its sensitivity to EO fluctuations. We evaluated, the effect of a single oral administration of amphetamine on [11C]carfentanil binding in the human brain. Twelve healthy male volunteers were examined with [11C]carfentanil PET, before, and 3 hours after, a single oral dose of d-amphetamine (either a "high" dose, 0.5 mg/kg, n=6, or an inactive "ultra-low" dose, 1.25 mg total dose, n=6). Regional binding potential (BPND) values were derived using a simplified reference tissue model with the occipital cortex as the reference region. The regional percent reduction in BPND from baseline to post-amphetamine scans (ΔBPND), at "high" and "ultra-low" amphetamine dose, was assessed in predefined automatically-delineated regions of interest (ROI) (Putamen, Caudate, Thalamus, Frontal Lobe, Anterior Cingulate, Insula) and manually-delineated ROI (Ventral Striatum, Amygdala, and Hypothalamus). An exploratory voxel-level analysis of group differences in DBPND was conducted using permutation-based nonparametric inference, with cluster-based thresholding correction for multiple comparisons. ΔBPND was significantly different from 0 in the "high" but not the "ultra-low" group, in Frontal Lobe, Putamen, Caudate, Thalamus, Anterior Cingulate, Insula ($p < 0.005$). The ΔBPND was significantly higher in the "high" than in the "ultra-low" group in the Frontal Lobe, Putamen and Thalamus ($p \leq 0.05$). Using the voxel by voxel approach, we observed a significantly higher DBPND in the "high" than in the "ultra-low" group, in putamen, ventral striatum, caudate, thalamus, and medial orbital gyrus in right cerebral hemisphere, and bilaterally in and superior, medial, and pre-central frontal gyri. This is the first direct demonstration of a dose-dependent, pharmacologically induced release of endogenous opioids in the human brain in vivo. Clinical data support the role of EO peptides in modulating the effects of acute amphetamine administration, as naltrexone attenuates the subjective effects of amphetamine (Jayaram-Lindström et al., 2004, J Clin Psychopharmacol, 24, 665-9). As dopamine receptors are co-localized with EO-synthesizing neurons, and the release of EO peptides after psychostimulants administration is mediated by dopamine receptors(Doron et al, 2006, Neuroreport, 23, 1633-6), it is likely that the dopamine system mediates the effects of amphetamine on EO release.
The study has been supported by the ECNP Research grant for young scientists and GlaxoSmithKline.

TC07

EFFECTS OF CELLULAR ENVIRONMENTS ON PET RADIOLIGAND BINDING – AN APPLICATION TO DOPAMINE AND OPIOID RECEPTOR IMAGING

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Imaging endogenous dopamine release using positron emission tomography (PET) has vastly increased our understanding of the role of the dopamine system, and dopamine2/3-receptors (D2/3DAR) in neurobiological disorders. There is now an increasing desire to measure release of other neurotransmitters using PET, such as opioid peptides, where increasing evidence suggests peptide release could be measureable with PET (Scott D.J. et al, 2007, Synapse, 61:707-714.). A greater understanding of the cellular processes and pharmacology underlying signal changes observed in vivo following release of endogenous substances would aid in the translation of this technology to other neurotransmitter systems. An internalisation process is thought to play a role in the change in signals observed for some receptors (Laruelle M., 2000, J. Cereb. Blood Flow Metab, 20:423-451.). We report the effects of three cellular environments (reflected by different physiological buffers) experienced by a receptor following agonist-induced internalisation on the binding parameters (Bmax and Kd) of D2/3DAR and opioid receptor (OR) radioligands. Three buffers were generated to reflect the different cellular environments: Extracellular (EC), Intracellular (IC) and Endosomal (EE), see Withey S.L. et al, 2010, NeuroImage, 52:S167. Saturation binding assays were performed using rat brain homogenates and the following radioligands: [3H]raclopride, [3H]spiperone, [3H](+)PhNO(all D2/3DAR), [3H]Diprenorphine(μ, κ, δ-OR), [3H]Naltrindole(δ-OR) and [11C]carfentanil(μ-OR). Assays were incubated at 37°C (60 minutes for D2/3DAR radioligands, 90 minutes for [3H]-OR radioligands and 30 minutes for [11C]-OR radioligands). Specific binding of D2/3DAR and OR were determined using haloperidol(1μM) and naloxone(10μM), respectively. All D2/3DAR radioligands studied exhibited a significant reduction in receptor affinity (Kd) in the endosomal environment compared to the extracellular: [3H]raclopride extracellular 2.01±0.16nM vs endosomal 9.45±0.82nM, [3H]spiperone extracellular 0.091±0.014nM vs endosomal 0.36±0.15nM and [3H](+)PhNO extracellular 0.56±0.13 vs endosomal 10.32±2.7 (all $P<0.01$). The three different environments had no effect on the D2/3DAR receptor availability (Bmax). The effect of altering cellular environments did not cause any change in the Kd for any of the OR radioligands. However, a significant reduction in Bmax of the OR was observed for all radioligands studied: [3H]Diprenorphine extracellular 286±22fmol/mg vs endosomal 127±26fmol/mg ($P<0.001$), [3H]Naltrindole extracellular 134±4.9fmol/mg vs endosomal 38±3.3fmol/mg ($P<0.001$) and [11C]carfentanil extracellular 81.94±11 vs endosomal 53.06±10.17fmol/mg ($P<0.01$). PET signal changes are generally reported in terms of binding potential (BP) which is defined as Bmax/Kd. These data suggest that following agonist-induced internalisation, a significant reduction in BP would be observed due to a reduction in Kd for the D2/3DAR, and a reduction in Bmax for the OR in the endosomal compared to the extracellular environment.

TC08

IMAGING THE DOPAMINE SYSTEM IN PATHOLOGICAL GAMBLING: AN [11C]-RACLOPRIDE PET STUDY

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Introduction: Changes in dopamine neurotransmission, including reduced D2/D3 receptor availability, have been widely reported in studies of drug addiction, but it is unclear whether these alterations reflect a consequence of long-term dopamine stimulation, or a pre-existing vulnerability. Studies of pathological gambling (PG) may help to resolve these pathways, as PG is associated with overlapping risk factors with drug addiction but the 'neurotoxic' sequelae are presumed to be minimal. While several indirect techniques indicate dopamine abnormalities in PG, no studies have assessed baseline D2 receptor availability directly in clinical PG.
Methods: Striatal D2/D3 receptor availability was assessed in 9 males with PG meeting DSM-IV criteria, recruited from the National Problem Gambling Clinic in London, UK. Participants underwent an [11C]-raclopride bolus PET scan, and were compared to 9 male age-matched controls. BPND values were extracted across functional subdivisions of the striatum (limbic, associative, somatosensory) based on the templates by Martinez et al (2003 J Cereb Blood Flow Metab 23, 285–300), with cerebellum as a reference region. Trait impulsivity was assessed using the UPPS-P (Cyders et al 2007 Psychological Assessment 19: 107-118), a self-report questionnaire that separates several facets of impulsivity including 'urgency', the tendency to commit impulsive acts during valenced mood states (positive urgency, negative urgency).
Results: There were no group differences in baseline D2/D3 receptor availability in the overall striatum (PG mean BPND=2.46, sd 0.26; Controls mean=2.44, sd 0.22; t16=.165, p=.871) or the three functional subdivisions. Within the PG group, there was a strong association between D2/D3 receptor availability and trait impulsivity. These inverse correlations were strongest for the two urgency facets, and were primarily observed in the limbic and associative subdivisions, where the effects survived partialling for age, which also predicted D2/D3 availability (Positive Urgency, Overall Striatal BPND: r6=-.941, p<.0005; Negative Urgency, Overall Striatal BPND: r6=-.881, p=.004).
Conclusion: We observed no changes in striatal dopamine D2/D3 receptor availability in individuals with PG, consistent with a recent dynamic [11C]-raclopride study reported by Linnet et al (2011 Addiction 106: 383-390). These results imply that previous D2/D3 reductions described in drug and alcohol addiction may occur as a consequence of long-term drug use. Nevertheless, individual differences in mood-induced impulsivity ('urgency') in the gamblers were associated with D2/D3 receptor binding, highlighting the relevance of this personality construct to disordered gambling and its link to dopamine neurotransmission.
Declaration: This work was supported by a Medical Research Council grant (G0802725). It was completed within the Behavioural and Clinical Neuroscience Institute, supported by a consortium award from the MRC and Wellcome Trust, and in collaboration with Addiction and Neurology Groups at MRC Clinical Sciences Centre, and with Imanet, GE Healthcare.

TC09

THIS ABSTRACT HAS BEEN WITHDRAWN

TC10

THE SSRI FLUVOXAMINE HAS NEUROPROTECTIVE EFFECTS IN AN MCAO RAT MODEL OF STROKE

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Introduction: SSRI's, including fluvoxamine, are effective antidepressants acting via increasing serotonergic transmission in the CNS. Recently SSRI's have been shown to promote neurogenesis and neuronal cell survival, increase concentration of growth factors and even suppress inflammation - the effects that might be effective in ameliorating acute and chronic brain trauma including ischemia(Jin et al. (2009) Brain Res. 1281:108, Li et al. (2009) J Neurosci Res. 87:112). However some controversy exists over whether SSRI's are beneficial or even harmful in various types of stroke. Here we set out to test if fluvoxamine is neuroprotective in a rat model of transient focal ischemia, middle cerebral artery occlusion (MCAO).
Methods: Using stratified randomization (by weight), 28 male Sprague dawley rats (380.1g ± 11.10 g) were randomly assigned to either the control (saline) or the treatment (fluvoxamine 25mg/kg) group. The middle cerebral artery (MCA) was occluded by a 5.0 intraluminal thread (Doccol Corporation, USA) under isoflurane anaesthesia (in O2/air 10:90) as previously described (Virley et al. (2000). J Cereb Blood Flow Metab. 20(3): 563). The reperfusion was achieved by withdrawing the thread after 60 minutes. Treatment was administered by 2 intraperitoneal injections: the first 30min before occlusion and the second at reperfusion. T2W MRI images were acquired at 24 hours and 9 weeks after MCAO on a 7T MRI system. Lesions were quantified by semi-automatically countering the hyperintense lesion in the T2W images by Jim software (Xinapse systems).
Results: Lesion sizes in the control group were (mean±sd) 121±74mm3 at 24h, and reduced to 70±64 mm3 at 9 weeks after MCA occlusion - of these 47% of animals had lesions encompassing cortical and subcortical tissue and 53% were subcortical-only (caudate-putamen), following a pattern previously described (Wegener et al. (2005) J Mag Res Imaging 21:340). In the fluvoxamine group, the lesions were 85±56 (24h) and 32±44 (9wk), and 44% animals had full lesions. Measurement of the lesions' change over time from acute to chronic revealed a significant effect of fluvoxamine treatment in the subcortical lesion cohort (p=0.04 Man Whitney two tailed t-test, 77% reduction in fluvoxamine group vs. 57% reduction in control group).
Conclusion: Fluvoxamine showed a small but significant neuroprotective effect on reducing the size of the subcortical stroke lesions in MCAO rats. This result corroborates and substantiates the findings of improved function in experimental stroke in rodents by SSRI's. This work was funded by the Department of Neuroimaging, Institute of Psychiatry

TC11

SIMULTANEOUS IN-VIVO PROTON SPECTROSCOPY AND ELECTROENCEPHALOGRAPHY: PRELIMINARY RESULTS AND EVIDENCE FROM A NOVEL METHODOLOGY

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Although electroencephalography (EEG) has been used to probe the neural correlates of human perception for nearly a century, the exact neurochemical underpinnings of both event related potentials (ERPs) and oscillatory activity in the human brain remain to be determined. Here, we present a novel methodology of combined EEG and event related proton magnetic resonance spectroscopy (ER-1H-MRS), which can be used non-invasively and concurrently, to probe both electrical and chemical activity in the human brain. 14 healthy right handed individuals participated. Informed consent was obtained and ethical approval granted. In the scanner, participants were shown drawings of familiar and unfamiliar objects in a repetition suppression paradigm previously shown to modulate gamma oscillations (Gruber & Muller, 2005, Cerebral Cortex,15, 109-116). They responded by pressing a button to indicate that the object was either familiar or unfamiliar. Each object, familiar and unfamiliar, was shown 3 times and each trial lasted 3 seconds and there were 256 per block, of which there was three. Time locked single voxel (15*15*20 mm) 1H-MRS data were collected from the lateral occipital cortex every 3s using a Philips 3T, (40 ms PRESS acquisition). EEG data were concurrently acquired using MR compatible hardware. Both spectral and EEG data were of good quality and the combined technique did not result in any significant degradation of signal or increase in noise. line width and signal to noise levels were similar to those normally acquired in research and clinical practice. Here we present, to our knowledge, the first successful evidence of concurrently acquired event-related 1H-MRS and EEG data. Utilizing this technique we find a strong positive correlation between Glu levels and evoked oscillatory activity in the gamma range. Additionally, we find increased glutamatergic activity in response to unfamiliar objects as opposed to familiar objects in the lateral occipital cortex. Finally, we also demonstrate a significant interaction between stimulus type and presentation, with familiar objects decreasing gamma activity when repeated and the opposite for unfamiliar objects. These results together, evidence the strong utility of this technique in probing cognition, with little to no evidence of signal degradation caused by the unique combination. This multi-modal imaging method has particular potential for clinical practice, where numerous conditions present with abnormal processing, as measured by EEG.
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TC12

NEURAL PROCESSING OF EMOTIONAL INFORMATION IS NEGATIVELY BIASED IN DYSPHORIA

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Introduction: Depression is associated with abnormal neural responses to emotional information processing. For example, neuroimaging studies of depressed patients have consistently reported amygdala hyperactivity in response to negative emotional stimuli. However, it is unclear whether this hyperactivity is also apparent as a function of dysphoria. Methods: The current study therefore scanned with fMRI 24 dysphoric participants (Beck Depression Inventory, BDI > 10) and 24 matched healthy controls (BDI < 5) during an emotion matching task. Participants were instructed to match facial expressions (fear or happy) and orientation of geometric shapes. Neural responses to fearful and happy faces were compared between groups to explore differences in neural activity.
Results: Dysphoric participants were observed to have greater activation to fearful than happy faces in the amygdala and fusiform gyrus compared to controls. In contrast, dysphoric participants had greater activation in the lateral orbitofrontal cortex to happy than fearful faces when compared with controls (small volume corrections applied for 10mm radius, FDR $p < 0.05$). Hyperactivity in the amygdala and fusiform gyrus combined with reduced activity in prefrontal control areas has been reported in depressed patients both at rest and in response to negative stimuli.
Conclusions: This pattern of neural activity is believed to contribute to biases in processing negative stimuli in depression. Similar results observed as a function of dysphoria support a continuum theory where emotional processing biases are also seen in symptomatic participants who fail to meet criteria for depression. Such effects validate this group for further investigations of emotional processes important in depression.

TC13

BRIEF COGNITIVE-BEHAVIOURAL TREATMENT NORMALISES INCREASED AMYGDALA RESPONSE TO THREAT IMAGES IN PATIENTS WITH PANIC DISORDER

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Background: Panic attacks are caused by misinterpretation of normal physical symptoms in a catastrophic way. Using an emotional regulation paradigm with fMRI in patients with panic disorder (PD), we have recently found hypersensitivity of limbic regions including the amygdala. In this study, we have tested the hypothesis that brief, exposure-based cognitive-behavioural treatment reduces limbic hypersensitivity to threat stimuli in patients with PD. Methods: Twenty-four patients with PD were randomly allocated to a treatment group receiving four sessions of CBT versus a waiting group not receiving any intervention. After this period, they were tested using functional MRI. They were presented with eight blocks of aversive pictures and instructed to either maintain or down-regulate the elicited negative affect. Volunteers were trained to use reappraisal as a strategy of down-regulation. FMRI data processing was carried out using FSL, with thresholds of $z>2.3$ and $p=0.05$. ROI signal extraction was carried out for brain areas identified as relevant in emotion regulation in our earlier research.
Results: Four sessions of CBT significantly reduced self-reported panic severity, catastrophic cognitions and agoraphobia. When maintaining negative affect (vs. down-regulating) during MRI imaging, activity in the left amygdala was decreased in patients who had received CBT treatment compared to waiting-group PD. Comparing percent signal change between treated PD patients and the healthy control sample of our earlier study indicated no differences between these two groups.
Conclusions: Increased amygdala response to threatening stimuli in PD patients is normalised by CBT treatment, after only four intervention sessions. These results suggest that reducing limbic sensitivity might be a relevant mechanism of action of cognitive-behavioural treatment similar to effects seen with pharmacological intervention strategies (Harmer et al 2009).

TC14

IMAGING VULNERABILITY FOR DEPRESSION

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Spontaneous fluctuations in blood oxygenation level-dependent (BOLD) signal, as measured by functional Magnetic Resonance Imaging (FMRI), has proved to be a valuable tool for probing neural function, architecture and psychopathology. Over the past decade a converging corpus has identified a series of canonical resting-state networks corresponding to divergent functions including; motor, visual and auditory processing, executive/cognitive control and self-referential processing. Moreover, there is increasing evidence to suggest that these networks may be disrupted in depression and it has been suggested that increased default-mode (also referred to as task-negative) network connectivity, mediated via a region of the dorso-medial prefrontal cortex (termed the dorsal nexus), may underlie the ruminative, introspective focus that is characteristic of depression (Sheline et al., PNAS, 2010, 107(24):11020-5). Here, we wished to test the hypothesis that increased connectivity from the dorsal nexus to the default-mode network (DMN) would be present in adolescents at increased familial risk of depression but with no personal history of mood disorder. We included 15 participants who had never personally suffered from major depression but who had a biological parent with a history of major depression (FH) and 15 healthy controls (HC). Resting-state data were acquired on a Siemens Sonata 1.5T whole-body scanner located at the Oxford Centre for Magnetic Resonance Research (OCMR), University of Oxford. During resting-state acquisition subjects were instructed to keep their eyes open and watch a fixation cross presented on a screen positioned at the foot of the scanner bore. Resting MRI analysis was carried out using Multivariate Exploratory Linear Optimized Decomposition into Independent Components implemented within FSL. We observed significantly greater DMN connectivity in FH participants to left dorso-medial prefrontal cortex, orbitofrontal cortex, left precuneus/lingual gyrus border, left fusiform and left middle temporal gyrus. There were no regions of increased connectivity in HC vs. FH participants, nor did we observe altered connectivity within other networks previously investigated by others [e.g. the Cognitive Control (also referred to as task-positive) or Affective networks]. The principal finding of the current report is that young people at increased risk for familial depression exhibit increased connectivity to the DMN from a region of the dorso-medial prefrontal cortex, a phenomenon similar to that described for acutely depressed patients (Sheline et al., PNAS, 2010, 107(24):11020-5). This raises the interesting question that altered DMN connectivity may represent a vulnerability marker for depression.

TD01

THE ROLE OF CHILDHOOD TRAUMA ON BODY MASS INDEX AND C-REACTIVE PROTEIN IN FIRST-EPISODE PSYCHOSIS

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The high incidence of metabolic abnormalities in psychosis patients has been mainly attributed to antipsychotic treatment. However, it has been shown that metabolic abnormalities are present also in drug naïve first-episode psychosis patients. It has been suggested that repeated psychological stress may play a role by inducing a chronic inflammatory process which may predispose to the development of metabolic abnormalities. The aim of the study is to investigate the association between psychosocial stress and inflammatory and metabolic biomarkers in subjects with first-episode psychosis and healthy controls. Body Mass Index (BMI), weight and waist circumference were measured in 96 first-episode psychosis patients (mean±SEM age: 27.0±0.6 years; gender: 62.5% males) and 99 healthy controls (age: 26.3±0.6 years; gender 67.7% male). High sensitive C reactive protein (hsCRP) and leptin were measured in a sub-sample of 37 patients (age: 28.5±1.1 years; gender: 65.8% males) and 49 controls (age: 26.3±0.6 years; gender: 73.5% males). In all subjects information on childhood trauma and recent stressors was collected. First-episode psychosis patients showed significantly higher BMI (24.8±0.5 vs. 23.3±0.4), higher hsCRP levels (0.7±0.2 vs. 0.2±0.1) and a higher number of childhood trauma events (1.2±0.1 vs. 0.6±0.1) compared with healthy controls. Levels of hsCRP were associated with BMI (Spearman's rho=0.49, p=0.012) and also with weight (Spearman's rho=0.47, p=0.012) in the patient group, but not in healthy controls. Patients with childhood trauma had higher BMI compared to patients without any trauma as well as controls (F=3.1, df=2,191, p=0.049). This was specific to childhood sexual abuse as patients with childhood sexual abuse had higher BMI compared to controls (p=0.004) and a trend for a higher BMI compared to patients without any childhood sexual abuse (p=0.055). Patients with childhood trauma also showed a trend towards higher levels of hsCRP (F=2.5, df=2,70, p=0.089). This effect was also specific to sexual abuse; patients with childhood sexual abuse had higher hsCRP levels compared to patients without any childhood sexual abuse (p=0.001) and controls (p<0.001). Our study shows an association between childhood trauma and the increased prevalence of metabolic and inflammatory abnormalities observed at the onset of psychosis. This suggests we might be able to identify and target more vulnerable individuals among patients with psychosis to prevent and treat poor physical health. Future longitudinal studies would need to clarify if the increase in inflammatory markers may, at least in part, mediate the link between early life stress and subsequent metabolic abnormalities in patients with psychosis.

TD02

SUBANAESTHETIC KETAMINE TREATMENT ALTERS PREFRONTAL CORTEX FUNCTIONAL CONNECTIVITY AND THE PROPERTIES OF FUNCTIONAL BRAIN NETWORKS

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Introduction: The quantitative analysis of network structure has been applied to elucidate the organisation of functional brain networks in both healthy humans and in schizophrenia (Liu et al., 2008. Brain.131:945-961). In both humans and preclinical models acute treatment with subanaesthetic doses of the NMDA receptor antagonist ketamine provides a translational model relevant to many of the symptoms of schizophrenia. Here we characterise ketamine-induced alterations in functional brain network structure to further elucidate the mechanisms underlying the schizomimetic effect of this drug. Methods: Cerebral metabolism (66 brain regions) was determined in control (saline, 2mls.kg-1, male, C57BL/6J, n = 9) and ketamine-treated mice (30mg.kg-1, i.p, n = 9) by semi-quantitative 2-deoxyglucose autoradiography (Dawson et al., 2010. Schizophrenia Bulletin. DOI: 10.1093/schbull/sbq090). Overt alterations in metabolism were statistically analysed by t-test. The global properties of the brain network in each group were characterised in terms of the mean degree, average path length, mean clustering coefficient. In addition, centrality analysis (degree, betweeness and closeness) was used to identify important hub regions in these networks. Hub region identification was determined by statistically comparing real with calibrated random (Erdös-Rényi) graphs. Statistical differences in global network architecture between groups were analysed using ANCOVA (correlation threshold as the covariate). Alterations in regional centrality between groups were analysed by comparing the z-score for each region, generated relative to random networks, using t-test with Bonferroni correction. Ketamine-induced alterations in neural system clustering and functional integration between neural systems were determined using the Generalized Singular Value Decomposition (GSVD) algorithm (Xiao et al., 2011. BMC Systems Biology, under review). Significance was set at $p<0.05$ throughout. Results: Ketamine-treatment induced overt hypermetabolism in the prefrontal cortex (PFC), along with overt hypometabolism in discrete thalamic nuclei. The functional brain network in ketamine-treated animals had a significantly increased mean degree ($F(1,21) = 493.56$, $p<0.001$), reduced average path length ($F(1,21) = 160.26$, $p<0.001$) and increased mean clustering ($F(1,21) =160.26$, $p<0.001$) as compared to that in controls. In control animals 11 regions were identified as important hubs ($z>1.96$ and $p<0.05$). In ketamine-treated animals the number of hub brain regions was increased, with a significant increase ($z>2.56$ and $p<0.05$) in centrality evident in 5 PFC, 5 thalamic and 2 amygdala nuclei. In control animals a functional interaction existed between the PFC-amygdala and PFC-septum/DB neural systems that was significantly lost ($p=0.026$ and $p=0.048$, respectively) in ketamine-treated animals. In contrast the PFC became more functional coupled to neuromodulatory nuclei ($p=0.007$) in ketamine-treated animals. Conclusions: This study is the first to identify how a schizomimetic dose of ketamine impacts on functional brain network structure and functional integration between discrete neural subsystems in the brain. These results provide new insight into the mechanisms underlying brain dysfunction in schizophrenia. This work was funded by the Psychiatric Research Institute of Neuroscience in Glasgow (PsyRING).

TD03

THE EFFECTS OF ACUTE ANTIPSYCHOTIC ADMINISTRATION ON CORTISOL AND INFLAMMATORY MARKERS IN HEALTHY VOLUNTEERS

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In patients with first episode psychosis, elevated levels of cortisol and pro-inflammatory cytokines have been reported and recent studies indicate that antipsychotics can play a role in moderating these abnormalities (Mondelli et al. 2010, Schizophrenia Research 116:234-242; Ryan et al. 2004, Psychoneuroendocrinology 29:1065–1070; Zhang et al. 2005, Neuropsychopharmacology 30:1532–1538); however it is still unclear if this is a consequence of changes in psychopathology or of their direct pharmacological action. The effect of antipsychotics on cortisol and cytokines levels in the absence of psychopathology, has only partially been investigated and remains unclear. This study investigates the effects of aripiprazole, a novel atypical antipsychotic with partial agonism activity at D2 and 5-HT1A receptors, and haloperidol on cortisol, interleukin (IL)-6 and leptin, in the same healthy individuals. Haloperidol (3mg) and aripiprazole (10mg) were administered to 20 healthy Caucasian males (age:23, SD:4.5yrs) in a randomized, double-blind cross-over placebo controlled design. Volunteers had no past psychiatric history, recent recreational drug or tobacco use. Salivary cortisol samples were acquired at -10, +105 and +190 minutes post intervention. Blood samples were acquired at +200 minutes post intervention to assess IL-6 and leptin levels. The area under the curve (AUCg) of cortisol levels was derived from the trapezoid formula (Pruessner et al., 2003). Data was available on N=18 and intervention effects were explored using aone-way repeated measures ANOVA with bonferroni post hoc comparisons. Cortisol levels (AUCg) were significantly altered by both antipsychotics ($F(2,34)=26.006$, $p=.0001$) such that compared with placebo, haloperidol was associated with a significant cortisol reduction ($p=.0001$) whilst a significant elevation in cortisol was observed after aripiprazole ($p=.005$). Direct comparison of the drugs indicated that aripiprazole was associated with significantly higher cortisol levels than haloperidol ($p=.0001$). A significant main effect of intervention was also evident on IL-6 levels ($F(2,20)=3.5$, $p=0.049$), indicating that IL-6 was significantly lower after haloperidol than placebo ($p=0.039$). There was no significant effect of intervention on leptin. In contrast with a recent study reporting an absence of effect of haloperidol on cortisol levels (Cohrs et al. 2006, Psychopharmacology 185:11-18), we instead show a significant reduction in cortisol, in addition to IL-6, levels after haloperidol, in healthy individuals. This finding is suggestive of a possible common (dopaminergic) pathway modulating these two stress biomarkers. The association of aripiprazole with increased cortisol levels has never been previously reported, and might be driven by this drug's novel pharmacological action on the dopamine and serotonin system. Our findings support the notion that stress biomarkers are directly affected by antipsychotics through their specific pharmacodynamic properties. Acknowledgments The study was supported by the American Psychiatric Institute for Research and Education (APIRE)and the NIHR Biomedical Research Centre for Mental Health, South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, King's College London

TD04

OLANZAPINE – RELATIONSHIP BETWEEN DOSE, PLASMA CONCENTRATION, RECEPTOR OCCUPANCY AND RESPONSE: A SYSTEMATIC REVIEW

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Objective: To conduct a systematic review in order to examine the relationships between olanzapine dose, plasma concentration, dopamine occupancy and clinical outcome and evaluate the potential for therapeutic drug monitoring (TDM).
Method: An electronic search using Embase, Medline and Pubmed was conducted and the literature was systematically reviewed. Studies that met the inclusion criteria were examined and the relationships between olanzapine dose-concentration and dose-response were analysed using a random effects meta-regression. The relationship between olanzapine dose and dopamine (D2) occupancy was analysed using a random effects model using individual patient data (IPD) as observations and each study as units (clustering variables).
Results: A total of six hundred and forty three papers were retrieved from the electronic search after eliminating all duplicate papers. The systematic exclusion process resulted in fifteen studies which were included in the meta-regression of olanzapine mean concentrations (27 observations) and seven studies allowed for analysis of median concentrations (10 observations). A linear relationship between mean plasma concentration and dose was observed (adjusted $r2 = 0.85$). Ten studies (providing 20 observations) were included in the analysis for dose-response of olanzapine. The relationship between effect size and dose showed a typical dose response curve with slow rise in slope above 10mg. Doses above 10mg gave rise to effect sizes > 0.5. The effect of dose was not significant and it was not a good predictor of effect size (adjusted $r2 = 0.12$). For the dose-occupancy relationship, six studies were included with 114 IPD observations. Five studies also provided additional information on age and gender. Dose only explained 32% of the overall variation observed in dopamine occupancy. Doses from about 13mg a day were sufficient to block 65% of dopamine receptors. Doses in excess of the maximum licensed dose of 20mg did not lead to importantly higher receptor occupancies, though the number of observations at such doses was low. Age and gender were not significant predictors of receptor occupancy.
Conclusions: There appears to be a direct linear relationship between olanzapine dose and concentration, with dose being a good predictor of plasma concentration. Dose was not found to be a good predictor of effect size and doses above 10mg per day gave rise to only modest improvements in effect size. These conclusions are consistent with the observation that D2 receptor occupancy reaches the threshold for response (65%) at around 13–14mg a day.

TD05

SCREENING FOR THE METABOLIC SIDE EFFECTS OF ANTIPSYCHOTIC MEDICATION IN PATIENTS UNDER THE CARE OF ASSERTIVE OUTREACH TEAMS: RESULTS OF A POMH AUDIT-BASED QUALITY IMPROVEMENT PROGRAMME

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People with severe enduring mental illness have an excess burden of physical comorbidity and mortality. The four aspects of the metabolic syndrome, obesity, hypertension, impaired glucose tolerance and dyslipidaemia make a major contribution to this poorer physical health, and treatment with antipsychotic medication may worsen a given patient's metabolic profile. The National Institute for Health and Clinical Excellence schizophrenia guideline (CG82) recommends an annual physical health screen, assessing each feature of the metabolic syndrome. Since 2006, the Prescribing Observatory for Mental Health (POMH) has been conducting a quality improvement programme of such screening in psychiatric patients receiving antipsychotic medication under the care of assertive outreach teams. Annual clinical audits have used the NICE recommendation as an audit standard. We report here on the data collected from 2006 to 2010. All UK mental health Trusts were invited to participate. For each audit, a bespoke data collection tool was used, with on-line submission of the clinical data collected. After every audit, each Trust received a customised report of their performance, benchmarked anonymously against the other participating Trusts. Between baseline and first re-audit at a year, change interventions including an educational poster were provided to participating Trusts and have remained available since. For each annual audit, the number of Trusts that chose to participate and the number of patients for whom data were submitted were as follows: 2006 (21 Trusts; 1996 patients), 2007 (21; 1516), 2008 (13; 1035), 2009 (21; 2522), and 2010 (29; 3058). The proportions of patients screened for all four aspects of the metabolic syndrome at each time point were 11%, 23%, 18%, 22%, and 24%, the proportions screened for some but not all aspects were 43%, 52%, 50%, 50% and 49%, and the proportions who received no screening related to metabolic parameters were 46%, 25%, 31%, 28% and 28%. The findings suggest that audit-based quality improvement programmes can boost clinical practice in relation to physical healthcare screening. In the total national sample, an initial improvement in screening rates was observed between baseline and first re-audit. However, while this was maintained over subsequent years, there was no further progress overall, although a small number of Trusts achieved incremental improvements over time. The findings also reveal that only a minority of community psychiatric patients prescribed antipsychotics is screened for the metabolic syndrome in accordance with best practice recommendations and therefore potentially remediable causes of poor physical health remain undetected and untreated.

TD06

PSYCHOTROPIC PRESCRIBING PATTERNS AMONG ADOLESCENTS IN NORTHERN IRELAND PRESENTING WITH PSYCHOTIC SYMPTOMS DURING A FIVE YEAR PERIOD

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Aims: To investigate prescribing patterns among adolescents within Northern Ireland presenting to psychiatric services with psychotic symptoms.
Background: Review research demonstrates a global increase in the prescription of psychotropic medications among children and adolescents over recent years. The increase in antipsychotic prescriptions in the USA is particularly marked but has also been demonstrated in the UK. Risperidone has been shown to be the most commonly prescribed antipsychotic among adolescents. In the UK, many prescriptions for psychotropic medications are 'off-licence'. Method: A log was kept of all new presentations of children and adolescents with psychotic symptoms between 1 July 2001 and 30 June 2006 across Northern Ireland. Presentations were either via outpatient services or in several cases through direct hospital admission. Clinical case notes were subsequently studied and information recorded for various demographic factors and prescribing patterns in instances where psychotropic medication was prescribed. ICD-10 and DSM-IV diagnoses were generated using the Operational Checklist for Psychotic Disorders (OPCRIT) computer algorithm. Results: 113 adolescents were studied, of which 63.7% were male and 36.3% female. 73.5% of patients were admitted to hospital during the study period. 88.5% were prescribed some form of psychotropic medication, with 11.5% not prescribed medication. 62% of patients prescribed psychotropic medication received solely an antipsychotic as the first type of medication prescribed. 13% received solely an antidepressant as their first psychotropic. 12% of patients were simultaneously commenced on both an antidepressant and antipsychotic as their first exposure to psychotropics. 4% received a benzodiazepine as their first medication. Risperidone (46%) was the most frequently prescribed of first-line antipsychotics, followed by olanzapine (24%) and chlorpromazine (13%). 88.5% of first line antipsychotic prescriptions were consistent with licensed indications, this percentage reducing with successive changes to only 55.6% of fourth line antipsychotic prescriptions. Fluoxetine (48.8%) was the most frequently prescribed of first-line antidepressants, followed by sertraline (23.3%), mirtazapine and citalopram (both 9.3%). 79.1% of first-line antidepressant prescriptions were consistent with licensed indications, this percentage reducing similarly to that seen among the antipsychotics to only 16.7% of third line antidepressant prescriptions. In the cases where a psychotic illness was diagnosed, 41.7% of diagnoses were of schizophrenia, 45.8% of affective psychosis, 8.3% of schizoaffective disorder and 4.2% of schizophreniform disorder. Conclusions: The findings of risperidone and fluoxetine as the most commonly prescribed first-line antipsychotic and antidepressant respectively are consistent with previous studies among child and adolescent populations. The increase in levels of 'off-label' prescribing with successive medication changes reflects the small arsenal of licensed medications clinicians have at their disposal in the child and adolescent setting..

TD07

MEDICINES RECONCILIATION: ADHERENCE TO MEDICATION ON ADMISSION TO A PSYCHIATRIC WARD

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In 2007, a NICE/NPSA 'Technical patient safety solutions for medicines reconciliation on admission of adults to hospital' was issued. The aim of medicines reconciliation (MR) in this context is to ensure that medicines prescribed on admission correspond to those being taken before admission. Details to be recorded include the name of the medicine(s), dosage and frequency, and also medication adherence immediately prior to admission. More than one source of information should be checked, as no single source (e.g. GP records or mental health service records) is likely to be completely reliable. In 2009, the Prescribing Observatory for Mental Health (POMH-UK) initiated an audit-based, quality improvement programme on MR. Forty-two Trusts participated in the baseline audit, submitting data for 1,790 newly-admitted patients from 375 clinical teams. At re-audit 18 months later, 43 Trusts submitted data for 2,296 patients from 455 clinical teams. In these national samples, checking of two or more medication information sources, thus making MR possible, occurred for 71% of patients at baseline and 79% at re-audit. At baseline, the proportion of patients for whom medication was prescribed who had a statement in their clinical records about adherence varied across services, being higher for those admitted to an acute adult ward (58.5%) or forensic ward (54.5%) than an elderly ward (38.5%), which may reflect that elderly patients are often assumed to be taking their medication as prescribed and that carers and/or residential home staff may be available to confirm adherence. The proportion of patients admitted to acute adult wards who were documented as having poor adherence was 43%, which is in line with other reported prevalence figures for poor adherence in mental health. In the re-audit sample, 18% of those patients prescribed medication were recorded as being adherent while 38% were documented as non-adherent. Considering diagnostic subgroups, for the 790 patients with an ICD-10 F20-29 diagnosis (schizophrenia spectrum disorder) 36% had no statement about adherence, 17% were reported as adherent and 47% as non-adherent. For the 636 patients with an ICD-10 F30 -39 (affective disorders) the respective figures were 48%, 17% and 36%. These national surveys found that in more than a third of patients there was no documentation of medication adherence at the point of hospital admission. This suggests that poor adherence, despite its potential adverse clinical impact, may often go unrecognised, with consequent underutilisation of appropriate remedial interventions to address compliance with the prescribed medication regimen.
POMH-UK is funded via subsciptions from member healthcare organisations.

TD08

OLANZAPINE PLASMA CONCENTRATION AND DOSE: FINDINGS FROM A 10 YEAR REVIEW OF A THERAPEUTIC MONITORING SERVICE

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Background: Olanzapine therapeutic drug monitoring (TDM) is the measurement of plasma olanzapine concentrations in an appropriate blood sample, which may be helpful in guiding dosage. We aimed to investigate the relationship between olanzapine dose and plasma concentration based on TDM data from a clinical service. Methods: We audited data from 5856 blood samples submitted for routine plasma olanzapine analysis to a therapeutic monitoring laboratory 1999-2009. Samples taken post-mortem or submitted for suspected self-poisoning were excluded. Plasma olanzapine was measured by high-performance liquid chromatography with UV detection and more recently with mass spectrometric detection, conforming to FDA/CDER standards. Descriptive analyses and multi-linear regression analysis were conducted to investigate predictive factors for olanzapine plasma concentration. Dose (mg/d) groups employed in the data analysis were 2.5-5, 7.5-10, 12.5-15, 17.5-20, 22.5-25, 27.5-30, 32.5-40, >40. Results: 5856 samples from 3207 patients were analysed. 77% of males and 62% of females were smokers at the time of sampling. Prescribed dose information was available for 3371 (58%) samples. Daily doses ranged from 2.5 to 95mg. For every dose a wide range of plasma concentrations were measured. For doses up to 20mg/d, only 22-34% were within a target range of 20-39µg/L. As dose increased, plasma concentrations were more likely to be in the potentially toxic range of >60µg/L (up to 20mg/d: 2-22%; >20mg/d: 30-59%). For dose range 17.5-20mg/d: the proportion of samples in the plasma concentration ranges were <2µg/L: 4%, 2-19µg/L: 18%, 20-39µg/L: 34%, 40-59µg/L: 22%, 60+µg/L: 22%. Ninety-two samples were from patients aged <18 years and the same pattern of results was apparent, but with higher mean concentrations in each dose band. The multivariate linear regression model for patients aged 18 and over included dose, smoking status, sex, age, and body weight and predicted 24% of the variance in plasma olanzapine . Females and non-smokers had higher plasma olanzapine concentrations for a given dose than males and smokers. Conclusion: For each dose of olanzapine, plasma concentrations varied considerably. The variability observed was explained by increasing dose, smoking habit, male gender and to a small extent by body weight. However, the degree of adherence, timing of sample post-dose, and interaction with concomitant medication may also contribute to the variability observed. Olanzapine TDM may have a useful role in routine clinical practice for patients of all ages and particularly so if dosage above 20mg/d is contemplated. Funding: An investigator-initiated grant and the supply of laboratory internal standards of pure olanzapine and LY170222 was provided by Eli-Lilly.

TD09

CAUSES OF MORBIDITY AND MORTALITY IN SCHIZOPHRENIA

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Introduction: Schizophrenia is a common disorder with high rates of morbidity and mortality. Suicide is a known and significant contributing factor of mortality in these patients, but recent evidence highlights that two thirds of overall mortality may be due to physical causes such as cardio-respiratory diseases, thrombo-embolism, diabetes and cancer. This is further complicated by a host of genetic and environmental factors including lifestyle of patients, reduced access to healthcare and potential adverse effects of antipsychotic treatment. Advent of atypical antipsychotics promised greater control of negative symptoms in schizophrenia and an improved side effect profile. However, concerns were raised about increasing mortality secondary to adverse effects of atypical antipsychotics on the cardiometabolic profile. Aim: This is an overview of causes of morbidity and mortality in schizophrenia and a careful consideration into the use of antipsychotics. Method: Medline and PubMed searches were conducted using the Medical Subject Heading (MeSH) terms 'schizophrenia' AND 'mortality AND/OR morbidity'. The search was conducted on relevant articles or abstracts published in the English language from 1985 to 2011.
Results: Data suggests a genetic predisposition to impaired glucose tolerance and insulin resistance in people with schizophrenia, independent of other factors. This is further compounded by poor diets, lack of exercise, smoking, alcohol and illicit drug use. In addition, cognitive deficits in schizophrenia combined with poor access to health care contribute to increased morbidity and mortality. For example there is reduced uptake of breast cancer screening, fewer invasive cardiac procedures and fewer admissions to secondary care for ischaemic heart disease. Even though antipsychotics are known to increase risk of metabolic syndrome by their effects on insulin resistance and dyslipidaemia, FIN-11 study clearly shows the protective affects of antipsychotics and their role in reducing mortality (Tiihonen et al, 2009, Lancet, 374, 620-627). Conclusion: Reducing morbidity and mortality will require consideration of the numerous causes, and systematic management of each. The use of antipsychotics reduce mortality but do require careful consideration of patients overall health and lifestyle. Effective communication and management within multidisciplinary psychiatric team as well as with all clinicians from primary and secondary care will be pivotal in the optimum management of these patients. Funding - No financial sponsorship

TD10

PLASMA CLOZAPINE AND NORCLOZAPINE IN RELATION TO PRESCRIBED DOSE AND OTHER FACTORS IN PATIENTS AGED <18 YEARS: DATA FROM A THERAPEUTIC DRUG MONITORING SERVICE, 1994-2010

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Background: Clozapine is used in children and adolescents for the treatment of early onset schizophrenia that has proved resistant to other antipsychotics. The evidence for its efficacy in this age group is limited to a few small-scale studies. However, young people are reported to be more sensitive than adults to some side effects of clozapine, most notably weight gain and metabolic abnormalities. Furthermore, data on the plasma clozapine concentrations attained in this age group are sparse. Method: We studied information from clozapine assay request forms and analysis results (clozapine therapeutic drug monitoring) from patients from the UK and Eire aged < 18 years at the time of the request, 1994–end 2010. Multiple linear regression analysis was performed to investigate the relationship between plasma clozapine and dose, age, sex, body weight, plasma clozapine:norclozapine ratio, and smoking habit. Results: There were 1,408 samples from 454 patients. Clozapine was not detected (plasma concentration < 0.01 mg/L) in 0.9 % of samples (prescribed clozapine dose up to 425 mg/d). Plasma clozapine was either < 0.35 mg/L, or ≥ 0.60 mg/L in 36 % and in 31 % of samples, respectively; in 6.4 % samples plasma clozapine was ≥ 1.0 mg/L. Although plasma clozapine was broadly related to prescribed dose, there was much variation: 11 % of samples had plasma clozapine > 0.6 mg/L at prescribed clozapine doses up to 150 mg/d (66 % < 0.35 mg/L), whilst 11 % of samples had plasma clozapine < 0.35 mg/L at doses of 650 mg/d and over (63 % > 1.0 mg/L). The factors studied had proportionately similar influences to those observed in adults, and together explained 44 % of the variance observed in plasma clozapine. Females had higher median plasma clozapine concentrations than males, irrespective of smoking habit, despite being prescribed lower clozapine doses. There was a clear tendency to higher clozapine doses in older children and adolescents, but this was probably due to increased prevalence of smoking with age. Conclusions: These data illustrate the routine use of clozapine therapeutic drug monitoring in children and adolescents. Plasma clozapine should be measured during dose titration and an assay should be repeated with increasing age or weight, or if smoking habit changes. All assay results should be considered in the light of the clinical presentation including the presence of adverse effects

TD11

THE ALPHA7 NEURONAL NICOTINIC RECEPTOR (NNR) MODULATOR TC-5619 WAS EFFICACIOUS AND GENERALLY WELL TOLERATED IN AN ADD-ON TRIAL IN COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

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Introduction: Dysfunction of α7 NNRs is thought to be a possible important factor in the pathophysiology of schizophrenia. TC-5619 has shown benefit in preclinical models of schizophrenia and was generally well tolerated in phase 1 clinical trials.
Methods: 185 outpatients (18 – 65 years; male 69%) from the US and India were randomized. All had stable schizophrenia without other psychiatric or unstable medical conditions. Subjects were stabilized (≥ 2months) on either quetiapine or risperidone. 46% were tobacco-users. Subjects were randomized to 12 weeks of add-on placebo (n = 91) or TC-5619 (n = 94) 1mg orally once a day to Week 4; 5mg to Week 8; and 25 mg to Week 12. The primary endpoint tested executive function: Groton Maze Learning Test (GMLT) from the computerized CogState Schizophrenia Battery (CSB). A positive outcome was defined as superiority (1-sided p-value < 0.10) for TC-5619 vs. placebo at Weeks 4, 8 or 12 using the Hochberg correction for multiplicity. Secondary outcome measures included: CSTB composite score; Scale for Assessment of Negative Symptoms (SANS); Clinical Global Impression - Improvement (CGI-I); Clinical Global Impression - Severity (CGI-S); Subject Global Impression – Cognition total score (a subject rated Likert scale assessing Memory, Attention and Speed of Thinking). Safety measures included; adverse event reports; physical examination; vital signs; serum chemistry and hematology; urinalysis; ECG; Abnormal Involuntary Movement Scale; Columbia Suicide Severity Rating Scale; and Calgary Depression Scale for Schizophrenia.
Results: Blinded analysis of GMLT data showed positive skew; thus GMLT data were log(10) transformed. GMLT results favoring TC-5619 met the success criteria (adjusted p = 0.054). CGI-I at week 4 and SANS, SGI-Cog at week 12 statistically favored TC-5619 (unadjusted p-values <0.05). The effect was stronger in tobacco users than non-users and stronger in the US sites compared to sites in India. TC-5619 was generally well tolerated, with no clinically significant change in any laboratory or vital sign measures. A similar number of AEs were reported in both cohorts except for nausea (5% TC-5619 vs. 0% placebo). There were 2 SAEs, both unrelated to drug: gastritis (placebo) and acute exacerbation of schizophrenia (TC-5619) in a subject who stopped taking quetiapine. Conclusions: The agreement between objective (GMLT), clinician rated (SANS, CGI-I) and subject-rated (SGI-Cog) variables, underscores the positive efficacy of TC-5619 in CDS.

TD12

EVALUATING NITRIC OXIDE SYNTHASE AS A POTENTIAL THERAPEUTIC TARGET IN SCHIZOPHRENIA.

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Schizophrenia is a complex and debilitating psychiatric syndrome that is not adequately treated by the drugs currently available. Experimental and clinical findings have identified a potential role of neuronal nitric oxide synthase (nNOS) in this disorder. For example, in rodents NOS inhibitors reverse behavioural deficits induced by the NMDA receptor antagonist phencyclidine (PCP) that have relevance to cognitive deficits seen in schizophrenia. To determine if PCP-treatment alters NOS activity in the brain, semiquantitative NADPH-diaphorase histochemistry was used with cryostat-sectioned brains of PCP-treated (5 mg.kg-1, i.p., n=6) and control (0.9% saline, i.p., n=6) adult male C57BL6J mice. This assay was also adapted for use with tissue homogenates in order to provide a more rapid and quantitative assessment of NOS activity. The specific rates (OD450/min minus buffer rate) of the linear phase of reactions were measured using homogenates of frontal cortex, striatum, hippocampus and cerebellum of PCP-treated (5 mg.kg-1, i.p., n=6) and control (0.9% saline, i.p., n=6) adult male C57BL6J mice. Data were analysed using Mann-Whitney tests. The relative optical density of diaphorase-stained neurones of PCP treated mice was increased in the prefrontal cortex (4.5 ± 2.2%, n.s.), striatum (3.6 ± 2.0%, n.s.), retrosplenial cortex (3.7 ± 2.9%, n.s.), and more notably in hippocampal regions, i.e. dentate gyrus (13.4 ± 5.8%, n.s.) and CA1 (12.1 ± 6.1%, n.s.), compared to vehicle treatment. NADPH-diaphorase activity was also increased in homogenates of frontal cortex (4.7 ± 17.8%, n.s.), striatum (6.3 ± 6.1%, n.s.), and cerebellum (8.2 ± 12.9%, n.s.) of PCP-treated mice compared with vehicle treated mice. As with the histological approach mentioned above, the largest increase in diaphorase activity was observed in the hippocampus of PCP-treated mice (33.9 ± 8.5%, p = 0.02) compared with vehicle controls. The altered activity of NOS in the brain regions investigated may contribute to the cognitive deficits reported in PCP-treated mice. These results suggest that NMDA receptor hypofunction may contribute to the alterations of NOS activity seen in schizophrenia and that NOS represents a potential therapeutic target for the cognitive deficits seen in this disorder.
This work was supported by the Scottish Universities Life Sciences Alliance (SULSA).

TD13

USING NEXT GENERATION SEQUENCING TO INVESTIGATE DPYSL2 GENE VARIANTS IN SCHIZOPHRENIA

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Next generation sequencing is a powerful technology revolutionising our analysis and understanding of genomes. It is particularly useful for deep re-sequencing of the human genome to elucidate the genetic basis of complex polygenic disorders such as schizophrenia that arise from influences of multiple common and rare variants in many genes. Dihydropyrimidinase-like 2 (DPYSL2) is an emerging candidate risk gene for the disorder. We and others have shown association of DPYSL2 gene variants with schizophrenia in case-control association studies and our data show that DPYSL2 transcripts are differentially expressed in the prefrontal cortex from schizophrenia patients and from a rodent PCP model of cognitive deficits and that DPYSL2 single nucleotide polymorphism (SNP) alleles have effects on DPYSL2 transcript expression. Recently it emerged that differential expression of DPYSL2 protein in brain regions with clinical relevance to schizophrenia is one of the most reproducible findings across proteomic studies (English et al., 2011 Biological Psychiatry 69 (2): 163-172). DPYSL2 transcripts were sequenced from overlapping RT-PCR products generated from RNA isolated from the prefrontal cortex of 36 schizophrenia patients and healthy controls. Indexed libraries were generated from each sample, fragmented and paired-end sequencing by synthesis performed on the Illumina Genome Analyzer II. The data underwent quality control measures using an automated pipeline, then were aligned to the reference genome sequence using TOPHAT and further analysed using custom scripts. Coding variants for the aligned sequences were identified using BCFTools and VCFTools. This approach resulted in a massive depth of nucleotide coverage (10,000x) with approximately 500,000 reads of 85 nucleotides per sample, enabling confidence to be given to findings that differ from reference sequences. Alignment of this DPYSL2 sequence data to the Ensembl reference sequences has enabled the identification of novel coding variants, alternate splicing at the 5' end of the gene and novel exon isoforms with skipped exons. Next generation sequencing for deep re-sequencing is facilitating the elucidation of the genetic basis of schizophrenia by identifying common, rare and novel variants in schizophrenia risk genes. We demonstrate the utility of this approach with DPYSL2. This work was funded by the University of Glasgow Medical Fund and NHS Research Scotland (NRS), through NHS Greater Glasgow and Clyde.

TD14

PROFILING EFFECTS OF NMDA ANTAGONISTS ON INSTRUMENTAL RESPONDING IN D-AMINO ACID OXIDASE NULL MUTANT MICE

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N-Methyl-D-Aspartate receptor (NMDAR) antagonists are routinely used to pharmacologically model aspects of schizophrenia in animals. Changes in instrumental responding are a sensitive pharmacodynamic measure of behavioural disruption caused by NMDAR antagonists, where in rats at least, markedly different responses to different antagonists are observed. D-Amino Acid Oxidase (DAO) null mutant mice possess a non-functional mutation of the DAO enzyme, elevating levels of D-serine in selective brain regions beyond the normal range. In this study, we were interested in testing whether this change in D-serinergic tone has consequences for instrumental response performance in DAO null mutants following NMDAR antagonist administration. Male ddY/DAO +/+ and ddY/DAO -/- mice (Charles River, Kent) were trained in a variable interval 30s (VI-30) task in standard Med Associates operant boxes. When performance was stable, animals received an acute administration of an NMDAR antagonist, or its respective vehicle. Eight different antagonists were tested in separate studies: PCP, MK-801, ketamine, memantine, SDZ 220,581, Ro 25-6981, CP 101-606 and NVP-AAM077. Study order was pseudorandomly determined, and each animal only received a single dose of each antagonist or vehicle per study. DAO null mutant mice were generally capable of performing a VI-30 schedule, with little evidence of a significant main effect of genotype being present across studies. All NMDAR antagonists tested showed qualitative profiles broadly similar to those previously seen in rats. PCP, ketamine, memantine and NVP-AAM077 significantly decreased response rates at higher doses. MK-801, SDZ 220,581 produced bidirectional changes in responding (increase at low doses, decrease at higher doses). Ro 25-6981 and CP 101-606 both caused dose-dependent increases in responding; significantly so for the former compound. As for rats, these behavioural patterns in mice do not bear straightforward relationships to the known mechanistic classes of compounds tested. Some Drug x Genotype interactions were also observed, where the response increases and decreases produced by Ro 25-6981 and MK-801 respectively were significantly attenuated in null mutants. Other trend-level Drug x Genotype interactions were observed, suggesting that study replication may well be beneficial here. In conclusion, our results imply changes in D-serinergic tone in DAO null mutant mice can significantly influence the behavioural response to NMDAR antagonists. Such interactions are important both from the perspective of validation of animal models of schizophrenia, but also with regard to understanding how glycine site pharmacotherapy might treat aspects of schizophrenia.

TD15

VIRAL-MEDIATED KNOCKDOWN OF ERBB4 IN THE RODENT PREFRONTAL CORTEX ENHNACES COGNITIVE PERFORMANCE

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The importance of ERBB4 in the pathophysiology of schizophrenia has been established from genetic studies showing association of ERBB4 gene variants with schizophrenia, differential expression of brain region-specific transcripts in post-mortem brain from schizophrenia patients and from in vitro and in vivo analyses of its function in NRG1 signalling. In the CNS, ERBB4 has many important functions, including axonal navigation, proliferation of neuronal precursors and neuronal migration, actions which are considered dysfunctional in schizophrenia. However the precise neurobiological role of ERBB4 in eliciting disease symptoms is unknown. Viral-mediated gene manipulation is a useful tool for studying the function of a gene and its role in disease pathogenesis in a spatially and temporally controlled manner. Here we investigate a role for ERBB4 signalling in schizophrenia-related cognitive deficits Recombinant adeno-associated viral particles (rAAVs) expressing eGFP (enhanced green fluorescent protein) and either an Erbb4 shRNA(short hairpin RNA) or a scrambled Erbb4 shRNA were generated (by GSK), validated in vitro using NG108-15 cells and primary cortical cultures and then stereotaxically injected into the medial prefrontal cortex (mPFC) of adult male Hooded Lister rats (n=8 per group; Erbb4 shRNA rAAV, scrambled Erbb4 shRNA rAAV and vehicle). 5 weeks post-surgery the rats were assessed in the 5-choice serial reaction time task for assessing attention and response inhibition. Knockdown of Erbb4 protein was assessed by ELISA and protein extracted from the rat PFC was analysed by western blotting to investigate signalling deficits in the Nrg1/Erbb4 pathway. In vitro validation of the Erbb4 shRNA viral particles confirmed their functionality and showed reduced expression of Erbb4 mRNA in transduced cells with no non-specific off-target effects. Stereotaxic injection of the Erbb4 shRNA rAAVs into the rat mPFC resulted in sustained knockdown of Erbb4 protein producing downstream effects on Nrg1 levels and Akt1 activity. As well as causing molecular changes, cognitive performance was altered by Erbb4 knockdown in the mPFC. In the 5-choice serial reaction time task, performance accuracy was increased. This study is the first to demonstrate altered Akt1 activity and enhancement of cognitive performance following knockdown of Erbb4 expression in the mPFC. This integrated approach of quantification of gene knockdown, downstream biochemical characterisation and behavioural analysis provides a powerful means to investigate the neurobiology of schizophrenia. This work was funded by a GSK/BBSRC case PhD studentship for Clare Paterson.

TD16

ENVIRONMENT-ENVIRONMENT INTERACTIONS IN A SCHIZOPHRENIA-RELATED DISEASE MODEL: IMPACT OF POLY IC AND THC ON THE DEVELOPING BRAIN

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Schizophrenia is a serious neuropsychiatric illness that affects 1% of the population worldwide. Increasing evidence suggests a relationship between exposure to environmental risk factors during critical phases of neurodevelopment and subsequent onset of the disease in adulthood (Brown et al. 2000 Am J Psychiatry; 157:438-443, Pope et al. 2003 Drug Alcohol Depend; 69:303–310). We investigated the potential interplay between maternal immune activation (MIA) and adolescent exposure to cannabinoids on the precipitation of schizophrenia-related behavioural phenotypes. This was tested using a rodent model of MIA by the synthetic analogue of viral double-stranded RNA, polyinosinic: polycytidylic acid (Poly IC) followed by chronic peripubertal exposure to the principal psychoactive constituent of cannabis, 9-tetrahydrocannabinol (THC). We employed two different treatment regimesΔ designed to mimic differential patterns of cannabis abuse: high-dose daily vs. low-dose recreational use. On gestation day 15, pregnant Lister-hooded rats received either a single intravenous injection of Poly IC (4mg/kg) or phosphate buffered saline (PBS-vehicle). Male offspring were assigned treatment with 7mg/kg THC daily, 3.5mg/kg 3 times/week or vehicle i.p. throughout postnatal days 35-56 (n=12/group). Behavioural testing was carried out in adulthood (PD70+). Behaviours evaluated were amphetamine-induced locomotor activity, attentional set-shifting task (ASST) and prepulse inhibition (PPI). We found increased locomotor activity following amphetamine administration in all treatment groups. Interestingly, chronic intermittent treatment with low-dose (3.5mg/kg) THC during the peripubertal period caused an increase in sensitivity to amphetamine in Poly IC-treated offspring compared to PBS-treated offspring. Moreover, animals chronically treated with low-dose THC demonstrated significant deficits within the extradimensional shift phase of the ASST, a measure of cognitive flexibility, irrespective of prenatal treatment ($p<0.033$). % PPI significantly increased with increasing prepulse stimulus intensities for all groups ($p<0.0001$), however, there was no significant effect of either prenatal or peripubertal treatment on performance of PPI task. Data analysed using ANOVA. During the peripubertal period, the brain exhibits differential liability to the deleterious effects of THC resulting in perturbances in cognitive flexibility in adulthood. These effects were evident following low-dose intermittent rather than high-dose daily THC treatment indicating that neuroadaptive responses differ according to pattern of use. These deficits were not exacerbated by MIA. The possibility of an environment-environment interaction warrants further investigation given that low-dose intermittent THC treatment to MIA offspring enhanced responses to amphetamine compared to PBS-treated offspring. Overall these data provide new evidence that exposure to environmental insults during critical phases of neurodevelopment produces deficits in schizophrenia-related behaviours in adulthood. This study was supported by a Capacity Building Award in Integrative Mammalian Biology funded by the BBSRC, BPS, KTN, MRC and SFC.

TD17

POST-WEANING SOCIAL ISOLATION OF RAT PUPS IMPAIRS PERFORMANCE IN AN EXTRA-DIMENSIONAL SHIFT OF AN OPERANT REVERSAL LEARNING PARADIGM.

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Rearing rats in isolation from weaning is an established neurodevelopmental model of schizophrenia which induces a range of behavioural deficits that have translational relevance to some of the core symptoms of schizophrenia. Repeated administration of the N-methyl-D-aspartate (NMDA) receptor antagonist, phencyclidine (PCP) also causes behavioural changes akin to those seen in schizophrenia. This study investigated whether combining isolation rearing with neonatal PCP produces deficits in learning and memory using an operant reversal learning paradigm. Thirty-eight male Lister-hooded rats obtained on post-natal day (PND) 3 received either subcutaneous saline (1ml/kg; n=19) or PCP (10mg/kg; n=19) on PND 7, 9 and 11. After weaning (PND 23) rats were housed in groups of 3-4 (PCP n=10; Saline n=9) or singly (PCP n=10; Saline n=9) for 6 weeks during which isolated rats received minimal handling but had visual, auditory and olfactory contact with littermates. On PND 53 and 54 novel cage-induced locomotor activity (LMA) and two trial non-spatial novel object discrimination (NOD) were assessed, respectively. On PND 121, food restricted rats were trained on an operant reversal learning paradigm. Initially rats were trained to respond on one of two levers to receive a food reward, and once criterion was reached the position of the reinforced lever was reversed. Following criterion attainment rats were tested in an extra-dimensional (ED) shift where the cue for correct lever was changed from the position of the lever to the presentation of a brief light cue above each lever. Neither isolation nor PCP affected LMA, however isolation rearing alone and in combination with perinatal PCP impaired NOD compared to group-housed controls (Gaskin et al, 2011; J. Psychopharmacol; this issue). Neither isolation nor PCP impaired performance in the simple reversal learning, however isolation, irrespective of PCP treatment, significantly increased trials to criterion during the ED shift ($p<0.05$; ANOVA). These data show that social isolation produces specific deficits in novel object recognition and ED set shifting which have translational relevance to some of the cognitive deficits in schizophrenia (Murray et al, 2008; Schizophrenia Bulletin; 34; pp 848-855). Neonatal administration of PCP did not potentiate the effects of isolation rearing in this task. These findings further validate isolation-rearing as a neurodevelopmental model of cognitive deficits seen of schizophrenia.
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TD18

TRANSMEMBRANE DOMAIN NRG-1 MUTANT MICE SHOW SEX-SPECIFIC DEFICITS IN EPISODIC-LIKE MEMORY

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Introduction: Neuregulin-1 (NRG1) is an at risk haplotype for schizophrenia [Harrisson, PJ et al.,2006 Biol. Psychiatry; 60,132-40]. Mutant mice heterozygous (HET) for the NRG1 gene or its receptor ErbB4 have been shown to display cognitive deficits reminiscent of those demonstrated in schizophrenia in tasks such as pre-pulse inhibition. People with schizophrenia have been shown in many studies to have disrupted episodic memory defined as memory for items embedded in spatiotemporal context [Leavitt,VM et al. 2009, Neuropsych. Rev.3,312-323]. In order to investigate the translational relevance of reduced function of TM-NRG1 behaviourally, we investigated whether mice heterozygous for the TM-domain NRG1 gene, would display impaired episodic memory in a task that requires simultaneous memory for "what", "when" and "where". Methods: HET TM-NRG1 (NRG1 +/-) and wildtype (WT) (NRG1 +/+) male and female littermates (40-44 weeks) were used. An object recognition task based on exploration of objects in an open field was used; consisting of 2 sample and one test phase. In the sample phases, mice were sequentially allowed to explore four copies of an object A (old object) and an object B (recent object). In the test-phase, animals were tested on two copies of object A (A1 and A2) and two copies of object B (B1 and B2). Object A2 was displaced to a different location from that used in sample-phase 1 while object A1 remained at its original position. Both Objects B1 and B2 were left at their original positions as in sample 2. Each of the stages was separated by a 50min inter-trial interval, and mice allowed to explore objects for 10min per stage. A discrimination ratio (DR) was calculated as exploration time at old objects/ time spent at old+ recent objects (A/A+B) in the test-phase. Results: WT mice showed increased exploration of old objects compared to the recent objects indexed by DR >0.5 (one sample T-test versus 0.5, $P<0.05$). A significant sex by genotype interaction on DR was found ($P<0.05$, ANOVA). There was a significant reduction in DR compared to WT in male NRG1 (+/-) only. Female NRG1 (+/-) mice showed significantly enhanced DR compared to their WT littermates ($P<0.05$).
Conclusions: These findings demonstrate that reduced function of TM-NRG1 gene has sex-specific effects on episodic-like memory impairing it in males and improving it in females. This suggests that this model may have relevance for investigating memory dysfunction in schizophrenia, particularly in the context of sexually dimorphic memory impairment. This work was supported by The Wellcome Trust [WT084592]

TD19

5-HT6 RECEPTOR ANTAGONIST SB-271046 REVERSES POST WEANING SOCIAL-ISOLATION INDUCED COGNITIVE DEFICITS IN THE RAT

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The 5-HT6 receptor antagonist, SB-271046, improves learning and memory in many rodent paradigms (Fone, 2008 Neuropharmacology 55, 1015); however, the role of 5-HT6 receptor antagonists in treating the cognitive symptoms of schizophrenia is unclear. Previous studies have shown that 5-HT6 antagonists exert their pro-cognitive effects by modulating central cholinergic and glutamatergic neurotransmission. Therefore, the present study explored the ability of acute, systemic administration of a single dose of SB-271046 (10 mg/kg) to reverse the long-term behavioural changes elicited in rats reared in social isolation; a neurodevelopmental model of schizophrenia (Fone and Porkess, 2008 Neurosci. Biobehav. Rev., 32, 1087). Male Lister hooded rats (n=40)obtained after weaning on PND 22-24 were either group-housed (GH; 3-4 rats/cage) or isolation-reared (IR) for 6 weeks during which time they received minimal handling but had visual, auditory and olfactory contact with each other. At subsequent weekly intervals, animals received vehicle (1 ml/kg i.p.) or SB-271046 (10 mg/kg i.p.) 20 minutes prior to monitoring novel arena-induced locomotor activity, novel object discrimination (NOD) and pre-pulse inhibition (PPI) of acoustic startle. All animals also received drug or vehicle immediately after training in a contextual fear conditioning (CFC) paradigm. IR animals demonstrated increased locomotion that was reversed by SB-271046 (ANOVA; Time $p<0.0001$; Drug $p=0.3292$; Interaction $p=0.0790$). GH vehicle-injected rats successfully discriminated novel from familiar objects in a two trial object discrimination task using a 2h inter-trial interval. Isolates injected with vehicle failed to discriminate novel from familiar object in the choice trail (Object $p<0.001$; Treatment $p=0.17$; Interaction $p=0.15$). This NOD deficit in isolates was fully reversed by SB-271046 such that animals explored the novel significantly longer than the familiar object (mean exploratory activity GH vehicle 23.8 + 7 and 16.9 + 7 sec; GH SB-271046 19.4 + 3 and 14.1 + 6 sec; IR vehicle 16.8 +5 and 14.5 + 7 sec; IR SB-271046 22 + 7 and 14.2 + 4 sec at novel and familiar object respectively). % PPI increased with increasing PPI intensity but this was unaffected by SB-271046 in any group. IR-induced a CFC deficit which was completely reversed by post-training administration of SB-271046 (Trial $p<0.0001$; Treatment $p=0.0001$; Trial x Treatment $p=0.967$). The reversal of some post-weaning social isolation-induced behavioural and cognitive deficits by SB-271046 indicates a role for 5-HT6 receptors and suggests that they might be involved in the genesis of some symptoms of schizophrenia.

TD20

DIFFERENTIAL EFFECTS OF PCP IN AN EFFORT BASED REWARD TASK AND A SUCROSE PREFERENCE TASK: IMPLICATIONS FOR MODELLING THE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

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Anhedonia and avolition have been associated with the negative symptoms of schizophrenia. These symptoms have received limited attention and remain relatively understudied in comparison to positive and cognitive symptoms of schizophrenia and as such there remains a considerable challenge for preclinical models to mirror these symptoms in order to develop suitable drug therapies. Phencyclidine (PCP) an NMDA receptor antagonist has been widely accepted as a suitable preclinical drug treatment for reproducing the positive, negative and cognitive symptoms of schizophrenia. The present study examines PCP's ability to alter the normal functioning of the reward system in the rat using two tasks designed to tap into different aspects of the reward system. Male hooded Lister rats were tested acutely and subchronically with PCP (2.58mg/kg i.p.) in two behavioural tasks designed to examine different aspects of the reward system. The first task was designed to examine motivational and/or anticipatory components of reward by measuring an animal's maximal effort expenditure in a T-Maze effort based reward task. In the T-maze animals were presented with a choice of climbing a wire barrier to obtain a high reward or take a non-effortful arm choice for a low reward. The second task was designed to measure consumatory aspects of reward by measuring sucrose preference, rats were presented simultaneously with 2 bottles, one filled with tap water the other filled with a sucrose solution (10% w/v) over a three hour period with fluid intake measured at 1 hour intervals. Theoretically; high loading of an anhedonic effect in consumption related reward systems would reduce high arm reward choices and reduce sucrose intake, whereas motivational effects would only reduce high arm/high reward choices leaving sucrose consumption rates relatively unchanged. Rats initially showed a reduced preference for the high arm/high reward following acute PCP treatment 30 minutes post injection, which was not seen 72 hours post PCP. The Subchronic PCP regime also produced evidence of reduced high arm/high reward choices 30 minutes and 24 hours post acute PCP challenge. In contrast to this, sucrose preference levels remained relatively stable throughout the entire testing period. The main findings suggest that acute and subchronic treatment of PCP results in motivation and/or anticipatory deficits of the reward system leaving consumatory aspects relatively intact.

TD21

A PRELIMINARY STUDY INTO THE EFFECT OF SUB-CHRONIC PCP SUBUNIT GENE EXPRESSION IN THE RODENT BRAIN ADMINISTRATION ON GABAA

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Introduction: An accumulation of evidence for abnormalities of the GABAergic system in schizophrenia has emerged with numerous post-mortem studies consistently reporting deficits relating to interneurons that contain GABA as their neurotransmitter. Of particular importance to the cognitive deficits are the parvalbumin (PV) containing subset of neurons. This population of neurons play a vital role in the synchronisation of pyramidal firing and normal cognitive function. Specific deficits in PV-immunoreactive cells have consistently been reported in schizophrenia (Lewis et al., 2005, Nature Reviews Neuroscience (4):312-24). We have consistently shown that a sub-chronic PCP treatment regime in rats induces long lasting cognitive deficits that are accompanied by alterations in GABAergic markers in both the prefrontal cortex and the hippocampus. (Neill et al, 2010, Pharmacology and Therapeutics 128:419-432). The aim of the current study was to investigate the effect of sub-chronic PCP administration on gene expression, with particular attention being paid to GABAA receptor subunits.
Methods: Adult female hooded-Lister rats received bi-daily injections of PCP (2mg/kg i.p) or vehicle for 7 days, followed by a 7 day PCP washout. Following this brains were removed, dissected into regions of interest (frontal cortex, hippocampus, striatum and cerebellum) and placed into RNAlater solution, in preparation for RNA extraction and analysis. Briefly, tissue was homogenised in 1ml Trizol reagent and RNA extracted using Invitrogen mini columns. After conversion to cDNA using a Qiagen reverse transcription kit, gene expression was quantified using SYBr Green qRT-PCR using a GAPDH normalising gene. A paired t-test on relative mRNA levels was used to analyse the data. Results: Sub-chronic PCP treatment resulted in significant reductions of all GABAA receptor α1-5 subunits in the frontal cortex ($P<0.05$). Other changes included significant reductions in δ subunit levels in the hippocampus ($P<0.01$) and significant reductions in α2 subunit levels in striatal tissue ($P<0.05$) in PCP treated rat brain compared to control. Conclusions: Sub-chronic PCP treatment markedly reduced the level of GABAA receptor subunits in the frontal cortex, hippocampus and striatum. This decrease was particularly robust in the frontal cortex, where reduced mRNA levels for 5 out of the 6 α subunits were observed. The molecular mechanism by which PCP produces these expressional changes has yet to be elucidated. These preliminary findings suggest that loss of GABAA receptors in the frontal cortex could play a role in the cognitive deficits found in the sub-chronic PCP model.

TD22

COMBINING REARING IN SOCIAL ISOLATION WITH PERINATAL PCP TREATMENT AS A PRECLINICAL MODEL OF SCHIZOPHRENIA

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The heterogeneous symptoms of schizophrenia make it difficult both to treat and to model in rodents. The current study combines two developmental models of schizophrenia: administration of the N-methyl-D-aspartate (NMDA) receptor antagonist, phencyclidine (PCP), to rat pups on post natal days (PND) 7, 9 and 11, and subsequent rearing in social isolation from weaning. The objective was to determine whether the combined interventions produced more robust behavioural deficits with greater translational relevance than either alone. 43 male Lister-Hooded rat pups were administered PCP (10mg/kg, s.c.) or saline control on PND 7, 9 and 11, and subsequently weaned on PND 23 resulting in 4 groups: group-housed controls (n=10), isolate controls (n=10), group-housed PCP-treated (n=11), and isolate PCP-treated (n=12). Five weeks post-weaning, rats were monitored in a battery of behavioural tests to assess their locomotor activity (LMA) in response to acute PCP (3.2mg/kg), novel object discrimination (NOD), prepulse inhibition (PPI) of acoustic startle and spatial learning and memory in a Morris Water Maze (MWM). Perinatal PCP significantly increased the LMA response to acute PCP ($p=0.0446$, main effect of perinatal drug treatment, 2way ANOVA). During the NOD task, all group-housed rats significantly discriminated between novel and familiar objects in the choice trial, whereas isolation-reared rats (irrespective of PCP treatment) explored both objects equally (GH-Con: $p<0.001$, GH-PCP: $p<0.01$, Iso-Con and Iso-PCP: $p>0.05$, Bonferroni post-hoc following 2way ANOVA). Only rats receiving perinatal PCP showed a significant impairment in PPI at 84 and 80dB prepulse levels ($p=0.0042$ and $p=0.0182$ respectively, main effect of PCP treatment, 2way ANOVA), regardless of subsequent housing condition. Although no impairment was seen in the isolation reared or PCP treated rats during learning of the initial fixed platform position in the Morris Water Maze, following a rule change, (moving the platform between trials to a fixed distance from the wall) both treatments impaired short-term, within-day improvements in platform location compared to controls, with an additive effect in the isolation-PCP combination treatment group ($p=0.0041$, overall effect of treatment by 2way ANOVA). Perinatal PCP treatment and isolation rearing of rat pups both produce behavioural deficits in adult rats, but combined treatment causes a wider range of cognitive impairments than either treatment alone. In conclusion combining perinatal PCP with isolation rearing may be a robust and useful preclinical model of schizophrenia but its predictive validity in tests with antipsychotic drugs requires evaluation.
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TD23

IMPACT OF MODAFINIL ON ACQUISITION AND SUBSEQUENT PERFORMANCE OF PCP –TREATED RATS IN THE 5-CHOICE SERIAL REACTION TIME TASK

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Cognitive deficits are central to schizophrenia, and account for the numerous difficulties observed integrating into society and employment, however current antipsychotics have been shown to have little effect on these symptoms (Buckley and Stahl. 2007. Acta. Psychiatr. Scand. 115(2): 93-100; Emsley. 2009. Expert Opin. Investig. Drugs. 18: 1103-1118). Modafinil is a potential cognitive enhancer although its actions are not fully understood. Increasing glutamatergic transmission within the pre-frontal cortex, a brain region considered to be a key component in cognitive function, may reverse the cognitive deficits and is of major interest. Modafinil has similar clinical effects to stimulants such as amphetamine and methylphenidate (Turner et al. 2003. Psychopharmacology. 165: 260-269), but lacks the associated side effect profile and abuse potential (Jasinski. 2000. J. Psychophamacol. 14: 53-60). This study aimed to determine whether phencyclidine (PCP) treatment impairs acquisition and performance in the 5-Choice Serial Reaction Time Task (5-CSRTT) (Robbins. 2002. Psychopharmacology. 163: 362-380) and if modafinil can restore any deficits observed using male Lister-Hooded rats. PCP did not cause a significant deficit in the acquisition of the baseline 5-CSRTT, although modafinil produced a trend to increase acquisition of the task. Manipulations of the basic task using variable stimulus duration (vSD) and variable inter-trial interval (vITI) highlighted a significant increase in premature responses [$F(2,11)=30.27$, $p<0.001$, n=8-9] and an increase in response latency [$F(2,34)=7.73$, $p=0.009$, n=8-9] when under the influence of PCP. In addition, under conditions of vSD, a significant interaction of PCP pre-treatment and modafinil treatment was seen [$F(1,139)=4.11$, $p=0.045$, n=8-9] causing decreased accuracy, which suggests sustained attention was further impaired after modafinil treatment. Data were analysed by three-way ANOVA with Tukey's post-hoc test. Cognitive ability was also assessed in another task, the novel object recognition (NOR) task, to determine if cognitive training can be translated to another cognitive task. However, no significant effects of PCP or modafinil were detected. In conclusion, the low-dose of PCP pre-treatment did not affect the ability of rats to acquire the 5-CSRTT task but produced deficits in inhibitory control and response latency under conditions of increased cognitive load. Whilst modafinil did not show a clear ability to enhance acquisition of the task or restore PCP-induced deficits in inhibitory control and reaction time , these studies provide a basis for further assessing the impact of cognitive training under modafinil on cognitive performance.
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TD24

DECISION-MAKING IN SCHIZOPHRENIA STUDIED WITHIN AN ECONOMICS GAME PARADIGM

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Introduction: Loss aversion behaviour, whereby losses weigh more heavily than equal-sized gains, has been demonstrated in individual decision-making paradigms. Research has shown that patients with schizophrenia exhibit diminished or absent loss aversion, with reductions in loss aversion correlated with proxy illness measures such as duration of illness and total time spent in hospital within an inpatient sample (Trémeau et al, Schizophrenia Research, 2008, 103: 121-128). No link to state illness severity was found in that study, though a trend was suggested with the PANSS Positive (symptoms) score. Methods: Here, 16 individuals with schizophrenia and 16 control participants, matched by age and sex, played two versions of the Iterated Prisoners' Dilemma, one version with only positive pay-offs and another version with positive and negative pay-offs, with the second version being derived from the first by subtracting a constant value from all pay-offs. Participants played against a computer player incorporating two pre-programmed strategies. Results: The control group demonstrated significantly lower cooperation rates when playing the Iterated Prisoners' Dilemma with negative pay-offs, compared with the version with only positive pay-offs. The loss aversion response exhibited by the control group allowed improvements in performance when playing the version with negative pay-offs, compared with the version with only positive pay-offs. However, this loss aversion response was not seen in the schizophrenia group. Furthermore, lower levels of psychopathology as determined by the PANSS Positive (symptoms) score were associated with loss aversion outcomes more similar to the control group. The schizophrenia and control groups were not balanced for IQ. However, the negative correlation between loss aversion outcomes and the PANSS Positive (symptoms) scores remained significant, even after taking account for IQ using multiple linear regression. Illness duration and total time spent in hospital were not significantly correlated with reductions in loss aversion outcomes, which may be explained by recruitment from both inpatient and outpatient services. Conclusions: These results replicate previous findings that diminished loss aversion is associated with schizophrenia. However, it provides additional evidence that reductions in loss aversion are related to state severity of illness, in particular to positive symptoms as measured by the PANSS. Diminished loss aversion may be explained by reduced attribution of salience to rewarding events. Abnormal attribution of salience has been proposed in contemporary studies of schizophrenia (Kapur, American Journal of Psychiatry, 2003, 160:13-23) (Gradin et al, Brain, forthcoming). The results presented here form the basis for further investigation with functional neuro-imaging.

TD25

NEURAL CORRELATES OF LANGUAGE LATERALISATION: A BIOLOGICAL MARKER OF SCHIZOTYPY?

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Neuroanatomical correlates of schizotypal personality and schizophrenia have been found in multiple brain regions. The current study aimed to identify these neural correlates particularly of the behavioural measure of language lateralisation representing schizotypy. The "global-local" task (Navon, 1977, Cognitive Psychology, 9, 353-383.), with words stimuli in comparison with numerals stimuli, was used to examine individual differences of lateralisation in 25 individuals. The degree of schizotypy was measured by Oxford-Liverpool Inventory of Feeling and Experiences (O-LIFE;Mason et al., 1995,Personality of Individual Differences, 18, 7-13. ;Mason et al., 2005,Schizophrenia Research, 78, 293-296.). The gray matter volume was analysed using MRI (Magnetic resonance image). Response time in the local over global advantage in words stimuli significantly correlated with the impulse non-conformity subscale of O-LIFE and was regressed onto the whole brain using a voxel-based morphometry (VBM) approach in SPM5. Several neural correlates were found mainly in the parietal regions contrary to our hypothesis in which the temporal regions were predicted as correlates. However, these correlates correspond to the functions of self perception and language processing which are assumed to be disrupted in the symptoms of schizophrenia (Garrity et al., 2007, American Journal of Psychiatry, 164, 450-457.). Furthermore, the superior global advantage in words stimuli found in the task is consistent with the account of reduced lateralisation in schizotypy (Crow, 1997, Trends in Neuroscience, 20, 339-343.). We conclude that in healthy individuals, altered parietal lobe processing may be associated with these aspects of schizotypy.
This study was not sponsored by any external fundings since it was conducted as the first author's MSc project.

TD26

FIRST EPISODE PSYCHOSIS PATIENTS DISPLAY IMPAIRED COGNITION ON THE CAMBRIDGE NEUROPSYCHOLOGICAL TEST AUTOMATED BATTERY (CANTAB) – A STUDY COMPARING SOUTH ASIAN TO CAUCASIAN PATIENTS.

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Cognitive deficits are now recognised as a core symptom of schizophrenia. A number of studies report profound deficits in cognitive function in both long term and first episode patients (Ojeda et al, 2007). There is evidence to suggest a higher prevalence of psychosis amongst ethnic minority populations than in Caucasian populations in the UK (Kirkbride et al., 2006). However to date there is limited research focusing on the relationship between the illness and cognition in minority populations. The aim of this study is to make a direct comparison of cognitive deficits found in South Asian patients compared to Caucasian patients, using the CANTAB. A total of 35 first episode psychosis patients, 20 South Asian (16 male and 4 female) and 15 Caucasian (8 male and 7 female) were recruited into the study along with 20 controls, 15 Asian (12 male and 3 female) and 5 Caucasian (3 male and 2 female). Patients were recruited from the Bradford and Airedale Early Intervention Service. The severity of clinical symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS). The Wechsler Test of Adult Reading was used to estimate pre-morbid IQ and other demographic data were collected, i.e. age, gender, educational attainment. Closely matched controls were recruited from the same catchment areas as the patient group. All subjects completed a comprehensive battery of neuropsychological tests from the CANTAB. The domains tested, visual memory, executive function, working memory, spatial memory and attention have all been identified as being impaired in schizophrenia patients (Ceaser et al., 2008). Patients and controls showed no significant differences in demographic factors: age, gender, pre-morbid IQ and years in education. Patients PANSS scores showed no significant differences between groups. There were no significant differences in the severity of deficits between ethnic groups (patients or controls); however there were significant differences in patients when compared to the control groups regardless of ethnicity in the following domains; visual memory (PRM) ($p<0.001$), executive function (IED) ($p<0.001$), working memory (SOC) ($p<0.01$), spatial planning (SOC) ($p<0.01$), spatial memory (SRM) ($p<0.05$) and attention (CRT) ($p<0.05$). First episode psychosis patients display significant cognitive deficits across all domains tested using the CANTAB. Severity of these deficits is independent of ethnic origin. This study is the first to demonstrate that cognitive deficits exist across all patient groups who have experienced a first episode of psychosis regardless of age, gender, pre-morbid IQ, years in education and ethnic origin.

TD27

SEX HORMONES AND SCHIZOPHRENIA: AGE AT PUBERTY ONSET AND GENDER DIMORPHISM IN FINGER LENGTH.

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Introduction: Sex hormones are increasingly being investigated for their influence on brain development. Differences in intra-uterine exposure to these hormones has been suggested as a contributing aetiological factor, possibly through gender dimorphism in developmental trajectories. Lengths of second and fourth digits have been studied as proxy measures for prenatal oestrogen and androgen exposure respectively. There are different findings in the literature regarding finger length (FL) since Arato et al found schizophrenic patients tended to have a 'feminine' phenotype of index and ring fingers (2004, Progress in Neuro-psychopharmacology and Biological Psychiatry,vol-28,191-4). There is also interest in differences in the age of onset of puberty between schizophrenic patients and the healthy population. Ruiz et al (2000, Journal of Psychiatric Research,vol-34,349-353) found the mean age of menarche was significantly higher than in females in the general population. In this series of studies we are investigating whether anthropomorphic measures or age of onset of puberty might be phenotypic indices to correlate within a gene/environmental model. Here we focus on two measures which are 'difference between the relative FL of 2D and 4D' and "age at onset of puberty".
Methods: 99 patients with a SADS-L diagnosis of schizophrenia and 183 healthy controls were included. The distance to the tips of the index and ring fingers was measured from the tip of third digit. Differences between the relative lengths of 2D and 4D (r4D-r2D) were used as the measure for analysis. Participants self-reported age at puberty onset for comparison between the two groups and by gender.
Results: There was no significant difference in r4D-r2D group comparisons between schizophrenic patients and controls. However in the sub-group analysis for gender, there was a significant difference (ANOVA)in the male right hands, with schizophrenic patients having a more 'feminine' pattern of index and ring fingers than same-sex controls ($p<0.05$). Age at onset of puberty was slightly earlier in male controls and slightly later in female controls but not at conventional levels of significance.
Conclusions: Our finding of feminine phenotype in schizophrenic male r4D-r2D difference suggests a low androgen/estrogen ratio during intrauterine life, and strengthens the evidence for the role of sex hormones in the development of schizophrenia and the possible relevance of gender dimorphism to the condition. The lack of a significant finding in puberty onset contrasts with previous work as we only found non-significant differences.
No external funding received for this study.

TE01

EARLY IMPROVEMENT AND ENDPOINT RESPONSE IN THE ACUTE TREATMENT OF GENERALIZED ANXIETY DISORDER WITH PREGABALIN OR VENLAFAXINE-XR

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Recent post-hoc analyses of pooled randomized placebo-controlled trial data with escitalopram or duloxetine in the treatment of generalized anxiety disorder (GAD) suggest that a response is unlikely, if no signs of improvement are observable after four weeks of double-blind treatment. We wished to determine which early improvement criteria best predicted an eventual response to short-term treatment of GAD with pregabalin or venlafaxine-XR. We pooled data from four double-blind, placebo-controlled treatment studies. The performance of a range of early improvement measures in predicting endpoint response was assessed, using both logistic regression models and receiver operator characteristic (ROC) curve analysis. We found that an improvement in symptom severity (defined as a reduction in HAMA-A score by 6 points or more) at Weeks 1 and 2 was associated with a high probability of achieving an endpoint response in patients treated with pregabalin (~67%), and at Week 2 with venlafaxine-XR (~60%). A Clinical Global Impression-Improvement (CGI-I) score of 3 or less at Week 2 was associated with a high probability of achieving endpoint response and a high sensitivity for both pregabalin (OR, 5.33; sensitivity, 0.91) and venlafaxine-XR (OR, 2.47; sensitivity, 0.86). However, use of CGI-I score of 3 or less at Week 2 had low specificity (pregabalin, 0.33; venlafaxine-XR, 0.29): in other words, this measure is associated with a high 'false positive' rate as a screening test. For both pregabalin and venlafaxine-XR, use of the CGI-S at Week 2 was less sensitive than the CGI-I as an indicator of eventual treatment response (pregabalin, 0.83; venlafaxine-XR, 0.78). Our findings suggest that observing at least a minimal early improvement, by Week 1 for pregabalin, and by Week 2 for venlafaxine-XR, is a simple and reliable way of predicting the likelihood of an endpoint treatment response in patients with GAD. The randomised controlled trials within the pooled analysis, and the analysis itself were funded by Pfizer.David Baldwin neither sought nor will receive funding for his work in this investigation.

TE02

VENLAFAXINE AND PREGABALIN REDUCE CO2-INDUCED SYMPTOMS OF ANXIETY IN AN EXPERIMENTAL HUMAN MODEL

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Studies have shown that inhalation of 7.5% CO2 for 20 minutes can model Generalised Anxiety Disorder (GAD) in healthy volunteers, whilst the single full breath inhalation of 35% CO2 activates the stress and fear response. Previous studies have shown that subjective and objective symptoms of anxiety induced by 7.5% CO2 inhalation can be attenuated by anxiolytics such as lorazepam and paroxetine (Bailey, JoP, 21, 2007). Venlafaxine, a serotonin-noradrenaline reuptake inhibitor, and pregabalin, which increases gamma-aminobutyric acid (GABA), were used to further investigate these models of human anxiety. Fifty-four participants, 29 male and 25 female, aged 20 to 43 years (mean 23.1, sd 4.68), were randomised to either placebo, venlafaxine or pregabalin groups. Study treatments were incremented over a 3 week period, to reach efficacious doses of 150mg venlafaxine and 200mg pregabalin by the CO2 challenge day. Participants inhaled 7.5% CO2 and air for 20 minutes (single-blind presentation), and a single vital capacity of 35% CO2. Subjective ratings (Visual Analogue Scales (VAS), Panic Symptom Inventory (PSI), GAD Criteria Inventory (GAD-C) and Spielberger State Anxiety Inventory (SSAI)) were recorded before and after each inhalation. This was followed by 5 days dose-tapering to minimise withdrawal effects. Health checks were performed weekly. As shown in previous studies (Bailey, Dep Anx, 21, 2005; Bailey, JoP, 21, 2007) the 7.5% and 35% CO2 inhalations increased ratings of panic and anxiety, and increased blood pressure and heart rate. During the 7.5% CO2 inhalation, there were non-significant trends towards feeling less nervous in the pregabalin group, and towards feeling less tense and worried in both groups, compared with placebo. During the 35% CO2 inhalation, scores of PSI panic ($t=2.24$, $df=34$, $p=0.03$), GAD-C anxiety ($t=2.15$, $df=34$, $p=0.04$), and VAS scores of fear ($z=2.27$, $p=0.02$) were significantly lower on pregabalin compared with venlafaxine. More adverse events were reported on venlafaxine than pregabalin. These findings are consistent with studies of GAD patients, where venlafaxine and pregabalin show anxiolytic properties but the side effects of venlafaxine can be problematic. These findings are also consistent with those reported by Bailey et al. (JoP, 21, 2007), where healthy volunteers treated with 21 days of paroxetine prior to 7.5% CO2 inhalation showed a marginal decrease in anxiety. This study adds to the validation of this model, and supports its use in proof of concept studies. Study supported by the P1vital CNS Experimental Medicine Consortium (members AstraZeneca, GlaxoSmithKline, Lundbeck, Organon (a subsidiary of Merck) and Pfizer).

TE03

NOVEL SEROTONIN TRANSPORTER POLYMORPHISM IN THE COMMON MARMOSET (CALLITHRIX JACCHUS) CONTRIBUTES TO ANXIOUS BEHAVIOUR

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Introduction: The serotonin transporter (5-HTT) mediates the reuptake of serotonin from the extracellular space. Transcriptional levels are regulated by a polymorphic variable-number of tandem-repeat promoter elements (5-HTTLPR). Alleles of varying lengths have been found in humans and primates, the 14-(short, s) and 16-repeat (long, l) alleles being the most frequent in humans. The lower expressing s allele has been implicated in the aetiology of psychological traits and psychiatric disorders including anxiety and depression. Consistent with this, structural and functional brain differences have been found between s and l-carriers, such as a functional uncoupling between PFC and amygdala, key circuitry for emotional regulation. However, to date there have been few in vivo studies focused on the functional effects of the polymorphism in species other than humans. The common marmoset Callithrix jacchus is a well-established animal model to study the cognitive and emotional functions of the serotoninergic system and identification of a functional 5-HTTLPR-like region in the marmoset gene would be useful for future functional studies. Methods: We performed PCR from marmoset genomic DNA using primers based on sequence homology between human and other mammals and obtained a 2.4kb-fragment from the promoter region of the 5HTT gene. In order to explore the variability in the repeat number, genotyping of the marmoset colony was assessed by PCR and subsequent sequencing. Expression levels were measured by real time PCR. Anxious behaviour was assessed in the Human Intruder Test (HIT). Results: We have identified a tandem-repeat region (26 repeats) analogous to the human 5-HTTLPR, although a repeat length polymorphism was not detected in our marmoset colony. However, a dinucleotide polymorphism (AC/CT) within the repeat region have been identified. Expression analysis suggests that this novel polymorphism regulates gene expression in a dose-dependent manner, with AC homozygotes showing lower levels than the CT homozygotes. Analogous to the human s allele, the lower expressing AC allele carriers showed higher levels of anxiety in the HIT.
Conclusions: Our findings suggest that this novel polymorphism not only regulates gene expression levels but it may also be correlated with an anxiety-like behavioural trait in marmosets. Future studies are necessary to dissect the molecular mechanisms by which the marmoset 5-HTT AC/CT polymorphism modulates the individual differences in anxious behaviour. AMS is supported by the James S McDonnell Foundation. The work is funded by a Medical Research Council (MRC) Programme Grant to ACR and performed within the Behavioural and Clinical Neuroscience Institute, University of Cambridge, funded jointly by the Welcome Trust and MRC.

TE04

NK1R-/- MICE DISPLAY PERSEVERATIVE BEHAVIOUR IN THE 5-CHOICE SERIAL REACTION TIME TASK BUT NOT IN THE MARBLE BURYING PARADIGM

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In the 5-Choice Serial Reaction-Time Task (5-CSRTT), NK1 receptor knockout mice (NK1R-/-) display behaviours that resemble key diagnostic features of Attention Deficit Hyperactivity Disorder (ADHD) including impulsivity, inattentiveness and perseveration (Yan et al, 2011, PLoS ONE 6: e17586). Perseveration was particularly robust and seen at all training / testing stages of the 5-CSRTT. Here, we studied marble burying, an alternative measure of perseveration (and controversially a model for obsessive-compulsive disorder (OCD)), in NK1R-/- mice or mice treated with the NK1 antagonist RP67580. Covered Perspex boxes (l, 30cm, w, 19cm, h, 18cm) were filled with sawdust to a depth of 5cm. 20 marbles were placed on the sawdust in a regular pattern about 4cm apart and animals were left to explore for 30min. The number of marbles buried more than two thirds of their depth was counted. Male NK1R+/+ and NK1R-/- mice (129/SvXC57BL/6 crossed with an outbred MF1 strain) were tested with no injection. The study was replicated with naïve C57BL/6 mice given vehicle (saline with 10% Tween) or NK1 antagonist RP67580 (5mg/kg), injected i.p. 30min before the test. N=6 for all groups. NK1R-/- mice bury fewer marbles than their wild-type counterparts ($t(1,10) = 2.6$, $P<0.05$). RP67580 decreased the marble burying behaviour, thus mimicking the behaviour of NK1R-/- mice, although vehicle injection also decreased marble burying activity ($F(2, 15) = 7.3$, $P<0.01$). NK1R-/- mice show robust perseverative responding in the 5-CSRTT, an operant procedure, but not in species-typical digging behaviours. Marble burying is reduced by a wide range of anxiolytic drugs and has been proposed as a model for OCD. However, while reduced marble burying in NK1R-/- mice might be predicted from previous pharmacological assays relevant to depressive illness and anxiety, the reduction of marble burying by a stressor (vehicle injection) in wild-type mice was unexpected and may suggest that a more complex interpretation of mouse marble burying and digging behaviours is required. In summary, the comparison of two assays for perseveration lead to opposite conclusions but point to the complex nature of this behavioural trait and the difficulty of using natural behaviours as models for human cognitive disorders.
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TE05

FURTHER DEVELOPMENT OF A TRANSLATIONAL AFFECTIVE TONES DISCRIMINATION TASK: EFFECT OF ACUTE ANXIETY

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The Affective Tones Discrimination Task (ATDT) is a novel paradigm based on the rodent cognitive affective bias task (Harding et al, 2004, Nature, 427(6972): p312-312). The task requires individuals to form an association between tone cues and emotional outcomes, obtain reward or avoid punishment. Following training, participants are presented with ambiguous tone cues and response bias and latency are quantified. Response selection during ambiguous cues is hypothesised to reflect affective state. This study investigated the effects of anxiety on performance in the ATDT using a 20 minute inhalation of 7.5% CO2, a human model of generalised anxiety disorder. Healthy volunteers (n=32) were recruited from the University of Bristol. Participants completed a training session which consisted of indentifying reward (achieve monetary reward) and avoidance (avoid aversive sound) tones (500Hz and 1000Hz) presented in a pseudo-random order for 5 seconds for a total of 16 trials (8/tone). The test session (120 trials total) included additional intermediate ambiguous probe tones at frequencies between the reward and avoidance tones coupled with the inhalation of normal air or 7.5% CO2, in pseudo-randomised order and counterbalanced. A total of six, ambiguous probe tones were used at 20Hz intervals either side of the 750Hz midpoint. Mean correct response and median response latency to each tone were recorded. Participants were then given a series of self-report measures of mood. Two participants (CO2 group) did not meet the inclusion criteria (>90% accuracy for reference tones) so were excluded from analysis. CO2 significantly increased measures of anxiety ($ps<0.05$). Number of correct responses to ambiguous probe tones were dependent on the degree of ambiguity (repeated measures ANOVA; $F[2,27] = 64.672$, $p < 0.001$). Participants also took longer to respond to more ambiguous tones ($F[2,27] = 7.651$, $p = 0.002$). CO2 tended to slow response times for all tones ($F= 2.885$, $p = 0.1$) with a trend toward a Gas x Valence interaction ($F[1,28] = 3.226$, $p = 0.083$). CO2-inhalation increased anxiety scores and resulted in some changes in task performance but did not induce a response bias. Participants in the CO2-inhalation group were slower to respond, especially to ambiguous tones nearest to reward. These data suggest CO2-inhalation may interfere with overall ability to perform the task and decrease motivation to obtain reward. Further studies are required to determine whether these effects are specific to anxiety or arise from non-specific cognitive impairment resulting from the CO2-inhalation. MRM is a Professor of Biological Psychology at the University of Bristol; ESJR is a senior lecturer at the University of Bristol; MHA is funded by a BBSRC studentship.

TE06

INHALATION OF 7.5% CO2 MODULATES ATTENTION NETWORK FUNCTION

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Inhalation of 7.5% carbon dioxide increases anxiety and autonomic arousal and provides a novel experimental model of generalized anxiety. We recently demonstrated that 7.5% CO2 challenge in healthy volunteers can mimic the attentional disturbances previously observed in anxious populations i.e. hyper-vigilance towards and deficient inhibition of visual threat stimuli (Garner et al. 2011, Neuropsychopharmacology). Observed individual differences in and covariation between subjective, autonomic and neuro-cognitive response to CO2 challenge suggests a need to better understand factors which modulate response to CO2 challenge. The present study compared the effect of 7.5% CO2 vs air on the efficiency of three attentional networks: alerting (maintaining an alert state), orienting (the selection of information from sensory input) and executive control (resolving cognitive conflict), and further examined whether individual differences in trait anxiety predicted the effect of CO2-challenge on subjective mood, autonomic arousal and attention network function. 23 healthy volunteers (12 females mean age = 20.3 yrs, SD =1.1 yrs) attended a single test session in which they completed a modified Attention Network Test whilst inhaling 7.5% CO2 and air (gas order counterbalanced across participants). The Attention Network Test combined a cued reaction time task and flanker task, and required participants to make a speeded response to a central arrow target (flanked by distracter stimuli) that was cued by either a temporal-onset (alerting) or spatial location (orienting) visual stimulus. CO2 inhalation significantly increased state anxiety, negative affect, heart rate and systolic blood pressure, consistent with previous findings ($Fs(2, 44) < 10.11$, $ps < .01$). Paired t-tests confirmed that inhalation of CO2 led to significant increases in alerting and orienting network function $ps < .05$; but did not affect executive control. Trait anxiety was associated with increased negative affect, heart rate and systolic blood pressure during CO2, and further associated with greater orienting (an effect mediated by the strong correlation between CO2-induced blood pressure and orienting). Findings provide evidence that 7.5% CO2 inhalation boosts efficiency in orienting and alerting networks, and that individual differences in trait anxiety can predict response to CO2 challenge. Increased utilization of visuo-spatial information in high trait anxious individuals during CO2-challenge is consistent with i) neuro-cognitive models that emphasize hypervigilance and stimulus-driven processing in anxiety via interactions between amygdala and prefrontal cortex, and ii) evidence that CO2 triggers related fear behaviour in small animals via direct innervation of the fear-network. Funding: None to declare.

TE07

THE EFFECTS OF LOCALISED LESIONS OF THE VENTRAL PREFRONTAL CORTEX ON A BEHAVIOURAL MODEL OF ANXIETY IN MARMOSETS

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Anxiety, when transiently expressed as a reaction to aversive stimuli, is a necessary everyday response. However, when it progresses to a constitutive state, it becomes pathological and a hindrance to normal daily performance. The neural components of negative emotion are traced back to the prefrontal cortex (PFC) including the orbitofrontal cortex (OFC) (Davidson 2002 Biol Psychiatry 51:68-80; Milad and Rauch 2007 Ann NY Acad Sci 1121:546-561). However, it is unclear how precise regions within the PFC and OFC influence fearful or anxious behaviours. Both all-encompassing (Brodmann areas 11, 12, 13, and 14) and more restricted (areas 11 and 13) lesions of the OFC decrease fear/anxiety responses in primates (Kalin et al. 2007 Biol Psychiatry 62:1134-1139; Machado and Bachevalier 2008 Psychoneuroendocrinology 33:926-941). Conversely, selective OFC lesions in rats exacerbate fear responses (Lacroix et al. 2000 Behav Neurosci 114:1119-1130). Moreover, studies in humans suggest the existence of independent dimensions of neurocognitive function in trait anxious subjects. To address these issues, we used a "snake model test" to model anxious reactions in marmosets and to investigate the effects of anterior OFC (antOFC, n=4) or ventrolateral PFC (vlPFC, n=5) lesions. Anxiety was measured as the average distance the animal spent away from a model snake as well as the number of calls (tsik and tsik-egg) elicited in the presence of the snake. One-way ANOVAs were conducted to statistically compare the control, antOFC, and vlPFC groups. Animals with antOFC lesions averaged a greater distance from the snake, suggesting that they were impaired in appropriately regulating fear. In addition, the number of tsik (but not tsik-egg) calls decreased in both antOFC and vlPFC-lesioned animals compared to controls (n=5). The fact that all animals made tsik-egg calls suggests that tsik-egg calls represent the emotionality component of anxiety (fearfulness). Tsik calls are essentially mobbing vocalisations and reflect the proactive (aggressive) coping dimension of anxious behaviours (Cross and Rogers 2006 Horm Behav 49:237-245). We suggest that distance from a predator also reflects “fear”. Finally, we propose that this pattern of responding in the presence of a model snake is consistent with a role of the OFC in regulating fear responses, and a role of the vlPFC in regulating attentional and strategic responses to anxiety-provoking stimuli.
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TE08

INTERMITTENT VOLUNTARY WHEEL RUNNING IS REWARDING AND AFFECTS COGNITION: ROLE OF THE STRESS HORMONE CORTICOSTERONE

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Corticosterone (CORT) modulates drug abuse behaviour and is self-administrated in rats. Recently, we demonstrated that mice acquired and reinstated corticosterone self-administration after a withdrawal period suggesting that it had rewarding properties (Ebada et al, BAP Summer Meeting, 2009). Voluntary wheel running is rewarding, activates the hypothalamic pituitary adrenal (HPA) axis and is believed to improve cognition. The present study aimed to investigate whether corticosterone contributes to the rewarding and cognitive effects of acute or chronic intermittent (1h) voluntary wheel running. Male C57BL/6J mice were individually housed and assigned to acute or chronic exercise sessions. In the acute study, mice had several training sessions until they showed clear motivation for wheel running (3 successive wheel running sessions with the third session's running distance over 0.3 km/h). On the day of the acute session, mice were divided into three groups (n=9-12); saline-treated non-exercising or exercising control groups and metyrapone (inhibitor of corticosterone synthesis; 35mg/kg, i.p)-treated exercising group, and underwent a 1hour-voluntary running session. Immediately after running, mice were killed and blood samples were collected for the measurement of plasma corticosterone levels. In the chronic study, mice were assigned to two groups (n = 10), sedentary and exercising, and were subjected to repeated 1-hour voluntary wheel running sessions (5 days/week) for 5 weeks. Memory performance was evaluated using the spontaneous alternation test (before and after the exercise regimen) and the novel object recognition test. Mice were killed after a final running session to examine the effect of chronic intermittent wheel running on plasma corticosterone levels. In both acute and chronic studies, non-exercising mice had access to static wheels. Metyrapone-treated mice ran less than control exercising mice ($P<0.05$) and there was a positive correlation between plasma corticosterone levels of exercising mice and distance run during the acute session ($r = 0.375$, $P<0.05$). In the chronic exercise study, running mice exhibited a gradual increase in the distance covered over the five weeks and showed a significant rise in their plasma corticosterone levels as compared to sedentary mice ($P<0.001$). Sedentary but not running mice showed improvement in spatial alternation performance ($P<0.05$). While neither of the two groups showed recognition memory impairment, there was a negative correlation between discrimination index of the running mice and their last week's mean running distance ($r = -0.74$, $P <0.05$). These data suggest that exercise-induced corticosterone release is important for the rewarding and memory modulating effects of wheel running. This work is a part of PhD scholarship of Mohamed Ebada which is funded by National Organization for Drug Control and Research (NODCAR), Cairo, Egypt

TE09

ENHANCED NOCICEPTIVE RESPONDING IN A RAT MODEL OF ANXIETY IS ASSOCIATED WITH ALTERATIONS IN LEVELS OF ENDOCANNABINOIDS AND RELATED LIPIDS IN DISCRETE BRAIN REGIONS

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Stress or anxiety can enhance pain responding/perception in rodents (Imbe, 2006, Front Biosci 11:2179-92) and humans (Rhudy and Meagher, 2000, Pain, 84:65-75), a phenomenon referred to herein as anxiety-related hyperalgesia (ARH). The neurochemical mechanisms mediating ARH are poorly understood. The endocannabinoid system modulates both pain- and anxiety-related behaviour (Finn, 2010, Immunobiology, 215:629-646). Here, we investigated nociceptive responding in Sprague Dawley (SD) and Wistar-Kyoto (WKY) rats, two strains that differ with respect to baseline anxiety-related behaviour. In addition, the study examined if altered nociceptive responding was associated with changes in levels of endocannabinoids (anandamide [AEA] and 2-arachidonoylglycerol [2-AG]) and related N-acylethanolamines (palmitoylethanolamide [PEA] and oleoylethanolamide [OEA]) in discrete brain regions. Anxiety-related behaviour of adult male SD and WKY rats (285-320g, n=12 per group) was assessed in the open field and elevated plus maze tests. The hot plate and formalin tests were used to assess nociceptive behaviour to acute thermal and persistent inflammatory stimuli respectively. Levels of endocannabinoids and N-acylethanolamines were measured using liquid chromatography-tandem mass spectrometry in brain regions harvested 33 min post-saline or formalin injection. All data were analysed by ANOVA followed by Fisher's LSD post-hoc test where appropriate and $p<0.05$ was deemed significant. WKY rats spent significantly less time in the centre zone of the open-field and in the open arm of the elevated plus maze compared with SD counterparts, indicating an anxiogenic phenotype. WKY rats exhibited significantly lower hot plate withdrawal latency and increased formalin-evoked nociceptive behaviour compared with SD counterparts, indicating a hyperalgesic phenotype. WKY rats not receiving formalin had significantly higher levels of 2-AG, OEA and PEA in the ventrolateral periaqueductal grey (PAG), 2-AG in the lateral PAG and OEA and PEA in the rostroventromedial medulla (RVM), compared with SD counterparts. Formalin-evoked nocicpetive behaviour in SD rats was accompanied by decreased levels of AEA, OEA and PEA in the right lateral PAG and increased levels of 2-AG, PEA and OEA in the RVM. In contrast, the enhanced formalin-evoked nociceptive behaviour in WKY rats was associated with decreased levels of AEA, 2-AG, PEA and OEA in the RVM. Moreover, anxiety-related hyperalgesia in WKY rats was associated with increased levels of 2-AG in the PAG except in the left dorsolateral PAG, increased PEA in the left ventrolateral PAG, lateral PAG and right basolateral amygdala (BLA) In conclusion, ARH is associated with alterations in endocannabinoids and related lipids in discrete brain regions involved in anxiety and nociceptive responding.

TE10

VARIATION OF EXPERIMENTAL CONDITIONS IN FEAR POTENTIATED STARTLE LEADS TO A NEW SHORTENED STUDY PROTOCOL

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Introduction: The fear potentiated startle paradigm (FPS) is a frequently used model to evaluate anxiolytic properties of drugs. The model consists of conditioning rats to a visual cue (conditioned stimulus, CS) which is combined with an aversive foot shock (unconditioned stimulus, US). During the subsequent test phase, the startle response to an acoustic stimulus is enhanced when presented in combination with the CS, and represents a measure of fear potentiation. FPS is a time-consuming model and is characterized by high variability between animals. We investigated variation of several parameters in order to decrease this variability.
Methods: Male Sprague Dawley rats (250-350g, n=10-16 per group) were used. San Diego Instruments startle reflex chambers were used to deliver different types of stimuli and to measure startle response. During the conditioning phase, we investigated various parametric features such as number of conditioning sessions (1-2) and trials per session (10-20), length of CS-US interval (0.2-51.2 sec) and length and intensity of foot shock delivered (0.5-1 sec, 0.3-1.8 mA). Following conditioning, expression of fear was measured using intervals of 4-48 hours. During the expression test, we also investigated how the choice of reference response (habituation pulses {1-30}, startle responses intermixed with conditioned responses {20 each}) or the length of the startle sampling window (100-200 msec) affected %FPS calculation. % FPS was calculated as the proportional difference of acoustic startle response during the light stimulus relative to in the dark.
Results: Coefficient of variation (CV), a measure of variability, ranging between 0.5-0.9 in the standard procedure (double training + 48 h test interval). None of the parameters varied improved variability; CV ranged between 0.5-1.0, not different from the standard condition. However, by reducing the number of training sessions from 2 to 1 and the conditioning-test interval from 24 to 4 hours, reproducible fear responses, ranging between 100-250 %, were measured in four independent studies. Comparable values, ranging 80-200 %, were measured under standard conditions, double training and 48 h test interval.
Conclusion: To our knowledge, this is the first demonstration that one single training session of 10 trials results in reproducible levels of fear measured after a short interval of 4h following conditioning. The degree of variability could not be improved by any parameter investigated.

TE11

ANXIOLYTIC EFFECTS OF NOVEL KAPPA-OPIOID RECEPTOR ANTAGONISTS IN THE ELEVATED PLUS MAZE

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Introduction: Activation of kappa-opioid receptors (KOR) has long been known to produce dysphoric effects (Pfeiffer et al., 1986, Science, 233:774-776) and KOR antagonists have been suggested as potential treatments for mood disorders (Mague et al., 2003. J Pharmacol Exp Ther, 305:323-330). We have reported previously that 5'-(2-Aminomethyl) naltrindole (5-AMN) and 5'-(2-Methylamidino) butyl naltrindole (5-MABN) are potent, long-acting KOR antagonists in vivo using the tail withdrawal assay (Bailey et al., 2010, J Psychopharmacol, 24: A42). Here, we have investigated the effects of 5-AMN and 5-MABN on anxiety-related behaviours in mice. Methods: CD-1 male mice, 8-9 weeks old (University of Bath) were gently handled daily for 1 week prior to treatment. Animals were group housed (n=3-4) and randomly assigned to saline control (0.9% w/v saline) or drug-treated groups (n=10 per group). At day 0, mice were injected (10 ml/kg; ip) with 0.9% w/v saline, 5'-AMN (1 mg/kg), 5'-MABN (1 mg/kg and 10 mg/kg) or norBNI (1 mg/kg and 10 mg/kg). On test days, 7, 14, and 21 days post-injection of KOR antagonist or saline, mice previously injected with KOR antagonists received saline, 30 min prior to behavioural testing. Control groups previously injected (at day 0) with saline were administered diazepam (1 mg/kg) or saline 30 min prior to testing. Behavioural effects were studied in an automated elevated-plus maze system for mice with Motor Monitor software (EPM; Campden Instruments). In the EPM mice explored the maze freely for 5 min, under low light intensity (100 lux) before being returned to the home cage. Data were analysed using a repeated measures one-way ANOVA, and Tukey-Kramer post-hoc test (Stat View 5 software). Results: In the EPM, there was no significant effect of drug-treatment on overall locomotion ($F(6, 12)=1.1$, $P=0.369$). However, there was a significant effect of drug-treatment on the time spent in the open arms ($F(6, 12)=4.6$, $P=0.0006$). Post-hoc testing revealed that at day 7 post injection diazepam (1 mg/kg), norBNI (1 and 10 mg/kg), 5'-AMN (1 mg/kg) and 5'-MABN (10 mg/kg), all significantly increased the time spent in the open arms compared to saline-treated control mice (all P's <0.05). 5'-AMN (1 mg/kg) was the only KOR antagonist that significantly increased the time spent in the open arms at 21 days post-injection, compared to saline-control. Conclusion: 5'-AMN, 5'-MABN and norBNI displayed anxiolytic-like effects in the EPM, without any significant sedative effect. The anxiolytic-like effects of 5'-AMN were very long-lasting in agreement with our previous in vivo study. We are currently investigating the antidepressant potential of these compounds. Supported by the University of Bath, The Royal Society (SJB), and NIDA DA07315 (SMH).

SO01

DO PEOPLE DEVELOPING PSYCHOSIS IN THE CONTEXT OF CANNABIS USE HAVE BETTER COGNITIVE FUNCTION BECAUSE THEY HAVE FEWER NEURODEVELOPMENTAL RISK FACTORS?

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Variables associated with cannabis use that have emerged from our own and other psychosis studies include a younger age at illness onset, poor prognosis and, for reasons that remain uncertain, better cognitive function. Our aim was to explore the nature of the relationship between cannabis use (and frequency of use), cognition, age at onset, and social and clinical outcomes, in a cohort of first-episode schizophrenia. Ninety-nine patients with first-episode schizophrenia and no history of alcohol or substance abuse other than cannabis were classified as either lifetime users or never-users of cannabis. The cannabis users had an earlier age at illness onset, and there was a strong linear relationship between age at first cannabis use and age at onset, with 94% reporting first cannabis use that pre-dated the development of prodromal symptoms. The cannabis users also demonstrated better cognition at psychosis onset, explained by higher premorbid IQ, and better social function; neither measure changed over the subsequent 15 months. Comparing low-frequency (twice a week or less) and high-frequency users (daily or almost daily) of cannabis, the only differences in functioning or outcome were that the former demonstrated modestly superior current cognitive function, including significantly higher IQ. It has been proposed that early cannabis users show better cognitive function because the drug has a neuroprotective effect on the developing brain prior to psychosis onset. This hypothesis predicts that high-frequency users would have better cognitive function than low-frequency users, but we found the opposite to be true. An alternative explanation, commensurate with our findings, is that individuals developing schizophrenia in the absence of cannabis use have different premorbid vulnerabilities, which are neurodevelopmental and reflected in poor cognition. This also aligns with our observation that the cannabis users had better social function at onset than never-users, independently of premorbid IQ and in the context of a lack of difference in symptom profile or duration of untreated psychosis. In summary, our data suggest that those who develop psychosis in the context of cannabis use have better cognitive function because they have fewer neurodevelopmental risk factors. Cannabis use, regardless of frequency of use, may bring forward the onset of psychosis in people who otherwise have good prognostic features, as indicated by level of premorbid cognition and social function. The earlier age of onset in cannabis users may therefore be a consequence of a toxic action of cannabis rather than an intrinsically more severe illness.

PD1

THE RELATIONSHIP BETWEEN STRUCTURAL, FUNCTIONAL AND EFFECTIVE CONNECTIVITY IN SUBJECTS OF HIGH GENETIC RISK IN SCHIZOPHRENIA

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Measures of gyrification, functional and effective connectivity have been reported to be aberrant in schizophrenia, but the nature of any association between them is unclear. We investigate the relationship between measures of gyrification, functional and effective connectivity in subjects at high genetic risk for schizophrenia. We hypothesised that the different connectivity measures suggest altered development of short- and long-range connectivity in this high risk phase of schizophrenia, and that those with most disrupted connectivity measures would be most likely to become ill. Brain connectivity measures were collected from individuals assessed as part of the Edinburgh High Risk Study (EHRS) who provided both structural imaging data from which we derived GI measures and functional imaging data on the Hayling sentence completion paradigm from which we derived functional and effective connectivity measures. Cortical folding and tissue measures were extracted using automated gyrification index (A-GI) methodology. A-GI detects fissures and extracts the prefrontal lobe. The results are exported and the GI calculated by dividing the inner by the outer contour. Measures of functional connectivity were assessed using a correlation based approach based on fMRI data. Statistical dependencies between regional time series were computed. Two seed regions were selected: the right inferior frontal gyrus (x=55, y=21, z=1) and the left thalamus (x=-8, y=-13, z=6). Effective connectivity measures were analysed using Dynamic Causal Modelling (DCM). DCM relates neuronal activity in different brain regions with a dynamical systems approach. Bayesian Model Selection and Model Space Partitioning were used to explain the effects in the fMRI data. The relationship between GI and functional connectivity revealed significant positive and negative associations. Positive correlations were found between prefrontal GI and lateral-medial connectivity ($p=0.018$, $p=0.017$ for right and left hemispheres respectively). A negative correlation was found between prefrontal GI and prefrontal to thalamic connectivity ($p=0.016$). In controls, no significant correlations between prefrontal GI measures and prefrontal lateral-medial connectivity ($p=0.7$, $p=0.3$ for right and left hemispheres respectively) and prefrontal to thalamic connectivity ($p=0.8$, $p=0.9$) were found. We suggest that the positive relationship between prefrontal GI and prefrontal connectivity reflects intact short-distance connectivity in the prefrontal cortex, while the negative correlation between prefrontal GI and prefrontal-thalamic connectivity reflects disrupted long-distance connectivity, and short-range connectivity is increased at the expense of the long-range connectivity. The ongoing effective connectivity analysis will allow further understanding of the underlying causality of the relationship between GI measures and functional connectivity. Funding: MRD is supported by Dr Mortimer and Sackler Foundation. TWJM is supported by Dr Mortimer and Sackler Foundation and TMRC. HCW is supported by a Dorothy Hodgkin Fellowship from the Royal Society (DH080018). The Edinburgh High Risk Study was funded by an MRC programme grant. Scanning was conducted at the Scottish Brain Imaging Research Centre which is supported by SINAPSE (Scottish Imaging Network, a Platform for Scientific Excellence, www.sinapse.ac.uk). MRD, TWJM, HCW and SML have previously received financial support from Pfizer (formerly Wyeth) in relation to imaging studies of people with schizophrenia.

PD2

BRAIN NETWORK FUNCTIONAL CONNECTIVITY IN CLINICAL IMAGING STUDIES: PROMISES AND PITFALLS

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The human brain possesses unrivalled biological and computational complexity, yet is prone to dysfunction at the systems level in various forms of neuropsychiatric disease. Thus far, neuroimaging explorations of functional connectivity have yielded interesting, but also challenging, implications for systems and clinical neurosciences, shifting common neuropsychiatric paradigms towards investigation of dysfunctional organisation at the level of neural networks. However, concrete applications of these techniques to critical questions of cognition and behaviour, clinical diagnosis, treatment efficacy and prognosis in neuropsychiatric disorders are yet to be fully realised. Of growing interest – particularly for their potential to allow us to overcome some of the limiting factors in this field – are 'resting-state network' (RSN) phenomena (Cole et al., 2010, Front Syst Neurosci 4:8). RSNs are a set of distinct, large-scale neural activation patterns. They consistently display strong functional connectivity and are usually measured using functional MRI during undirected wakefulness (Beckmann et al., 2005, Philos Trans R Soc Lond B Biol Sci 360:1001-13). RSNs are thought to reflect the ensemble activity of neuronal populations serving specific, core functions and have been shown to be abnormal in multiple neuropsychiatric disorders associated with aberrant cognition and reward processes, including addiction (Cole et al., 2010, Neuroimage 52:590-9). With particular reference to RSNs, we will first consider some advantages and disadvantages of statistical approaches commonly used to elucidate the fundamental functional network architecture of the dynamic brain from neuroimaging data. We will then consider key benefits and interpretative limitations arising from initial applications of these techniques to questions relevant for psychopharmacology. Specifically, we will discuss data examining the influence of dopamine and nicotine challenges on RSNs in healthy and neuropsychiatric populations, along with the relevance of these findings for treating pathological cognition and reward processes underlying disorders such as addiction. Finally, we will consider the future importance of systems-level connectivity measures in clinical imaging and drug discovery, highlighting a possible use for RSNs to bridge existing gaps between molecular and pharmacodynamic markers of neurotransmitter function and drug action.

PD3

THE APPLICATION OF GRAPH THEORY ALGORITHMS TO BRAIN IMAGING DATA GAINED IN A PRECLINICAL CONTEXT

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Graph theory algorithms have recently been applied to quantitatively define the properties of functional brain networks in humans, providing added insight into their organisation in healthy individuals and their disrupted organisation in disease states, including schizophrenia (Liu et al., 2008. Brain.131:945-961). The value of applying these algorithms in a preclinical context is yet to be tested. Here we apply both established and novel graph theory algorithms to functional brain imaging data gained in a preclinical model relevant to schizophrenia, subchronic phencyclidine (PCP) treatment (Pratt et al., 2008. British Journal of Pharmacology. 153:S465-S470). Cerebral metabolism was determined in control (saline, male, Lister Hooded, n = 7) and PCP-treated (2.58mg.kg-1, i.p, 1 x daily for 5 days, n = 9) rats by semiquantitative 14C-2-deoxyglucose imaging (Dawson et al., 2010. Schizophrenia Bulletin. Epub: doi:10.1093/schbul/sbq090). Overt alterations in metabolism were analysed by t-test. Global brain network properties were characterised in terms of mean degree, average path length and mean clustering coefficient. Centrality analysis (degree, betweeness and closeness) was used to identify important hub regions in the networks. Hub regions were statistically identified by comparing real and calibrated random graphs. Statistical differences in global network architecture were analysed using repeated measures ANOVA. Alterations in regional centrality between groups were analysed by comparing regional z-scores using t-test with Bonferroni correction. GSVD analysis (Xiao et al, 2011. BMC Systems Biology 5:72) was used to characterise differences in regional clustering between the groups. Significance was set at $p<0.05$ throughout. Subchronic PCP-treatment induced overt hypometabolism in prefrontal and select thalamic regions. The functional brain network in PCP-treated animals was significantly less connected (reduced mean degree [$F(1,21)= 1178$, $p<0.001$]) and had a reduced efficiency for information transfer (increased average path length ($F(1,21)= 197.19$, $p<0.001$) and reduced mean clustering ($F(1,21)= 185.44$, $p<0.001$) as compared to that in controls. In control animals several thalamic regions and the locus coeruleus were identified as hubs ($z>1.96$ and $p<0.05$). Of these regions the reticular and centromedial thalamus, nucleus reuniens and locus coeruleus lost their hub status in PCP-treated animals ($z>2.576$ and $p<0.05$). GSVD analysis revealed that the PFC and hippocampus are functionally segregated in PCP-treated but not control animals. This study is the first to apply graph theory algorithms to functional brain imaging data from a preclinical model relevant to schizophrenia. PCP-induced alterations in global network properties parallel those reported in schizophrenia and provide new insight into the mechanisms underlying brain dysfunction in schizophrenia.

PD4

STATE-DEPENDENT INTERACTIONS OF CORTICAL AND HIPPOCAMPAL NETWORKS IN A NEURODEVELOPMENTAL MODEL OF SCHIZOPHRENIA

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Cognitive deficits in schizophrenia affect multiple domains including learning and memory, attention, and behavioural flexibility, thereby confounding the rational design of pharmacological treatments. Recent studies emphasise the importance of rhythmic activity in neuronal networks for cognitive processing during both wake and sleep, and abnormal oscillations have been correlated with severity of symptoms in schizophrenic patients. Whilst the pathophysiological mechanisms of aberrant network activity in schizophrenia remain poorly understood, future therapies should therefore aim to normalise neuronal activity at this level. Here we investigated in vivo network activity during sleep and wake in a rat neurodevelopmental model of schizophrenia generated by exposure to the mitotoxin methylaxoxymethanol (MAM) at embryonic day 17 (E17). We aimed to characterise state specific oscillatory activity in cortical and hippocampal networks during sleep, resting wake and high cognitive load states using either chronic intracranial dual site cortical EEG recordings or dual site prelimbic cortex and hippocampus tetrode recordings. Animals were recorded in their home cage for extensive characterisation of sleep wake cycles and trained in a spatial working memory test on an end-to-end T-maze. We identified a fragmented sleep-architecture phenotype in MAM-E17 rats, and observed non rapid eye movement (nREM) specific changes in cortical and hippocampal oscillatory activity and synchronisation. Moreover, MAM treated rats showed oscillatory abnormalities specific to the wake behaving state, which included an increased occurrence of fast hippocampal ripple oscillations (120-250Hz) during cognitive behaviour. The current results present an extensive survey of oscillatory network activity during relevant behavioural states in a preclinical model of schizophrenia. The MAM-E17 model recapitulates sleep abnormalities evident in schizophrenia, and establishes a novel link between abnormal sleep architecture and disrupted cortico-limbic interactions during nREM sleep. The impaired sleep architecture is accompanied by increased hippocampal network activity during cognitive load, which contribute to aberrant learning of associations. Our results increase mechanistic understanding of cognitive deficits in schizophrenia and establish a model for testing novel pharmacological intervention.

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GL1

NO HEALTH WITHOUT MENTAL HEALTH

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The separation of psychiatric training and treatment from the rest of health care has many disadvantages and few remaining benefits. As mental disorders are now viewed as brain disorders, training that focuses on the mind and ignores the brain, robs psychiatry of a rich intellectual and scientific base. As mental health treatments are administered independent of other health care, the common co-morbidities (substance abuse, heart disease, diabetes) are rarely given adequate attention. As a result of these co-morbid medical conditions, people with serious mental illness die 25 years early (in the U.S.). Indeed, the major economic costs of health care for those with mental illness are actually the costs of co-morbid medical conditions. But most important, the treatment of mental illness is essential for overcoming these other health care challenges. As a society, we will not achieve overall health until we successfully treat mental illness.

PW1

UNDERSTANDING THE ROLE OF STRESS PATHWAYS ON THE PROGRESSION OF SYMPTOMS AND NEUROPATHOLOGICAL HALLMARKS OF ALZHEIMER'S DISEASE

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Introduction: Stress is a predisposing factor for Alzheimer's disease, whereas positive lifestyle factors, such as mental activity and moderate exercise, are protective to the condition although they themselves activate stress pathways. Our recent work have provided strong evidence that low levels of stress, induced by the repeated exposure to a novel environment, are protective during the early stages of Alzheimer's-like pathology in a transgenic mouse model. The overall aim of my current research is to identify the brain mechanisms responsible for the therapeutic-like effect of mild novelty stress as they could be targeted for the development of novel treatments. Our most recent work indicates that the corticotrophin-releasing factor receptor 1 (CRF1), a key modulator of behavioural and neuroendocrine responses to stress, is a strong candidate.

Methods : Mice over-expressing the amyloid-precursor protein (APP) and preselinin 1 (PS1) genes known to cause the familial form of Alzheimer's disease were used. We first tested the involvement of CRF1 and CRF2 receptors in the responses to novelty stress using selective antagonists administered i.c.v. to 4-month-old APP/PS1 mice. CRF mediates increased neural activity via the CRF1 and the glutamatergic NMDA receptors and there was no effect of CRF2 antagonism. We thus investigated the involvement of CRF1 and/or NMDA receptors activation on repeated novelty-induced improvement in cognition. Antagonists to the CRF1 and/or NMDA receptors were administered i.p. to 4-month-old APP/PS1 mice prior to each novelty sessions (4/week, 5 weeks). Changes in recent contextual fear memory were assessed at the age of 5.5 months, followed by post-mortem analysis of the level of markers of synaptic density in the hippocampus and frontal cortex.

Results : APP/PS1 mice showed different behavioural and neuroendocrine responses to acute novelty, which are partially mediated by the CRF1 receptor. Repeated novelty-induced improvement in recent memory in APP/PS1 mice was blocked by CRF1 and NMDA antagonism individually, but not in combination, suggesting that CRF1 activation mediates the observed beneficial cognitive effects independently of NMDA activation. The novelty-induced increased in synaptic density was blocked by all three treatments in the hippocampus, whereas it was preserved in the frontal cortex by co-treatment with the CRF1 and NMDA antagonists.

Conclusions: Overall, this work further highlight the beneficial effect of a stimulating environment on the early stages of Alzheimer's disease progression via activation of stress pathways and could pave he way to the development of improved treatment strategies targeting some stress mediators.

PW2

NEUROLOGICAL CONSEQUENCES OF HEAVY KETAMINE USE

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Ketamine use has increased dramatically over the past decade, with it now being the fourth most popular illicit recreational drug. Physical health consequences associated with its use have now emerged, including 'ketamine induced ulcerative cystitis', a chronic and disabling condition that can lead to cystectomy in some individuals. Over several years researching the drug, I have built up a profile of its cognitive and phenomenological effects, ketamine appears to induce in heavy users profound memory impairments and some schizophrenia-like symptomatology. However, despite severe physical health and psychological consequences, little is still known about the neurological consequences of taking the drug heavily. This study compared 18 heavy ketamine users with 19 age, IQ, gender and poly-drug use matched controls. Data were collected on symptoms, cognition, glutamate /glutamine levels and functional differences between ketamine users and controls on an associative learning task. Ketamine use is associated with lower levels of thalamic glutamate which were correlated with level of dependence on the drug in ketamine users. There were also indications of other neurological changes underpinning learning deficits in this population. Future research to assess the reversibility of these learning deficits and neurochemical changes in ketamine users upon cessation of use.

PW3

THE GABA-BENZODIAZEPINE RECEPTOR, ITS SUBTYPES AND ALCOHOL MISUSE: INSIGHTS FROM IMAGING AND PHARMACOLOGICAL CHALLENGE STUDIES

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Introduction. The GABA-benzodiazepine receptor has long been known to be involved in many of alcohol's central effects. Neuroimaging using 123I-iomazenil single photon emission tomography (SPET) and 11C-flumazenil and 11C-Ro15 4513 positron emission tomography (PET) alongside pharmacological challenges have been crucial to increasing our knowledge in man. The a5 benzodiazepine subtype is of particular interest due to its putative role in 'alcohol-liking' and memory. Whilst 11C-flumazenil PET predominantly images the a1 subtype, 11C-Ro15 4513 is relatively selective for a5 benzodiazepine subtype with high levels of binding in limbic regions such as the nucleus accumbens and hippocampus. Methods. Abstinent alcohol dependent individuals were recruited for neuroimaging studies and non-dependent drinkers for pharmacological challenge studies.
Results. Reduced benzodiazepine receptors levels were seen in the frontal lobe using 123I-iomazenil SPET. This is consistent with impaired executive functions commonly seen in alcoholism. To investigate whether tolerance occurs in man, the function of benzodiazepine receptor was explored with a pharmacokinetic-pharmacodynamic 11C-flumazenil PET study. Whilst no difference in beta-EEG response or saccadic eye movements to a midazolam challenge was seen between abstinent alcoholics and controls, reduced time asleep was seen in alcoholics. It is likely that benzodiazepine receptor subtypes underlie these differential responses. In abstinent alcoholics, binding of 11C-Ro15 4513 was not significantly reduced in the frontal cortex, but was significantly reduced in the nucleus accumbens and hippocampus in abstinent alcoholics compared with controls. The a5 subtype is extra-synaptic and provides tonic inhibition therefore such a reduction will result in less inhibition within the nucleus accumbens and consequently greater activity in efferent projections. The levels of 11C-Ro15 4513 binding in the hippocampus were significantly and positively associated with performance on a hippocampal task, delayed verbal memory, in alcoholics but not controls. In heavy drinkers, an inverse agonist at the a5 subtype reversed the memory impairing effects of an acute dose of alcohol. We propose that in abstinent alcoholics, the tonic inhibition from a higher level of a5 subtype results in appropriate function of hippocampal glutamatergic neurons, which are likely to be dysregulated due to chronic alcohol exposure. Whereas in non-dependent individuals an acute alcohol challenge stimulates all the benzodiazepine receptors impairing glutamatergic function and the inverse agonist then allows the a5 to provide tonic inhibition.
Conclusion. The benzodiazepine receptor continues to be a focus of research in alcohol misuse and a growing understanding of the role of the various subtypes gives us new targets for treatment.