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Abstract Book 2010

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human volunteers that suggest that CBD and THC may have opposing effects on some of the neural substrates of human memory (Bhattarcharya et al., 2008). Smokers of high CBD strains showed an attenuation of the acute THC-induced memory impairment and reduced overall cognitive and mood difficulties compared to THC smokers. These findings support the use of higher CBD strains in cannabis, as they may offer relief from the acute effects of THC while reducing harmful effects. In terms of harm reduction, users should be made aware of the higher risks associated with smoking low CBD strains of cannabis.

Neuropsychopharmacology, 35:764-74).

In a recent, large scale naturalistic study, we have collected samples of cannabis and analyzed the levels of different cannabinoids. Although high THC cannabis has become increasingly available over recent years, little is known on changes in levels of other cannabinoids as these are not routinely measured in routine drug testing. The relative THC/CBD ratio of cannabis varies significantly depending on the strain and method of cultivation. In terms of psychopharmacological effects, high THC strains are associated with transient schizophrenia-like positive and negative symptoms, perceptual alterations, and cognitive deficits. In a subsample of more than 250 healthy individuals, who were more sensitive to the effects of Δ9-THC, we found that low CBD strains were more detrimental than high CBD strains. This suggests that other components of cannabis may contribute to the “beneficial” effects of cannabis.

The relative THC/CBD ratio of cannabis varies considerably. In terms of harm reduction, users should be made aware of the higher risks associated with smoking low CBD strains of cannabis. In a recent, large scale naturalistic study, we have collected samples of cannabis and analyzed the levels of different cannabinoids. Although high THC cannabis has become increasingly available over recent years, little is known on changes in levels of other cannabinoids as these are not routinely measured in routine drug testing. The relative THC/CBD ratio of cannabis varies significantly depending on the strain and method of cultivation. In terms of psychopharmacological effects, high THC strains are associated with transient schizophrenia-like positive and negative symptoms, perceptual alterations, and cognitive deficits. In a subsample of more than 250 healthy individuals, who were more sensitive to the effects of Δ9-THC, we found that low CBD strains were more detrimental than high CBD strains. This suggests that other components of cannabis may contribute to the “beneficial” effects of cannabis.
SO1

ADVANCES IN IN VIVO CANNABINOID RECEPTOR PHARMACOLOGY

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The hemp plant Cannabis sativa has acquired much interest over the last few years, not only because of problems associated with its abuse, but also because of the possible therapeutic potential of its constituents. More than 60 cannabinoids and terpenoids have been described to date and we became particularly interested in extracted cannabis-relatives termed 9-Tetrahydrocannabinol (THC) and areAphyltocannabinoids. They are derived from chemically enriched and purified from plant extracts. Of particular medicinal 9-Tetrahydrocannabinarvin (THCV), CannabigerolAarelevances are compounds such as: 9-TetrahydrocannabinarvinicA(CBG), Cannabichromene (CBC), Cannabidiol (CBD), or acid (THCVa). They were tested as sole active ingredient (>95% purity assessed by NMR) or as naturally occurring extract from plants cross-fertilised to generate high amounts of the respective cannabinoid in their extract. Such extracts, termed botanical drug substance or BDS, also consist of numerous 9-THC in various amounts. Initially, we conducted Acominations including pharmacokinetic analysis of the pure compounds to determine tmax and time course of elimination after intraperitoneal and oral administration in rat and mouse. Cannabinoid levels were monitored by LC/MS/MS in plasma and brain and were readily identified with peak values attained within 1-4 hours. Onset was slower following oral administration relative to intraperitoneal injection, but metabolism of all compounds returned to baseline within 24 hours. Both, pure or corresponding BDSs were assessed in an Irwin screen for central and/or peripheral drug effects in mice. High doses of cannabinoid administered intraperitoneally caused subtle anomalies such as reductions in ambulatory movements, reactivity, body posture and defecations. Overall, however, cannabinoids were safe and devoid of toxicity apart from THCVa for which considerably more negative effects were observed. Finally, purified cannabinoids and extracts were tested in paradigms with predictive validity in terms of psychiatric disorders such as open field and forced swim test in mice and apomorphine-induced stereotyped behaviour in rats. Overall, pure CBD weakly reduced stereotyped behaviour in high doses >30mg/kg, but had no effect on in the forced swim test despite lower locomotion in the open field. CBG was much weaker and doses of 120mg/kg did not affect behaviour apart from a small reduction in ambulatory activity. THCV reduced stereotyped behaviour and locomotion at doses of >0.3mg/kg, but had no effect on immobility in the forced swim test. Similar results were obtained for extracts. However, overall effects were weak to moderate relative to reference compounds that are currently in clinical use.

SO2

“GONE TO POT”: EVIDENCE FROM LABORATORY STUDIES WITH Δ9-THC

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Introduction: Converging lines of evidence suggest a relationship between cannabinoids and psychosis. Laboratory studies with Δ9-THC have been a useful approach to investigate this relationship. Methods, Results and Conclusions: We have characterized the dose related behavioral, subjective and cognitive effects of intravenous Δ9-THC in more than 250 healthy individuals, in a series of placebo controlled double-blind, randomized and counterbalanced laboratory studies. Δ9-THC produces an array of transient schizophrenia-like positive and negative symptoms, perceptual alterations, and cognitive deficits. In a subsample of more than 25 subjects, we studied the psychophysiological effects of Δ9-THC. Similar to the deficits observed in schizophrenia and some other neuropsychiatric disorders, Δ9-THC reduced amplitude of the P3a and P3b in healthy individuals: Δ9-THC impairs the allocation of attention and context updating to a greater extent than the orienting of attention to novelty. Cannabis is frequently misused by individuals with schizophrenia - and while cannabis appears to have a negative impact on the course and expression of schizophrenia, individuals with schizophrenia report deriving “benefits” from its use. We characterized the effects of Δ9-THC in patients with schizophrenia (n=13) and found Δ9-THC transiently exacerbated symptoms without producing any obvious “benefits”. Furthermore, schizophrenia patients were more sensitive to the effects of Δ9-THC. The discrepancy between the negative effects of Δ9-THC in the laboratory and “benefits” of cannabis reported by individuals with schizophrenia suggest that other components of cannabis may contribute to the “beneficial” effects of cannabis in this population.

SO3

DIFFERENTIAL EFFECTS OF CANNABINOIDS IN CANNABIS SMOKERS

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Cannabis contains a myriad of different chemicals, more than 60 of which are unique to the plant and called cannabinoids. The main psychoactive ingredient is delta9-tetrahydrocannabinol (THC) and this produces the effects that users seek (Curran et al., 2002 Psychopharmacology 164: 61-70). When given intravenously to healthy humans, THC produces psychotic-like and anxiogenic effects (D’Souza et al., 2004 Neuropsychopharmacology 29: 1558-1572). In contrast, cannabidiol (CBD), another major constituent of most strains of cannabis, appears to have anti-psychotic properties, is anxiolytic (Guimares et al., 1990 Psychopharmacology 100: 558-559) and may be neuroprotective in humans (Hermann et al., 2007 Biol. Psychiatry 61: 1281-1289). The relative THC/CBD ratio of cannabis varies greatly. Although high THC cannabis has become increasingly available over recent years, little is known on changes in levels of other cannabinoids as these are seldom measured. We found that users with high levels of THC in hair and low CBD demonstrated greater levels of schizophrenia like symptoms than users with higher levels of CBD (Morgan & Curran, 2008, Br J. Psychiatry, 192: 306-307). In a recent, large scale naturalistic study, in which we have collected samples of cannabis smoked and analysed this for levels of cannabinoids, we have found that individuals smoking high CBD strains of cannabis show different patterns of acute effects than those smoking low CBD strains. Smokers of high CBD strains showed an attenuation of the acute THC induced memory impairment and reduced ‘attentional bias’ to cannabis and food stimuli. There were no differences between the groups in the acute psychotomimetic effects of CBD. These findings concur with recent preclinical findings that suggest CBD may reduce the salience of drug cues (Ren et al., 2009, J. Neuroscience 29:14764-9.) and findings in healthy human volunteers that suggest that CBD and THC may have opposing effects on some of the neural substrates of human memory (Bhattarcharya et al., Neuropsychopharmacology, 35:764-74). In terms of harm reduction, users should be made aware of the higher risks associated with smoking low CBD strains of cannabis like ‘skunk’ and encouraged to use strains containing higher levels of CBD.
SO4

THE BROAD BIPOLAR SPECTRUM: IMPLICATIONS FOR THE TREATMENT OF BIPOLAR DEPRESSION

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Depression is a heterogeneous diagnosis which encompasses a wide range of clinical presentations and which may be better viewed as part of a broad bipolar spectrum. A growing body of research suggests that many individuals with depression experience clinically relevant manic symptoms. A small proportion of these individuals will have undiagnosed bipolar disorder but the majority have manic symptoms which fall below the DSM-IV threshold for a formal diagnosis of bipolar disorder. Drawing on data from epidemiological and treatment studies, as well as from our work in Cardiff, this presentation will assess whether diagnostically sub-threshold manic symptoms in major depression have important implications for the assessment and treatment of both unipolar and bipolar depressive disorders, with particular reference to the use of antidepressants.

SO5

ANTIDEPRESSANTS AND ANTIPSYCHOTICS: CLINICAL ACTION, LONG-TERM EFFECTS ON DEMENTIA, SUICIDES AND MORTALITY

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Background: Antidepressants (AD) are criticised for having: a late onset of action, a very small effect compared to placebo (PLO), and for being dangerous by increasing suicidality and inducing hypomania and rapid cycling. None of these statements is sufficiently evidence based. Findings: The onset of action of AD is early; the main effect occurs within the first days and most responders improve within the first twelve. During this period careful observation and optimal dose adjustment are important. Patients showing no improvement within the first two weeks are mostly non-responders. As long as given, AD induce and maintain a biological remission process, which is identical for placebo- and drug-responders and is associated with multiple genes. The response to both AD and PLO is strongly dependent on baseline severity. With increasing severity of depression, PLO response decreases and AD response increases. Most RCT with PLO are carried out in unrepresentative samples of mild depressives without suicidality, which can give misleading and results that are not generalisable to severe depressives. A switch from depression to hypomania occurs in bipolar depressives and depressives with hidden sub-threshold bipolarity; the latter is present in 33%-40% of all DSM-IV major depressives. AD induce response more often than PLO; the switch is dependent on the response (non-responders cannot switch), a fact not taken into account in reports on AD induced switch rates. There is also no sufficient statistical evidence that AD induce rapid cycling. Ever since the introduction of AD, it has been known that they can increase suicidal ideation in some patients, who react with agitation or mixed states. There are also reports from in short term AD clinical trials of a significant increase in suicide attempts among younger depressives. The latter observations from large sample sizes ultimately led to a general FDA warning. By contrast, AD given over years in low doses can decrease suicide rates significantly. A strong anti-suicidal effect is also found for Clozapine and Lithium long-term treatment in mood disorder patients. In addition, these drugs can attenuate or may even prevent senile dementia. Cardiovascular mortality is not correlated with long-term AD treatment but with the proportion of mania; pure manics had the highest. Taking all long-term effects together, there is no reason to stop long-term prophylactic medication in the elderly but it can often be decreased. Conclusion: AD deserve a better reputation; a key problem, however, is their improper use.

SO6

GENETICS OF THE MOOD-PYSCHOSIS SPECTRUM: CLINICAL IMPLICATIONS

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Mirroring clinical practice, it has been conventional for psychiatric research, including the search for predisposing genes, to proceed under the assumption that schizophrenia and bipolar disorder are separate disease entities with different underlying etiologies. These represent the traditional dichotomous classification of the so-called “functional” psychoses and form the basis of modern psychiatric diagnostic practice. Recently positive findings have been emerging in molecular genetic studies of psychoses. However, the pattern of findings shows increasing evidence for an overlap in genetic susceptibility across the traditional classification categories - including association findings at DISC1 and NRG1. Genome-wide association studies (GWAS) provide greater power to explore the relationship between mood and psychotic illness. Within the context of the Wellcome Trust Case Control Consortium (WTCCC) we have studied 2700 mood-psychosis cases and 3000 controls and several other large-scale studies have been undertaken, including studies of structural genomic variation. The emerging evidence suggests the existence of both relatively specific as well as more general relationships between genotype and psychopathology. For example, in our dataset variation at GABAA receptor genes is associated with susceptibility to a form of illness with mixed features of schizophrenia and bipolar disorder. Genome-wide significant associations at CACNA1C in bipolar disorder and ZNF804A in schizophrenia show evidence for a contribution to susceptibility across the traditional diagnostic boundaries. The elucidation of genotype-phenotype relationships is at an early stage, but current findings highlight the need to consider alternative approaches to classification and conceptualization for psychiatric research rather than continuing to rely heavily on the traditional dichotomy. As psychosis susceptibility genes are identified and characterized over the next few years, this will have a major impact on our understanding of disease pathophysiology and will lead to changes in classification and the clinical practice of psychiatry.
SO7

HOW TRANSLATABLE ARE THE CURRENT ANIMAL MODELS OF DEPRESSION AND MANIA

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Over 30 years ago in his seminal forced swim test paper Roger Porsolt wrote “A major problem in the search for new antidepressant drugs is the lack of animal models which both resemble depressive illness and are selectively sensitive to clinically effective antidepressant treatments”. This statement remains as true today as it did when Porsolt believed that the test would bridge the gap from preclinical research to humans. The wide spectrum of disruptions that characterizes depression and bipolar illness highlights the difficulties researchers are posed with as they try to mimic these disorders in the laboratory. Criticism has been directed towards the “traditional” preclinical models, which can often be better described as tests of antidepressant-activity. Nevertheless, they have greatly advanced our understanding of psychiatric disorders. However, the lack of translation of results from preclinical animal models to patients has led in the last few years to a number of different approaches being employed. These aim to provide more information regarding the pathophysiology of depression and bipolar disorders and ultimately lead to drugs with novel mechanisms of action. Endophenotype-based approaches, which attempt to assay a single symptom or marker, have the benefit of simplifying complex disorders and the possibility of increasing the relevance of findings across a number of psychiatric disorders given their substantial co-morbidity. Another direction, in light of the evidence purporting social stress to be a risk factor for depression and bipolar disorders is the development of social stress paradigms. Such models are believed to be more relevant to the human situation than non-social stress paradigms. Genetic predisposition is known to be a factor in the aetiology of depression and bipolar and selective breeding paradigms, as well as assessment of different inbred strains, can lead to important information regarding the underlying pathophysiology of depression. Additionally, research in the clinical arena has become more sophisticated and is providing potential avenues to incorporate into preclinical paradigms. These emerging findings will not only enable closer comparisons to be made but also to determine whether findings from preclinical models remain true in humans. It is hoped that such approaches will lead to greater insight into the underlying aetiology of depression and bipolar disorders but as implicated by the opening statement only time will tell.

SO8

MODULATION OF THE GLUTAMATERGIC SYSTEM: FROM RAT TO HUMAN

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Pharmacological MRI provides a powerful means to study the effects of neuropsychiatric drugs on the patterns of brain activity in humans and in pre-clinical species, and to elucidate the neurobiological substrate of their pharmacological activity. Acute administration of glutamate NMDA receptor (NMDAR) antagonists such as phencyclidine (PCP) or ketamine induce symptoms that closely resemble those of schizophrenia in humans, a finding that has led to the hypothesis that a decreased NMDAR function may be a predisposing or even causative factor in schizophrenia. Here, we have applied phMRI to study the brain circuitry underlying the psychotomimetic action NMDA blockers in the anesthetized rat, and to investigate how these functional changes are modulated by drugs that possess distinct pharmacological mechanisms. Specifically, we found that NMDA blockade by PCP at sub-anaesthetic doses results in the activation of discrete cortico-limbomodal regions, consistent with human findings. This effect was strongly suppressed by pretreatment with compounds that can reduce neuronal excitability and modulate glutamatergic transmission such as the sodium channel blocker lamotrigine, and the mGlur5/2 agonist LY354740. Similarly, blockade of the NMDA binding-site of glycine, an obligatory co-agonist of glutamate at this receptor, strongly reduced the response to PCP, thus corroborating the pivotal role of cortical glutamatergic neurotransmission in the psychotomimetic action of NMDAR antagonists. Pretreatment with the selective D2 dopamine antagonist raclopride did not significantly affect the response to PCP, a finding that argues against a primary role for dopamine D2 receptors in the functional response elicited by NMDAR antagonists. Finally, the antipsychotic clozapine produced a region-dependent suppression of PCP-response, with moderate inhibition in the cortex, and total response suppression in the thalamus. This wealth of data provides valuable insight into the neural circuitry engaged by PCP and into the neurochemical determinants of the complex response to NMDA blockade. Moreover, the recent confirmation of these findings in human healthy volunteers strikingly demonstrates the translational potential of pharmacological MRI.

SO9

FUNCTIONAL MRI IN AWAKE ANIMALS: IMAGING THE NEURAL CIRCUITRY AND PHARMACOLOGICAL CONTROL OF AGGRESSION, SEX, AND FEAR

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Functional magnetic resonance imaging (fMRI) in awake animals is a window on the brain allowing behavioral neuroscientists the ability to image the brain activity associated highly emotional behaviors like aggression, sex and fear. With fMRI in awake animals it is possible to resolve patterns of neuronal activity across the entire brain with high spatial and temporal resolution. Synchronized changes in neuronal activity across multiple brain areas can be viewed as functional neuroanatomical circuits coordinating the thoughts, memories and emotions for particular behaviors. To this end, fMRI in conscious rats combined with 3D computational analysis was used to identifying the putative distributed neural circuits involved in aggressive motivation, sexual motivation and conditioned predatory fear and how these neural circuits are affected by drugs altering vasopressin and serotonin neurotransmission. Data will be presented showing changes in brain activity associated with aggressive motivation. Socially dominant male rats can be positioned in the MR scanner and their brain imaged in response to the presentation of a strange dominant male. The subsequent change in brain activity reflects aggressive motivation toward the intruder and shows a robust pattern of activation in the thalamus, cortex and hypothalamus similar to that preceding a generalized seizure. When a drug is given to block vasopressin receptors or increase serotonin neurotransmission, aggressive motivation is suppressed along with the increase in brain activity. Interestingly, in the presence of vasopressin receptor blockade and suppressed aggression, dominant males still show sexual motivation and heightened brain activity toward sexually receptive females. In contrast, fluoxetine, a selective serotonin reuptake inhibitor, reduces aggressive responding but impairs sexual behavior. Data will be presented on a newly developed, unique model of predatory fear conditioning using a live sable ferret as the unconditioned stimulus. In short, rats exposed to a ferret while experiencing the taste of sucrose show a dramatic increase in brain activity in the limbic cortex and hippocampus weeks later in response to the taste of sucrose alone. Indeed the brain activity associated with the memory is far greater than the initial exposure to the predator. Treatment with an orally active vasopressin receptor antagonist blocks the sucrose-associated traumatic memory but the initial innate fear response.
Background An emerging theme in the neuroscience of emotion is the question of how acute stress shapes, and distorts, social-emotional behavior. The prevailing neurocircuity models of social-emotional behavior emphasize the central role of the amygdala. Acute stress leads to increased central levels of norepinephrine (NE) and cortisol (CORT), and evidence suggests that these endogenous neuromodulators synergistically influence amygdala responses to social-emotional stimuli. Methods We hypothesized that amygdala responses to emotional facial expressions would be susceptible to pharmacologically induced increases in central NE and CORT levels. To specifically test this hypothesis, we measured amygdala activation to emotional faces using functional magnetic resonance imaging in 62 healthy subjects under four pharmacological conditions: (1) single oral dose of placebo, (2) 4 mg of the selective NE-reuptake inhibitor reboxetine (RBX), (3) 30 mg of hydrocortisone, or (4) both drugs in combination. Results We found that a decrease in amygdala activation to positive facial emotion was coupled with an increase in amygdala activation to negative facial emotion in the RBX-CORT combined challenge condition. Conclusions In conclusion, a pharmacologically induced elevation of central NE and CORT levels in healthy subjects created a negative response bias in the amygdala that did not exist at baseline. Our results implicate a causative role of NE-CORT interactions in the emergence of a negative bias of cognitive and emotional functions which is germane in stress-related affective disorders.

S11

MEASURING NUCLEAR RECEPTOR ACTIVATION IN MAN: PMR OR ASL?
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Signal detection in pharmacological BOLD MRI (pMR) can be difficult if the pharmacological action of the agent of interest has a slow and prolonged onset of action as is the case with corticosteroids. In addition, since many analytic techniques are model driven and rely on plasma concentration, they may not be a robust representation of brain events. Finally pMR is not quantitative only representing relative changes and the interpretation of negative signals can be difficult. Arterial spin labelling (ASL) is a MRI technique that allows the quantification of perfusion in the brain and therefore has more potential as a robust technique to measure drug action in the brain. Here we describe the concomitant use of BOLD and arterial spin labelling (ASL) in the same placebo controlled experiment in order to determine the site of action of the glucocorticoid agonist hydrocortisone. pMR analysis was carried out in SPM5 using plasma input curves as input functions. ASL data was collected at the beginning and end of experiment. ASL data revealed a pattern of decreased perfusion that encompassed thalamo-fronto-striatal areas medial temporal lobe (amygdala and hippocampus) and hypothalamus. The pattern on pMR was more limited in extent but with a larger signal from the hypothalamus that reflected an earlier time course. The two signals may relate to different time courses and/or downstream effects. In the discussion other processing techniques will be discussed including data driven approaches.

S12

SEX, STEROIDS AND COGNITION – DO WE THINK WITH OUR GONADS?
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The rhythmicity of the gonadotropic axis exhibits several frequencies from the episodic through ultradian to circadian which in sexually mature women is exemplified by the menstrual cycle. Men also exhibit circadian rhythm as plasma testosterone is highest in the morning and lowest in the evening. The axis is under control of gonadotropin releasing hormone (GnRH), which intermittently stimulates the pituitary gonadotropes to release follicle stimulating hormone (FSH) and luteinizing hormone (LH) which control germ cell production and steroidogenesis. The sex steroids exhibit pleiotropy not only do they influence reproduction and secondary sexual characteristics but their influence in the central nervous system extends beyond the pituitary and the hypothalamus. The sexual differentiation of the brain begins in utero and many neurones receptors for the sex steroids. The effects of the sex hormones are often interrelated and dependent on various enzymes, for example aromatase (which is active in the brain) which converts androgens into oestrogens and carrier proteins such as sex hormone binding globulin. The sex hormones can also influence neuroplastic change and affect cognitive processes. Data suggest that these effects are domain specific, for example, men usually outperform women on visual-spatial tasks whereas women higher scores on tests of verbal fluency. However, it is difficult to correlate such performances with bioavailable hormone levels. The situation in women is complicated further by the fact that the ratio of oestrogen to progesterone also influences cognition as exemplified in studies of pregnant women where hormone levels far exceed the fluctuations seen throughout the menstrual cycle. Chronobiology also influences steroid production most obviously in women at the menopause but bioavailable testosterone levels also decline in men. Evidence is accumulating that some cognitive domains are adversely affected by this phenomenon but hormone supplementation has yielded equivocal results. The classical mechanism of action of the sex steroid is via intranuclear receptor systems and the distribution of these and their subtypes is well documented across the central nervous system. The steroids also modulate other pathways such as their regulation of lipid signalling; in particular, the prostaglandin pathway, for example, PGE2 has been shown to play a role in hippocampal neurogenesis. Such indirect effects may go some way to explain the lack of obvious correlation between cognitive functioning and bioavailable steroid levels.
S13

FEMALE RATS ARE SMARTER THAN MALES: IMPORTANCE FOR TRANSLATIONAL RESEARCH.

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Translational research has become an endevour involving steps from in vitro experimental evaluation, its translation into experimental animals and finally into humans. However, the translation from one level to the next faces a number of difficulties which are currently of major interest for the development of novel therapeutics. Women and men have different risks for developing certain neurological, psychiatric, neuroendocrine and neuroimmunological disorders which ought to be considered when evaluating new therapeutics through existing and during the development of new experimental models. There are significant sex differences in normal brain structure and function and in behavior which are critical to consider for understanding and treating human diseases of the nervous system. Preclinical studies, both historically and today, remain largely focused on male subjects, and do not address adequately the specific neurobiological principles which govern these processes in females. Recent research has confirmed clear sexual dimorphisms during cognitive paradigms where females are shown to 'outperform' male rodents (e.g. Ghi et al., 1999. Pharmacology Biochemistry & Behaviour 64; 761-766. Sutcliffe et al., 2007. Behavioural Brain Research 177; 117–125). In addition, the stage of the oestrous cycle has been observed to impact upon strategies employed and overall performance (e.g. Sutcliffe et al., 2007. Behavioural Brain Research 177; 117–125: Walf et al., 2006. Neurobiology of Learning & Memory 86; 35 – 46). Extensive evidence from preclinical animal studies indicate that sex steroids, in particular oestrogen, but also the progestins', are neuroprotective with accumulating evidence supporting a key role for ERß in cognition. ERß knock-out mice show not only profound memory impairment in hippocampal dependent tasks but also show deficits in hippocampal neuronal activity (Walf et al., 2008. Behavioural Neuroscience 122; 974-981). Recently, ERß activation increases levels of synaptic proteins (Glutamate receptor 1,GluR1 and post synaptic density 95), enhances LTP in hippocampal slices (CA1 region), increases dendritic branching and spine number, increases cyclic-AMP response element binding protein (CREB) phosphorylation and improves spatial memory (Liu et al., 2008. Nature Neuroscience 11, 334–343). Despite these findings there is still a significant lack of focus on sex differences. This situation is primarily due to the increased cost of studying sex-related differences, and to the technical challenges in controlling for cyclical hormonal variations in female animals. Appreciation of gender influences and hormonal status are paramount and researchers not only need to develop more hypothesis driven research strategies to understand gender differences but also to collect necessary data regarding ovarian cycle status and the influence of gonadal steroid fluctuations on brain function in both normal behaviours and in the case of psychiatric disorders.

S14

SEXUALLY DIMORPHIC EFFECTS OF COMT ON COGNITION AND IN PSYCHIATRIC DISORDERS

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Introduction: Sex differences can affect brain function, and its dysfunction in psychiatric disorders. Genetic factors contribute to these sex dimorphisms, but few candidate genes underlying these sex differences have been identified. The catechol-O-methyltransferase (COMT) gene, which encodes an enzyme that metabolises catechol compounds, including dopamine, is a leading candidate in this regard. Methods: I will review evidence for a sexually dimorphic influence of COMT upon psychiatric phenotypes and brain function, and discuss potential mechanisms by which this may occur. Results: COMT’s enzyme activity is sexually dimorphic in human populations. In addition, the neurochemistry and behaviour of COMT knockout mice, and that of rats treated with COMT inhibitors, differs between male and female animals. Furthermore, several genetic associations between COMT and psychiatric phenotypes reportedly show differences between men and women. Thus, COMT is associated with obsessive compulsive disorder in men but not women, and potentially with anxiety-related phenotypes in women but not men. These sexually-dimorphic effects of COMT are usually attributed to the regulation of its transcription by oestrogens; however, a careful examination of the literature suggests that additional mechanisms are also likely to be important. Conclusions: Although some of the reported differences are unconfirmed or minor, there are accumulating and in places compelling data showing that COMT has markedly sexually dimorphic effects on brain function, and its dysfunction in psychiatric disorders. These findings suggest that there are likely to be sex differences in associations between the functional COMT Val158Met polymorphism and brain-related phenotypes. Sexual dimorphisms in the relationships between the autosomal genes and brain function will likely emerge, since sex differences in the genetic regulation of brain function are likely to be the rule, rather than the exception.

S15

THE ROLE OF OESTROGEN IN PSYCHOSIS AND ITS TREATMENT

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Due to their lipophilic nature, ovarian sex steroids easily pass into the brain where they bind to widespread receptors. In susceptible females, reproductive events that lead to changes in sex steroid production have repeatedly been shown to influence the course of mental illness. Several illness characteristics suggest that oestrogen has a protective effect for schizophrenia. For women, the onset is later than in men, and the disease course is in general less severe until the perimenopausal years when the number of onsets increases. In addition, schizophrenia symptom severity inversely correlates with day to day changes in oestradiol levels in premenopausal women. During pregnancy, when the production of female sex steroids gradually increases to levels 100 – 200 higher than prior to conception, the risk of hospital admission for first or recurrent episodes probably decreases whereas the precipitous fall of sex steroid levels after childbirth is followed by an increase in the subsequent weeks. The effect of childbirth on the course of bipolar disorder is even more pronounced and it has been suggested that the dramatic increase in first presentations and recurrences immediately after childbirth is caused by the effects steroid withdrawal on a latent dopaminergic dysfunction. This hypothesis is supported by a preliminary neuroendocrine study in drugfree women with bipolar disorder. However, oestrogen has numerous other actions in the brain which might be involved in modulating the course of mental illness. This includes actions on other neurotransmitter systems as well as neurotrophic and neuroprotective effects. The preventative use of oestrogen for bipolar recurrences after childbirth has only been partially successful. However, a larger body of evidence supports a therapeutic effect of oestrogen in the treatment of acute schizophrenia, although some clinical trials have shown no effect. A promising approach for further study is the application of selective estrogen receptor modulators that have antagonist action in breast tissue but agonist action within the brain.
S16

IMPACT OF VAGUS NERVE STIMULATION ON THE NOREPNEPHRINE, SEROTONIN, AND DOPAMINE SYSTEMS IN THE RAT BRAIN

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**INTRODUCTION.** Vagus nerve stimulation (VNS) is a non-pharmacological intervention for treatment-resistant depression. Its mechanism of action has not been elucidated. Rat brain recordings have shown that VNS increases the firing rate of NE neurons after one hour, and that of 5-HT neurons after 14 days (J Pharmacol Exp Ther 318: 890, 2006). The current VNS studies were aimed at: 1) assessing 5-HT neurotransmission, 2) examining DA neuronal firing, and 3) determining the parameters that produce an optimal activation of 5-HT neurons. Methods. Rats were implanted with a VNS electrode and a stimulator subcutaneously in the back area. It was turned on for 14 days using standard (0.25 mA, 20 Hz, 500 µsec, 30 sec ON-5 min OFF), for 12 or 24 hours per day, or various parameters (current: 0.25-1 mA; frequency: 1-144 Hz; pulse width: 130-750 µsec; 30 sec ON every 0.8-30 min). Two and four pulses at 200 Hz every two sec were also used. The NE toxin DSP-4 was used to lesion NE neurons of the locus coeruleus. Dorsal raphe 5-HT, ventral tegmental area DA, and hippocampus CA3 pyramidal neurons were recorded under choral hydrate anesthesia. Results. The enhancement of the firing rate of 5-HT neurons by VNS was abolished by the DSP-4 lesion. VNS increased the degree of activation of postsynaptic α1-adrenoceptors in the raphe. In VNS treated rats, but not in controls, the 5-HT1A antagonist WAY 100635 increased the firing activity of CA3 pyramidal neuron. A two-week VNS treatment decreased DA neuronal firing. The standard VNS parameters, except for the stimulation intensity, produced the largest increases in 5-HT neuronal firing. Finally, the 12-hour stimulation was as effective as continuous stimulation. Conclusions. VNS initially increases the firing activity and pattern of NE neurons, and subsequently those of 5-HT, but decreased that of DA neurons, presumably as a cascade effect. VNS treatment, like classical antidepressants, enhanced the tonic activation of forebrain postsynaptic 5-HT1A receptors. The VNS parameters used clinically, with the exception of the current intensity, correspond to the optimal ones that best activate 5-HT neurons in the rat brain. However, enhancing further the charge led to a loss of VNS effect on 5-HT neuronal firing. Twelve hours per day of stimulation, intervals of 10 and 15 min, and bursts are sufficient to achieve VNS efficacy on 5-HT neuronal firing activity. This could lead to a longer battery life, and possibly minimize side effects during the day.

S17

NEUROENDOCRINE MODULATION AND FUNCTION IN TREATMENT RESISTANT AFFECTIVE DISORDERS

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Introduction Recent evidence has shown that many patients with affective disorders (both unipolar (UP) and bipolar (BP)) exhibit hypothalamic-pituitary-adrenal (HPA) axis dysfunction and hypercortisolaeima. In UP disorder the HPA axis dysfunction is found in patients who are more severe and treatment-resistant, although it is not always found in chronic depression and it is usually a state phenomenon only found during episode, although it can be a predictor of relapse. In bipolar disorder HPA axis dysfunction and hypercortisolaeima occurred during euthymia as well as during episodes of mood disturbance. The elevated cortisol may have negative impact in the patient in terms of both cognitive and affective outcome. Cortisol is known to modulate many processes in both animal and human models. Hypercortisolaeima is also known to change the neurobiological effects of some psychotropic medication and to impact on memory function. The question therefore is whether the administration of treatments that regulate or modify HPA axis activity may be beneficial in affective disorders. Methods The use of antiglucocorticoid therapy in both UP and BP disorder will be reviewed including discussion of a recent Cochrane review on this topic. Data will also be presented from a programme of research into the effects of Mifepristone (RU486) a glucocorticoid receptor antagonist in depressed BP patients unresponsive to antidepressants. Results There is suggestive but not conclusive evidence that various ways of interfering with impact of cortisol in the brain can improve outcomes in patients with affective disturbances. The mechanism of any efficacy remains uncertain although the themes of pre-existing hypercortisolaeima and serotonergic modulation appear to be the most exciting. The best data in UP depression is from study of the cortisol inhibitor metapyrone and this result will be presented in greater detail along with the design of a large pragmatic study to test this agent in the UK. In BP disorder pilot data from a crossover study of Mifepristone indicated that adjunctive administration selectively improves spatial memory compared with placebo and this effect has recently been confirmed in a larger parallel design trial. In this latter study a novel object location memory task informed by pre-clinical experimental data has been used to further explore the selectivity of these effects. Conclusions These results will be discussed in term of both the efficacy of antiglucocorticoid treatments in affective disorders and also increasing our understanding of the role of glucocorticoids in cognitive processing.

S18

THE IMPACT OF P-GLYCOPROTEIN ON ANTIDEPRESSANT FUNCTION.

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The Blood-brain barrier (BBB) is crucial for an optimal function of the central nervous system (CNS). Transport of molecules into the brain is tightly controlled by the endothelial cells that convey minimal permeability to non-lipophilic large molecules. Antidepressants and antipsychotics are small lipophilic molecules that can enter the brain through passive diffusion. Their passage is however limited by the efflux transporter P-glycoprotein (P-gp). This protein is remarkable, for it can extrude hundreds of structurally divergent molecules: the majority of psychiatric drugs are substrates for this pump. P-gp is also a major efflux transporter, its pump capacity is very large for certain substrates, as has been confirmed in knockout models. Inhibition of P-gp is seen in models of neuroinflammation, leading to an increased access of proinflammatory cytokines and other solutes, that contribute to a breakdown of the BBB and neuronal damage. The function of P-gp may be modulated by drugs that inhibit or induce P-gp function. Consequently, CNS side effects may be based on drug related P-gp modulation. On the other hand, P-gp inhibitory agents could be used to improve CNS penetration of psychiatric drugs, and accordingly abate drug resistance. Non response in major depressive disorder may also be related to gene variation of the encoding gene, ABCB1. Positron emission tomography (PET) can now be used to quantify P-gp function in vivo, which may enable researchers to improve the understanding of drug disposition and the role of P-gp. Recent PET studies have suggested that P-gp may be a susceptibility factor in depression. At the same time, chronic use of an antidepressant may lead to P-gp upregulation in the BBB, thereby limiting its own access to the brain. Further insight into the role of P-gp may lead to improved therapeutic strategies, that possibly contribute to the puzzle of treatment resistant depression.
S19

UNDERSTANDING MST AND DBS IN TREATMENT RESISTANT AFFECTIVE DISORDERS: NEUROIMAGING FINDINGS AND CLINICAL EFFECTS
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The main focus of studies on the underlying neurobiology of major depression has focused on the description of biological differences between patients and healthy subjects such as alterations of monoaminergic or endocrine systems. The relative importance of the various biological changes has not been elucidated; correlation with specific symptoms of the disease has rarely been attempted. Psychotropic drugs work by altering neurochemistry to a large extent in widespread regions of the brain, many of which may be unrelated to depression. We believe that more focused, targeted treatment approaches that modulate specific networks in the brain will prove a more effective approach to help treatment-resistant patients. In other words, whereas existing depression treatments approach this disease as a general brain dysfunction, a more complete and appropriate treatment will arise from thinking of depression as a dysfunction of specific brain networks that mediate mood and reward signals, in particular, the cortical–limbic–thalamo–striatol network. Transcranial Magnetic Stimulation is a non-invasive method of brain stimulation, which is evaluated for the treatment of major depression. A novel form of this treatment, Magnetic Seizure Treatment (MST), in which stimulation parameters are selected, that can reliably and reproducibly induce therapeutic seizures has been developed. Results of a recent randomized, within-subject, double-masked trial comparing ECT and MST in ten patients indicate that MST appears to have less subjective and objective side-effects and is associated with faster recovery of orientation. Although ECT has an unparalleled and well-documented efficacy in severe depression it is associated with cognitive side effects. Deep brain stimulation (DBS) is a well-established procedure that refers to stereotactic placement of uni- or bilateral electrodes in a given brain region with electrodes connected to a neurostimulator implanted under the skin of the chest. It is a FDA approved method for control of severe forms of tremor in Parkinson’s disease, essential tremor and primary dystonia. DBS is currently being researched actively for its as putative application in treatment resistant disorders like obsessive-compulsive disorder and major depression. Results from stimulation to different targets within the cortical–limbic–thalamo–striatol network have been presented in the last five years. As of today it cannot be assumed that DBS and MST will cure treatment refractory depression. Clinical usefulness of these approaches still needs to be demonstrated convincingly. Hypothesis guided interventions to different targets may reveal more information on the underlying neurobiology of depression and will likely lead to promising putative new antidepressant approaches.

S20

VENTRAL STRIATAL ACTIVITY AND DOPAMINE RELEASE IN HUMANS WITH FMRI AND PET: TOWARD IDENTIFICATION OF NEUROBIOLOGICAL MARKERS FOR SUBSTANCE ABUSE
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An increasingly large body of fMRI research supports the role of ventral and dorsal striatal regions in reward processing, while evidence from animal studies and human neuroimaging studies support the role of dopamine release in reward-related ventral striatal (VS) functioning. Understanding the relationship between (VS) function and dopamine release may help to develop a potential biomarker for those at high risk for alcohol and substance use disorders, unipolar depression, bipolar disorder, and attention-deficit/hyperactivity disorder. Here we describe a potential method to probe this relationship. Three healthy right-handed females, (age 23±2 years), underwent an fMRI scan during a well validated monetary reward task and then three [11C]raclopride PET scans, using a bolus plus constant infusion paradigm, each separated by a week: one at rest/baseline, (BL) one during a motor control task, (MCT) and one during the same monetary reward task, (MRT), as for the fMRI. fMRI analysis was completed using Statistical Parametric Mapping version 5 software with a statistical threshold of p < 0.05, corrected for multiple comparisons. D2 receptor binding potential was estimated using the BPND, (binding potential non-displaceable), derived by equilibrium analysis. There were significant VS fMRI BOLD signal changes, (25 voxels, MNI coordinates: 12, -3, 0, t = 42.02, corrected p = 0.02) to reward versus motor control task. There was also greater region-specific displacement of [11C]raclopride in the VS than other striatal regions to reward versus the motor control task, (VS = BL 2.59±0.12, MCT 2.53±0.08 and MRT 2.45±0.07, Associative Striatum = BL 2.81±0.05, MCT 2.74±0.11 and MRT 2.71±0.08; Sensorimotor striatum = BL 3.61±0.09, MCT 3.39±0.03, MRT 3.47±0.19). (There is insufficient power, at this stage, to demonstrate significance). An interesting observation that is the fact that the motor control and reward task led to selective increases in DA release in the sensorimotor striatum and ventral striatum, respectively. This is consistent with a specific effect of reward on VS dopamine related to the BOLD signal changes we found in the same region. These preliminary results demonstrate the potential ability of this technique to measure physiological dopaminergic transmission in the functional subdivisions of the striatum and relate this to VS BOLD responses on the same task. Further subjects are currently being assessed using the same technique to confirm and expand this finding and develop an fMRI marker of striatal dopamine functioning.

S21

A ROLE FOR DOPAMINE IN REWARD AND AVERSION: WHAT ELECTROPHYSIOLOGICAL STUDIES IN THE RAT CAN TELL US
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Midbrain dopamine neurons play a key role in reward processing. In particular it has been suggested that they encode a reward prediction-error rule. It is widely assumed that these neurons represent a functionally-homogeneous group. This view is difficult to reconcile with evidence suggesting that dopamine neurons may also code for aversive events and arousal. I will discuss recent evidence, that we and others have provided, suggesting there are in fact several functionally- and anatomically distinct groups of dopamine neurons coding for these events in different ways. In particular, using combined single-cell labelling in rats, we find that subgroups of dopaminergic and non-dopaminergic neurons in the ventral tegmental area (VTA) respond distinctly to aversive stimuli. In addition, I will present recent data concerning the functional properties of dorsal raphe dopamine neurons, which may signal arousal. The broad conclusion is that there is considerable functional heterogeneity within the dopamine system. I will discuss the implications this view holds for understanding addiction.
S22
IMAGING THE ROLE OF DOPAMINE IN HUMAN OPIOID ADDICTS
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The central role played by the dopaminergic mesolimbic system in reward, drug expectation, motivation and learning or conditioning to the incentive salience of a stimulus is well established. In man, previous [11C]-raclopride positron emission tomography (PET) studies have demonstrated increases in dopamine with stimulants correlating with the high’. However increases in dopamine levels related to ‘high’ have not been consistently shown for nicotine, cannabis/THC or alcohol. Increases in dopamine have been shown in man in response to salient cues and expectation of a positive drug effect. Substance dependence has also been shown to be associated with reduced dopamine D2 receptor levels for alcohol and stimulants. The effect of opioid drugs on dopamine release is much less well characterised in humans. Therefore we have conducted two studies in human opioid addicts using [11C]-raclopride PET. In the first study, 14 heroin addicts on methadone maintenance treatment underwent two [11C]-raclopride PET scans following an injection of placebo and either 50mg intravenous diamorphine or 10mg subcutaneous hydromorphone in a double-blind, random order design (Daglish et al 2008; BJPsych 193:65-72). Neither opioid agonist resulted in an increase in striatal dopamine levels despite pronounced subjective and physiological effects. This dissociation implies that dopamine may not be critical in mediating the ‘high’ from opioids in dependent humans. In addition the level of dopamine D2 receptors was no different between opioid addicts and controls. The aim of our second study was to determine whether the expectation of reward increased brain dopamine levels in opioid dependence. 10 heroin addicts on maintenance treatment underwent three [11C]-raclopride PET scans. During the first scan subjects received 50mg intravenous diamorphine, during the second scan, 0.1mg intravenous diamorphine and nothing for the third ‘baseline’ scan. Subjects were blinded to the dose of diamorphine received on the first and second scans. Preliminary results show no increase in striatal dopamine levels to expectation of reward, despite evidence of expectation having been generated. Our studies suggest that dopamine may not play the same role in addiction to opioids as it does in other substances. It may be that opioids result in small increases in dopamine which are not reliably detectable with [11C]-raclopride PET. Nevertheless, the absence of a dopamine response to expectation and administration of opioid agonists contrasts with that found with stimulant drugs and fundamental questions still remain about the role of dopamine in human opioid addiction. Funded by MRC. In collaboration with Imanet, GE Healthcare.

S23
PET IMAGING STUDIES OF DOPAMINE RECEPTORS IN RODENT MODELS OF ADDICTION
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Over the last decade there has been a renewed effort to understand why many people can apparently maintain prolonged recreational drug use without ever progressing to what could be regarded as compulsive or harmful drug use. Increasing evidence suggests that certain personality traits, including impulsiveness and the seeking out of intense forms of sensation and novelty may predispose to drug use and addiction. Consistent with this view we have recently shown that a naturally-occurring form of impulsivity in rats predicts both the escalation of intravenous cocaine self-administration (Dalley et al, 2007 Science 315: 1267-1270) and the subsequent development of compulsive drug taking (Belin et al, 2008 Science 320: 1352-1355). We have also demonstrated using micro-positrion emission tomography (microPET) and the PET tracer 18F-fallypride – a selective, high-affinity DA D2/3 receptor antagonist – that high impulsivity is inversely related to DA D2/3 receptor availability in the ventral but not dorsal striatum (Dalley et al, 2007). Low DA D2/3 receptor function in the ventral striatum, and putatively within its largest sub-region – the nucleus accumbens (NAcB) – may thus be a neurobiological endophenotype that predisposes to excessive cocaine intake. This talk will focus on recent experimental approaches to define with greater precision the neural and psychological specificity of trait-like impulsivity in rats. Using voxel-based morphometry, in-situ hybridisation, targeted administration of selective DA-ergic compounds into the core and shell sub-regions of the NAcB, evidence will be provided for several abnormalities in the NAcB of high impulsive rats, including a loss of grey matter, reduced DA D2 gene expression and supporting evidence from behavioural experiments that impulsivity is exacerbated by administering D2 receptor antagonists directly into the shell sub-region of the NAcB. Taken together our findings indicate that trait-like impulsivity in rats may be mediated in part by DA receptor dysfunction in the NAcB, which interacts with drug exposure to accelerate the transition to compulsive drug seeking and taking. The relevance of these data to human drug addiction will be discussed with particular emphasis on the functional involvement of the brain DA systems in mediating the transition from controlled drug use to habitual and ultimately compulsive patterns of drug use. Supported by the MRC and Wellcome Trust within the University of Cambridge Behavioural and Clinical Neuroscience Institute.

S24
ISOLATION REARING FROM WEANING: A NEURODEVELOPMENTAL MODEL
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Exposing mammals to early-life adverse events, such as peer isolation, profoundly affects brain development and adult behaviour and may contribute to the occurrence of psychiatric disorders such as schizophrenia in genetically predisposed individuals. The molecular mechanisms underlying these environmental-induced developmental adaptations are unclear and best evaluated in animal paradigms. Rearing rat pups from weaning in isolation from littermates, to prevent social play and contact, causes robust, long-term changes in behaviour, brain structure and function. These include abnormal habituation to aversive environments, impaired sensorimotor gating, cognitive rigidity, reduced prefrontal cortical volume and decreased cortical and hippocampal synaptic plasticity. As described in this presentation these behavioural, morphological and neurochemical abnormalities strongly resemble some of the core symptom domains of schizophrenia. Therefore unravelling the mechanisms that trigger these sequelae will improve our knowledge of the aetiology of neurodevelopmental psychiatric disorders, enable identification of longitudinal biomarkers of dysfunction and permit predictive screening for novel compounds with potential antipsychotic efficacy. The current talk will compare the ability of atypical antipsychotics and potential novel therapeutic compounds acting through modulation of serotonergic, glutamatergic, cholinergic and dopaminergic mechanisms, to reverse a battery of behavioural alterations produced in isolation reared rats. Furthermore, the combined impact of treating pregnant rats on gestational day 17 with the anti-miotic agent, methylazoxymethanol acetate, and subsequent rearing of the rat pups in isolation on resultant behaviour and brain structural will be presented. We are very grateful for financial support from the BBSRC, Epix Pharmaceuticals, F.Hoffmann-La Roche, GSK and Servier.
PHENCYCLIDINE TREATMENT: A PHARMAOCOLOGICAL MODEL OF SCHIZOPHRENIA
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Cognitive deficits in schizophrenia remain an unmet clinical need. All patients exhibit some form of cognitive impairment with patients typically performing 2 standard deviations below the mean. Accordingly, a major focus for current preclinical research is to understand the mechanisms behind cognitive deficits in schizophrenia. Improved understanding of the neuro and psychopathology of such symptomatology depends on the availability of carefully validated animal models. Such animal models form a critical stage in the identification and development of novel therapies. There are seven recognised domains of cognition affected in schizophrenia as outlined by MATRICS (www.matrics.ucsd.edu): working memory, attention, verbal learning and memory, visual learning and memory, reasoning and problem solving, speed of processing and social cognition, some of which may be modelled in animals with much work still to be done (Young et al. 2009 Pharmacol. & Ther. 122:150). There is much evidence that at least some of the pathology and symptomatology (particularly cognitive and negative symptoms) of schizophrenia results from a dysfunction of the glutamatergic system. This may be modelled in animals through the use of NMDA receptor antagonists, such as phencyclidine, PCP. This symposium presentation will examine the validity and usefulness of the NMDA receptor antagonist model of schizophrenia in rodents. We use a sub-chronic dosing regime with PCP (2 mg/kg twice daily for 7 days followed by at least 7 days drug free) to induce robust, enduring cognitive disturbances of relevance to schizophrenia in male hooded-Lister rats as assessed in a battery of cognitive tests relevant to MATRICS. We then investigate subsequent reversal of the deficit by atypical and classical antipsychotics and novel compounds (seeNeill et al. Pharmacol. & Ther. 2010 for review). This dosing regime of PCP also leads to reductions in social behaviour of relevance to negative symptoms of schizophrenia. In addition neurobiological changes are also produced such as reduced hippocampal parvalbumin immunoreactive cell density, time-dependent alterations in gamma oscillations in the hippocampus and decreased BDNF mRNA in several brain regions. PCP-treated animals show impaired prefrontal cortical dopamine release in retention in the novel object recognition test, a deficit of which may be critical to restoration of cognitive function in patients. Our conclusion, although not incorporating a neurodevelopmental or genetic component, fits well with the dopamine hypothesis of schizophrenia. This well validated model provides a reliable means for testing efficacy of novel drug candidates.

INSIGHTS INTO THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA USING GESTATIONAL ADMINISTRATION OF MAM IN RODENTS
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Introduction: Schizophrenia is a genetically linked disorder, and increasing evidence suggests that this disorder arises as a result of disruption early in gestation. We found that this pathophysiology can be mimicked in a rodent by administration of the DNA methylating agent methyl azoxymethanol acetate (MAM) at gestational day 17. Methods: MAM was administered to pregnant dams at gestational day 17, and the offspring tested as adults. Electrophysiological recordings were made in the ventral subiculum of the hippocampus and from the ventral tegmental area dopamine neurons. Dopamine neuron population activity was assessed by passing an electrode through the ventral tegmental area in 9 pre-defined tracks and counting the number of dopamine neurons firing spontaneously, along with their firing rate and pattern. Cortical thickness was assessed stereologically. Response to amphetamine was tested in an automated activity monitor, and startle responses using San Diego Instruments cameras. Oscillatory activity was recorded in the ventral subiculum and prefrontal cortex of awake rats. Results: MAM-treated rats tested as adults exhibited features characteristic of schizophrenia, including limbic cortical thinning with increased neuron packing density, deficits in prepulse inhibition of startle and reversal learning, deficits in latent inhibition, and hyper-responsiveness to phencyclidine and amphetamine. Examined using electrophysiological techniques, we found that ventral hippocampal neurons recorded from MAM-treated rats were hyperactive compared to saline-treated controls, and that this hyperactivity corresponded to a loss of parvalbumin interneuron staining and evoked gamma oscillatory activity; also features found in schizophrenia. Moreover, this hippocampal hyperactivity was correlated with increased dopamine neuron function. Thus, in MAM-treated rats, there was an increase in the proportion of dopamine neurons firing spontaneously. This is proposed to result in an increase in the “gain” of the phasic dopamine signal generated in response to stimuli. Inactivation of the ventral subiculum in the rodent model was found to reverse the dopamine neuron overdrive as well as the behavioral hyper-responsivity to amphetamine, providing an important link between the hippocampus and dopamine system regulation. Conclusions: We propose that a deficit in parvalbumin interneuron function in the ventral subiculum of the hippocampus leads to an abnormally high responsiveness of the dopamine system to stimuli that underlies psychosis. Since this hyper-responsivity appears to be driven by abnormal drive from the ventral subiculum, these data suggest that novel therapeutic approaches that target restoration of ventral subicular function may be a more effective therapeutic avenue in the treatment of schizophrenia in humans.

THE EFFECT OF DIFFERENT TREATMENT STRATEGIES ON COGNITIVE PERFORMANCE IN SCHIZOPHRENIA: BALANCE BETWEEN CLINICAL AND PRECLINICAL STUDIES
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Cognitive performance is nowadays widely regarded as a useful tool to describe cognitive dysfunction and its remediation in patients suffering from schizophrenia. Impaired brain plasticity may be the reason behind some of the most crucial impairments of the disorder. Cognitive remediation should be based both on the usage of procognitive antipsychotic agents and cognitive training facilitated by such drugs. There have been numerous attempts to study and describe the conditions underlying the observed changes in the brains of affected patients. Animal models have been used as the necessary preclinical prerequisite to a more precise understanding of both functional and dysfunctional cognition. It was, however, feared that such models do not necessarily translate into similar clinical results. But similar test methodology for reaction time, selective attention and, finally, executive tasks such as set shifting tasks, are nowadays widely available both for animal and human domains and the same experimental philosophies are employed both in psychometric and experimental approaches. Comparisons between preclinical and clinical studies are mainly based on three basic principles. First, the principle is that alterations of neurotransmitter functions are causing similar and predictable changes both in animals and in humans. The second is that basic cognitive functional systems will undergo similar changes both in rodents and humans when they are altered in a similar way. The third principle is that brain alterations induced by psychotropic agents - such as phencyclidine - in both animals and humans may help to understand cognitive changes and their remediation in both species and can therefore be translated from one species to the other. This presentation aims at presenting evidence for the advantage of such translational approaches and the dramatic strategic changes and new challenges that these findings have introduced to the understanding of psychopharmacology, drug development and both agent-based and cognitive training-related strategies in the field of schizophrenia. Callicott J, Bertolino A, Mattay V, et al., Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited, Cerebral Cortex, 2000; 10: 1078-1092. Galhofer B, Jaanson P, Mittoux A, et al., Course of Recovery of Cognitive Impairment in Patients with Schizophrenia: A Randomised Double-blind Study Comparing Sertindole and Haloperidol, Pharmacopsychiatry, 2007; 40: 275À€â€¢,36e286. Rodefer JS, Murphy ER, Baxter MG, PDE10A inhibition reverses subchronic PCP-induced deficits in attentional set-shifting in rats, Eur J Neurosci, 2005;21(4):1070-6.
HOW IMPORTANT IS PLACEBO IN ANTIDEPRESSANT TRIALS?

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Placebo-controlled trials are required to adequately assess the efficacy of novel antidepressant drugs. In both the USA and Europe, regulatory authorities require placebo-controlled studies for marketing authorization. The selective publication of placebo-controlled antidepressant trials and its effect on apparent efficacy is well recognized and there is currently controversy on this topic. Placebo-controlled trials are mainly designed for regulatory approval purposes; to meet both ethical and safety requirements, they tend to recruit patients with a mild form of disease. Although placebo-controlled trials can be efficient because they need smaller sample sizes than non-placebo-controlled trials, difficulties in carrying out these trials when effective treatments are known to exist can introduce artifacts into clinical trials. Response to placebo across antidepressant trials has been shown to vary and has clearly increased in the past two decades, with a similar increase occurring in the fraction of patients responding to active medication as well. The issue of changes in trial outcomes over time is still under debate; however, the change in placebo response does not seem to be directly explained by changes in study characteristics. Inflation of baseline severity, for example, is likely to be a cause for the temporal rise in placebo response rates, which increases the proportion of failed trials. As placebo-controlled trials of antidepressants become increasingly difficult to do, it is perhaps time to reconsider the standard requirements. A recent multiple treatments meta-analysis suggested that sertraline is better than other new-generation drugs in terms of efficacy and acceptability, and could be used as a standard comparator in phase III and also in pragmatic (or effectiveness) trials to increase the real-world applicability of the results. Although the sample-size requirements might be larger than in the ideal placebo-controlled trial, the increased real-world applicability of the results would offset this disadvantage. Furthermore, the need of new treatments to show either greater efficacy or acceptability than an existing standard therapy would serve as a disincentive to the development of me-too agents that offer little to patients other than increased costs.

HOW CAN WE JUDGE WHICH TREATMENTS ARE SUPERIOR? EXPERIENCE WITH ANTIDEPRESSANTS

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There are two ways of investigating potentially superior antidepressants. The most scientific and convincing method is to compare the efficacy directly in a double-blind randomised head to head study under conditions of fair comparison. This method avoids the potential biases inherent in meta-analysis and makes sure that the populations studied are comparable. It follows the regulatory approach where only randomised double-blind placebo-controlled studies establish efficacy. This method has determined that only escitalopram, venlafaxine and clomipramine have definite evidence of being superior on the protocolled primary analysis with two or more placebo-controlled studies which demonstrate superiority in 2 such studies. The second method is to add together all the studies and make a judgement from a meta-analysis. Regulatory authorities have come to distrust meta-analysis as it is post hoc secondary and prone to bias. The conclusions of Cipriani et al, who reported in 2009 that only escitalopram and sertraline were superior in both efficacy and tolerability, were based on meta-analysis. Unfortunately several studies included in the analysis were patently biased and the comparison unfair because a dose rise was permitted on one antidepressant, eg. sertraline or venlafaxine, but not the other. Confidence in the result is therefore weakened. The important issue, however, is that both methods have concluded that not all antidepressants are the same and assumptions of similarity by committees such as NICE are inaccurate. We need to concentrate our efforts to promote the superior and best tolerated antidepressants and stop assuming that all generic antidepressants should be preferred despite the strong evidence to the contrary. Depression is a serious disorder and deserves to be taken seriously.

HOW SHOULD WE BE MEASURING CLINICAL OUTCOME IN PSYCHIATRIC TREATMENT TRIALS?

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There is little or no reason to believe that the components of life leading to health and a sense of wellbeing would be substantially different for individuals suffering from mental illness compared to anyone else. What constitutes “the good life”, and how can it be measured? To love and to be loved; To feel supported and safe? To be part of “meaningful” activities? These are aspirations for every human being, so, shouldn’t we focus more on identifying the steps towards attaining them rather than focussing primarily on symptom reduction? How relevant are symptom ratings as outcome measure in “real life” treatment trials? Does for example a reduction of rated psychosis symptoms lead to a better life (and/or improved health) in a delusional patient whose self esteem might be highly dependent and boosted from the sense of being a target of interest for his perceived persecutors? Should we aspire to help everyone attain social and vocational fulfilment rather than symptom reduction? And if we choose to aim for that would it be possible to identify relevant proxys of progress?
CONTROLLED TRIALS: DO THEY TELL US WHAT WILL BENEFIT OUR DEPRESSED PATIENTS?

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For the practitioner, the purpose of clinical trials is to provide information that can guide treatment and management decisions. However, we appear to have entered a ‘new age of uncertainty’ regarding therapeutic approaches to depression: Recent work has assertively challenged the value of antidepressants in depression other than the most extreme forms. Conversely, recent metaanalyses indicate that not only are antidepressants widely effective but also that there are clinically significant efficacy differences between antidepressants. Furthermore, an emerging body of evidence suggests that some psychotherapies rival the effectiveness of the pharmacotherapies. The knowledge of the therapeutics for depression is highly assumption-dependent. For example it is well known that subject selection for antidepressant trials is highly constrained and that study populations may be unrepresentative of clinical populations. The use of evidence is also assumption-dependent: Increasingly, the interface between the clinician and the data is a guideline, which may offer advisory or prescriptive interpretations of the evidence. But such syntheses of the evidence are commonly characterised by the ecological fallacy, narrow domain of application and limited utility. It is suggested that of all the data theoretically available only a tiny proportion influences clinical decision making at the level of the patient encounter. Clinicians, while assenting to evidence based practice, may in fact proceed largely on the basis of clinical intuition and heuristics. New approaches to generating clinically relevant data may be required, either replacing or supplementing the approaches of conventional randomised controlled trials.

LITHIUM: STILL A MAJOR TOOL IN THE MANAGEMENT OF AFFECTIVE DISORDERS

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For more than 50 years, lithium has been widely recognised as a powerful tool in the management of affective disorders. Even today, lithium is considered the mood stabilizing drug par excellence, at least for maintaining long-term stability in patients with bipolar disorder. It is worth noticing that lithium has survived as a main treatment despite the fact that it has not been promoted by any drug company during the last many years. However, since lithium has often been used as an internal reference in pivotal trials conducted for approval of alternatives to lithium, the pharmaceutical industry indeed has provided convincing data on lithium over the years. Besides the psychiatric indications outlined below, lithium has some minor extra-psychiatric indications. An ideal mood stabilizer is able to control acute symptoms of mania and of depression and to prevent the reoccurrence of symptoms of either pole. As to the antimanic efficacy, modern parallel-group designed trials have confirmed earlier positive findings. However, due to the narrow therapeutic index requiring blood monitoring and due to a relatively late onset of action, which is related to the safety issues, lithium monotherapy generally has a limited place in the acute treatment of more severe manic states. For acute bipolar depression, there are conflicting results, in particular due to recent industry-generated studies showing no advantage of lithium over placebo. The well-documented beneficial role of add-on lithium in unipolar depressive patients insufficiently responding to antidepressants confirms some antidepressant potentials of lithium. Recent long-term trials have added substantially to the documentation of the long-term stabilizing properties of lithium in bipolar disorder. In particular, it has now been shown, that lithium is efficacious as maintenance treatment independently of any acute response to the drug. It has also been convincingly demonstrated that lithium not only prevents mania, but also depression in bipolar disorder. This is in accordance with earlier studies showing that lithium also acts preventive in recurrent major depressive disorder. It is still debated whether lithium has a specific anti-suicidal effect beyond its recurrence preventive effects. Beyond the beneficial clinical effects, lithium has multiple unwanted clinical effects involving other organ systems than the CNS. However, when lithium treatment is properly and skilfully managed and monitored, the more serious effects can be avoided.

GENETIC MODULATION OF LITHIUM SENSITIVITY

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Bipolar mood disorder, or manic-depression, is a major psychiatric illness treated using mood stabilizer drugs such as lithium (Li+) and valproic acid (VPA). Although triggered by lifetime events, there is a strong genetic risk of developing bipolar disorder, however this is a complex trait and no consensus candidate genes have yet emerged from studies in individual family studies. An alternative investigative approach is to seek insight from the therapeutic mechanisms of the mood stabilizer drugs. Li+, the most widely used mood stabilizer, is an effective prophylactic agent with both anti-manic and anti-depressant properties. Li+ treatment reduces inositol synthesis and suppresses inositol phosphate (IP) based signalling, suggesting that attenuation of IP signalling could modify the neurological processes underlying bipolar mood disorder. Consistent with this hypothesis, the structurally unrelated mood stabilizers VPA and carbamazepine also deplete inositol, indicating a broader association between mood stabilizers and IP signalling (1). To understand why Li+ is an effective therapy, we are using the social amoeba Dictostelium as a model system. Li+ has a strong effect on Dictostelium chemotaxis due to reduced PI3P signalling (2). This both pinpoints an alternative signalling system targeted by Li+ and provides a useful phenotype for further genetic analysis. Elevated expression of the inositol monophosphatase gene, impA1, confers Li+ resistance and elevates PI3P synthesis in response to chemotactic signals, indicating that the effects of Li+ ultimately arise via reduced inositol production. A genetic screen for altered Li+ sensitivity identified a lithium resistant mutant, lisA, that leads to elevated IP signalling. LisA encodes the Dictostelium orthologue of the serine protease prolyl oligopeptidase (PO). We have established that PO acts to control modulate IP signalling via changes in expression of the inositol biosynthetic and metabolic genes (3). We have pursued this mechanism further, and I will report on a new class of Dictostelium mutants with chemotaxis phenotypes that are “cured” by Li+ treatment. 1. Williams et al (2002) Nature 417: 292-295. 2. King et al. (2009) Disease Models & Mechanisms 2: 306-312. 3. King et al (2010) PLOSone (in press)
S34

TARGETING NETWORKS, AKT/GSK3 SIGNALLING IN THE ACTIONS OF MOOD STABILIZERS

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Psychotropic drugs acting on monoamine neurotransmission remain the principal form of pharmacological treatments for neuropsychiatric conditions such as schizophrenia, depression, ADHD and bipolar disorder. Several lines of research involving behavioural and biochemical approaches in normal and/or genetically modified mice provide evidence for an involvement of the protein kinases glycogen synthase kinase-3 (GSK3) and Akt in the behavioural functions of dopamine and serotonin (5-HT). These kinases have also received attention for their role in the actions of psychoactive drugs including lithium, antidepressants and antipsychotics. Furthermore, investigations of the mechanism by which D2 dopamine receptors regulate Akt/GSK3 signalling strongly support the physiological relevance of a new modality of G protein-coupled receptor (GPCR) signalling involving the multi-functional scaffolding protein beta-arrestin 2. Here we provide an overview of how this dual function of components of the GPCR desensitization machinery relates to the mechanism of action of mood stabilizers and summarize recent insights into the relevance of the Akt-GSK-3 signalling cascade for the etiology of bipolar disorders.

S35

TRANSLATIONAL STUDIES ON THE EFFECTS OF LITHIUM

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INTRODUCTION Magnetic resonance techniques are well established, having provided innumerable insights in the field of neuroscience. Harnessing the magnetic resonance ph- nomenon can yield structural images of exquisite detail, allow inferences to be made about brain function and enables the chemical composition of human tissues to be examined in vivo. In translating preclinical findings to human studies, magnetic resonance techniques are invaluable --- in the case of lithium, caution must be advised. Substantial amounts of preclinical data support the notion that lithium interacts with dopaminergic systems to bring about its effects on mood and cognition. Decades of clinical research implicate dysfunction of such systems in the affective disorders, most notably the manic presentations of bipolar disorder. Through its actions on potentially related pathways, lithium is now considered to have neuroprotective effects. Whether these effects can be established in humans remains a matter for debate. METHODS MRI studies were conducted at Newcastle Magnetic Resonance Centre using normal human participants and a 3T scanning system. We applied a methamphetamine model of mania in a placebo-controlled study of lithium, investigating its effects on neuropsychological and fMRI parameters. A variety of structural and quantitative scans were performed, with the intention of investigating the effects of lithium on grey matter volumes. All studies were approved by a local Ethics Committee. RESULTS Lithium appears to attenuate the effects of methamphetamine, diminishing BOLD contrast brain regions innervated by dopamine. Its effects on brain structure are sensitive to the analysis algorithm applied, in a manner that suggests an alternative explanation to the grey matter volume change. CONCLUSIONS Dopaminergic theories of lithium's action are largely upheld when translated into human studies. The neuroprotective effects of lithium have yet to be convincingly demonstrated in clinical studies, in large part due to the complex interaction between lithium and the magnetic resonance phenomenon.

MA01

INFLAMMATORY AND NEUROTROPHIC FACTORS UNBALANCED IN LEUKOCYTES OF FIRST EPISODE PSYCHOSIS PATIENTS

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Introduction: stress is known to play an important role in psychotic illnesses, and literature has shown that stressful life events have a determining role in their pathogenesis of the illness. With the aim to better clarify the molecular pathways involved, we have used peripheral blood leukocytes strongly support the physiological relevance of a new modality of G protein-coupled receptor (GPCR) signalling involving the multi-functional scaffolding protein beta-arrestin 2. Here we provide an overview of how this dual function of components of the GPCR desensitization machinery relates to the mechanism of action of mood stabilizers and summarize recent insights into the relevance of the Akt-GSK-3 signalling cascade for the etiology of bipolar disorders.

Background: the study of brain structure in schizophrenia has attracted increasing interest, because of the suggested progression of brain structural abnormalities. The aim of this study is therefore to investigate the association between amygdala volume, childhood trauma and cognitive function. Conclusions: our data demonstrate that first-episode psychosis is associated by amygdala volume reduction compared to age and gender matched non-psychotic controls. Furthermore, patients with psychosis have increased incidences of childhood trauma, and childhood trauma again is linked to amygdala volume abnormalities and cognitive impairments. The aim of this study is therefore to investigate the association between amygdala volume, childhood trauma and cognitive function. Conclusions: our data demonstrate that first-episode psychosis is associated by amygdala volume reduction compared to age and gender matched non-psychotic controls. Furthermore, patients with psychosis have increased incidences of childhood trauma, and childhood trauma again is linked to amygdala volume abnormalities and cognitive impairments.

Conclusion: These results suggest an altered balance between brain protective factors like BDNF and pro-inflammatory biomarkers that in turn, regulating apoptotic mechanisms and neuronal survival, could contribute to the development of psychosis and its associated brain structural abnormalities.
MA02

PSYCHOTIC SYMPTOMS, HPA AXIS AND STRESS IN FIRST EPISODE OF PSYCHOSIS

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Introduction. Stress is known to play an important role in psychotic illnesses, and literature has shown that stressful life events have a determining role in their clinical course. Psychosis has been associated with abnormalities in hypothalamic-pituitary-adrenal (HPA) axis, namely elevated levels of daytime cortisol—the main hormone involved in the stress response—and a blunted cortisol awakening response (CAR). Furthermore, while healthy controls showed increasing levels of daytime cortisol with a higher number of stressful life events, patients with psychosis were characterized by an opposite relationship. Literature showed there is a relationship between HPA axis function and different patterns of clinical symptoms but findings have been inconsistent: some authors found correlations with negative symptoms, while others reported associations with depressive, disorganized or positive symptoms. Investigating these associations among patients at their first episode of psychosis (FEP) can reduce the incidence of bias due to progression of illness or prolonged drug treatment. Aim of the present study is to investigate the relationships between stress, HPA axis activity and psychotic symptom dimensions. Methods. Sixty-six subjects with FEP (mean age 30.1 ±8.8, 39.4% females) were recruited from the South London and Maudsley (SLAM) NHS Foundation Trust, as part of the Genetic and psychosis Study. Symptoms dimensions were investigated using OPCRIT and PANSS, while stressful events were assessed using the Brief Life Events Questionnaire. Salivary cortisol was collected at awakening, at 15, 30, 60 minutes after awakening and at noon and 8pm. CAR and diurnal cortisol were measured as areas under the curve. Pearson, Spearman and partial correlation analyses were used as appropriate. Results. CAR negatively correlated with negative symptoms measured with OPCRIT (R=-0.26; p=0.048). Unexpectedly, diurnal levels of cortisol showed negative correlations with positive (R=-0.30; p=0.044) and excited (R=-0.30; p<0.034) dimensions measured with PANSS. Moreover, the number of stressful life events positively correlated with PANSS positive and excited dimensions (R=0.48; p<0.001 and R= 0.32; p=0.022 respectively) and OPCRIT positive dimension (R=0.26; p=0.048). When adjusting for the number of stressful life events diurnal cortisol was not correlated with symptom dimensions any longer. Conclusions. Our findings suggest that blunted CAR is partly explained by the severity of negative symptoms. In contrast, the high cortisol levels during the day seem not to be explained by either stressful events or psychotic symptoms, as previous models suggested. Further longitudinal studies would be needed to clarify the complex interplay between these factors and potential causal relationships.

MA03

IS THERE A LINK BETWEEN AMYGDALA VOLUME, COGNITIVE FUNCTION AND CHILDHOOD TRAUMA IN FIRST-EPISTODE PSYCHOSIS?

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Background: Considerable evidence suggests that the human amygdala plays an important role in higher cognitive functions in addition to its well known role in emotional processing. Moreover, abnormal amygdala volume has been reported in patients with psychosis, and cognitive impairments are one of the core features in psychosis. Furthermore, patients with psychosis have increased incidences of childhood trauma, and childhood trauma again is linked to amygdala volume abnormalities and cognitive impairments. The aim of this study is to investigate the association between amygdala volume, childhood trauma and cognitive function in first-episode psychosis. Methods: We recruited 87 patients with first-episode psychosis (mean±age:27.2±8.0; gender: 64% males), and 63 controls (age: 28.0±7.7 yrs; gender: 41% males) as part of the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study. MRI scans were acquired with a GE Sigma 1.5-T system. The whole brain was scanned with a 3D inversion recovery prepared fast spoiled GRASS (SPGR) T1-weighted sequence. The images were acquired in the coronal plane with 1.5 mm contiguous sections. TR was 13.8 ms, TI was 450 ms, TE was 2.8 ms, and the flip angle was 20°, with one data average and a 256 × 256 × 128 pixel matrix. The MRI images were transferred to a Sun workstation and displayed using DISPMI image display software. Regions of interest were outlined using a mouse-driven cursor. DISPMI automatically calculated the area of the region marked which was multiplied by the voxel dimensions to give the volume in mm3. Furthermore, all participants underwent standardised neuropsychological test battery to assess general cognition, memory, processing speed, executive function, visuo-spatial abilities, verbal intelligence, and language. Moreover, in a subsample of the patients (N=46) information of childhood trauma was available from the Childhood Experience of Care and Abuse Questionnaire (CECA-Q). Chi-square test was used to compare categorical variables between patients and controls. ANCOVA was used to compare amygdala volume between patients and controls covaried for total brain volume. Furthermore, partial correlation was conducted investigating amygdala volume and cognitive function, corrected for total brain volume. Lastly, a separated correlation analysis was performed investigating childhood trauma, amygdala volume and cognitive function. Results: As expected, patients scored significantly worse on all the cognitive tasks presented compared to controls (p<0.05). Moreover, we found a significant (p<0.05) reduction of amygdala volume (~4%) in first-episode psychosis compared to controls. Further, amygdala volume was significantly (p<0.05) positively correlated with cognitive performance in the patients, indicating that a more “normal” amygdala volume was related to better cognitive function. In the patients significant (p<0.05) correlation was also observed between childhood trauma and cognitive impairments, together with a significant (p<0.05) negative correlation between childhood trauma and amygdala volume. However when investigating childhood trauma and cognition, controlling for amygdala volume, no correlations were longer detected between childhood trauma and cognitive function. Conclusions: Our data demonstrate that first-episode psychosis is associated by amygdala volume reduction compared to age and demographically matched control group. Moreover, our data indicate a complex relationship between amygdala volume and cognitive function, together with childhood trauma exposure in the first-episode psychosis.
MA04

ARIPIPRAZOLE: TWO YEAR OUTCOMES IN A RETROSPECTIVE, NATURALISTIC STUDY

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Introduction: The efficacy of aripiprazole has been examined in randomized controlled trials. The aim of this study was to investigate the drug’s effectiveness in a clinical setting, using two year outcomes in schizophrenia or schizoaffective disorder. Methods: All patients prescribed aripiprazole in an acute mental health trust between July 2004 and January 2007 were identified from pharmacy records. Data were collected by retrospective case note review. Subjects were categorized either as those remaining on aripiprazole at two years, designated “continuers”, or individuals who had discontinued treatment. Patients’ treatment histories were reviewed to determine whether or not they had previously received clozapine. Results: 143 patients received aripiprazole. Of these, 32 were prescribed it for indications other than schizophrenia or schizoaffective disorder and 14 received aripiprazole as an augmentation strategy with clozapine and were therefore excluded. A further five patients were lost to follow up. Thus, data were available for 92 patients, 27 (29%) of whom remained on treatment at 2 years. The most common reason for treatment discontinuation was lack of response, accounting for 36 subjects (39%, n=92). Ten of these patients received aripiprazole for fewer than 42 days, whilst 16 had previously been treated with clozapine. Patients treated with clozapine were no more likely to discontinue aripiprazole than those who had not (p=0.81, Fisher's Exact test, n=92). Of the remaining patients, 16 (17%, n=92) discontinued due to adverse effects, 10 (11% n=92) refused, and 3 (3% n=92) discontinued due to other reasons. Conclusion: The percentage of patients discontinuing aripiprazole within 2 years was comparable to that seen with risperidone long-acting injection (RLAI) in a similar naturalistic study (Deslandes et al., 2009 Int J Psychiatry Clin Pract. 13(4): 298-302). The most common reason for aripiprazole discontinuation was lack of response, which accounted for 36 patients. Of these, 26 might have been expected to show a poor response either due to an inadequate treatment trial, (duration <42 days), or previous use of clozapine, suggesting treatment resistance. Interestingly, prior treatment with clozapine did not appear to be associated with increased discontinuation overall. Discontinuation due to adverse effects accounted for 17% of patients treated with aripiprazole, compared with 10% seen in the naturalistic study of RLAI. However, a significant proportion of aripiprazole discontinuations occurred early in treatment, perhaps as a result of the switching strategy employed on initiation. Sources of funding: This work was conducted by NHS staff as part of their normal duties, no external funding was received. Acknowledgements: The authors thank Mrs W. Davies for the opportunity to conduct this work.

MA05

LARGE EFFECT OF BASELINE TREATMENT WITH LONG-ACTING ANTIPSYCHOTIC DRUGS ON RANDOMISED TREATMENT OUTCOMES

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Introduction: In the CUiLASS 1 Trial (Jones et al 2006 Arch Gen Psych 63, 1079-1087) patients with an inadequate clinical response or intolerance were randomised to either a first generation antipsychotic (FGA) drug or a (non-clozapine) second generation antipsychotic (SGA) with assessments at baseline, 12, 26 and 52 weeks following randomisation. The primary outcome was quality of life (QOL) measured using the QLS, with secondary outcome measures including symptoms (PANSS), depression (CDSS), overall functioning (GAF), drug attitude (DAI) and adherence (Kemp). Non-neurological side effects (ANNERS) and neurological side effects (Simpson-Angus, AIMS, Barnes) were also assessed. Would outcome during the course of the trial be affected by the delivery route of the antipsychotic drug prescribed at trial entry? Methods: Forty per cent (N=90) of the 227 patients entering the CUiLASS 1 Trial were being treated with a depot FGA antipsychotic prior to randomisation. Results: Fitting multi-level mixed-effects models using Stata 11 and including demographic variables and baseline attitudes to medication as predictors showed that: 1. QLS was significantly reduced (-5.7 points; CI -10.1, -1.4) at final visit in those receiving depot before randomisation. There was no significant difference in this effect between those who were randomised to first or second generation antipsychotics during the trial. 2. The same pattern of results held for PANSS total score and GAF. 3. Modelling centre as a separate level had little effect on coefficients of baseline covariates. 4. Baseline DAI score indicating adherent attitudes predicted better outcome on all three measures (p<0.001). Conclusions: Participants randomised from depot medication at baseline had a significantly worse one-year outcome regardless of subsequent allocation to FGA or SGA than those taking oral medication at baseline. This may be due to reduced adherence. Once participants were randomised into the study, adherent attitudes were predictive of outcome. The effect was present whether the patient was randomised to a first or second generation antipsychotic during the course of the trial.

MA06

LOW VIOLENCE RATES ON PICU DESPITE REDUCTION IN USE OF COMBINATION OR HIGH-DOSE ANTIPSYCHOTIC PRESCRIBING.

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Introduction NICE guidelines regarding the management of schizophrenia, bipolar affective disorder and disturbed/violent behaviour do not support the use of high-dose or combination antipsychotic prescribing regimens. However, such practice is not uncommon in the management of psychiatric inpatients in the UK, and management of disturbed behaviour is the usual reason given for it (Paton et al. 2008 British Journal of Psychiatry 192 (6); 435-9). Psychiatric intensive care units (PICU) are designed for the management of patients in an acutely disturbed phase of a serious mental disorder who pose a high risk of violence. ES1 is a PICU serving an inner-city population in SE London and over the past 4 years efforts have been made to minimise the use of high-dose and combination antipsychotic prescribing by utilising alternative strategies such as staff-training, de-escalation, seclusion and relying on benzodiazepines and/or promethazine for PRN use and rapid tranquilisation. We report the results of a service evaluation which aimed to determine whether a reduction in the use of combination/ high-dose antipsychotic prescribing was achieved, and if so, whether this led to an increase in the rate of violence on the ward and the use of seclusion. Methods Antipsychotic prescribing data was obtained with permission, from the POMH-UK study (Paton et al. 2008 British Journal of Psychiatry 192 (6); 435-9). Data on violence and the use of seclusion were obtained from ward audit records. Results 392 patients were admitted in the study period- 105 in 2006, 94 in 2007, 94 in 2008 and 99 in 2009. All were male. 69% were black, 27% were white and 3% were Asian. The most common diagnoses were paranoid schizophrenia (50%), bipolar affective disorder (23%) and schizo-affective disorder (16%). The rate of antipsychotic polypharmacy fell from 66% to 13% during the study period. The rate of high-dose antipsychotic prescribing fell from 58% to 0%. There was no increase in the use of supervised confinement and the assault rate fell each year from 1.8 (2006) to 0.5 (2009) assaults per patient admitted per year. Conclusion Despite a reduction in the rate of high-dose and combination antipsychotic prescribing there was a dramatic decrease in the rate of assault during the period studied. This was achieved without an increase in the use of seclusion. Our results suggest that violent behaviour can be managed effectively on a PICU without the use of high dose/combination antipsychotic strategies.
MA07

A QUALITY IMPROVEMENT PROJECT TO IMPROVE THE ASSESSMENT OF SIDE EFFECTS IN PATIENTS PRESCRIBED DEPOT ANTI PSYCHOTIC MEDICATION

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Antipsychotic drugs are associated with a diverse range of unpleasant, disabling and potentially harmful side effects. Some of these, such as weight gain, movement disorders and sexual problems, may negatively impact on medication adherence and therefore mental health, whereas others such as impaired glucose tolerance and dyslipidaemia may go unnoticed by a patient but have serious consequences for physical health. Thus, detection and treatment of remediable side effects may improve treatment outcome. The Prescribing Observatory for Mental Health (POMH) invited mental health NHS Trusts to participate in a quality improvement programme to improve the quality of assessment of side effects in patients prescribed a depot antipsychotic. Such patients have regular contact with health professionals when receiving their injections, providing an opportunity for routine monitoring of side effects. A baseline clinical audit in October 2008 measured prescribing practice against the following audit standard: all patients should have a review of side effects at least once each year. Following the audit, each Trust received detailed, benchmarked data, allowing comparison of Trust and clinical team prescribing practice with that of other participating Trusts nationally. In addition, an educational slide set that allowed raising awareness of antipsychotic side effects was made available. Re-audit was conducted 15 months later. Data were submitted at baseline for 5,804 patients from 500 clinical teams in 38 Trusts, and, at re-audit, for 5,037 patients from 392 clinical teams in 35 Trusts. At baseline, examining clinical records over the past year revealed a general statement that side effects were present or not present in 54% of cases. A physical examination related to side effects had been documented in 11%, blood tests in 12%, body weight or body mass index (BMI) in 27%, and assessment for extrapyramidal side effects in 31% and sexual side effects in 9%. A systematic checklist or rating scale had been used in 12% of cases. The respective figures at re-audit were 56%, 19%, 31%, 21%, 34%, 15% and 17%. Although all the changes seen between baseline and re-audit are positive, a gap remains between documented practice and the audit standard. The baseline audit figures were the same when the data for Trusts that did not participate at re-audit were removed. There was marked variation between Trusts which was more apparent at re-audit than at baseline. Therefore, for many patients, potentially remediable side effects from antipsychotic drugs may go undetected, and therefore untreated, despite frequent contact with a healthcare professional.

MA08

ALPHA-7 NACHR AGONISTS OR POSITIVE ALLOSTERIC MODULATORS DO NOT REVERSE MK-801-DISRUPTED PPI OF ACOUSTIC STARTLE IN RAT

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General psychosis is characterised by positive, negative and cognitive symptoms, but also by sensorimotor gating deficits. Prepulse inhibition of acoustic startle (PPI), a measure of sensorimotor gating, is a generally used translational tool to screen for antipsychotic properties of experimental compounds. Psychostimulants acting on the glutamatergic (e.g. MK-801) or the dopaminergic system are used to induce schizophrenia-like symptoms in rodents: these drugs have been shown to disrupt PPI while having only minor effects on the startle response per se. Several lines of evidence support a role for the alpha7 nicotinic acetylcholine receptor (α7-nAChR) in learning and memory, and the prototypic non-selective agonist nicotine has been shown to enhance cognition in a number of animal models. Selective α7-nAChR agonists have also been shown to normalise sensory gating deficits in animal models. Nicotine reversed sensorimotor gating deficits induced by dopaminergic stimulation without affecting disruption by glutamatergic stimulation (Suemara 2009, Br J Pharmacol 142:843), Dunlop (2009, JPET 328:766) showed reversal of MK-801-disrupted PPI in Long Evans rats by the α7-nAChR partial agonist SSR-180711. Following treatment with α7-nAChR modulator drugs (SSR-180711 (1.25-20 mg/kg), PNU-120596 (2.5-40 mg/kg) PNU-282987 (1.25-20 mg/kg), AR-R17779 (1.25-20 mg/kg), NS-1738 (1.25-20 mg/kg), nicotine (0.08-1.25 mg/kg)) and MK-801 (0.1 mg/kg sc) (30 and 15 min before test respectively), Wistar rats were placed in a startle chamber with a background white noise (65 dB). The session began with a 5-minute habituation period, followed by 10 startle alone pulses (120 dB) to habituate the animals. Three pre-pulse intensities of 69, 75 or 81 dB were delivered alone and in combination with the startle alone pulse. All trial types were presented 9 times in a pseudo-random order and responses were collected over a 20 minute period. Robust PPI levels were observed in control groups while consistent disruption of PPI was seen at all pre-pulse intensities after MK-801 challenge (rm-ANOVA: all p<0.01). None of the tested α7-nAChR modulators improved MK-801-disrupted PPI after oral or subcutaneous administration (all p>0.05). Risperidone (0.31 mg/kg) reversed the MK-801-induced deficit in this model (all p<0.01). Effects on startle response were measured following SSR-180711 (20 mg/kg, 1w-ANOVA: p<0.001) or nicotine (starting at 0.08 mg/kg, p<0.05) treatments. In addition, we were also unable to replicate reversal effects of SSR-180711 in Long Evans rat using exactly the same conditions according to Dunlop. In conclusion, these data suggest that activation of α7-nAChR does not affect MK-801 induced PPI-deficit in this rat model.

MA09

THE ALPHA-7 NICOTINIC ACETYLCHOLINE RECEPTOR AGONIST PNU 282987 DOES NOT IMPROVE VIGILANCE IN MICE AS ASSESSED IN THE 5-CHOICE CONTINUOUS PERFORMANCE TEST: CONTRASTING RESULTS WITH NICOTINE

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Introduction: Impaired attention/vigilance is commonly observed in several neuropsychiatric disorders, including schizophrenia, bipolar disorder, attention deficit hyperactivity disorder, and Alzheimer’s disease. Recognising that vigilance is commonly assessed in humans using the continuous performance test (CPT), which includes target and non-target stimuli, we developed the 5-choice continuous performance test (5C-CPT) for use in mice to assay putative pro-vigilance drugs. Nicotine improves vigilance in several of these disorders as well as normal subjects in the CPT, but exerts undesirable side-effects. Identifying the mechanism of nicotine-induced improvement in vigilance would provide a target for developing a drug with an improved therapeutic profile. Methods: We used the 5C-CPT to assay the effects of nicotine and the alpha7 nicotine acetylcholine receptor (nAChR) agonist PNU 282987 on vigilance performance in mice. Two cohorts of mice were trained to perform the 5C-CPT. Once stable, performance was challenged over 250 trials with variable stimulus durations (vsD; 0.75, 1.25, and 2.5 s). During these challenges, nicotine (0, 1, 10, and 100 μg/kg) and PNU 282987 (0, 3, 10, and 30 mg/kg) were administered in a four-day subchronic design. Results: Nicotine improved vigilance as measured by d prime (F(3,42)=3.2, p<0.05), primarily due to an increased hit rate (F(3,42)=5.1 p<0.005). No effects on other measures were observed. A PNU 282987 by vsD interaction was observed (F(6,70)=2.4, p<0.05), driven by a trend toward increased false alarm responding at 30 mg/kg during longer stimulus durations (F(2,18)=3.2, p<0.05). No other effects were significant. Conclusion: Nicotine improves vigilance in normal mice in the 5C-CPT, consistent with human CPT performance. These data provide further support of the cross-species translational validity of the 5C-CPT. This nicotine-induced improvement in vigilance was driven by an increased hit rate, also consistent with humans. Stimulation of alpha7-nAChRs via PNU 282987 administration did not however affect vigilance performance. Therefore at the doses tested, PNU 282987 does not exert a nicotine-like effect on vigilance. Although these doses are effective in other paradigms, further doses of PNU 282987 should be explored. Moreover, the effects of PNU 282987 have yet to be studied in putative animal models of neuropsychiatric disorders. The development of this assay in mice allows genetic as well as pharmacologic models of such disorders to be utilized when evaluating the effects of PNU 282987. These studies were funded by R21-MH085221 as well as by a NARSAD Young Investigators Award (JWY)
MA10

NICOTINIC AGONISTS BUT NOT CLOZAPINE OR LY404039 INCREASE KETAMINE-INDUCED DEFICITS IN A RODENT ODOR SPAN TASK

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Background The NMDA receptor antagonist ketamine produces cognitive deficits in humans including attention and memory. Previous studies using a variety of cognitive tasks have shown nicotine can enhance performance in normal non-compromised rodents. This study aimed to develop a rodent model of cognitive deficits using ketamine to assess the ability of nicotinic agonists and clinically-effective antipsychotic agents (clozapine and the novel mGlu2/3 agonist LY404039) in restoring these deficits using a rodent model of non-spatial working memory; the odor span task (OST). Methods Two cohorts of 24 and one cohort of 12 male hooded Lister rats were trained in the OST; this task involved identification of a novel odour from an increasing number of presented odours, until demonstrating asymptotic performance. Sub-chronic exposure to ketamine (10 or 30mg/kg IP) or vehicle daily for 5 consecutive days produced a dose-dependent impairment in the OST (p<0.001), replicable across the 3 studies and found to be stable over 10 weeks. Analyses were carried out using 2-way ANOVA for repeated measures, followed by Bonferroni post-hoc tests where appropriate. Results Tested acutely, nicotine (0.05 and 1.0mg/kg) and the alpha 7 selective agonist PHA543613 (1 and 3 mg/kg) improved performance in ketamine-treated animals (p<0.001:p<0.05), with nicotine restoring performance in ketamine-treated animals and also improving control subjects; the largest effect following 0.05mg/kg nicotine (p<0.001). Despite improving performance in ketamine-treated subjects, PHA543613 did not fully restore baseline OST performance. There was also evidence of an impairment following all doses of PHA543613 in control animals (p<0.05). The antipsychotics, LY404039 (0.3, 1, 3 and 10mg/kg) and clozapine (1, 3 and 10mg/kg) failed to reverse ketamine-induced deficits (p=0.07:p=0.1) in a dose that otherwise impaired OST performance in control animals (p<0.01). Conclusions These data suggest that the sub-chronic ketamine regimen employed in the OST may be useful in examining novel treatments to restore cognitive impairments associated with neuropsychiatric disorders such as schizophrenia. More importantly, this study highlights the role of neuronal nicotinic receptors, particularly the alpha 7 subtype as a viable target for such an intervention. This approach could be exploited further by the assessment of a novel series of type 1 and II alpha 7 allosteric modulators in restoring ketamine-induced deficits. This work was funded by Johnson and Johnson, Belgium.

MA11

ACTIVATION OF A7 NICOTINIC RECEPTORS IMPROVES PHENCYCLIDINE-INDUCED DEFICITS IN COGNITIVE TASKS IN RATS: IMPLICATIONS FOR THERAPY OF COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

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Introduction: Nicotinic a7 acetylcholine receptors (nAChRs) have been highlighted as a target for cognitive enhancement in schizophrenia (Gray & Roth, 2007, Schizophrenia Bulletin, 33: 1100-1119). In this manuscript, we have consistently shown that a sub-chronic phenylcyclidine (PCP) dosing regime in adult female rats produces robust, long lasting cognitive deficits (Grayson et al., 2007, Behavioural Brain Research, 184: 31-38; McLean et al., 2008, Behavioural Brain Research, 189: 152-158; McLean et al., 2009, European Neuropsychopharmacology, 19: 440-450). The aim of this study was to investigate whether the deficits induced by sub-chronic PCP in reversal learning and novel object recognition could be attenuated by the selective a7 nAChR full agonist, PNU-282987. Methods: Adult female hooded-Lister rats received sub-chronic PCP (2 mg/kg) or vehicle i.p. twice daily for seven days, followed by 7-days washout. In cohort 1, PCP-treated rats then received PNU-282987 (5, 10, 20 mg/kg; s.c.) or vehicle and were tested 1 hour later in the reversal learning task. In cohort 2, PCP-treated rats received PNU-282987 (10 mg/kg; s.c.); 1 hour pre-treatment for 15 days and were tested in the novel object recognition test on day 1 and on day 15, to test for tolerance. Reversal learning data was analysed by a one-way ANOVA followed by post-hoc Dunnett’s t-test. Data for the novel object task i.e. time at the novel versus familiar objects were analysed using paired t-tests, and the discrimination indices and line crossing data were compared using a one-way ANOVA followed by post-hoc Dunnett’s t-test. Results: Sub-chronic PCP produced significant deficits in both cognitive tasks (P<0.01:0.001). PNU-282987 attenuated the PCP-induced deficits in reversal learning at 10 mg/kg (P<0.01) and 20 mg/kg (P<0.001), and in novel object recognition at 10 mg/kg on day 1 (P<0.01) and on day 15 (P<0.001). Conclusions: These data show that PNU-282987 has efficacy to reverse PCP-induced deficits in two paradigms of relevance to schizophrenia. Results further suggest that 15 day once daily dosing of PNU-282987 (10 mg/kg s.c.) does not cause tolerance in the rat. This study suggests that activation of a7 nAChRs may represent a suitable strategy for improving cognitive deficits of relevance to schizophrenia. S McLean was funded by a GSK postgraduate studentship and this study was partially funded by Johnson and Johnson.

MA12

DOPAMINE D2-RECEPTOR MODULATION OF SPOONTANEOUT, DIRECT BEHAVIOUR: IMPLICATIONS FOR SCHIZOPHRENIA AND ADHD

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Dopamine has multiple functions, modulating behaviour at the level of sensory input, information integration and motor expression (Schultz 2007 Annu. Rev. Neurosci. 30, 259-288 for review). The different dopamine receptors have previously been shown to subserve differential roles across such behavioural measures. In this study we investigated the role of dopamine D2 receptors (DRD2) during different aspects of behavioural control. DRD2 are implicated in both schizophrenia and ADHD development. For example, sulpiride (an antagonist primarily of DRD2 ) is commonly used as a neuroleptic in the treatment of schizophrenia, and methylphenidate, a psychostimulant used in the treatment of ADHD, may also act via DRD2. Using the SSR (stop signal reaction time) task, we investigated the effects of systemic sulpiride and therefore the significance of the DRD2 system over a number of behavioural measures including trial initiation, signal processing and general motor competency. We also investigated the potential role of DRD2 to mediate effects of systemic methylphenidate (1 mg/kg) on sensory input, information integration and motor expression, using a low dose of sulpiride (20mg / kg). To further assess the role of systemic methylphenidate (2mg / kg) in initiation-type behaviour we introduced a range of foreperiods into the task (500, 2000 and 4000ms), which are known to speed motor response times. Results: Trial initiation was significantly impaired in a dose-dependent manner by sulpiride [F(2, 38)=12, p<0.0002], whilst signal processing [F(4, 71)=0.6, p<0.7] and general motor competency [F(2.5, 58)=0.8, p<0.5] were unaffected. Methylphenidate (1 mg/kg) speeded initiation [MPH vs vehicle: F(1, 23)=17, p<0.0005]. Sulpiride (20 mg / kg) partly antagonised this initiation-speeding effect of MPH [Sulpiride/MPH vs Vehicle/Vehicle: F(1, 23)=3.5, n.s.]. Foreperiod significantly reduced initiation [F(2, 37)=23, p<0.00001] and methylphenidate (2mg / kg) further speeded initiation at each interval used: 500ms [MPH vs vehicle: F(1, 21)=34, p<0.00001], 2000ms [F(1, 22)=12, p<0.0033], 4000ms [F(1, 23)=27, p<0.00003]. Summary: Trial initiation is highly sensitive to dopaminergic manipulations, whereas other standard performance measures are not affected in a normal population of rats. The DRD2 system is key to modulating trial initiation behaviour, without having any gross motor effect, or impacting on signal processing. In psychiatric conditions where hyper-arousal is diagnosed, it is likely that DRD2-mediated drugs operate in a significant manner through their effects on initiation.
MA13

ENHANCED LATENT INHIBITION AFTER HALOPERIDOL MICROINJECTION IN SHELL, BUT NOT CORE, OF THE NUCLEUS ACCUMBENS; COMPARISON WITH THE EFFECTS OF 6-HYDROXYDOPAMINE

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Introduction: Latent inhibition (LI) refers to the process whereby non-reinforced pre-exposure to a stimulus retards subsequent learning of an association with that stimulus. LI can be abolished or enhanced by lesions to nucleus accumbens (NAc). Relatedly, the role of the distinct NAc subregions and mediation via inhibitory versus excitatory dopamine (DA) receptor subtypes is not firmly established. We have found that reduced DA function produced by 6-hydroxydopamine injection within the medial shell leads to enhanced LI under conditions that disrupt LI in controls (few pre-exposures). Here we tested whether haloperidol (0.5μg in 0.5μl) micro-injected bilaterally at coordinates targeted on shell but not core NAc would similarly enhance LI. Methods: Guides cannulae were implanted under general anaesthesia using coordinates adapted from the 6-hydroxydopamine lesion study, positioned 2mm dorsal to the shell and core injection sites. After a minimum of 1 week to recover, rats were water deprived and placed to drink in their allocated conditioning boxes for a total of 5 days. LI was subsequently measured in a threestaged motivated conditioned emotional response procedure. Rats in the LI groups received 10 pre-exposures of a noise stimulus; behavioural control groups received equivalent box exposure. On the next day there were 2 noise-shock conditioning trials. Conditioning was followed by reshaping and test sessions on each of the following days, to re-establish drinking and to determine the level of conditioned fear in the different groups. Haloperidol was administered by micro-injection, 15 min prior to conditioning sessions only. Half the controls were injected with saline at shell coordinates and half were injected at core coordinates. Results: LI was demonstrated as reduced suppression in the pre-exposed compared to the non-pre-exposed group when haloperidol was injected in shell, t(21)=2.3, p<0.05; this effect amounted to an enhancement relative to the corresponding saline-injected control group in which the LI effect was insignifcant, t(9)=1.54. LI was similarly insignificant after haloperidol injection in core, t(21)=1.24; however saline injection at core coordinates left LI intact, t(9)=3.12, p<0.05. Conclusions: Similar to the effects of 6-hydroxydopamine, haloperidol enhanced LI when injected in shell but not core. Together these results underscore the dissociable roles of core and shell subregions of the NAc in mediating the expression of LI and suggest that specifically reduced activity at DA D2-like receptors within the medial shell leads to enhanced LI. Although these experiments with few pre-exposures were not standard to test for LI abolition, haloperidol and 6-hydroxydopamine in core attenuated LI. Thus reducing the actions of DA within NAc produces the opposite pattern of results to that obtained with electrolytic and excito-toxic lesions to shell versus core (Weiner, 2003, Psychopharmacology, 169, 257-297). This work was supported by the Wellcome Trust (ref. 082940).

MA14

ATTENUATION OF D-AMPHETAMINE-INDUCED DISRUPTION OF CONFLICT RESOLUTION BY CLOZAPINE IN RATS

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The stroop task can be viewed as a conditionally instructed discrimination paradigm and is highly sensitive to prefrontal cortex dysfunction. Haddon and Killcross (2006, J. Neurosci., 26(1):2933–2940) developed an operant task for rats which is analogous to the response conflict demonstrated by the stroop task. Previous research has shown that disruption of forebrain dopamine systems impairs the use of high-order information to guide goal-directed performance, and that this deficit may be related to impaired use of task-setting cues in patients with schizophrenia. The main aim of this study was to test this hypothesis by examining the effects of acute d-amphetamine administration and/or the atypical antipsychotic clozapine on the contextual control of response conflict in rats. Sixteen male lyster hooded rats were trained on two biconditional discrimination tasks - one auditory and one visual, each trained in contextually distinct operant chambers. At test, compounds of the auditory stimuli are presented that signal either the same (congruent) or a different (incongruent) response. During incongruent test trials, animals used the context in which the test was carried out to disambiguate responding. That is, rats respond according to the element of the compound that was trained in the test context. Rats were given systemic d-amphetamine (1.5 mg/kg, i.p.) and/or clozapine (5 mg/kg i.p.) A within-subjects design was used in which rats were exposed to each drug condition (vehicle/vehicle, clozapine/vehicle, vehicle/amphetamine, clozapine/amphetamine) in a fully counterbalanced sequence. Data from congruent and incongruent discriminations were analysed within subjects ANOVAs with drug condition and response (correct, incorrect) as factors. The main effect of drug (p<0.001) was observed and significantly more correct than incorrect responding was observed (p<0.001) in both congruent and incongruent test trials. Specific drug effects on congruent and incongruent responding were analysed by paired t-tests. Acute systemic application of vehicle/d-amphetamine (1.5 mg/kg i.p.) disrupted correct performance on the incongruent test trials (p<0.05) but not the congruent test trials (p>0.01). Congruent and incongruent performance was not impaired by clozapine. However, clozapine selectively reversed the d-amphetamine induced deficit in performance during the incongruent test trials (p<0.01). These results show that the atypical antipsychotic clozapine is able to reinstate contextual control of biconditional discriminations impaired by acute administration of d-amphetamine. Acknowledgement: AC Reichelt is supported by a BBSRC Case studentship in association with Eli Lilly.

MA15

A SINGLE LOW DOSE OF AMPHETAMINE DISRUPTS PPI IN DOPAMINE D2 RECEPTOR DEFICIENT MICE

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Introduction: Amphetamine disruption of pre-pulse inhibition (PPI) is an animal model of hyperdopaminergia-induced sensory motor gating impairment and parallels impairments in schizophrenics. Studies using dopamine D2 receptor (D2R) null mice suggest that the D2R is necessary for amphetamine-induced disruption of PPI (Ralph et al., 1999, J. Neurosci.19, 4627-4633). These studies however used a high dose of amphetamine. High and low doses of amphetamine can have dissociable behavioural and neural effects. We investigated whether PPI disruption induced by one or two low doses of amphetamine is abolished in D2R-/- mice. Methods: D2R null (D2R -/-) and wildtype (D2R +/+ ) littermates 10 -16 weeks were used. Two PPI protocols were used, in the first protocol there was one acoustic startle session (day 1). In the second, mice received one habituation session (day 1, in chamber for 25mins) and one acoustic startle session (day 2, startle trials to120dB pulse alone and pre-pulse+pulse trials). The pulse alone trial consisted of six x 40 ms 120-db pulses of broadband noise at the beginning and end of the series. PPI was the magnitude of startle to the pre pulse trial (a 20-ns noise pre pulse, with a 100 ms delay followed by 60-μB pulse of broadband noise). Mice were injected 30 minutes prior test either on Day 1 or Day 2 with either amphetamine (2.5 mg/kg i.p.) or saline (0.9% W/v). Results: In the protocol with habituation, WT showed a significant effect of increasing pre-pulse on %PPI (P<0.001) however there was significant deficit in PPI in D2R -/- mice (effect of genotype: P=0.005) precluding any further comparisons with amphetamine treated mice. In the protocol that included a habituation session there was a significant effect of increasing pre-pulse on % PPI in both WT and D2R -/- mice (P<0.001). There was a significant effect of drug treatment (P<0.0001) both single and double doses of amphetamine disrupted PPI in WT, but only the single amphetamine dose disrupted PPI in D2R -/- mice (genotype x drug treatment interaction, P<0.05). Conclusions: These findings demonstrate that prior conclusions about the requirement of the D2R for amphetamine effects in PPI does not generalise to all doses. Second, they suggest a dissociation between one and two doses of amphetamine with respect to the D2R. Third, they suggest the importance of protocol in phenotypic effects on PPI in mice. We acknowledge the support of the Wellcome Trust.
MA16

SUB-CHRONIC PCP IMPAIRS WORKING MEMORY IN FEMALE RATS, EVIDENCE FROM PERFORMANCE IN THE 16-HOLEBOARD MAZE

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Introduction: We have consistently shown that sub-chronic treatment with phencyclidine (PCP) produces a marked impairment in several tasks of relevance to cognitive dysfunction in schizophrenia in the rat (Neill et al. 2010 Pharmacol & Ther, in press). Patients with schizophrenia consistently demonstrate impairments in working memory (Silver et al. 2003 Am J. Psych 160: 1809-1816). The 16-holeboard maze (16-HBM) was developed by Oades & Isaacson 1979 (Behavioural Biology 24: 327-337) and is believed to measure working memory in the rat. We have recently demonstrated pharmacologically specific deficits in this task following acute treatment with psychotomimetics, PCP, d-amphetamine and scopolamine. Aim: The aim of this study is to evaluate the effects of sub-chronic treatment with the psychotomimetic, PCP on performance in the 16-HBM. Methods: Adult female (n=16) hooded-Lister rats were food restricted to 95% of free feeding body weight and handled daily, habituated to eating food pellets from all 16-holes in the 16-HBM for 7 days prior to any behavioural training. Rats were trained for a maximum of 2 min for 10 trials to search for food pellets that are placed in the same 4 holes for 9 consecutive days. On the tenth day, rats were randomly assigned to receive sub-chronic PCP (2 mg/kg, b.i.d, i.p, n=8) or vehicle (saline 0.9%, n=8) for 7 days followed by 7-days washout prior to testing and subsequently tested in the 16-HBM. The testing procedure was identical to the training sessions. Data are expressed as the mean ± SEM (n=8 per group) and analysed using ANOVA and/or Student’s t-test. Results: Sub-chronic PCP produced a significant (P<0.05) increase in re-visits to food rewarded holes (from 0.45 ± 0.08 to 1.08 ± 0.12) and a trend towards an increase in non-food rewarded hole re-visits (from 0.61 ± 0.11 to 1.42 ± 0.4) over the 10 trials when compared to the vehicle group. Latency to complete the trials was unaffected by sub-chronic PCP treatment. Conclusion: These data show that sub-chronic treatment with PCP induces a specific disruption in spatial working memory measured in the 16-HBM. These results support the spatial working memory deficits observed using the delayed spatial win-shift procedure following sub-chronic ketamine treatment (Enamoto & Floresco 2009 Prog in Neuro-Psychol & Biol Psych 33: 668-675). This suggests that the 16-HBM could be useful in elucidating the underlying mechanisms surrounding working memory deficits observed in schizophrenia. B.Grayson is funded by b-neuro.

MA17

ALTERATIONS IN FUNCTIONAL BRAIN NETWORK STRUCTURE INDUCED BY SUBCHRONIC PHENCYclidINE (PCP) TREATMENT PARALLEL THOSE SEEN IN SCHIZOPHRENIA

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Quantitative analysis of complex 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; Micheleyannis et al., 2006. Schizophrenia Research. 87:60-66). These methods are yet to be applied to brain imaging data from translational models relevant to this disorder. Here we investigate network structure in functional brain networks in a preclinical model relevant to schizophrenia (Pratt et al., 2008. British Journal of Pharmacology. 153:S465-S470). Cerebral metabolism (64 brain regions) was determined in control (saline, male, Lister Hooded, n = 7) and PCP-treated rats (2.58mg.kg-1, i.p, 1 x daily for 5 days, n = 9) by semi-quantitative 2-deoxyglucose autoradiography (Dawson et al., 2009. Journal of Neuroscience Research. 87:2372-2385). 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 and small-worldness. In addition, centrality analysis (degree, betweenness and closeness) was used to identify important “hub” regions in these networks. Small-world properties and hub region identification were determined by statistically comparing real with calibrated random (Erdős-Rényi) graphs. Statistical differences in global network architecture between groups were analysed using repeated measures ANOVA. 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. Significance was set at p<0.05 throughout. Subchronic PCP-treatment induced overt hypometabolism in prefrontal and select thalamic regions, as previously reported (Cochran et al., 2003. Neuropsychopharmacology. 28:265-275). The functional brain network in PCP-treated animals had a significantly reduced mean degree (F(1,21)= 1178, p<0.001), increased average path length (F(1,21)= 197.19, p<0.001) and reduced mean clustering (F(1,21)= 185.44, p<0.001) in comparison to that in controls. The network in PCP-treated animals also displayed a significantly higher small-worldness (F(1,21)= 77.84, p<0.001) than that in controls. In control animals several thalamic regions and the locus coeruleus were identified as important hubs (z=1.96 and p<0.05). Of these regions the reticular (ventral and dorsal) and centromedial thalamus, nucleus reunions and locus coeruleus lost their hub status in PCP-treated animals (z=2.576 and p<0.05). This study is the first to apply the quantitative analysis of network structure to functional brain imaging data from a preclinical model relevant to schizophrenia. PCP-induced alterations in global network properties parallel those reported in schizophrenia (Liu et al., 2008; Micheleyannis et al., 2006). Furthermore, these results provide new insight into the mechanisms underlying brain dysfunction in schizophrenia. This work was funded by the EPSRC Bridging the Gap program at the University of Strathclyde.
MA18

SIGNAL DETECTION THEORY REVEALS SUB-CHRONIC PCP-INDUCED IMPAIRMENTS IN THE 5-CHOICE CONTINUOUS PERFORMANCE TEST IN THE RAT

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Attention and behavioural inhibition can be assessed in rodents using the 5 Choice Serial Reaction Time Task (5-CSRTT). Attention is assessed by measuring accuracy and omissions, whilst impulsivity is indicated by premature responding. The original 5-CSRTT is essentially a go-task, where the animal responds to the stimulus. The 5 Choice Continuous Performance Test (5C-CPT) is an adaptation of the traditional 5-CSRTT that includes no-go trials in which a correct response is made when the animal withholds from responding to irrelevant stimuli. The inclusion of both the go and no-go trials enables signal detection theory (SDT) to be used in the analysis and may give insight into animal’s vigilance level and response strategy. 32 Female hooded-Lister rats were trained in the 5C-CPT to criterion (>75% accuracy and <25% omissions in the go trials and >65% correct rejections in the no-go trials). The stimulus duration (SD) was 1s, the variable inter-trial interval (ITI) had a mean duration of 5s and a 2s limited hold (LH) was used. Animals were dosed with PCP (2.5mg/kg or 5mg/kg i.p.) following the sub-chronic regime (7-days bi-daily followed by 7-days washout) used in previous studies at Bradford showing impairments in cognition in several tasks of relevance to schizophrenia. The first experiment assessed animals’ performance when tested using the standard training conditions. The second experiment involved changing the constant SD to a variable SD (0.25s – 1.0s) for the 30 minute test session. Data are mean ± SEM (n=10 – 11), grouped into trial bins and analysed using repeated measures ANOVA followed by Planned Comparisons. There were no significant differences in performance between the vehicle and PCP treated animals when tested using standard training conditions. When the animal’s performance was challenged by using the variable SD, SDT revealed significant differences in performance between the vehicle and PCP treated animals. When performance was analysed over the duration of the session, PCP treatment resulted in a significant reduction in hit rate (p<0.05 – p<0.01), a significant increase in the false alarm rate (p<0.001) and a significant reduction in the sensitivity index (p<0.05 – p<0.001). There was no significant effect of sub-chronic PCP treatment results in impairment in performance of the 5C-CPT only when the variables of the task are manipulated, suggesting PCP treatment results in cognitive inflexibility. The impairments highlighted by SDT are indicative of attentional impairment and increased impulsivity, which indicate a vigilance deficit and an inability to discriminate between trial types. Sam Barnes funded by B-nuro.

MA19

TOPRAMATE INDUCED PSYCHOSIS: PRESENTATION AND TWELVE MONTH FOLLOW UP

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Topiramate has been primarily a treatment for epilepsy and prophylaxis against migraines.(Winum J.-Y. et al, 2009, Medicinal Research Reviews, 29/3, 419-435) Recently there has been increased use of topiramate in bipolar affective disorder (Lung F.-W. et al, 2009, World Journal of Biological Psychiatry, 10, 74-77), borderline personality disorder (Lieb K., 2010, British Journal of Psychiatry, 196/1, 4-12) post traumatic stress disorder (Alderman C.P. et al, 2009, Annals of Pharmacotherapy, 43/4, 635-641) and weight control secondary to antipsychotic medication or in eating disorders (McElroy S.L. et al, 2009, CNS Drugs, 23/2, 139-156). The importance of topiramate induced psychosis needs to be highlighted in view of the vulnerability of psychotic patients towards psychotic episodes. A small number of cases have been reported in neurological journals (Mula M., Monaco F., 2000 Epileptic Disorders, 11, 1-9) however it is rarely recorded in European psychiatric literature. In February 2009 a 19 year old male with epilepsy, diabetes and mild mental retardation secondary to a hypoxic brain injury at birth was admitted following destructive actions towards his family property and uncharacteristic hostility. He was experiencing auditory hallucinations, misidentification of family members, thought interference and delusions of control. His level of distress was high and did not respond to verbal or medical de escalation. He was restrained by the police who used CS gas prior to the admission and sustained multiple injuries but was not subdued. He required nursing in seclusion. During the admission period it was noted that he had recently had an adjustment of his medication from sodium valproate to topiramate and at time of admission was on 100mg topiramate twice per day. This was discussed with the neurological treating team and a change to phenytoin was made due to a need for anticonvulsant cover and prompt discontinuation of the topiramate thought to be the cause of his psychosis. Since discontinuation of the topiramate his psychotic symptoms settled within four days and he was discharged shortly afterwards. He was monitored by the early intervention services and at 12 months post discharge had not had recurrence of any symptoms despite not receiving antipsychotic medication since his admission. This case supports other similar reports regarding topiramate induced psychosis and offers additional evidence of the absence of psychosis following discontinuation of the medication. In the trend of topiramate being prescribed for psychiatric conditions it is important for psychiatrists to be aware that it may trigger a psychotic illness.

MA20

COMMUNITY TREATMENT ORDERS, CONDITIONS AND PSYCHOTROPIC MEDICATION: BASELINE DATA ANALYSIS FOR A PROSPECTIVE NATURALISTIC ONE YEAR FOLLOW UP STUDY

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Background: Community treatment order (CTO) legislation commenced in November 2008 in England and Wales. Rates of CTO use were higher than anticipated, resulting in difficulties with timely authorization of medication by second opinion appointed doctors (SOADs). The commonly used combination of CTO use with antipsychotic long acting injections (LAIs) has been previously noted. The aims at baseline of this prospective one year follow up observational study in the first year of CTO legislation, were to: (i) identify patient characteristics for those commenced on a CTO; (ii) identify the nature of psychotropic medication prescribing at CTO initiation. Hypothesis: patients with schizophrenia have higher than average rates of LAI use as compared with national prescribing data. Methods: The setting was the South London and Maudsley NHS Foundation Trust, which provides secondary care level psychiatric services plus tertiary referral inpatient facilities and forensic wards. Consecutive sampling was conducted for all patients whose CTO was registered in the Trust in the first year of CTO legislation (03/11/08-31/10/09). Only the first CTO for each patient was included. Measures included: sociodemographic variables, psychiatric diagnosis, CTO date of initiation, statutory reasons and stated conditions, psychotropic medication and date of SOAD authorization. Results: There was geographical variability in rates of CTO use between the 4 sub-regions. 52% of the 195 patients were of black ethnic origin. 53% had stated conditions regarding their place of residence and 29% were required to allow access into their homes. 9% were prescribed an antipsychotic, 28% a mood stabilizer, 8% an antidepressant, 5% a benzodiazepine. First generation antipsychotic LAIs were the most commonly prescribed group of antipsychotics (37%). 64% of those with schizophrenia on a CTO were prescribed an antipsychotic LAI. The mean BNF5's antipsychotic dose was 61.6% and 7.2% of the total sample had antipsychotic (combined) doses exceeding 100%BNF dose limits. 9.7% were prescribed two antipsychotics. 21% were LAI-naive prior to CTO initiation. Only 14.9% had SOAD certification completed within the required timeframe. Conclusions: Variation in CTO use exists for geographical areas. Conditions of CTOs may not follow the least restrictive principle, particularly for requirements regarding a patient’s place of residence; clearer guidance for setting of conditions is required. The finding of 64% of those with schizophrenia on a CTO being prescribed an LAI; this is almost double the rate reported (35%) for patients with schizophrenia on UK acute inpatient wards (Barnes et al, 2009, BJPsyCh, 95(suppl 52): s37-s42). Funding: Own Account.
**MB01**

**DIFFERENTIAL REACTIVITY TO THE ELECTRICAL STIMULATION OF THE DORSAL PERIAQUEDUCTAL GRAY IN MALE AND FEMALE RATS**

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Introduction: It is well established that susceptibility to affective disorders differs widely between genders. The regular cyclical variation in hormonal concentration during the menstrual cycle may be related to the susceptibility of women in developing psychopathologies such as anxiety and panic disorders, especially during the late luteal phase of the cycle which is characterized by a rapid decline of plasma progesterone levels. The aim of this study was to evaluate gender responsiveness and the influence of oestrous cycle of female rats during electrical stimulation (ES) of the dorsal part of periaqueductal gray matter (dPAG), since it is involved in the brain neural circuitry responsible for the integration of defensive behavior and it is one of the main structures involved in the physiopathology of panic attacks.

Methods: Male and female Wistar rats (250g) were implanted with electrodes into the dPAG and submitted to the procedure of ES of this structure during 4 consecutive days. Female rats were stimulated in all stages of the estrous cycle (proestrus – P; oestrus – O; early diestrus – ED and late diestrus - LD). Only rats cycling regularly were used in the experiments. The time of freezing behavior was also recorded after escape threshold (post-stimulation freezing). Statistical analysis was performed using a repeated measures (RM) one-way ANOVA, followed by Tukey’s post hoc comparisons (significant level was set p<0.05).

Results: Female rats showed a significant decrease in the thresholds for freezing behavior in O as well as in LD compared to P and ED (F3,33 = 7.64; p < 0.05). On the other hand, there were no significant differences in the freezing and escape thresholds as well as in post-stimulation freezing in male rats (F3,27 = 1.70; 2.80; 1.14; p> 0.05, respectively). Conclusion: The increased reactivity of the neural substrates of fear in the dPAG of female rats observed in LD has revealed remarkable hormone-linked changes in the intrinsic excitability of the PAG circuitry that is reflected by significant changes in behavior. This finding provides further evidence for the implication of the falling levels of progesterone and associated neuroactive metabolites in the differential sensitivity between male and female to brain aversive stimulation related to panic disorder. Funding agency: FAPESP (São Paulo - Brazil)

**MB02**

**STRUCTURAL NEURONAL PLASTICITY MARKERS AND BDNF ARE DIFFERENTIALLY ALTERED IN THE HIPPOCAMPUS, FRONTAL CORTEX AND PLASMA IN A RAT GENETIC MODEL OF DEPRESSION**

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The Flinders Sensitive Line (FSL) rats obtained by selective breeding of Sprague Dawley (SD) are a well established genetic model of depression. FSL rats naturally display increased immobility in the forced swimming test (FST), indicative of a depressive-like phenotype, which is rescued by antidepressant drugs. The present study investigated the depressive-like phenotype of the FSL and the expression of microtubular proteins, synaptic markers and brain-derived neurotrophic factor (BDNF) in the hippocampus and frontal cortex (FC). Additionally, BDNF was also analysed in the plasma. Male FSL (n=8) and SD (n=8) rats (2 months old) were submitted to the FST. Immobility counts were scored every 5-sec for 5-min in the pre-test session of the FST (15-min, day-1) and during the 5-min test session of day-2, as previously described (Bianchi et al. 2002 Exp. Brain Res. 143-191). Eighteen-hours later the hippocampi and FC were dissected for western blot analyses of microtubular proteins (Tyr-Tub, Glu-Tub, Delta2-Tub and Acet-Tub), synaptic markers (synaptophysin, PSD-95 and spinophilin) and BDNF (pro-BDNF and mature-BDNF). Additionally, plasma was obtained from trunk blood for ELISA analyses of total and free mature BDNF. The FST immobility counts were analysed as day-2/day-1 ratio using a one-way ANCOVA approach with the day-1 immobility, adjusted for strain differences, fitted as a covariate. FSL rats showed a significant increase (p<0.01) in immobility behaviour to 129±4% of SD rats, confirming their depressive-like phenotype. This was accompanied, relative to SD rats, by significant decrease of the pre-synaptic marker synaptophysin (67±12%; p<0.01) and of the post-synaptic marker PSD-95 (74±5%; p<0.05) in the hippocampus. Furthermore, mature/pro-BDNF (index of BDNF metabolism) was also significantly decreased (p<0.05) to 75±8% of SD animals. Hippocampal microtubular proteins and spinophilin were unchanged in FSL compared to SD. In the FC, Tyr/Glu-Tub (index of microtubule dynamics) was significantly decreased (p<0.05) to 80±5% compared to SD. The other proteins analysed were unchanged in the FC of FSL compared to SD. Finally, mature/total-BDNF was significantly increased (p<0.05) in FSL plasma to 150±17% of SD rats. FSL showed depressive-like phenotypes paralleled by molecular changes suggesting alterations in neuronal structure and mature-BDNF production in the hippocampus and decreased microtubule dynamics in the FC. Interestingly, mature BDNF levels in the hippocampus and plasma showed an inverse correlation. The present findings further support the hypothesis that alterations in cytoskeletal dynamics and neuronal structure may be involved in the pathogenesis of depression. Supported by internal MAPREG funding.
ISOLATION-REARING INDUCES DEPRESSIVE-LIKE PHENOTYPE ACCOMPANIED BY ALTERATIONS IN STRUCTURAL NEURONAL PLASTICITY MARKERS AND BDNF IN THE RAT HIPPOCAMPUS WHICH ARE RESCUED BY CHRONIC ADMINISTRATION OF MIANSERIN

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Isolation-rearing from weaning in rats produces behavioural and hippocampal changes at adulthood. Mianserin is an atypical antidepressant displaying antagonistic properties at both the adrenergic and the serotonergic receptors. The present study investigated the depressive-like phenotype induced by isolation-rearing and parallel hippocampal changes in microtubular proteins, synaptic markers and brain-derived neurotrophic factor (BDNF). The efficacy of chronic administration of mianserin in rescuing such alterations was evaluated. Male Sprague Dawley rats were reared undisturbed in grouped or in isolation from weaning (post-natal day 21-25) for 30 days. From housing day 31, isolated and grouped rats received chronic (22 days; n=6 for each cohort) daily i.p. administration of water (400µl/rat) or mianserin (5mg/kg). The novel object recognition (NOR, 1h ITI) task was employed on housing day 50. The forced swimming test (FST) was applied on housing days 51-52 to analyse immobility behaviour. Eighteen-hours after the last injection the hippocampi were dissected for western blot analyses of microtubular proteins (Tyr-Tub, Glu-Tub, Delta2-Tub and Acet-Tub), synaptic markers (synaptophysin, PSD-95 and spinophilin) and BDNF (pro-BDNF and mature-BDNF). ANOVA and Fisher’s LSD were used for statistical analysis of behavioural data, while the t-test was used for the molecular ones. The discrimination (D2)-index in the NOR was significantly increased (p<0.05) in isolates (0.16±0.09) compared to grouped rats (0.47±0.04). Moreover, immobility counts in the FST were significantly increased (p<0.05) to 120±2 of grouped rats. Tyr/Glu-Tub (index of microtubule dynamics) was significantly decreased (p<0.001) in the hippocampus of isolates to 75±3% of grouped rats. Furthermore, mature/pro-BDNF ratio (index of BDNF metabolism) was significantly decreased (p<0.05) to 77±6% of grouped animals. Hippocampal Delta2-Tub, Acet-Tub and the synaptic markers were unchanged. Mianserin recovered the NOR deficits of 30% and rescued the FST alterations induced by isolation-rearing. Moreover, relative to isolated vehicle-treated rats, mianserin significantly increased hippocampal Tyr/Glu-Tub (p<0.05) to 116±4% and decreased the neuron-specific Delta2-Tub (p<0.001) to 67±3% and the stable form Acet-Tub (p<0.001) to 69±6% in isolates. BDNF and the synaptic markers were unchanged. Isolation-rearing induced recognition memory deficits in the NOR and depressive-like phenotype (i.e. increased immobility in the FST) paralleled by decreased microtubule dynamics and mature-BDNF production in the hippocampus, suggesting alterations in brain development and/or neuronal plasticity. Importantly, mianserin induced a partial recovery of recognition memory and a rescue of the depressive-like phenotype in isolates. Such antidepressant efficacy was accompanied by increased hippocampal neuronal microtubule dynamics supporting the involvement of cytoskeletal proteins in antidepressant response. Supported by internal MAPREG funding.

ANTIDEPRESSANT ACTIVITY OF AGOMELATINE IN THE FORCED SWIMMING TEST IS ACCOMPANYED BY MODULATION OF CYTOSKELETAL MICROTUBULAR PROTEINS AND SYNAPTIC MARKERS IN THE RAT HIPPOCAMPUS

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Changes in molecular correlates of structural neuronal plasticity including cytoskeletal proteins and synaptic markers have been associated with the treatment of major depression. Consistently, chronic administration of antidepressant drugs have shown efficacy in rescuing the hippocampal neuronal structure alterations induced by animal models of depression. Here we investigated the effects of agomelatine, a novel antidepressant drug with melatonergic (MT1/MT2) agonist and 5-HT2C receptor antagonist properties, on microtubular proteins and synaptic markers in the rat hippocampus. Moreover, the antidepressant efficacy of agomelatine was assessed in the forced swimming test (FST) model of depression following chronic administration. Adult male Sprague Dawley rats (250-300g) received acute (single injection) or chronic (once a day for 22 days) i.p. administration of hydroxyethylcellulose 1% (vehicle; 400µl/rat) or agomelatine (40mg/kg) between 17.00-18.00h. On day 21 and 22 of chronic administration the animals were submitted to the pre-test and test of the FST, respectively, as previously described (Bianchi et al. 2002 Exp. Brain Res. 143 191). Immobility counts were scored every 5-sec during the 5-min of the test session of the FST. The rats were sacrificed 1h (acute treatment) or 18h (chronic treatment) after the last drug injection and the hippocampi dissected for western blot analyses of microtubule dynamics markers (Tyr/Glu-Tub, Delta2-Tub and Acet-Tub) and synaptic markers (synaptophysin, PSD-95 and spinophilin). Total α-tubulin and β-actin were used as house-keeper proteins and the student t-test was employed for statistical analyses. Acute agomelatine administration significantly increased (p<0.05) the neuronal-specific Delta2-Tub in the hippocampus to 120±2% of vehicle. This rapid effect on neuronal microtubules was not paralleled by any change in synaptic markers. Furthermore, under chronic conditions, agomelatine exerted clear antidepressant activity in the FST by significantly decreasing (p<0.05) immobility behaviour to 78±5% of vehicle. This antidepressant effect was accompanied, relative to vehicle treated rats, by a significant increase (p<0.05) in hippocampal Tyr/Glu-Tub (index of microtubule dynamics) and Delta2-Tub to 136±6% and 118±2%, respectively. Finally, spinophilin (dendritic spines marker) was also significantly decreased (p<0.05) to 75±9% of vehicle. The stable form Acet-Tub, synaptophysin (pre-synaptic marker) and PSD-95 (post-synaptic marker) were unchanged. Taken together, our data demonstrated antidepressant activity of agomelatine accompanied by modulation of cytoskeletal microtubular proteins and synaptic markers in the rat hippocampus. The observed increase in microtubule dynamics may promote phenomena of structural neuronal plasticity such as dendritic spines remodelling. These findings suggest an involvement of cytoskeletal microtubule dynamics and structural neuronal plasticity in antidepressant response. Supported by Servier.
MB05
IMPAIRED PREFRONTAL ACTIVATION AND FRONTOLIMBIC CONNECTIVITY IN YOUNG PEOPLE AT FAMILIAL RISK OF DEPRESSION
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Introduction: The processing of aversive stimuli in patients with major depression is associated with increased neural activity in limbic areas while activity in cortical regulatory regions is diminished. The aim of the present study was to examine whether related neural abnormalities might be present in young people at increased familial risk of depression but with no personal history of illness. Method: We used a blocked design functional magnetic resonance imaging protocol on a 3T Varian scanner in 29 young people (age 16-21 years) who had a biological parent with a history of major depression (FH+), and 30 age and gender-matched controls with no parental depression (FH-). Participants completed a perceptual task involving the matching of fearful and happy expressions interleaved by blocks of a sensorimotor task. fMRI data were analysed with FSL v4.1.4. Group x task interactions were analysed at the whole brain level (cluster-based thresholding at z = 2 and a corrected p < 0.05). Significant between group differences were further analysed using Psychophysiological Interactions (PPI), a measure of functional connectivity. Mean parameter estimates were extracted, converted to percent signal change and subjected to repeated measures ANOVA. Results: Relative to controls, FH+ participants had diminished responses in left dorsolateral prefrontal cortex (DLPFC) to presentation of fearful faces (t(54), = 3.20, P = .002), but similar responses to happy faces (t(54) = -3.36, P = .002). A functional connectivity analysis indicated that FH+ individuals had lowered connectivity between the left DLPFC and left amygdala (maximum Z = 2.1, coordinates of peak voxel: x = -22, y = -6, z = -16). Conclusions: A significant group x emotion interaction found in left DLPFC, showed impaired activation in FH+ versus healthy participants. Our findings suggest dysfunction in a frontolimbic circuit in FH+ individuals reflecting impaired emotion regulation prior to clinical depression. Thus, similar to MD patients, young people at increased familial risk of depression show decreased cortical regulation of aversive stimuli and impaired functional connectivity between this cortical region and the amygdala. Diminished cortical regulation of aversive emotional experience could place vulnerable individuals at increased risk of experiencing maladaptive reactions in stressful circumstances and may represent a target for cognitive remediation strategies aimed at preventing depression in vulnerable young people.

MB06
ALTERATION OF PERIPHERAL BENZODIAZEPINE RECEPTOR GENE EXPRESSION AND NEUROSTEROID CONCENTRATION IN MAJOR DEPRESSION
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The peripheral benzodiazepine receptor (PBR) is located in peripheral organs such as spleen testis, ovary and adrenal gland and in glial cells in the brain, where it is involved in steroidogenesis (Papadopoulos et al., 2006, Neuroscience, 138, 749-756). A previous study demonstrated that PBR protein expression was increased after exposure to acute stress (Johnson et al., 1998, Biol Psychiatry, 43, 306-309). Moreover, PBR protein has also been reported to be decreased in chronic and repeated stress, panic, anxiety disorders, and suicidal patients (Soreni et al., 1999, Biol Psychiatry, 46, 484-488). Furthermore, increases in neurosteroid concentration, allopragnenolone, and PBR expression have also been observed following antidepressant administration (Weizman et al., 1995, Journal of Affective Disorders, 33, 257-261). However, the relationship between PBR gene expression and neurosteroid alterations in major depressive disorder (MDD) is still unclear. Therefore, the aims of this study were to investigate PBR gene expression and alteration of serum progesterone, a neurosteroid, in major depressive disorder patients. Twenty-two patients (female; n=19, male; n=3, age 41±18 year) who have been firstly diagnosed by a psychiatrist meeting DSM-IV criteria for major depression and 35 healthy subjects (female; n=18, male; n=17, age 32±8 year) who have no psychiatric and drug abuse histories, were recruited. Peripheral blood was collected for RNA extraction and followed by PBR gene amplification using RT-PCR. Serum progesterone was determined by electrochemiluminescence (ECLIA). All data were analyzed by ANOVA. The result showed a significant decrease in PBR gene expression in major depressive patients with suicide attempt (n=8) when compared with both controls (p = 0.003) and a non-suicide attempt group (p = 0.001; n=14). Moreover, a significant decrease in serum progesterone was observed in depressed patients (p=0.049). The findings of the present study indicate a decrease of PBR gene expression in MDD with suicide attempt may be induced from chronic stress that is in consistence with previous reports (Chelli et al., 2008, European Neuropsychopharmacol, 94,595-603). Reduction of progesterone concentrations was also observed in MDD. The results provide a novel evidence to support PBR function in MDD with suicide attempt and contribute a support of neurosteroid deficit in MDD. This study was supported by the Naresuan University Research Fund and TRF-master research grants. The authors gratefully acknowledge the Psychiatric Clinic, Naresuan University Hospital for collecting the demographic data.

MB07
EFFECTS OF CORTICOSTEROIDS ON EEG HEMISPHERIC ASYMMETRY IN HUMANS: A REVIEW OF THE LITERATURE
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Background: Depression is associated with changes in hypothalamic-pituitary-adrenal (HPA) axis activity as well as hemispheric asymmetry of electroencephalography (EEG) and these are hypothesised to be linked. A number of studies have revealed that administration of corticosteroids to healthy subjects causes EEG asymmetry, although with conflicting results. The aim of this work was to systematically assess the evidence for asymmetric EEG activity in relation to corticosteroids. Methods: An electronic search using Ovid search of Medline (between 1950 and March 2010), Embase (between 1980 and March 2010) and PsychInfo (between 1806 and March 2010) was conducted using (EEG or ERP; asymmetry or laterality, and corticosteroid or cortisol) in the abstract, title or keyword. Additional papers were sought by examination of the reference lists of identified studies. Studies were included only if they were original investigation of EEG activity in humans. Animal studies and studies of sleep EEG in humans were excluded. Results: 14 studies were identified to fulfil the inclusion criteria. Additional papers were sought by examination of the reference lists of identified studies. Studies were included only if they were original investigation of EEG activity in humans. Animal studies and studies of sleep EEG in humans were excluded. Conclusions: These studies demonstrate similar pattern of EEG hemispheric asymmetry to that seen in depression. Abnormal cortisol levels may, at least in part, account for the cortical activity asymmetry related to depression and may prove to be useful as a biomarker of depressive illness. Further work is required to explore this utility of cortical asymmetry to monitor and/or predict response to treatment, and indeed whether asymmetry is a valid treatment target in its own right. HAA is supported by NIHR Academic Clinical Fellowship.
MB08

INFLAME-BEAT: DEPRESSION IS ASSOCIATED WITH HIGHER IMMUNOLOGICAL AND METABOLIC DISTURBANCES IN PATIENTS WITH HEART DISEASE

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One of the most neglected areas of healthcare research is the effects of physical illness on an individual’s mental health. Depression in patients with coronary heart disease (CHD) increases the risk of cardiac morbidity and mortality. Indeed, depression is more prevalent in patients with CHD than in general population. For reasons that are not entirely clear, depression may amplify the symptoms of physical illness and increase the risk of death in such populations. Studies suggest that clinicians are less likely to prescribe antidepressants to individuals who are physically ill due to uncertainty of drug efficacy for patients concerned. INFLAME-BEAT is a 2-year project to investigate putative biomarkers to diagnose mood disorder patients and to identify individuals at risk of mood disorders which is characterized by an activated inflammatory response system (IRS); to study human blood cells to further understand the pathogenesis of inflammation-related mood disorders and the pharmacological mechanism of anti-inflammatory drugs that could potentially influence depressive behaviour. Recruitment methods: This study stems from a qualitative NIH-funded project investigating depression in patients with coronary heart disease (CHD) in primary care. General practitioners are remunerated to keep a record of CHD registers. Patients with sCHD are recruited from practice CHD registers. Clinical assessments included Beck depression inventory (BECK), and Patients Health Questionnaire (PHQ), Hospital Anxiety and Depression Questionnaire (HADS), Brief illness perception questionnaire (BIPQ), general Health Questionnaire (GHQ), and Short Form Survey (SF-36). Blood was collected for plasma measurement of CRP, cortisol, and Full Blood Count. Patients were considered depressed if they scored > 13 on the PHQ. Unpaired T test was used to examine the difference between two groups. From a total of 43 patients, 35 (81.4%) had sCHD and 8 (18.6%) had sCHD and depressive symptoms (sCHDdep). sCHDdep patients did not differ in relation to age (sCHDdep =68 ± 4, CHD = 72 ± 3, p=0.09) or Body mass index (sCHDdep =29 ± 7, CHD = 27 ± 1.6, p=0.20) when compared to CHD patients without depression. Indeed, sCHDdep patients had more depressive symptoms as shown by higher scores on the PHQ (sCHDdep = 17.1 ± 1.4, sCHD = 3.5 ± 0.6, p=0.000), HADS (sCHDdep = 41 ± 5.8, sCHD = 15 ± 1.7, p=0.000), BECK (sCHDdep = 20.8 ± 3.7, sCHD = 10.2 ± 2.8, p=0.03), sCHDdep patients had signs of severe problems and psychological distress when compared to sCHD patients without depression as shown by higher scores on the GHQ (sCHDdep = 19.4 ± 1.6, sCHD = 15.05 ± 0.49, p=0.037). Depressed patients had lower levels of haemoglobin (sCHD 13.7 ± 0.304, sCHDdep 12.85 ± 0.15), increased levels of RDW (sCHD 13.71 ± 0.162, sCHDdep 15.00 ± 1.2), lower levels of lymphocytes (sCHD 1.9 ± 0.154, sCHDdep 1.36 ± 0.1) and lower levels of basophils (sCHD 0.063 ± 0.014, sCHDdep 0.035 ± 0.005). There was no difference in the levels of cortisol or CRP in sCHD and sCHDdep. The presence of depressive symptoms seems associated with increased risk for cardiovascular disease possibly due to the lower levels of the protective HDL, lower levels of lymphocytes and basophils, but higher levels of neutrophils. These may contribute to worsening of cardiovascular outcome in sCHD patients with depression and suggests that doctors will maximise a patient’s treatment and recovery from the mental and physical symptoms of illness if depressive symptoms are relieved. This project is funded by the NARSAD Young Investigator Award, the Biomedical Research Centre, UK and the European Union Framework 7 MOODINFLAME grant agreement FP7-HEALTH-2007-2.2.1-8.

MB09

EVALUATION OF A TRANSLATIONAL EMOTIONAL TONES DISCRIMINATION TASK IN HUMANS AS A POTENTIAL METHOD FOR ASSESSING AFFECTIVE BIAS

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Negative emotional bias has been attributed to affective disorders such as depression and anxiety. These important features of the human psychiatric condition have been largely overlooked in pre-clinical studies because of a lack of suitable translational methodology. A cognitive affective bias (CAB) task was developed for rats based on an emotional go/no-go paradigm (Harding et al, 2004, Nature, 427(6972): p312-312). To complete the reverse translation, we have now developed an equivalent task for human subjects (Robinson et al, 2008, J. Psychopharm, Suppl, 22(5) A53, TB10). The present study aimed to further evaluate this human model of emotional cognitive biases and assess its potential for use in a clinical population. Healthy volunteers (n = 40) 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 (500 Hz and 1000 Hz) presented in a pseudo-random order for 5 seconds for a total of 16 trials (eight per tone). The test session included additional intermediate ambiguous probe tones at frequencies between the reward and avoidance tones. A total of six, ambiguous probe tones were used at 20 Hz intervals either side of the 750 Hz midpoint. Participant winnings (up to a maximum of £10) were determined by their response accuracy. Mean response selection and median response latency to each tone were recorded. Participants were then given a series of self-report questionnaire measures of mood. Repeated-measures ANOVA of response choice indicated a significant main effect of ambiguity (p=0.05) and a marginal main effect of valence (p=0.053) with a significant ambiguity x valence interaction (p=0.05). Correlation analysis using a bias score showed significant correlation to VAS anxiety (p=0.05) and a trend level positive correlation to STAI state anxiety (p=0.10), controlling for depressed mood as measured by the BDI and PHQ-9 strengthen both VAS anxiety (p=0.036) and STAI state anxiety (p=0.035). These data suggest that this task is sensitive to differences in incentive salience between positive and negative stimuli among healthy volunteers. Associations between participants’ affective state and task performance suggest that this task may be sensitive to differences between healthy volunteers and patients. Further investigation with either a larger cohort of the general public or comparison against a clinical population is needed to further validate the task. These data support the translational potential for this task. MRM is a Reader in Experimental Psychology at the University of Bristol ESJR is an RCUK Academic Fellow supported by the British Pharmacological Society, integrative pharmacology fund MHA is funded by a BBSRC studentship.
MB10
SWEETNESS AND LIGHT: SWEET TASTE THRESHOLDS AS SURROGATE MARKERS FOR SEROTONIN LEVEL CHANGES AFTER BRIGHT LIGHT EXPOSURE IN HEALTHY SUBJECTS
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Bright light exposure increases serotonin (5-HT) levels in healthy subjects (Rao et al. 1992 Acta Psychiatri Scand. 86(2):127-32). Compared to dim lighting, bright light exposure prevented mood worsening in subsyndromal seasonal affective disorder (SAD) patients (aan het Rot et al. 2008 Eur Neuropsychopharmacol 18(1):14-23). SAD is also associated with blunted sweet but not salt taste perception (Arbisi et al 1996 Psychiatry Res. 59(3):171-82). 5-HT levels are difficult to measure but significant and rapid changes in sweet and bitter, but not salt, taste thresholds occur following SSRI administration in healthy subjects (Heath et al. J Neurosci 2006 26(49):12664-71). The study hypothesis was that short-term exposure to bright light would enhance sweet, but not salt, taste perception. Eleven healthy non-smoking adults (male:female=2:9, mean age 30 years, range 22-42) were recruited to a cross-over study in which sweet and salt taste perception were measured before and after 30 minutes of dim (<20 lux) and bright (10000 lux) light. The order of exposure to dim and bright light and the order of taste presentation were randomised across tests, with a 30-minute washout period in between light conditions. Salt and sucrose recognition thresholds (Heath et al. 2006), and intensity and pleasantness of concentrated (1M) salt and sucrose solutions were measured in each subject. Visual analogue scales assessed mood, anxiety, alertness and sleepiness at baseline and after each light condition. Participants also completed questionnaires to assess general health and mood. Ten subjects completed the study; one was excluded on grounds of ill-health at testing. Bright light exposure resulted in a significant reduction in sucrose, but not salt recognition threshold (sucrose, p=0.041 – threshold 13mM before (10 to 17mM, 95% CI): 17mM after (15 to 19mM); F(1,236)= 4.234, salt, p=0.7 - 10mM before (8 to 12mM); F(2,236)=0.4). Dim light exposure had no effect on either sucrose or salt recognition threshold. There were no significant effects on taste intensity or pleasantness. The results show that a short period of bright light exposure decreases sweet taste recognition threshold, with no effect on other measures of sweet taste perception, or on salt taste perception. This change in threshold could reflect an increase in 5-HT availability and suggests that even 30-minutes of bright light may significantly increase 5-HT availability. Sweet taste recognition threshold may therefore represent a marker for altered 5-HT availability and merits further work in clinical populations.

MB11
DEPRESSION AS AN EVOLUTIONARY ADAPTATION: ANATOMICAL ORGANISATION AROUND THE THIRD VENTRICLE
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Currently available antidepressants are no longer seen as the panaceas they once were. Only a proportion of the depressed population responds to them, they have a high relapse rate and a therapeutic lag of several weeks. The notable lack of progress in developing more efficacious drug-based antidepressant therapies over the past half century should be a powerful stimulus for the search for new approaches. This paper will outline the hypothesis that depression is an evolutionary adaptation that emerged where individuals needed to remain within a social group that had become hostile to their presence (e.g. displaced dominant making a transition to lower social status). The major effect of such social change is damage to reproductive potential and depression is now triggered by such damage from a range of sources. This analysis predicts that females would be most prone to depression because of the sexual asymmetry in the costs of human reproduction, whereby females are the most heavily investing sex. This is seen at all levels, from the size of the ova compared to sperm, the energetic costs of gestation and the foreclosed opportunities to attract further mates for a significant period after giving birth. The behavioural cluster associated with depression includes adoption of a hunched posture, avoidance of eye contact, loss of appetite for food and sex and sleep disruption. This behavioural cluster serves to reduce an individuals’ attack provoking stimuli and so facilitates their ability to remain within a hostile social environment. When viewed in this context, it becomes clear that many of the brain areas that mediate these behaviours (e.g. the pineal, hypothalamus and amygdala, whose main output, the stria terminalis passes through) all lie in close physical proximity to the Third ventricle. In consequence, it is proposed that depression has its origins within this ventricle. The increased volumetric changes seen in the third ventricles of depressives and changes in other closely associated structures are in agreement with predictions based on the current hypothesis and it is hoped that this will be of heuristic value in the search for more effective drug-based antidepressant therapies.

MB12
IMPAIRED FACIAL DISCRIMINATION IN MAJOR DEPRESSIVE DISORDER AND THE EFFECTS OF ACUTE ANTIDEPRESSANT ADMINISTRATION IN HEALTHY SUBJECTS
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Background Major depressive disorder is reported to be associated with social abnormalities such as withdrawal and altered ability to identify emotions in others. Brain regions implicated in emotional information processing are reported to be abnormal in depressed patients. We therefore hypothesised that depressed patients would be impaired in recognition of facial expressions. Some evidence suggests that antidepressant administration can alter the recognition of emotions in healthy controls. Therefore, our second hypothesis was that acute antidepressant administration would alter recognition of facial expressions in controls. Methods Seventeen patients with major depressive disorder and 21 matched healthy controls were assessed for their discrimination accuracy and response bias to different emotions (happy, sad, anger, disgust, fear) using a facial recognition task. Fifteen of these controls took 20 mg of citalopram for 3 days and were re-tested on the 4th day. The order of testing controls in the unmedicated and medicated conditions was counterbalanced. To measure how well participants discriminated individual emotions (targets) among other facial expressions (distractors), discrimination accuracy scores for every emotion were calculated according to signal detection theory with logistic distributions. Results Group by emotion ANOVA of discrimination scores revealed patients were significantly impaired in recognition of facial expressions of happy (p < 0.05), sad (p < 0.003) and disgust (p < 0.01) when compared with unmedicated controls. Controls were significantly impaired in labelling sad emotions when acutely medicated with citalopram (p < 0.05). Limitations As patients were receiving long term medication, confounds due to medication remains possible. Conclusions The findings add to the accumulating evidence for emotional recognition impairments observed in depressed patients which might explain the reported social impairments observed in depressed patients. Acute administration of citalopram was found to affect emotional processing of sad faces in healthy controls. Keywords: Major depressive disorder, emotion, citalopram, facial recognition
DEPRESSION AS AN EVOLUTIONARY ADAPTATION: ANATOMICAL ORGANISATION AROUND THE THIRD VENTRICLE

MB12

THE DISTRIBUTION OF ANXIETY AND DEPRESSIVE SYMPTOM SEVERITY AND MENTAL WELL-BEING SCORES IN A SINGLE OCCUPATIONAL GROUP: CROSS-SECTIONAL STUDY IN UK VETERINARY SURGEONS

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Introduction: Anxiety and depressive symptoms are common in community and clinical samples, but the distribution of symptom severity in particular occupational groups has not been studied extensively. As veterinary surgeons have a suicide proportional mortality ratio around four times that of the general population, they form a suitable profession in which to study the distribution of psychological symptoms and other measures of emotional well-being. Method: A questionnaire was mailed twice to 3200 veterinary surgeons (approximately 20% of the membership of the Royal College of Veterinary Surgeons, excluding those practising overseas or retired). Anxiety and depressive symptoms were assessed with the Hospital Anxiety and Depression Scale (HADS) and mental well-being with the Warwick-Edinburgh Mental Well-Being Scale (WEMWBS). Results: Evaluable questionnaires were returned by 1796 participants, a response rate of 56.1%. The demographic and occupational profile of respondents was fairly representative of the UK veterinary profession. The prevalence of anxiety, depression, and co-morbid anxiety and depression ‘probable cases’ (i.e. HADS sub-scale score ≥ 11) was 26.3% (95% CI: 24.3 to 28.4%), 5.8% (95% CI: 4.8 to 7.0%) and 4.5% (95% CI: 3.6 to 5.6%) respectively. Anxiety symptom severity approximated to Normal distribution (mean score = 7.95; SD=4.08; median=8; IQR= 5 to 11). By contrast, depressive symptom severity was positively skewed, with most respondents having relatively minor symptoms (mean score =4.70; SD=3.47; median=4; IQR= 2 to 7). Mental well-being scores (mean score=48.82, SD 9.08, median=49, IQR 43 to 55) approximated to Normal distribution. Conclusions: In comparison with normative data for a non-clinical sample of the UK adult general population (Crawford et al 2001 Br J Clin Psychol 40, 429-434), veterinary surgeons reported higher levels of anxiety and depressive symptoms. These levels of psychological distress suggest that ready access to and knowledge of lethal means is not the sole factor underlying the greater suicide risk within the profession. It seems possible that the suicide rate in a given occupation is related to the distribution of affective symptom severity within that profession, but this requires further examination in other occupational groups. The pattern of depressive and anxiety symptoms in this population provides no evidence for a clear threshold of severity for ‘caseness’: hence it would be arbitrary to make treatment decisions based on symptom severity alone. Funding for this study was provided by Veterinary Times and BUPA Giving.

MC01

DISTURBED SLEEP AND DAYTIME DROWSINESS IN PATIENTS WITH MOOD AND ANXIETY DISORDERS AND THEIR FIRST-DEGREE RELATIVES: BETWEEN-GROUP COMPARISON

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Introduction. Disturbed sleep is a distressing and clinically important depressive symptom, which reduces quality of life, and often persists despite otherwise successful treatment with antidepressants or cognitive-behaviour therapy. Depressed patients report poorer perceptions of sleep quality and duration than matched controls with similar overall sleep timing, and a distortion of sleep perceptions has also been seen in their non-depressed first-degree relatives. We wished to examine the relationships between habitual sleep and wakefulness patterns, insomnia, depressive and anxiety symptom severity, and attitudes and beliefs about sleep in patients with mood and anxiety disorders and in their first-degree relatives. Methods. A cross-sectional questionnaire-based study in NHS tertiary referral mood disorder service outpatients, with completion of the Hospital Anxiety and Depression Scale (HADS), Horne Ostberg Questionnaire (HOQ) for ‘morningness’ and ‘eveningness’ in human circadian rhythms, Medical Outcome Study Sleep Scale (MOSSS), Epworth Sleepness Scale (ESS) and Dysfunctional Beliefs and Attitudes about Sleep Scale (DBASS-16). First-degree relatives nominated by participating patients completed the same questionnaires. Results. The clinical sample comprises 82 patients (25 men and 57 women) and the relative sample comprises 31 individuals (13 men and 18 women). As expected, the mean severity of depressive and anxiety symptoms was significantly greater in the patient group compared to the relative group (HADS-total score 21.51 [SD 10.37] vs. 12.13 [SD 8.04], respectively; t=5.09, p<0.001). The patient group reported significantly more problems sleeping, compared to relatives (MOSSS sleep problems index 1, 42.30 [SD 20.38] vs. 31.4 [SD 18.61], respectively; t=-2.59, p=0.05 and MOSSS sleep problems index 2, 44.81 [SD 20.49] vs. 32.83 [SD 18.91], respectively; t=-2.93, p=0.001). Mean total scores on the DBAS-16 differed significantly between the two groups (patients 78.23 [SD 30.61], relatives 64.71 [SD 27.48]; t=-2.145, p=0.034) but there were no significant differences between the patient and relative groups in daytime drowsiness (ESS score 7.95 [SD 5.34] vs. 7.48 [SD 4.91], respectively). Conclusions. As expected, when compared to a non-clinical sample of first-degree relatives, outpatients attending a tertiary referral mood and anxiety disorder service had significantly more severe depressive and anxiety symptoms, and reported significantly greater disturbance and problems during sleeping. The magnitude of dysfunctional attitudes and beliefs about sleep was greater in the patient population than in relatives, but there were no significant differences in daytime drowsiness between groups.
MC02

RELATIONSHIPS BETWEEN DISTURBED SLEEP, ANXIETY, AND COGNITIVE CONTROL IN HEALTHY VOLUNTEERS

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Introduction: Anecdotal and clinical observations suggest that individuals who experience disturbed/poor sleep report greater negative affect and day-to-day cognitive impairment. However while increased levels of anxiety and depression have been frequently reported in individuals with primary insomnia, observable deficits in attention and cognitive control are less evident. Previous null results might in part reflect the relative insensitivity of tasks used to profile cognitive and attentional deficits in insomnia vs. healthy controls; and thus future clinical studies are likely to benefit from the identification of tasks in analogue studies that can clarify associations between sleep disturbance, affect and cognitive control in healthy individuals. Furthermore, this approach may further our understanding of cognitive mechanisms that increase emotional disorder in those with poor sleep; and increase both maladaptive cognitive activity in poor sleep and worry about sleep in those with anxiety and depression. Method: 84 undergraduate volunteers attended a single test session in which they completed self-report measures of sleep quality (Pittsburgh Sleep Quality Index - PSQI), current sleepiness (Stanford Sleepiness Scale), trait anxiety, worry and depression (e.g. Profile of Mood States). Participants also completed subjective measures of attention control (Attention Control Scale, ACS), cognitive control (Cognitive Failures Questionnaire) and computerized measures of attention (orienting, alerting & executive attention sub-tests of the Attention Network Task-ANT) and response inhibition (Stop-signal reaction time - SSRT). Results: Reduced sleep quality was associated with increased self-report anxiety, depression and cognitive failure (CFQ), ps < .05. Reported daytime dysfunction due to sleepiness and current sleepiness (Stanford) were similarly associated with increased negative affect, increased cognitive failure (CFQ), reduced attention control (ACS), and increased errors of commission and reduced response inhibition on the Stop-signal task, ps < .05. Current sleepiness was further associated with reduced executive attention (sub-test of the ANT); a relationship which remained after controlling for negative associations between executive attention (ANT) and trait anxiety/worry, and self-report cognitive control, ps < .05. Observed group levels of sleep quality, anxiety and mood fell within ranges typically observed in sub-clinical samples. Conclusions: We observed significant relationships between poor sleep, daytime sleepiness, negative affect and subjective and objective measures of attention and cognitive control in healthy undergraduates. Future studies should confirm the extent to which deficits in cognitive/attention mechanisms that help regulate cognition and emotion can account for the observed covariance between disturbed sleep and negative affect in disorders of sleep, anxiety and mood.

MC03

LINEAR DISCRIMINANT ANALYSIS AND SEMI-AUTOMATIC SLEEP-WAKE SCORING IN MICE

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Increasing interest in sleep research as well as its pharmacological modifications and growing demand for screening of genetically modified animals requires reliable sleep scoring programs. Presently existing solutions suffer from poor performance, low flexibility and often do not use optimized sleep stage-discriminating variables. Using a head-mounted data logger (Neurologger 2), EEG was recorded from parietal cortex overlaying the dorsal hippocampus in ten male and female C57BL/6 mice freely behaving under home cage conditions. Neck muscle activity (EMG) was also recorded. Multiple sets of EEG frequency variables were used for analysis. Parameters included conventional power spectrum and period-amplitude analysis. Manual sleep staging was compared with the scoring performance of the supervised classifier: Linear discriminant analysis (LDA). Upper theta and gamma activity was particularly high during REM sleep and waking. Among a total of 73 different tested variables, four were most effective for sleep-wake stage separation (judged according to automated versus manual staging): 1. amplitudes of upper-gamma-, 2. delta- and 3. upper theta-frequency bands and 4. the integral of bandpass filtered neck muscle EMG. Small sets (5%) of manually scored training data were used for Linear discriminant analysis. The LDA staging performance was verified by calculating test sensitivity, specificity, positive predictive value and negative predictive value. High theta and gamma activity during rapid eye movement (REM) sleep are particularly useful for sleep-wake stage separation. Linear Discriminant Analysis performs best in supervised automatic staging procedures. Reliable semi-automatic sleep scoring with Linear discriminant analysis substantially reduces analysis time. The study was funded by a DFG grant (SFB 636/806) to A.D.

MD01

ATTENTIONAL BIASES IN A CLINICAL POPULATION OF PATIENTS WITH ALCOHOL USE DISORDERS (AUDs): THE IMPACT OF CO-MORBIDITY

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Alcohol use disorders (AUDs) are a significant, global, public health problem. They frequently co-occur with other measures of psychological and behavioural distress, and in clinical samples this results in significant levels of psychiatric co-morbidity. However, despite the high prevalence of co-morbidity in AUDs, there is much less evidence on how attentional biases to disorder specific cues interact with each other, and the impact that this may have on understanding the natural history and recovery processes in patients with co-morbid conditions. Patients with AUDs, at various stages of treatment, were recruited from a specialist community alcohol service. All patients completed: the Alcohol Use Disorders Identification Test (AUDIT); Mini International Neuropsychiatric Interview (MINI); details of clinical history; visual dot probe task (VPT); Modified version of the Stroop task; and cravings questionnaires (Desire for Alcohol Questionnaire –DAQ, and urge to drink now).Data was analysed using descriptive statistics and correlation between alcohol-related attentional biases, and scores of self-reported measures of alcohol misuse and depression and anxiety scores. Data was collected on 113 patients (63.7% male). Mean length of AUD was 15.26 years, and only 18.6% of participants were currently employed. Sixty-six patients (58.4%) reported abstinence at the time of participation. Of those still drinking the median number of units of alcohol consumed per week was 89.2 (IQR 35-189). The majority of patients (67%) had a family history of AUDs. Levels of co-morbidity were high with 87% scoring for one or more co-morbid psychiatric diagnosis. Current depressive symptoms reached diagnostic thresholds in 71% of patients, and 39% had a life-time history of a manic or hypomanic state. Reaction time to alcohol-related words was slower than to non-alcohol related words, with a significant difference in attentional bias towards the alcohol-related words (t=2.8; p=0.007). There was also a significant bias towards depression-related words on the VPT (t=-2.15; p=0.034). Patients seeking treatment for severe alcohol use disorders have high levels of co-morbid psychopathology, and significant social impairment. Attentional biases to alcohol-related words were present in this sample and an understanding of how they interact may help to delineate underlying mechanisms.
THE EFFECTS OF D-CYCLOSERINE AND CUE EXPOSURE ON THE PROCESSING OF ALCOHOL-RELEVANT CUES IN HEAVY RECREATIONAL DRINKERS

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Background: In heavy recreational drinkers and alcoholics, environmental 'cues' associated with alcohol can gain abnormal salience, being able to hijack attention and elicit craving in the absence of alcohol itself. These cues are an important aspect in the maintenance of hazardous drinking and the progression from recreational use to alcoholism. Cue-exposure therapy (CET) may be a way to reduce the salience of alcohol cues via extinction learning. The present study examined a role of CET in altering attention to alcohol-related cues. It was hypothesized that CET would reduce attention to alcohol cues. Methods: 21 participants received 2 sessions of cue exposure procedure and either placebo (n = 10) or 125mg DCS (n=11) on each occasion. Cue exposure consisted of extended imaginal scripting and handling of glasses of wine or beer. Attentional bias to alcohol-related cues was measured by a dot-probe task in which pictures were presented at short and long stimulus onset asynchrony (SOA) to differentiate automatic and strategic processing. Outcome measures were reaction time (RT) and eye-tracking data. Results: Participants showed a significant attentional bias to alcohol-related pictures before treatment at the short SOA only (p = .002). This bias disappeared after cue exposure treatment (p = .11). No effect of DCS was found from RT, eye-tracking data are currently being analysed. Conclusions: The attention-grabbing effects of alcohol-related cues appear to operate only at the automatic level. Cue exposure procedures may be effective in reversing these automatic attentional processes in hazardous drinkers and alcoholics. DCS does not appear to increase the efficacy of CET in overcoming behaviourally-measured attentional bias.

MU-OPIOID RECEPTOR (OPRM1) A118G POLYMORPHISM IS ASSOCIATED WITH SALIVARY CORTISOL-CORRELATED STATE ALCOHOL CRAVING IN ALCOHOLICS

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INTRODUCTION Stress and appetite regulation have been the focus of recent alcohol craving studies due to their interactions with the limbic reward pathway, in which opioidergic neurotransmission plays an indispensable role. Previous human studies showed a functional mu-opioid receptor (OPRM1) polymorphism, A118G, may participate in modulation of alcohol craving level and influence the efficacy of abstinent-management medication in alcohol-dependent subjects. This study explores the association between OPRM1-A118G and state alcohol craving, and the possibility of regulation of state alcohol craving by cortisol and leptin levels. METHODS Ninety-two Caucasian alcohol-dependent subjects (54 males and 37 females) were recruited during in-patient detoxification treatment. On a morning between Day 3 and Day 5 (at 7 a.m.), state craving level of alcohol was measured by the Alcohol Urge Questionnaire, followed by collection of saliva and overnight-fasting blood samples. Salivary cortisol and plasma leptin levels were measured by ELISA on a subset of 60 subjects without other substance dependence or psychiatric co-morbidity (except depressive symptoms). Genotyping of OPRM1 A118G polymorphism was done on all 92 subjects by restriction fragment length polymorphism. RESULTS Genotyping results showed that most of the participants were AA homozygous at OPRM1 A118G polymorphism (73 subjects; 80.2%) with fewer AG heterozygous (18 subjects; 19.8%) and no GG homozygous. AA individuals were found to have significantly higher state alcohol craving levels than AG individuals (Mann-Whitney U test p = 0.018), but the two groups did not differ significantly in salivary cortisol or plasma leptin levels. A significant correlation between salivary cortisol and state alcohol craving levels was only observed in AA individuals (Spearman's correlation coefficient = 0.381; p = 0.015). No correlation between BMI-corrected plasma leptin levels and state alcohol craving was observed in either group. CONCLUSIONS These preliminary data suggest that OPRM1 A118G AA genotype is associated with higher state alcohol craving, which is correlated with a higher cortisol level, in alcohol-dependent subjects during in-patient detoxification treatment. For AG individuals, though state alcohol craving is lower, the lack of correlation with cortisol level suggests that stress hormonal regulation may not play a major role in craving in these individuals. However, it may simply represent a lack of statistical power due to the low prevalence of the G allele. Correlation between leptin and state alcohol craving is not supported. It should be noted that the alcohol craving level was measured when subjects were in an abstinence focused, protected environment.

IMPULSIVE PERSONALITY PREDICTS RISKY SEXUAL BEHAVIOUR IN HEROIN ADDICTS

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Objective Substance abuse is known to be associated with risky sexual behaviour. Treatment for drug dependence over the recent past has been generally focused on harm reduction, driven by a desire to reduce blood-borne virus (BBV) transmission in many jurisdictions. This study presents new data on the overlap of drug use with risky sexual behaviour also associated with BBV transmission. Methods Questionnaires covering demographics, impulsivity and substance use were administered to 315 Sinhalese speaking male heroin addicts according to DSM-IV criteria. They were recruited from an open prison and its associated drug rehabilitation facility. Ethical approval for the study was obtained from the Human Research Ethics Committee, Faculty of Medicine, University of Peradeniya, Sri Lanka and voluntary written informed consent was obtained from all participants. The bivariate relationships between current risky sexual behaviour and possible predictors were examined using logistic regression. Variables that were significantly associated with each risky sexual behaviour were then entered into a multivariate logistic regression for that behaviour. Results In this population of male heroin users, impulsive personality traits, especially sensation-seeking, had the most consistent association with risky sexual behaviours. Total score on the Sensation-Seeking Scale (SSS) was significantly associated with: sex with multiple partners (OR:1.10, 95% CI:1.01-1.19), sex while intoxicated with drugs (OR:1.16, 95% CI:1.08-1.24), sex with another man (OR:1.31, 95% CI:1.19-1.45), sex while having a sexually transmitted infection (OR:1.09, 95% CI:1.04-1.15) and trading sex for money (OR:1.32, 95% CI:1.12-1.56). The next most consistent factor was the apparent protective effect of completing some level of secondary education. This was significantly associated with a reduced likelihood of sex with multiple partners (OR:0.38, 95% CI:0.17-0.86), sex with a CSW (OR:0.32, 95% CI:0.16-0.64) and sex while intoxicated with drugs (OR:0.43, 95% CI:0.23-0.81). Injecting drug use, polydrug use, and daily frequent heroin use were also significantly associated with some of the individual risky sexual behaviours. Conclusion The results suggest that future treatment intervention for heroin addicts should target individuals to engage in risky sexual behaviours. The association with lower educational achievement may suggest that some of this effect is mediated by peer-group effects in those who leave, or are excluded from, school at a younger age. For clinicians, this data provides further evidence for the importance of addressing all of the potential multiple risk behaviours for BBV transmission when treating drug using populations with the known high incidence of impulsive personality traits. LD was supported by a scholarship from Griffith University, Qld.
MD05

EFFECTS OF ACUTE ALCOHOL CONSUMPTION ON RESPONSE INHIBITION OF SALIENCE ATTRIBUTE

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Alcohol use has been associated with both prefrontal abnormalities linked with impaired behavioural control and limbic system dysfunction related to reward deficits. However, no study has yet examined the acute effects of alcohol on the association between the response inhibition and incentive salience. The aim of the present study was therefore to investigate: 1) the effects of alcohol on response inhibition of alcohol stimuli; and, 2) the effects of heaviness of drinking on response inhibition of alcohol stimuli. Healthy, heavy and light users of alcohol (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. Response inhibition of alcohol and neutral cues was measured using lexical and pictorial versions of an affective Go/No-Go task. Mixed-model ANOVAs of commission error data were conducted with two within-subjects factors of target (alcohol, neutral) and block (shift, non-shift) and two between-subjects factors of challenge condition and drinking status. Lexical commission error data indicated significant main effects of target (F[1, 90] = 51.43, p < 0.001) and shift (F[1, 90] = 55.86, p < 0.001), such that all participants made more errors towards alcohol word targets compared to neutral targets and more errors in shift blocks versus non-shift blocks. An interaction effect on commission errors between target and challenge condition was also observed (F[2, 90] = 4.74, p = 0.011), indicating that following an acute high dose of alcohol (0.6 g/kg) participants made more errors towards alcohol targets. Pictorial commission error data also indicated significant main effects of target (F [1, 90] = 50.66, p < 0.001) and shift (F [1, 90] = 30.36, p < 0.001). For pictorial cues, all participants made more errors towards neutral images versus alcohol images and more errors in shift blocks versus non-shift blocks. Our data indicate that, following an acute dose of alcohol, disinhibition is increased, reflected in more commission errors towards alcohol target words. These data are the first to tentatively support the presence of a synergistic impaired response inhibition and salience attribution (I-RISA) model following acute alcohol consumption. Additionally, our results suggest that all participants showed increased disinhibition towards lexical alcohol cues, but reduced disinhibition towards pictorial alcohol stimuli. At present it is not clear if this discrepancy in response inhibition towards alcohol stimuli reflects distinct cue-specific mechanisms of reward on inhibitory control. Funding: University of Bristol studentship.

MD06

COGNITIVE BIAS IN SOCIAL ALCOHOL CONSUMERS: DO STIMULI MATTER?

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Incentive–sensitization theory suggests that individuals consuming drugs on a regular basis will display cognitive bias towards drug-related cues. Research in social alcohol consumers has yet to examine the role of stimulus characteristics on alcohol-related cognitive biases. The following studies therefore examined whether the presence of cognitive biases in social alcohol consumers is stimulus-specific. In study 1, n = 72 (50% male) healthy light and heavy alcohol consumers completed a lexical and pictorial version of the modified alcohol Stroop task. In study 2, n = 72 (50% male) healthy light and heavy alcohol consumers completed a lexical and pictorial version of the visual probe task. Lexical reaction time data were analyzed within a 2 x 2 mixed model ANOVA, with cuetype / validity (alcohol, neutral) as a within-subjects factor, and drinking status (light, heavy) as a between-subjects factor. Pictorial reaction time data were analyzed within a 2 x 2 x 2 mixed model ANOVA, with cuetype / validity (alcohol, neutral) and stimulus set (active, passive) as within-subjects factors, and drinking status (light, heavy) as a between-subjects factor. In study 1, lexical Stroop data, indicated no significant main effect of cuetype (p = .90), while pictorial Stroop data indicated no significant main effect of cuetype (p = .18) or stimulus set (p = .76). A significant interaction between cuetype and stimulus set was observed (F [1,70] = 9.12, p = .004), indicating slower reaction times towards alcohol-related pictorial cues in the passive stimulus set, irrespective of drinking status. No further significant interactions were observed (ps > .30). In study 2, lexical visual probe data, indicated no significant main effect of validity (p = .48), while pictorial visual probe data, indicated no significant main effect of validity (p = .68) or stimulus set (p = .10). No further significant interactions were observed (ps > .51). Neither stimulus type (lexical, pictorial) nor stimulus set (active, passive) appears to influence the presence of attentional bias on a visual probe task. Within the modified alcohol Stroop task, selective processing towards alcohol-related cues was observed among a pictorial version within a particular stimulus set (passive). Results indicate the potential role of stimulus characteristics in the presence of cognitive bias.

MD07

SOBER SOCIAL DRINKERS WITH HIGHER LEVELS OF ALCOHOL USE EXHIBIT INCREASES IN ASPECTS OF IMPULSIVITY AND FINANCIAL RISK-TAKING

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Alcohol consumption has frequently been reported to increase aspects of impulsivity and risk-taking, but occasionally there are contradictory findings. However, because problem drinking is associated with a younger ‘age at first drink’, it appears that personality differences related to problem drinking pre-date the initiation of alcohol drinking. The present study investigated the relationship between typical levels of daily and weekly alcohol intake and responses (whilst sober) to three measures designed to assess aspects of impulsivity and risk-taking. Participants were recruited as an opportunity sample (n=80) and their responses to the AUDIT questionnaire (supplemented with additional questions) were used to allocate them to groups based on their typical (daily or weekly) levels of alcohol intake. Group responses on the Procrastination Scale, the Deferment of Gratification Scale and Bets 16 (a measure of risky financial decision making) were then compared using one-way ANOVAs supplemented with Tukey’s tests or the Kruskal-Wallis test supplemented with Mann-Whitney U tests (for Bets 16). Results indicated that increased levels of typical alcohol consumption, whether based on daily (non-drinkers, moderate drinkers, binge drinkers) or weekly (non-drinkers, sensible drinkers, hazardous drinkers and harmful drinkers) intakes, were associated with reduced self-reported Deferment of Gratification scores [F(3,76)=17.2, p<0.001], increased self-reported Procrastination scores [F(3,68)=16.0, p<0.001] and increased risky financial choices (Bets 16;p<0.001). Unexpectedly, non-drinkers and sensible drinkers had faster latencies for risky choices than safe choices whereas hazardous and harmful drinkers had faster latencies for safe choices than for risky choices. Overall, the results confirm that heavier social drinking is associated with increased impulsivity and risky financial decision making, even when participants are sober when tested. However, the slower risky choices (compared to safe choices) of hazardous and harmful drinkers argue against impulsive risk-taking in these groups.
Alcohol consumption is associated with behavioural disinhibition, impulsivity and increased risk-taking, although there have been occasional reports of alcohol reducing aspects of impulsivity e.g. discounting of delayed rewards [Orrtner (2003) Alcohol & Alcoholism, 38, 151-156]. However, because problem drinking is associated with a younger ‘age at first drink’, it appears that personality differences related to problem drinking pre-date the initiation of alcohol drinking. The present study investigated the relationship between typical levels of daily and weekly alcohol intake and responses to a behavioural measure of discounting of delayed reward (the Two Choice Impulsivity Paradigm; TCIP) and two self-report measures: The Financial Attitudes Test, which assesses Financial Risk Control (FRC) and Speculative Risk (SR) and the Stimulating/Instrumental Risk Inventory (SIRI) which assesses Stimulating Risk (StimR) and Instrumental Risk (IR). Participants were recruited as an opportunity sample (n=74) and their responses to the AUDIT questionnaire (supplemented with additional questions) were used to allocate them to groups based on their typical (daily or weekly) levels of alcohol intake. Participants were sober at the time of testing. Data were submitted to one-way ANOVA supplemented by Tukey’s tests. The TCIP required participants to make 40 choices between a small quick reward (5 points after 5 sec) and a larger more delayed reward (20 points after 20 sec) where each point was worth an imaginary £1. Group responses on the TCIP revealed that Binge drinkers chose more small quick rewards [Mean=28.8(SEM=1.5)] than all other groups, but made these choices with longer latencies than other groups. Sub-binge drinkers also chose more small quick rewards [Mean 15.9 (SEM=2.7)] than non-drinkers [Mean=8.5 (SEM=1.1)], but did not differ from moderate drinkers [Mean=14.0 (SEM=1.5)].

FAT results revealed that Binge drinkers [Mean=18.3, (0.7)] scored lower than non-drinkers [21.1, (0.6)] on Risk Control, but there were no between-group differences on Speculative Risk or SIRI measures. In conclusion binge drinkers, when tested sober, exhibited increased discounting of delayed rewards and reported lower levels of financial risk control.

MD09

THE EFFECTS OF REPEATED ETHANOL WITHDRAWAL ON SLEEP EEG MEASURES IN RATS AS AN INDEX OF WITHDRAWAL SEVERITY

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Sleep disturbances are a common complaint often reported as an enduring symptom in alcoholics undergoing detoxification. This withdrawal symptom is pronounced in alcoholics with a history of detoxifications. Sleep disturbances may increase susceptibility to relapse in abstinent alcoholics as sleep problems associated with repeated detoxification can often persist for an extended time. The present study evaluated the effects of multiple ethanol withdrawals in a rat model on sleep time and sleep architecture. Male Lister hooded rats were surgically fitted with radio-transmitters for continuous electroencephalogram (EEG) data collection. Baseline data were collected for 2 days, after which rats received one of 3 treatments: control diet (CON) or chronic ethanol treatment (7% ethanol) for 24 consecutive days with a single ethanol withdrawal (SVD) or multiple ethanol withdrawal episodes for 30 consecutive days including 2 intermediate withdrawal episodes during days 11 – 13 and 21 – 23 of chronic ethanol treatment (RWD). Rats consumed 10-15g/kg ethanol per day. EEG data were collected continuously for 22 hours on specific days of treatment. Data were subjected to automated analyses of 12-second epochs into wake, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Data was analysed using ANOVAs, all tests of significance performed at α=0.05. Ethanol withdrawal reduced time spent awake (wake%) during the light phase compared with control group (F 2,18 = 8.3, p = 0.03) and increased wake% during the dark phase (F 2,18 = 21.3, p <0.001). This was accompanied by a concomitant increase in NREM sleep during the light phase (F 2,18 = 10.05, p <0.001) and a decrease in NREM during the dark phase(F 2,18 = 10.43, p <0.001) compared with the control group. Although there was a general increase in REM sleep in the transition between the light phase to the dark phase, no significant group differences were found during the light phase (F 2,18 = 0.913, p = 0.41) or the dark phase (F 2,19 = 0.16, p = 0.86). There were no significant differences in sleep measures between singly and repeatedly withdrawn rats. The effects of ethanol withdrawal on sleep measures persisted 3 days after the final withdrawal. Ethanol withdrawal produces changes in sleep architecture in wake% and NREM% but did not affect REM%. Authors would like to thank the BBSRC and Pfizer for funding this study.

MD10

A ROLE FOR NO IN THE ANXIOGENIC EFFECT INDUCED BY ABSTINENCE TO CHRONIC ETHANOL CONSUMPTION

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Introduction: Abstinence to chronic ethanol consumption (CEC) leads to anxiogenic effects. NO levels are increased in this condition and the Dorsal Raphe Nucleus (DRN) has increased levels of the NO synthesizing enzyme Nitric Oxide Synthase (NOS). Therefore, the aim of our work was to investigate whether intra-DRN administration of L-NAME (a non-specific NOS inhibitor) or 7-Ni (nNOS inhibitor) attenuates the abstinence-induced anxiogenic-effect of CEC in rats. Methods: Male wistar rats with cannulas aimed at the DRN received water (W) or a 6% (v/v) ethanol (EtOH) solution to drink for one (acute) or twenty-one (chronic-CHR) days. After this, animals received only water for forty eight hours until test in the elevated plus maze (EPM). Five minutes before being tested in the EPM, animals received an intra-NDR injection of L-NAME (10nmol/0.2µL), 7-Ni (10nmol/0.2µL, in 15%DMSO), saline (SAL) or vehicle (Ve; DMSO 15%). Percentages of entries (%EOA) and time spent (%TOA) in the open arms were registered and analyzed by three-way ANOVA, considering the following factors: intake (EtOH x W; DRINK); period of intake (TIME), and intra-NDR treatment (DRUG). Significance was set at p<0.05. Results: Abstinence to acute ethanol consumption did not change %EOA (F1,160=3.9; p=0.05, W/SAL =24.7±3.3; EtOH/SAL=17.1±4.4) and %TOA (F1,160=5.6; p=0.05, W/SAL =8.2±2.7; EtOH/SAL =11.7±3.6). Intra-DRN treatments did not change the exploratory behaviour of rats submitted to acute ethanol consumption (%EOA: F1,160=11.1; p<0.05, %TOA:F1,160=0.8; p<0.05). On the other hand, abstinence to CEC, decreased %EOA (W/SAL=55.7±3.9; EtOH/SAL=10.8±3.6; TIME:F1,152=2.82, p<0.05; and DRINK:F1,152=6.50; p<0.05) and %TOA (W/SAL=23.3±3.2; EtOH/SAL=6.5±2.9; TIME:F1,152=3.5; p<0.05; and DRINK:F1,152=6.50; p<0.05). This effect was attenuated by intra-NDR administration of L-NAME, but not 7-Ni (%EOA: EtOH/LNAME=28.5±4.2; ETOH/7Ni=23.9±3.5; %TOA: EtOH/LNAME=10.8±3.4; ETOH/7Ni=14.5±2.8).

Discussion: Abstinence to CEC leads to anxiogenic effects that can be detected in the EPM. These effects were attenuated by intra-DRN treatment with L-NAME, but not 7-Ni, further suggesting a role for NO in this response. Affiliation: none Financial Support: CAPES and FAPESP.
CONCOMITANT USE OF CENTRAL NERVOUS SYSTEM DEPRESSANTS, IN PARTICULAR, IS IDENTIFIED AS A RISK FACTOR FOR HEROIN OVERTDOSE. STUDIES OF OVERTDOSE DEATHS HAVE REPORTED A SIGNIFICANT INVERSE RELATIONSHIP BETWEEN BLOOD ALCOHOL AND BLOOD MORPHINE CONCENTRATIONS AT POST-MORTEM [RUTTENBERG ET AL., 1984; ZADOR ET AL., 1996]. THIS STUDY USES AN ALCOHOL CHALLENGE TO INVESTIGATE THE ALCOHOL-HEROIN INTERACTION ON RESPIRATION. 10 OPIOID-DEPENDENT PARTICIPANTS RECEIVING OPIOID-SUBSTITUTION THERAPY (25-85mg METHADONE/16mg BUPIPRENORPHINE DAILY) AND 12 HEALTHY CONTROLS WERE RECRUITED. PARTICIPANTS WERE ADMINISTERED A 400ML DRINK CONTAINING 0.8% ALCOHOL (VODKA). MEASURES OF ALCOHOL EFFECT WERE COLLECTED AT BASELINE AND AT 15 MINUTE INTERVALS AFTER ALCOHOL CONSUMPTION. RESPIRATORY PARAMETERS (HEART RATE, RESPIRATION RATE, OXYGEN SATURATION, NASAL ETCO2) WERE COLLECTED. SPIROMETRY WAS USED TO RECORD TIDAL VOLUME AND MINUTE VOLUME AND INSPIRATION/EXPIRATION TIME.

SUBJECTS PERFORMED THE READING TASK TO ASSESS CENTRAL CHEMOREFLEX VENTILATORY SENSITIVITY TO CO2, BOTH BEFORE AND AFTER (105 MINUTES) FOLLOWING ALCOHOL CONSUMPTION. RESULTS WERE ANALYSED USING REPEATED MEASURES ONE-WAY ANOVA WITH BONFERRONI’S MULTIPLE COMPARISON TEST.

BREATH ALCOHOL CONCENTRATION (BAC) SIGNIFICANTLY INCREASED IN ALL PARTICIPANTS FOLLOWING CONSUMPTION OF 0.8%/KG ALCOHOL (P<0.0001). BAC WAS SIGNIFICANTLY HIGHER IN THE HEALTHY CONTROL GROUP WHEN COMPARED TO OPIOID-DEPENDENT PARTICIPANTS (P=0.0001). CONTROLLING FOR BAC (ETCO2/BAC), NASAL ETCO2 SIGNIFICANTLY INCREASED IN OPIOID-DEPENDENT PARTICIPANTS WHEN COMPARED TO HEALTHY CONTROLS POST ALCOHOL CONSUMPTION (P=0.0001). AT PEAK (105 MINUTES), THERE WAS A 8.14+6.5% INCREASE IN ETCO2 (COMPARED TO BASELINE) IN OPIOID-DEPENDENT PARTICIPANTS, BUT A -2.56+4.1% DECREASE, FOR HEALTHY CONTROLS. OXYGEN SATURATION, HEART RATE AND RESPIRATORY RATE DID NOT CHANGE SIGNIFICANTLY FOLLOWING ALCOHOL CONSUMPTION (BAC CONTROLLED, P<0.05). TIDAL VOLUME AND MINUTE VOLUME SHOWED A TREND TO INCREASE IN OPIOID-DEPENDENT SUBJECTS AND DECREASE IN HEALTHY CONTROLS, HOWEVER, THERE WERE NO SIGNIFICANT GROUP DIFFERENCES (P>0.05). RESULTS WERE ANALYSED USING ONE-WAY ANOVA WITH BONFERRONI’S MULTIPLE COMPARISON TEST. READING TASK INDICATED A DECREASED BASELINE RESPIRATORY DRIVE IN OPIOID-DEPENDENT SUBJECTS. IN AGREEMENT WITH EXISTING LITERATURE THESE RESULTS SUGGEST OPIOID-DEPENDENT PARTICIPANTS MAY HAVE AN IMPAIRED RESPIRATORY SYSTEM. IN ADDITION, THE SIGNIFICANT INCREASE IN NASAL ETCO2 SUGGESTS THAT ALCOHOL MAY MODULATE SOME RESPIRATORY PARAMETERS WHEN ADMINISTERED TO OPIOID-DEPENDENT PATIENTS BUT NOT HEALTHY CONTROLS, WHICH MAY EXPLAIN WHY MIXING BOTH DRUGS CAN LEAD TO DEATH. INVESTIGATING THESE RESPIRATORY CHANGES MORE FULLY IS IMPORTANT IN UNDERSTANDING HOW TO REDUCE OPIOID OVERTDOSE RISK FACTORS. IN ADDITION THESE FINDINGS MAY EXTEND TO CHRONIC OPIOID USERS IN OTHER SETTINGS, FOR EXAMPLE PAIN. FINANCIAL SUPPORT: MRC PROGRAMME GRANT (GO40075) AND STUDENTSHIP.
ATTENTIONAL BIAS FOR SMOKING-RELATED CUES IN SMOKERS WITH LOW LEVEL OF NICOTINE DEPENDENCE

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Cognitive aspects of tobacco use such as the attentional bias toward tobacco-related stimuli are important to understand how tobacco dependence develops. With repeated use of cigarettes, environmental stimuli related to the effect of this drug can alter the smoker’s attention, increase the desire to smoke and lead to repeated drug use. Attentional bias can occur during all the attention process: the initial process, measured in shorter exposure periods (≤200ms), and the maintenance of attention, measured at ≥ 2000ms. It is not known if smokers with low level of nicotine dependence would present attentional bias during all the process of attention. The aim of this study was to investigate attentional bias for smoking-related stimuli presented at different exposure times in young smokers and non-smokers using a visual probe task. The participants were 47 smokers (11 male; 36 female) and 50 non-smokers (13 male; 37 female) recruited among college students from universities. The mean age of smokers was 23 years (SD=2.82) and of non-smokers was 21 years (SD=2.82). Exclusion criteria were alcohol or drug dependence, regular use of prescribed psychiatric drugs and reported mental illness. Participants answered Fagerström Test for Nicotine Dependence (FTND); the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST); a Visual Probe Task (VPT) and pleasantness rating tasks. In VPT, there were 12 pairs of stimuli (tobacco-related photograph / control) presented in blocks with different exposure times (200, 500 and 2000 ms). After these stimuli, an arrow replaced one of them. Attentional bias was calculated by subtracting the average reaction time to respond to the arrow when it was replaced by tobacco-related stimuli from the average reaction time to respond to the arrow when it was replaced by control stimuli. A two-factor repeated measures ANOVA (General Linear Model) was applied to investigate the attentional bias in the three exposure times between the groups. Smokers showed a greater attentional bias for smoking-related cues than non-smokers in all stages of the attentional process (F (1.95) = 4.33, p < 0.05). Most of young smokers (76%; n = 35) showed a low level of nicotine dependence (M±SD: 2.22, 4.04) in FTND. Besides, smokers rated smoking related pictures more pleasantly than non-smokers (F (1.94) = 17.47, p<0.001). Young smokers already show attentional bias to smoking cues, meaning that smoking even for a few years and with low dependence can change the orientation and the maintenance of attention to this kind of stimuli.

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ASSOCIATION OF THE CHRNA5-A3-B4 GENE CLUSTER WITH HEAVINESS OF SMOKING

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There is consistent evidence from twin and adoption studies that genetic factors contribute to the aetiology of cigarette smoking. Nevertheless, despite a large number of candidate gene studies, few reported associations have proven to replicate reliably. Recently, variation in the 15q24 nicotine receptor cluster CHRNA5/A3/B4 has shown promise as a candidate region for smoking behaviour. Polymorphisms in this cluster have been linked to multiple smoking-related phenotypes (e.g., nicotine dependence; smoking quantity) and smoking related diseases (e.g., lung cancer). Two SNPs, rs16969696 in CHRNA5 and rs1051730 in CHRNA3, which are in high LD and have been found interchangeably in the literature, have generated particular interest. We sought to evaluate the strength of evidence for the association between the rs16969696 (k = 41 samples) and rs1051730 (k = 23 samples) SNPs and heaviness of smoking, as measured by daily cigarette consumption, including k = 15 samples which reported data on both SNPs. We used meta-analytic techniques to evaluate existing published data, and contacted study authors where necessary for additional data. We tested both dominant and recessive models of genetic action, and explored which SNP provided a stronger genetic signal. Meta-analysis indicated evidence of association between the rs1051730/rs16969696 variants and cigarette consumption under both recessive (d = -0.15, 95% CI: -0.47, -0.12, p < 1×10-9) and dominant (d = -0.01, 95% CI: -0.41, -0.08, p < 1×10-9) models of genetic action. The effect size estimate was larger for the rs1051730 variant compared to the rs16969696 variant for both recessive (d = -0.17 vs d = -0.11, p=0.025) and dominant (d = -0.12 vs d = -0.06, p=0.003) models of genetic action. In all cases there was no evidence of substantial between-study heterogeneity (I2 < 25%). Our data suggest a small effect of both the rs16969696 and rs1051730 SNPs on cigarette consumption, equivalent to a genotype effect of 1-2 cigarettes per day. These effects appear to act recessively, and the rs1051730 SNP may provide a stronger signal. Furthering our understanding of the genetic contribution of smoking-related behaviours may ultimately enable us to improve and personalise smoking cessation treatments, which may help to reduce the substantial global health concern associated with tobacco use. Funding: Wellcome Trust studentship.

TREATMENT EFFECTS OF ST JOHN’S WORT AND CHROMIUM (3+ ) IN A RANDOMISED DOUBLE-BLIND PLACEBO CONTROLLED TRIAL ON EARLY WAKING SALIVARY CORTISOL IN QUITTING SMOKERS – IS THIS RELATED TO RELAPSE?

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Purpose of study: To study the effect of St John’s wort (SJW) and chromium (Cr) versus placebo (i.e. PL-SJW and PL-Cr) treatments in quitting smokers. Is related to waking salivary cortisol? Methods: 143 smokers (>10/day) were recruited and randomly allocated into four treatment groups with each group taking two medications (SJW/PL-CR; CR/PL-SJW; SJW/PL-CR; PL-SJW/PL-CR). SJW (3x300mg/day) and Cr (40μg/day) treatments were administered 2 weeks prior to quit and for 12 weeks after. Mood and anxiety were measured by the Mood and Physical Symptoms Scale (MPSS) and State-trait Anxiety Inventory (STAI) respectively. Smoking abstinence at 4 weeks was rated a successful outcome. Abstinence was confirmed by exhaled CO concentration <10 ppm. Saliva for cortisol was collected every 15 minutes over a period of 1 hour following waking on days -14, 0 (quit day), 1, 3, 7, 14 and 28 respectively. Cortisol was analysed by radioimmunoassay. Data was analysed by ANOVA (with post-hoc t-tests). Results: There was no evidence that SJW reduced nicotine withdrawal symptoms or urges to smoke. Treatments were well tolerated. 6/71 on active SJW and 9/72 on placebo achieved prolonged abstinence at 4 weeks. At 6 months 3 SJW active and 6 placebo participants were still abstinent. The active treatments all demonstrated significant reductions of cortisol auc’s during the period from the start of treatments at 14 days post-quit to 7 days post-quit versus placebo. However, unlike for some treatments such as nicotine replacement therapy (NRT), reduction in cortisol output immediately post-quit does not relate to relapse or outcome success since the majority of participants taking active treatment relapsed prior to the 4 week cut-off. Actually, the rate of success was slightly greater in the placebo group. Cortisol data 7 days after quitting may reflect a return to smoking in some, especially those in the PL/PL group. Analysis of total MPSS mood scores in successful quitters showed no significant differences between active and placebo treatments (within-subjects [F=0.46; df=1,14; p=0.51], mood/treatment [F=0.78; df=1,14; p=0.39] and between-subjects [F=0.79; df=1,14; p=0.39]). Individual item scores such as depression were reduced. Analysis of STAI scores in successful quitters also showed no significant differences between active and placebo treatments (F=2.83; df=1,14; p=0.11). Conclusions: Trial showed that SJW and CR or their combination had no effect on enhancing smoking cessation rates. Data suggests that it might be difficult to interpret cortisol deficits with rates of relapse. CR may reduce weight gain. Sponsor: The study was supported by CR-UK.
MD17

INVESTIGATING THE SUBTYPES OF NICOTINIC ACHR INVOLVED IN CATECHOLAMINE RELEASE IN DIFFERENT REGIONS OF THE RODENT BRAIN

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Noradrenaline (NA) is important for spatial learning in hippocampus (HC) and alertness/attention in frontal cortex (FC) and has a role in withdrawal from drugs of abuse, including nicotine. Nicotine exerts its effects via nicotinic acetylcholine receptors (nAChRs) which are heterogeneous and widely distributed in the mammalian brain where they modulate many neurotransmitter systems. The aim of this study was to investigate the nAChR subtypes modulating NA release locally in vitro in rat FC and HC tissue. We also examined the effects of in vivo nicotine exposure on ex vivo NA release. Noradrenaline release was assessed using a 96-well plate filtration assay in rat brain prisms. [3H]Epibatidine binding was used to determine nACHr number after chronic nicotine treatment or withdrawal via osmotic minipumps. Statistical analysis was carried out in SigmaStat using ANOVA and t-tests as appropriate. Nicotine elicited release of [3H]NA in FC and HC prisms, but with higher potency in FC (EC50 6.17 uM, HC EC50 12.59 uM). [3H]NA release was also elicited in FC by β2* nAChR agonist 5-ido-A-85380 (SIA) in a concentration-dependent manner (EC50 5.8 nM). In HC 1000-fold higher concentrations of SIA were required to elicit comparable [3H]NA release (EC50 4.5 uM). This pharmacological profile implicates α4β2 and α3β4 nAChRs in FC and HC respectively, consistent with inhibition by β2*-selective antagonist DHβE in FC but not HC. After acute in vivo nicotine treatment (0.4 mg/kg s.c.) in vitro release of [3H]NA from rat brain prisms was unchanged. After chronic nicotine treatment via osmotic pumps in rats (4mg/kg/day, 14 days) responses to in vitro stimulation were also unchanged in either FC or HC, but whole brain [3H]Epibatidine binding increased to 135 +/- 8.7% of control (p=0.008). Three days after removal of minipumps there was no significant difference in nAChR levels from control animals. This in vitro study has established distinct pharmacological profiles for nicotinic modulation of NA release in FC and HC by β2* and β2* nAChRs respectively. This will be confirmed in vivo using microdialysis. The functional nAChR differences seen here raise the possibility of targeted treatments using subtype selective agonists. Funding was provided by a BBBSRC CASE studentship in collaboration with RenaSci Consultancy Ltd.

MD18

THE ELECTRONIC CIGARETTE: ACUTE EFFECTS ON MOOD AND CRAVING

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Electronic Cigarettes (e-cigarettes) are battery-operated devices that provide nicotine via an inhaled vapour. Since no tobacco is burned, inhaling nicotine in this manner should provide a safer alternative to regular cigarette smoking since it eliminates the harmful tars and carbon monoxide associated with tobacco smoking. Nevertheless, the efficacy of the e-cigarette as a smoking cessation aid or effective alternative to smoking has not been systematically explored. In this exploratory study, we investigated whether the e-cigarette (the ‘Super White’; The Electronic Cigarette Company) can reduce withdrawal symptoms (Mood and Physical Symptoms Scale; MPSS) and urge to smoke in minimally-deprived smokers (1 hour abstinence). 40 regular tobacco smokers were randomly allocated to either a nicotine or placebo condition and completed a 1-item urge to smoke scale and the MPSS before, and 5 minutes after, using the e-cigarette ad lib for 5 minutes. They also rated the extent to which they felt ‘a hit’ and ‘satisfied’ following use of the e-cigarette. Preliminary ANOVA’s reveal significant main effects of TIME (pre vs. post e-cigarette use) reflecting a dramatic reduction in urge to smoke and MPSS (F1,33 > 17.00, p < 0.001) but this was not qualified by an interaction with GROUP (nicotine vs. placebo e-cigarette; F1,33 < 2.50, ns); that is, there was no superior effect of nicotine. T-tests for between group comparisons revealed that...
MD20

BENEFICIAL EFFECTS ON MOOD AND COGNITIVE PERFORMANCE FOLLOWING "SHISHA" (WATERPIPE NICOTINE) USE

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Anecdotal media reports and increases in the numbers of Shisha cafes in cities, suggest that UK waterpipe smoking is becoming commonplace. Research to date has predominantly focussed on health concerns, though there has been some work on characteristics of users and indicators of addiction (e.g. Jackson & Aveyard, 2008; BMC Public Health, 8). The current study aimed to look for simple nicotine effects in a cross section of regular Shisha cafe clients, using a 16-item visual analogue mood scale and a letter cancellation task. We approached 30 people: 17 female, 13 male, aged 18-28 (mean age 22). Of these 19 did not use nicotine products outside of their visits to the cafe, and 11 were regular cigarette smokers (mean Fagerstrom score 7.18). Over two visits participants were asked to complete the mood scales and letter cancellation task both immediately before starting their Shisha session and again 20 minutes into their session (with the order being counterbalanced across participants). A repeated measures ANOVA showed that Shisha use produced a borderline reduction in drowsiness (p = 0.06), and significant increases in ratings of feeling excited (p<0.005), energetic (p<0.001), relaxed (p<0.005) and sociable (p<0.02). For the letter cancellation task there were also substantially significant improvements in performance and reductions in time taken to complete the task (both p<0.001), with no effects on errors. When cigarette smoker status was included in the analysis, significant interactions were found for the feeling states energetic (p<0.05) and relaxed (p<0.02), with smokers tending to show lower baseline scores and greater increases in ratings after Shisha use. These effects could be taken to demonstrate some degree of reversal of nicotine deprivation. However, given that these interactions were limited to just two of the measures, overall the data suggests that nicotine delivery via Shisha use produces beneficial effects over and above withdrawal in smokers. In sum, the data in this study show a range of positive effects following waterpipe (Shisha) nicotine delivery in a ‘real world’ social setting, in both smokers and non-smokers. Such findings highlight the need for more research to explore the allure of this rapidly growing social psychopharmacological phenomenon.

ME01

DIFFERENTIAL OCCUPANCY OF STRIATAL VERSUS EXTRASTRIATAL DOPAMINE D2/D3 RECEPTORS BY THE TYPICAL ANTPSYCHOTIC HALoperidol IN MAN MEASURED USING [18F]-FALLYPRIDe PET

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Introduction: The PET radioligand [18F]-fallypride binds to D2/3 receptors with high affinity, and represents a significant advance over previous dopaminergic tracers (Silfestein et al., 2004 Synapse;54:46-53.). We performed a tracer change study with placebo or low dose haloperidol to demonstrate selective D2/3 binding and to measure D2/3 density in striatal and extrastriatal subregions, and their occupancy by the typical antipsychotic haloperidol. Methods: Six healthy right-handed males aged 18-45 were recruited. Scanning was conducted on a GE VCT PET scanner. Participants received a low dose CT scan (10mA) for attenuation correction. List mode 3D acquisition commenced for 80 min, then 90 min, following a 10-minute rest period. A bolus of 250mHq radio-labelled [18F]-fallypride diluted up to 10ml with normal saline was given intravenously over 10 seconds and flushed with 10ml normal saline. At 90 minutes the scan recommenced, and at 110 minutes (according to randomization) the participant received Haloperidol (1mg) or Placebo injection via R antecubital cannula. Results: Scans were reconstructed as non-attenuation corrected PET images (to preserve anatomical information) and realigned, followed by formation of a mean image for transformation to the SPN PET template. Regions of interest were delineated for the right and left caudate, putamen, ventral striatum, amygdala, substantia nigra, the medial thalamus, and temporal cortex using a standardised brain atlas and inversely transposed to both the placebo and haloperidol PET studies, regional DA D2 receptor binding potentials were then calculated using the simplified reference region tissue model (Lammertsma et al, 1996 J Cereb Blood Flow Metab 16: 42-52.) implemented in MATLAB. Differences in binding potential images based upon data pre and post haloperidol/placebo challenge were conducted using Logan plots (Cunn et al, 1997 Neuroimage; 6:279-287.). Conclusions: The PET radioligand [18F]-Fallypride clearly demonstrated selective binding to striatal and extrastriatal brain regions in accordance with published results (Silfestein et al., 2004). Logan plots for striatal regions demonstrated rapid displacement of [18F]-fallypride by intravenous haloperidol, reducing binding in these regions by about 50%. However, in extrastriatal regions such as Thalamus and inferior Temporal Cortex the measured haloperidol-induced displacement was reduced by an order of magnitude to about 5%. These results indicate either differential occupancy of striatal versus extrastriatal D2/D3 receptor populations by low dose Haloperidol, or potentially a failure of SRTTM assumptions in the modelling of [18F]-Fallypride binding.

ME02

SPECIES COMPARISON OF THE BINDING PROPERTIES FOR THREE D2/D3-DAR RADIOLIGANDS WIDELY USED IN PET IMAGING

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The dopamine D2/D3 receptor ([D2/D3-DAR] has been extensively studied with the PET radioligands, [11C]Raclopride, [11C]Sipiperone and more recently [11C](+)Phenol. Rat and pig are commonly utilised with PET to assess in vivo proof of principle studies. The relative binding properties of these radioligands have not been compared between these two species. This report directly compares the binding characteristics of these three radioligands in rat and pig striata, and additionally reports the manner in which these radionuclides bind in ion conditions reflective of different cellular compartments. Homogenate binding assays, using rat (Sprague-Dawley, n=4) and pig (Yorkshire Landrace, n=4) striata, were performed using tritiated forms of the PET ligands, [3H]Raclopride, [3H]Sipiperone and [3H](+)Phenol. Three buffers were prepared to represent the physiological conditions of cellular compartments; Extracellular (EC)-50nM Tris HCl, 140mM NaCl, 5mM KCl, 1.5mM MgCl2, 1.5mM CaCl2, pH7.4; 37°C; Intracellular (IC)-50nM Tris HCl, 10mM NaCl, 140mM KCl, 0.5mM MgCl2, pH7.0, 37°C; Endosomal (EE)-20mM MES, 10mM NaCl, 140mM KCl, 0.5mM MgCl2, 0.003mM CaCl2, pH6.0, 37°C. Tissue was prepared in these buffers and incubated with increasing concentrations of each radioligand for saturation analysis. Assays were incubated at 37°C for 60mins, with haloperidol (1µM) to define specific binding. Data analysis was performed using GraphPad Prism and two-way ANOVA. The density (Bmax) of D2/D3-DAR is significantly higher in the striata of the rat for all radioligands in the EC condition (p<0.05). The Bmax in rat and pig for [3H]Raclopride (368 and 152fmol/mg protein) and [3H]Sipiperone (265 and 44fimol/mg protein) was approximately double that of [3H](+)Phenol (130 and 616fmol/mg protein) reflecting its agonist properties. Additionally, the binding affinities (Kd) in the rat were higher than that in the pig for all radioligands. For [3H]Raclopride and [3H](+)Phenol, a decrease in Bmax and Kd were observed when exposed to the EE ionic condition versus that in the EC and IC conditions. This abstract reports the density of D2/D3-DAR in the rat striata to be approximately twice that of pig. Additionally, the affinities of the three D2/D3-DAR radioligands were all lower in the pig striata versus the rat PET image data is generally reported in terms of Binding Potential (BP), where the BP=Bmax/Kd. These data suggest that BP’s generated for the pig would be lower than the rat in PET studies using these radioligands. Furthermore, the EE condition caused a marked decrease in the Kd and the Bmax for both [3H]Raclopride and [3H](+)Phenol in both species. These data suggest Raclopride and (+)Phenol could behave similarly in vivo, and it is possible that the agonist, (+)Phenol, would be more sensitive to endogenous DA turnover than the currently used antagonist, Raclopride. DQ is sponsored by a BBsRC/Case Award with GlaxoSmithKline.
ME03

VARENICLINE INCREASES STRIATAL Dopamine D2/3 RECEPTOR BINDING IN DRUG-NAÏVE RATS

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Background: In drug addiction, striatal dopamine (DA) is important for reward and learning. Increasing striatal DA D2/3 receptor availability is therefore postulated to be a possible treatment for drug addiction. Varenicline is an α4β2 nicotinic acetylcholine receptor partial agonist, currently registered and proven effective for smoking cessation by reducing craving towards nicotine and reducing withdrawal symptoms. Nicotine receptors are involved in modulating the DA signal. We hypothesize that varenicline modulates DA D2/3 receptor availability. If so, varenicline may be an effective treatment for addictions other than smoking.

Methods: Two separate experiments were performed. In a first one, twenty male drug-naïve rats were randomized to either daily subcutaneous injections with varenicline (2 mg/kg) or placebo for 14 consecutive days, and injected intravenously with the dopamine D2/3 radiotracer 123I-BZM. Phosphor storage imaging was used to determine ventral and dorsal striatal 123I-BZM binding as a measure of D2/3 receptor availability. In a second follow-up study, a replication study using several doses of varenicline ranging from 0.5 mg/kg and 2 mg/kg were used to assess dose-dependency and replicate previous finding on striatal DA D2/3 receptor availability.

Results: In the first experiment, we found significantly higher specific striatum-to-cerebellum binding ratios in both dorsal (13.9%; p = 0.014) and ventral (14.7%; p = 0.009) striatum for the varenicline group compared to the placebo group. In the second experiment, previous data were confirmed, and several doses did not induce a dose-dependent increase in DRD2 binding. Conclusions: In drug-naïve rats, varenicline increases DA D2/3 receptor availability and a 0.5 mg/kg dose seems already sufficient for this. We therefore believe that varenicline can be an effective pharmacotherapy in the treatment of alcohol and drug addiction.

ME04

PRAMIPEXOLE MODULATES BOTH VENTRAL STRIATAL-OCCIPITAL CONNECTIVITY AND RESTING STATE EEG ALPHA POWER

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Dopaminergic therapy in some patients with Parkinson’s disease is associated with negative consequences, such as hallucinations (predominantly visual) and disinhibited behaviour (Lawrence et al.2003)Lancet Neurol 2(10): 595-604) linked with dopamine dysregulation in the ventral striatum (Evans et al.(2006)Ann Neurol 59(5): 852-858). These consequences are particularly prevalent with a D3-prefering agonist pramipexole (Etminan et al.(2003)Drugs Saf 26(6): 439-444) perhaps linked to the rich dopamine D3-receptor expression in the ventral striatum (VS). Here we examine the effects of pramipexole on the functional connectivity (FC) of the VS during simultaneous resting state (RS) fMRI and EEG acquisition. Sixteen healthy males were scanned at 3T on four occasions following administration of pramipexole 0.5mg (predosed with 10mg domperidone to reduce nausea), paroxetine 20mg, or placebo (on 2 occasions) in a double-blind, randomised balanced design. Three hours post-administration RS-EEG was performed prior to and during 5 minute fMRI acquisition using a 64 channel Neuroscan Maglink RT. Standard preprocessing was used for the fMRI and EEG data (scanner-gradient, BCG and eyeline artefact removal). Parieto-occipital alpha EEG power timeseries served as regressors in the fMRI analysis. The effects of pramipexole on striatal FC maps (Di Martino at al.(2008)Cereb Cortex 18(12): 2735-2747) were tested with a second-level ANOVA. The influence of opening/closing eyes was subsequently assessed using a psychophysiological interaction (PPI; Gitelmanet al.(2003)Neuroimage 19(1): 200-207) analyses. Pramipexole enhanced connectivity between the VS and visual cortex (VC; P<0.05 corrected), but did not change VC activation associated with eyes open versus eyes closed blocks. In addition EEG-recorded alpha power across parieto-occipital electrodes was reduced (Main effect of drug: F(1,14) = 18.85; p<0.002) following pramipexole (outside scanner, n=15). This effect was only evident for the eyes-closed condition. Accordingly, the fMRI-PPI effect was also predominant in the eyes-closed condition. While VS-VC connectivity and EEG alpha power were altered by pramipexole, the drug did not alter the relationship between EEG alpha power and BOLD signal in the visual cortex. The observed enhancement of VS-occipital connectivity is likely mediated by the thalamus, the primary output target of the striatum (Alexander et al.(1986)Annu Rev Neurosci 9: 357-381) and a key generator of occipital alpha EEG (Lindgren et al.(1999)Biol Psychiatry 45(8): 943-952; Ben-Simon et al.(2008)PLoS One 3(12): e3984), and is thus a promising candidate mediator of both the observed effects of pramipexole. Our observations suggest a novel mechanism of action for pramipexole and define a potentially useful target network for patient-based investigations of this drug’s unusual side-effect profile.

ME05

7 DAY ANTI-DEPRESSANT MEDICATIONS CITALOPRAM AND REBOXETINE REDUCE RESTING-STATE FUNCTIONAL CONNECTIVITY IN HEALTHY VOLUNTEERS

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fMRI studies have revealed abnormalities in resting state functional connectivity (RSFC) in those with Major Depressive Disorder (Greicius et al., 2007 Biol Psychiatry 62(5): 429-437; Zhou et al., 2010 J Affect Disord 121(3): 220-230). However, the effect of antidepressant medications on human brain function is less clear and the effect of these drugs on RSFC is unknown. Thirty-nine volunteers matched for age and gender with no previous psychiatric history received either citalopram (SSRI), reboxetine (SNRI) or placebo for 7 days in a double-blind design. We used resting-state functional magnetic resonance imaging and seed based connectivity analysis to explore the functional connectivity of the nucleus accumbens, the medial and lateral orbitofrontal cortex, the amygdala and subgenual cingulate cortex. Mood and subjective experience were also measured before and after drug administration using self-report scales. Our analysis revealed that despite no differences in mood across the three groups, there was reduced connectivity between the anterior cingulated and nucleus accumbens (p=0.03) in both the citalopram and reboxetine group (p<0.001) compared to the placebo. Reboxetine also had reduced connectivity between the medial orbitofrontal cortex (p=0.03) and the nucleus accumbens. For the lateral orbitofrontal cortex seed we found reduced connectivity with the anterior cingulate (p<0.001), the caudate (p=0.001) and putamen (p=0.001) in the reboxetine group compared to the placebo group. And finally we also found when examining the activation pattern associated with the amygdala seed that reboxetine compared to citalopram had reduced connectivity within the caudate and putamen (p=0.001). These data suggest that antidepressant medications can differentially modulate RSFC outside of any change in mood and areas associated with emotional processing and reward in the brain. Such actions may be relevant to their functional effects in depression.
ME06

CORTICAL NEUROTRANSMITTER LEVELS IN YOUNG PEOPLE AT FAMILIAL RISK OF DEPRESSION: PROTON MAGNETIC RESONANCE SPECTROSCOPY FINDINGS

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Major depressive disorder is associated with changes in brain chemistry that may be elucidated using proton Magnetic Resonance Spectroscopy (MRS). In parieto-occipital regions, abnormal levels of neurotransmitters are found during episodes of major depression, with decreased GABA and increased glutamate reported. A similar pattern is also found in people who have previously been depressed but have now fully recovered. It is unclear whether these differences in GABA and glutamate reflect an underlying trait vulnerability to depression, or are an after-effect ('scar') of the episode of illness. To answer this question it is necessary to study people who are vulnerable to depression, but have not yet been depressed. A history of major depression in at least one parent is known to be associated with an elevated risk of developing depression. Young people (ages 16 to 21) with a family history of parental depression (FH+) were compared to a control group without such a history (FH-). All participants had no personal history of Axis I mental disorder and were free of any psychotropic medication. MRS measurements were taken from a 30x30x20mm voxel in parieto-occipital cortex using a Varian 3 Tesla scanner. Short-echo time PRESS, PRESS-J, and MEGA-PRESS acquisitions were obtained to allow quantitation of glutamate, GABA, and GLX (total glutamate + glutamine) relative to creatine as an internal control. Group differences were tested by multivariate analysis. MRS data were obtained for 24 participants with a family history of parental depression and 28 participants without a family history of depression. An effect of group was seen (F(6,43)=2.6, p=.032). FH+ participants had higher levels of glutamate within the voxel (p=.017), but did not differ from controls in levels of GABA (p=.65) or GLX (p=.89). These data suggest that increased glutamate levels in parieto-occipital cortex may represent a trait marker of depression vulnerability. By contrast, the lowered GABA levels seen after recovery from major depressive disorder may represent an effect of episodes of illness. Longitudinal studies are required to confirm this interpretation. This study was supported by the Medical Research Council.

ME07

EFFECT OF ANAESTHESIA ON PHARMACO-ELECTROENCEPHALOGRAPHY OF AMPHETAMINE

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Reports of heterogeneity of cerebral responses under different anaesthetics point to the need for further characterisation prior to choosing the suitable anaesthetic for a simultaneous pHMRI and EEG study. α-chloralose is mainly used in rat fMRI as it preserves BOLD response to forepaw stimulation better than volatile anaesthetics (Austin et al, 2005, NeuroImage 24, 92-100). However, many pHMRI studies employ gaseous anaesthesia. We chose amphetamine for its well-characterised ability to induce changes in cerebral blood flow, neural and metabolic activity, that have been correlated with dopamine release and behavioural activations (Detre et al, 1990, NMR Biomed, 3, 272-8; Segal & Kuczynski, 1987, J Pharmacol Exp Ther, 242, 917-26). The aim of the study was to assess the extent to which three frequently used anaesthetics affect brain EEG activity in response to amphetamine. SD rats were implanted with unipolar electrodes in the hippocampus, the entorhinal cortex and on the cortical surface. Seven days after electrode implantation, the animals were anaesthetised with either halothane, isoflurane (1% and 1.5% in 20:80 02:air mix respectively, n=6/group) or α-chloralose (65mg/kg iv bolus followed by 30 mg/kg/hr, n=4/group); a 60 min baseline EEG was recorded prior to administration of 1.4 mg/kg i.p. amphetamine, or vehicle. EEG was then recorded for further 90 min. EEG signals were processed in Matlab with a FFT and split into the delta, theta, alpha and beta frequency bands. Data was normalized to percentage of baseline prior to analysis. Under halothane, there was no significant effect of drug on the EEG (2-way ANOVA) although a trend was noted toward EEG power reduction in the entorhinal cortex, as well as reduction of delta and theta frequency band powers in the cortex. Under isoflurane, we observed a significant reduction in EEG power in the theta and alpha band for all three locations and in the beta band for the hippocampus and entorhinal cortex. In contrast, under α-chloralose there was no effect of amphetamine, but a reduction in EEG power over time was noted in both groups. The lack of amphetamine effect under chloralose is consistent with reported α-chloralose inhibition of dopamine transmission (Chen et al, 2000, ISMRM, Denver, USA). Decreases in EEG activity under isoflurane, and a similar trend under halothane, are consistent with the similar effects of amphetamine shown previously (Berridge & Morris, 2000, Psychopharm, 148, 307-13). Despite α-chloralose’s efficacy in IMR paradigms, volatile anaesthetics may be better choice for dopaminergic compounds. Funding provided by the BBSRC and GSK as a CASE award PhD

ME08

DETECTION OF ACUTE EFFECTS OF HYDROCORTISONE IN THE HIPPOCAMPUS USING PHMRI

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Evidence suggests that impaired hippocampal function is of key importance in the pathogenesis of depression. The hippocampus contains a high concentration of both mineralocorticoid (MR) and glucocorticoid receptors, and experimental administration of corticosteroids has been reported to mimic the impairments of declarative memory seen in depression (Hinkelmann, K. et al. (2009). Biological Psychiatry 66(9): 879-885; McAllister-Williams, R. H. et al. (2002). Psychopharmacology 160(1): 74-83). Our research investigated whether the direct effects of acute administration of hydrocortisone could be detected in hippocampal function both directly, and in modulating brain responses to cognitive activation, using pharmaceutical functional magnetic resonance imaging (pHMRI). 14 healthy volunteers (age 19-30) were recruited to this within-subject placebo controlled crossover study, with equal numbers of male and female participants. They received either 100mg hydrocortisone or saline as a rapid intravenous bolus given over 90 seconds during a high resolution pHMRI scan. Subsequently, subjects underwent the NBack task during fMRI scan and a different version of the NBack task out of scanner. Results were analysed with SPM8 using a time series analysis for the infusion and standard random effects analysis for the NBack task. Significant results are reported at P<0.001 in the hippocampus (region of interest). Hydrocortisone infusion caused a significant, time-dependent and focal increase in MR BOLD signal in hippocampus reaching a maximal effect after 16 minutes. During the NBack task following the saline infusion, the hippocampus showed an increase in BOLD signal after the hydrocortisone infusion. The activation seen with the task in dorsolateral prefrontal cortex was unaffected by hydrocortisone. Behaviourally there was a trend towards decreased performance at the highest level of both versions of the task following hydrocortisone administration (p<0.10). The results suggest that acute hydrocortisone has rapid direct and modulatory influences on hippocampal function, probably acting through membrane-bound MR. It has been suggested that these receptors act to modulate glutamate release in hippocampus (Olijslagers, J. E. et al. (2008). European Journal of Neuroscience 27(10): 2542-2550). Hydrocortisone infusion pHMRI may be a useful tool to investigate hippocampal corticosteroid receptor function in depression. Financial support from The University of Manchester Magnetic Resonance Imaging Facility and the NIHR Manchester Biomedical Research Centre is acknowledged.
ME09

FMRI- A NON-INVASIVE TECHNIQUE TO ASSESS CHANGES IN THE BRAIN FOLLOWING INTRAPERITONEAL GLUCOSE ADMINISTRATION IN A FASTED RAT MODEL

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Introduction: All neurons need to consume glucose to fulfill their metabolic needs. Glucosensing neurones regulate membrane potential and firing rates in response to ambient glucose levels, and are generally located in areas involved in neuroendocrine function, nutrient metabolism and energy homeostasis. Methods: A time-series of BOLD-MRI scans were acquired of fasted anaesthetised SD rats pre/post intraperitoneal (i.p.) administration of isotonic glucose or isotonic saline. Subjects were recovered for 40 minutes prior to collection of terminal cardiac blood samples for glucose measurements. SPM5 software was used to movement correct and normalise masked images to a rat brain template, prior to Gaussian smoothing (2x in-plane resolution). The random effects general linear model (2nd level analysis) was applied to test for changes in the BOLD signal between pre- and post images in the time-series. SPM[t] distribution was thresholded at p<0.001 (uncorrected for multiple comparisons). Results: Plasma glucose concentrations were significantly higher after glucose (223.2±53.4mg/dl, mean±sd) compared to saline (147.9±22.16mg/dl, P<0.05). Widespread increases in BOLD-MRI signal after glucose administration was observed in the cerebellum, brainstem, other hindbrain and midbrain regions, hippocampus, hypothalamus, thalamus and striatum. Less extensive but significant changes were observed following saline, with only small increases in the posterior cortex and hippocampus (unilateral). Both treatments showed significant BOLD-contrast decreases in the prefrontal cortex and olfactory regions, possibly related to i.p. volume administration. Significant activations were observed in the hypothalamic region which is consistent with the known presence of glucosensing neurones in the ventromedial nucleus containing higher proportions of GE neurones (Dunn-Meynell et al., 2002). Diabetes, 53: 549-598) and hippocampal areas where the neurones become more depolarized, (excitable) with increasing glucose concentrations (Huang et al., 2007). J. Neurosci. Res., 85: 1468-77). However, the changes observed following glucose dosing may also result from insulin action in the brain: insulinoma, arising from glucose-stimulated release of insulin from pancreatic beta cells. No transient decrease in activity in the hypothalamic as previously reported was observed (Smeets et al., 2007). Am. J. Physiol., 293: E754-8, Dunn-Meynell et al., 2002). Diabetes, 53: 549-598) following i.p. glucose administration. Our methodology may be insensitive to this transient small decrease but sensitive to changes occurring throughout the brain. Further studies are needed to determine the source of the changes in the BOLD-MRI signal following i.p. glucose administration. Conclusion: BOLD-MRI may be used to a non-invasive tool assess the functional role of nutrients in the brain under different physiological states. Funded by Department for Neuroimaging, IOP.

ME10

EFFECTS OF ACUTE TRYPTOPHAN DEPLETION ON CINGULATE CORTEX REACTIVITY AND BRAIN CEREBRAL BLOOD FLOOD – AN MRI STUDY

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Introduction: Experimentally, acute tryptophan depletion (ATD) is used to reduce human central serotonin levels. While full dose ATD (100g) often causes acute return of depressive symptoms in patients with a history of depression, low-dose ATD (31.5g) does not alter mood. However, low dose ATD has been shown to affect cognition [Munafo et al. J Psychopharmacol 2006; Hayward et al. Biol Psychiatry 2005]. Two fMRI studies showed that ATD increases neural response to conflict in Stroop tasks in healthy volunteers [Horacek et al. Physiol Res 2005, Evers et al. NeuroImage 2006]. However, no neuroimaging studies have been performed with recovered depressives using such methods. Tasks: We measured 21 currently unmedicated, recovered (>6 months), unipolar depressed patients (10 female). Subjects were randomly assigned 31.5g ATD, or a balanced mixture containing tryptophan (BAL) as a placebo control, between-subjects. MRI scanning began five hours later. A lexical counting affective Stroop task was used. 1-4 copies of a word were presented, subjects responded using a four-button box. Words were positive, neutral, socially threatening e.g. “humiliated” and physically threatening e.g. “injury.” Trails lasted 2s. 20s word blocks alternated with 20s fixation cross baseline. We also used arterial spin labelling (ASL) MRI in order to investigate the effects of serotonin manipulation on resting-state brain haemoperfusion. Results: As expected, low-dose ATD had no mood effects. ATD increased neural reactivity across all words in a cortical midline network of task-related areas, including the anterior cingulate cortex (ACC) (whole-brain fully corrected, thresholded Z>2.3 cluster significance P<0.05). Anatomical region-of-interest analysis confirmed greater activation in the rostral ACC (ANOVA main effect of group p=0.01) and trend greater activation in the dorsal ACC (p=0.054) in the ATD group vs the BAL group. ASL showed no group differences on resting-state haemoperfusion in any brain region (even at an extremely liberal uncorrected p=0.01 threshold), suggesting that low dose ATD has no effects on baseline blood flow. This provides support to the idea that observed effects of ATD on neural activation during tasks such as the fMRI data from this study, and other studies, is not driven by baseline haemodynamic effects. Conclusions: Low-dose ATD increased cortical midline (including ACC and PCC) responses in a Stroop task. This effect was not related to baseline haemoperfusion in these regions. This finding confirms earlier findings of increased ACC reactivity with ATD in healthy volunteers, and extends them to recovered depressives. Funding: Funded by the Medical Research Council.

ME11

EXPECTANCY AND SURPRISE INFLUENCE ATTENTION TO EMOTIONAL INFORMATION

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Background: Threatening stimuli capture attention particularly when unexpected. This implies the existence of a neural system which tracks threat expectancy and deployment accordingly. We assessed whether a Bayesian learning computational model (BLM), analogous to the Rescorla-Wagner model used to track reward expectation, predicted both behavioural and neuroimaging measures of attention to threat. We also assessed whether trait anxiety was associated with the use of expectancy to control attention to threat. Methods During functional magnetic resonance imaging (fMRI) 29 healthy volunteers (18 female) completed a task which varied the frequency of threatening stimuli. Trait anxiety was measured prior to scanning. For each individual a trial-by-trial estimate of threat expectation and surprise was obtained from the BLM. This model derived estimates were then entered into multiple regression analyses at the individual level in which reaction time and blood oxygen level dependent (BOLD) signal were the dependent variables. The regression analyses provide an estimate of the model’s ability to explain behavioural and neuroimaging measures of attention. For the reaction time data the regression slopes from individual subjects were tested against zero using a one sample t-test. fMRI analysis was performed using the default options of the FMRIB software library (FSL) package. This includes correction for multiple comparisons across the whole brain using Z=2.3 and p<0.05. Results Attention, as indexed by speed of response [t(28)=2.24, p<0.03] and visual cortex activity [p<0.001], was increased when a stimulus was expected to be threatening. The expectancy signal was also observed in the orbitofrontal cortex (OFC; p=0.002) and right amygdala [p<0.001] suggesting a possible role for these areas in generating the signal. Increased surprise, regardless of stimuli valence, was also associated with increased attention as indexed by both reaction time [t(28)=2.34, p=0.03] and activity in the visual cortex [p<0.001]. In addition, surprise activated the anterior cingulate cortex [ACC; p<0.001]. A higher trait anxiety was associated with decreased expectancy signal in both amygdale [p<0.001] and subcortical ACC [p<0.001]. Conclusions A network of areas including OFC, the amygdale and ACC are involved in tracking the expectation of threat and deploying attention accordingly. The attentional control difficulties associated with anxiety may result from suboptimal use of this system. This study was supported by the Wellcome Trust
Background Carrying the short (S) allele of the 5-HTTLPR polymorphism has been associated with anxiety related traits, elevated risk for depression and an exaggerated amygdala response to fearful faces, as well as reduced grey matter volume in subgenual cingulate and amygdala. These functional and structural differences might underlie impairments in fronto-limbic integration and result in elevated amygdala-mediated arousal increasing the risk of depression. The aim of the current study was to extend earlier structural findings in healthy volunteers genotyped for the functional triallelic 5-HTTLPR G substitution, rs25531 (S/La/Lg), where/polymorphism, including an embedded A Lg allele is considered functionally similar to and grouped together with the S allele (L=La; S=S and Lg). Methods We included 22 S^+^ non-carriers (L"L" genotype) (13 females, mean age 30.2 years females, 36.2 years males) and 91 S^+^ carriers (30 females; mean age 34.6 for females, 40.7 for males). All volunteers were free from any lifetime psychiatric or neurological disorders. Structural MRI data were acquired on a 3T scanner [TR=9.6ms, TE=4.6 ms, flip angle=8, voxel dimensions 0.94×0.94×1.2 mm]. Image preprocessing utilised an optimised voxel-based morphometry (VBM) protocol. Effects of 5-HTTLPR on gray matter volume were examined using an analysis of covariance model with age and gender as covariates of no interest. Gray-matter volume changes were assessed statistically with one-tailed t-tests using a threshold free cluster-based approach with correction for multiple comparisons at the whole-brain level. In addition, regions of interest (ROI) for bilateral amygdala and subgenual cingulate were used. The genetic variants of 5HTTLPR rs25531 polymorphism were determined by the PCR reaction, followed by digestion with MspI restriction enzyme. Results Whole brain analysis revealed significantly reduced gray matter volume in S^+^ allele carriers vs L"L" homozygotes in inferior frontal gyral (MN1=x=62, y=-14, z=22, superior temporal gyrus (x=-8, y=-16, z=36) and anterior cingulate (x=54, y=18, z=22). There were no significant between-group differences in any of the a priori regions. Also, there were no regions that displayed greater volume in S^+^ allele carriers vs L"L" homozygotes. Conclusions We observed reduced grey-matter volume in S^+^ allele carriers vs non carriers in frontal, superior temporal and cingulate gyri. These results are similar in direction, but differ in location, with respect to earlier studies investigating the effect of the 5-HTTLPR polymorphism on gray matter in healthy participants. There is a need for consensus in volumetric analysis approaches as different methodologies may account for the inconsistencies across studies.

Background: In humans, immediate reflexive reactions to emotional stimuli are not always adaptive. In fact, we are widely able to voluntarily regulate our emotions in favour of reaching certain longer-term goals in the future. Recent imaging studies on the voluntary control of behaviour in healthy volunteers have shown that successful suppression of negative affect is related to decreased activation in limbic areas and increased activation in prefrontal cortical areas such as the anterior cingulate, the dorsolateral (DLPFC) and the ventrolateral prefrontal cortex. Patients with panic disorder are threatened by physical symptoms that they rationally understand as being harmless. Nevertheless, anxiety takes over during a panic attack, even in the most inconvenient situations. We tested the hypothesis that panic disorder is related to insufficient regulation of negative affect. Methods: Eighteen patients with panic disorder (PD) and 18 healthy controls without any current or past DSM-IV diagnosis (HC) participated in an fMRI study. They were presented with eight blocks of aversive pictures and instructed to either maintain or suppress the elicited negative emotion throughout the block. Before the experiment, all volunteers were trained to use reappraisal as a strategy of down-regulating their emotion. This strategy involves reinterpreting a picture in a way that makes the observer feel less negative about it. For instance, tears could be seen as a sign of happiness instead of grief. FMRI data processing was carried out using FSL. Z-statistic images were thresholded using clusters determined by z=2.3 and a (corrected) cluster significance threshold of p=0.05. Results: In a whole brain-analysis, suppression of negative affect was associated with decreased activation in areas relevant in emotional processing, such as the thalamus, the prefrontal, and the insular cortex, as well as increased activation in prefrontal areas. No group differences were found. Conclusions: The task used in this study suggests no reduced capability of voluntary suppression of negative affect in patients with panic disorder compared to healthy controls. Implications for cognitive-behavioural therapy with these patients will be discussed.

CORTICAL BLOOD PERFUSION FOLLOWING MDMA (“ECSTASY”) ADMINISTRATION IN RATS DETERMINED BY SPIN LABELLING OF ARTERIAL WATER COUPLED TO MAGNETIC RESONANCE IMAGING

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3,4-methylenedioxymethamphetamine (MDMA) is a popular recreational drug of abuse. It acts to increase extracellular serotonin (5-HT) by inducing its release from neuronal stores and this action is thought to underlie its psychotropic properties. In addition however, MDMA carries a risk of adverse cerebrovascular events as 5-HT plays an important role in the regulation of cerebrovascular tone. Recent advances in magnetic resonance imaging (MRI) have enabled measurement of cerebral blood flow (CBF) by contrast agent free approaches such as bolus-tracking arterial spin labelling (bASL) (Kelly et al., 2010, Journal of Cerebral Blood Flow and Metabolism, 1-10). The aim of the current study was to assess regional CBF changes in cortical fields following MDMA administration to rats using bASL MRI. Male Wistar rats were administered either saline (0.89%) or MDMA (20 mg/kg i.p.) and 3 hours later anaesthetised with 0.1 ml ketamine (100 mg/ml) and 0.1 ml xylazine (2%). Animals were placed into 7-Tesla MRI scanner (Bruker BioSpec 70/30 magnet system) and respiratory rate monitored continuously. A high resolution MR anatomical scan [T2-weighted Rapid Acquisition with Relaxation Enhancement (RARE)] was conducted followed by a continuous ASL sequence. The sequence consisted of the preparation interval containing the inversion pulse followed by snapshot Fast Low Angle Shot (FLASH) acquisition. Perfusion-weighted images were generated by subtracting control images. A recently developed quantitative model of cerebral perfusion was fitted to the experimental data using a least-squares fit. Mean transit time (MTT), a measure that represents the time for labelled spins to traverse the vasculature, and capillary transit time (CTT), a measure of the dispersion of the labelled bolus at region of interest, values were generated. Both MTT and CTT are inversely proportional to blood flow. MDMA induced a reduction in MTT and CTT values in multiple cortical fields including insular cortex, and primary and secondary motor cortices in comparison to saline treated controls (P < 0.05; two-way ANOVA). These effects were not evident 24 hours following drug administration. In conclusion, MDMA provoked an acute increase in cerebral blood flow in rats. Arterial spin labelling is a reliable, contrast free method of assessing cerebral blood perfusion in an animal model and is amenable for determination of CBF changes in response to pharmacological stimuli. This study was funded by Trinity College Institute of Neuroscience, Trinity College Dublin.
ME15
THE EFFECTS OF Δ9-THC ON WORKING MEMORY-RELATED BRAIN FUNCTION: A PHARMACOLOGICAL MRI STUDY

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Introduction: Cannabis use increases the risk for developing schizophrenia (Moore T.H. et al., 2007, Lancet, 370, 319-28). This suggests that abnormal endogenous cannabinoid neurotransmission is involved in the pathophysiology of this psychiatric disorder. One striking parallel between acute effects of cannabis and the cognitive phenotype of schizophrenia is working memory (WM) impairment. Although brain function underlying these working memory deficits in schizophrenia has been studied extensively, the neurophysiological correlates of acute cannabis-induced WM impairment are unknown. The purpose of the present pharmacological MRI study was to investigate the effect of Δ9-THC, the main psychoactive component in cannabis, on WM-related brain function. Methods: Nine right-handed healthy males participated in a double-blind, randomized, placebo-controlled, cross-over pharmacological MRI study. All subjects underwent two functional MRI sessions receiving THC (6 mg) or placebo using a Volcano vaporizer. Working memory was assessed with a parametric Sternberg item-recognition task consisting of letter sets with increasing WM load containing 1, 3, 5, 7 and 9 consonants. In SPM5, brain activation was compared between placebo and THC sessions. Regions of interest were defined based on pooled group activation maps for the load 7 – load 1 contrast (thresholded at t=4.5, p<0.05, corrected, clusters ≥ 10 voxels). Results: Performance accuracy on the WM task decreased with load in both conditions. However, with THC the onset of the decline started at a lower processing load compared to placebo. In addition, THC enhanced reaction times for all WM loads. Pooled group activation maps yielded a commonly found network of activated regions, including the bilateral insula, left middle and inferior frontal gyri, left precentral gyrus, left inferior parietal gyrus, right cerebellum and anterior cingulate cortex. This network showed higher levels of brain activation with rising WM loads (p<0.001). Compared to placebo, however, THC attenuated the increase in activity in the left middle insula for the higher WM loads (p<0.05). Conclusion: Δ9-THC induced load-dependent decreases in both task performance and brain activation critically involved in WM-related processes such as maintenance and rehearsal of information. These results suggest that THC compromises WM system capacity. This is in line with neurophysiological correlates of working memory dysfunction in schizophrenia, indicating that either efficiency or capacity of the WM system is reduced (Manoach D.S. et al., 1999, Biol Psychiatry, 45, 1128-37). Thus, our results confirm similarities between acute cannabis intoxication and the cognitive phenotype of schizophrenia. Would a cannabinoid antagonist alleviate WM deficits of schizophrenia patients? This study is performed within the framework of Top Institute Pharma.

MF01
SEROTONERGIC MODULATION OF FIELD POTENTIALS IN THE MEDIAL PREFRONTAL CORTEX

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Patients suffering from affective disorders exhibit changes in serotonergic neurotransmission and in the function of the prefrontal cortex. Here we have used in vitro electrophysiology in male, litter hooded rat brain slices to investigate the role of 5-HT receptors on synaptic transmission in the medial prefrontal cortex (mPFC). Electrically evoked field potentials (FPs) were recorded in the mPFC and used as a measure of synaptic transmission. The effects of glutamate and GABA receptor antagonists and 5-HT receptor agonists were examined. FPs in the mPFC contained distinct components. There was an initial short latency component (PC) followed by late latency components (C1, 2, 3 and 4). Two way repeated measures ANOVAs (component as repeated measure) with post hoc t- tests were used to examine the effects of drugs on these different components. The AMPA/kainate receptor antagonist DNQX (20 μM) significantly inhibited C1, 2, 5 and 4, but not PC indicating that C1, 2, 3 and 4 are postsynaptic components and PC is a presynaptic component (DNQX main effect F1, 5 = 20.4; p<0.006). The GABAA receptor antagonist bicuculline (3 μM) enhanced specific components of the EP. There was no main effect of 3 μM Bicuculline but there was a significant interaction (F3,18 = -10.9; p<0.001), post hoc tests revealed significant enhancement of C1 and 4 and inhibition of C2. These results indicate that the EP is partially mediated by GABA. 5-HT (10 and 30 μM) differentially inhibited the FP components. 30 μM 5-HT significantly inhibited C1 (41%), 2 (60%) and 3 (25%) (main effect F1, 10 = 44.4; p<0.001), whilst 10 μM 5-HT had no significant effect. There was no main effect of the 5-HT1A agonist 8-OH-DPAT (30 and 100nM). However, at 100 nM there was a significant interaction (F1,4 =9.69; p<0.04), post hoc tests revealed a significant inhibition of C2 (11%). These results suggest that 8-OH-DPAT partially mimicked the effect of 5-HT. The 5-HT2A/C receptor agonist DOI had no effect on any component of the FP. Our results support those from previous studies showing that FPs in the mPFC are mediated by both glutamate and GABA. Our results also indicate that 5-HT inhibits postsynaptic FPs in a concentration dependent manner. The effect of 5-HT is partially mediated by 5-HT1A receptors; however there is no contribution from 5-HT2A/C receptors. Further studies will continue to investigate the receptors mediating the effect of 5-HT. This study was jointly funded by the MRC and Schering Plough.

MF02
EFFECTS OF IN UTERO ANTIDEPRESSANT ADMINISTRATION ON ADULT BEHAVIOUR IN THE RAT

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Depression is a condition affecting over 121 million people worldwide, with an almost 2:1 ratio of female to male sufferers. Moreover, it has been estimated that the prevalence of depression during pregnancy is around 10%, thus representing a treatment dilemma. Amitriptyline (aMi), a tricyclic antidepressant, made up almost 60% of antidepressants prescribed in the UK in 2007. As such, it is reasonable to assume that aMi could pass the placenta and be exposed to the developing fetus during pregnancy. Animal models are useful in this regard as they allow full experimental control over dose employed and dosing schedules, from which aetiological effects can then be determined. The present study investigates the effects of maternal oral administration of aMi on a range of behavioural parameters in the resultant offspring. Both male and female offspring were evaluated as previous studies suggest that there are sex differences in many behavioural tests. Pregnant females (n=4-5) received either vehicle (distilled water) or aMi (10 mg/kg) by oral gavage from gestational day 7 to 21. Open field (OF) and elevated plus maze (EPM) behaviour of separate offspring groups were then examined either at 1, 2, 3 or 4 months of age. Home cage locomotor activity and Morris water maze (MWM) tests were also carried out between the ages of 3 and 4 months. Data were analysed using Two-Way and Repeated Measures ANOVA with Post-Hoc tests. No effects of aMi treatment or sex were found at 1 month in either behavioural test. However, female offspring displayed significantly increased locomotor activity in the OF at 2 and 3 months, in the EPM at 2 and 4 months, and also in the home cage, when compared to their male counterparts. In addition, females had higher percentage open arm time spent in the EPM at 4 months. aMi-induced effects consisted of a reduction in open arm entries in the EPM in females at 2 months, reduced distance moved in males at 3 months, and an increased distance moved in females in the OF, when compared to their control counterparts. No changes in MWM behaviour were evident between groups. In conclusion, maternal oral administration of aMi produced sex-specific transient effects in the EPM and OF, without having any effect in the home cage or MWM. Sex has an effect on locomotor activity from 2 months, but does not lead to differences in spatial memory in adulthood. Research is funded by NUI, Galway Science Fellowship.
**MF03**

**THE KYNURENE PATHWAY IN HUMAN HIPPOCAMPAL STEM CELLS: REGULATION BY PRO-INFLAMMATORY CYTOKINES**

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Increasing amounts of data suggest that inflammatory responses have an important role in the pathophysiology of depression. In particular, it has been repeatedly shown that depressive patients have elevated levels of pro-inflammatory cytokines, including interleukin-1beta (IL-1beta) and IL-6. In addition, increased levels of pro-inflammatory cytokines induce the production of neurotoxic, and potentially neurodegenerative, end-products of the kynurenine pathway. A key player is the enzyme indoleamine 2,3-dioxygenase (IDO), which initiates this pathway by catalysing tryptophan into kynurenine. Kynurenine can then generate the neurotoxic quinolinic acid, an NMDA receptor agonist, through steps catalyzed by kynureninase (KYNU). Recent studies show that interferon-gamma and tumor necrosis factor-alpha mediate the upregulation of IDO. However, the exact regulation of the entire pathway by other pro-inflammatory cytokines is not well understood. This prompted us to investigate the effect of IL-1beta and IL-6 on the kynurenine pathway in human brain cells. We used a conditionally immortalized human hippocampal stem cell line (HPC0A07; ReNeuron, UK) as a model. Cells were incubated for 24 hours with either IL-1beta (10 ng/ml) or IL-6 (50 ng/ml). In order to analyze molecular mechanisms involved, cells were treated with the p38 mitogen-activated protein kinase (MAPK) inhibitor SB202190 (5microM) or the glucocorticoid receptor agonist dexamethasone (1microM). RNA was extracted and reversed transcribed to cDNA. Quantification of mRNA expression of IDO and KYNU was performed by quantitative PCR, using beta-actin and GAPDH as housekeeping genes. Our studies show an upregulation of mRNA for IDO (70-fold increase) and KYNU (12-fold increase) in response to IL-1beta. Co-treatment with either SB202190 or dexamethasone significantly reduced this upregulation. When cells were treated with IL-6, no significant changes in the expression levels of IDO or KYNU were observed. As we have previously shown that treatment with IL-1beta induces the production of IL-6 in these cells, the observed effect on IDO and KYNU regulation can be assigned to a direct effect of IL-1beta. These data show that IL-1beta regulates the kynurenine pathway by induction of enzymes contributing to the production of neurotoxic metabolites. The observation that dexamethasone decreases this induction indicates the involvement of the glucocorticoid receptor pathway. The signaling mechanisms are dependent on p38 activity. Our findings provide further information on the molecular pathways involved in the cytokine-induced neurotoxicity in the brain.

**MF04**

**ANTIDEPRESSANT-INDUCED CHANGES IN NEUROGENESIS ARE DEPENDENT ON THE GLUCOCORTICOID RECEPTOR**

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Antidepressants are known to increase adult hippocampal neurogenesis and to promote neuronal differentiation in animal models, but the underlying molecular mechanisms are still unknown. It has been shown that antidepressants enhance the function of the glucocorticoid receptor (GR) in cellular models, laboratory animals and humans. This effect is common for chemically unrelated antidepressants and ultimately results in enhanced GR-mediated gene transcription. Using a novel in vitro assay in human hippocampal stem cells, we want to investigate whether antidepressants increase neuronal differentiation by modulating the GR, and we want to explore changes in gene expression of the GR-target genes p27Kip1 and p57Kip2, which induce neuronal differentiation. A human hippocampal stem cell line (HPC03A07, ReNeuron, UK) was incubated with the antidepressant sertraline (SERT) and the GR-antagonist RU486. To investigate changes in neuronal differentiation, cells were treated for 10 days and immunocytochemistry for the neuronal marker microtubul-in-associated protein 2 (MAP-2) was applied to identify mature neurons. The fraction of MAP-2 positive cells over total cells was determined by cell counting. To investigate changes in stem cell proliferation, cells were treated for 72 hours, and the synthetic nucleotide 5-bromo-2-deoxyuridine (BrdU), which gets specifically incorporated into dividing cells, was added for 4 hours at the end of the treatment. Dividing cells were detected by immunostaining for BrdU. Gene expression was analyzed during cell proliferation by quantitative real-time PCR. In all experiments, data was analyzed by Student’s t-test and results are expressed as % of change from the vehicle treated control conditions (mean ± SEM). SERT (1 µM) increased the number of MAP-2 positive cells if treated for 10 days (+28.4%±2.4% compared with control, p<0.0021, n=5). Co-treatment with SERT and the GR-antagonist RU486 (50 µM) abolished this effect (-6.8%±11.5% compared with control, p>0.05, n=5). Moreover, SERT decreased the number of BrdU-positive, dividing cells (-16.4%±1.8% compared with control, p<0.0002, n=7). Co-treatment with RU486 (50 µM) also abolished this effect (-1.9%±4.1% compared with control, p>0.05, n=7). Furthermore, SERT increased the expression of the GR-target genes p27Kip1 (+51%±9.7% induction over control, p=0.036, n=5) and p57Kip2 (+48.1%±10.8% induction over control, p=0.042, n=5) after 12h of treatment. In conclusion, we demonstrate that sertraline increases neuronal neurogenesis and decreases neuronal differentiation by modulating GR in our cells. Our results indicate that this effect may be mediated by sertraline-induced expression of the GR-target genes p27Kip1 and p57Kip2. This work was funded by the Biomedical Research Centre and Medical Research Council.

**MF05**

**THE ROLE FOR SEROTONIN IN THE ANTIDEPRESSANT-INDUCED EXPRESSION OF NG-NITRO-L-ARGININE, IN THE RAT FORCED SWIMMING TEST**

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Nitric oxide synthase (NOS) inhibitors display antioxidant activity in the forced swimming test (FST) with a behavioural profile suggestive of a serotoninergic mechanism of action. The present study determined regional serotonin (5-HT) synthesis and metabolism changes associated with the nitric oxide synthase (NOS) inhibitor N(G)-nitro-L-arginine (L-NA) and the influence of 5-HT receptor blockade in the antidepressant-like actions of L-NA in the forced swimming test (FST). Regional effects of L-NA (5,10 and 20mg/kg, i.p.) on tryptophan hydroxylase (TPH) activity, the rate limiting enzyme for 5-HT synthesis, were determined by measuring accumulation of the transient intermediate 5-hydroxytryptophan (5-HTP) by high performance liquid chromatography, following in vivo administration of the amino acid decarboxylase inhibitor, NSD 1015 (100mg/kg, i.p.). All data were analysed by one or two way ANOVA followed by Dunnett’s or Student Newman Keuls post hoc test and results compared respectively. Differences between treatment groups were deemed significant when P<0.05. As previously reported, L-NA (5-20mg/kg, i.p.) dose dependently provoked an antidepressant-like response in the FST evident as a reduction in immobility and an increase in escape oriented swimming behaviour in the FST (P<0.05). L-NA (20mg/kg, i.p.) increased 5-HT accumulation, particularly in the amygdaloid cortex, following exposure to the FST (P<0.001). L-NA also provoked an increase in regional brain 5-HIAA concentrations (P<0.023) and in the 5-HIAA:5-HT metabolism ratio (P<0.001). Co-treatment with NSD-1015 failed to modify the antidepressant-like behavioural effects of L-NA in the FST. Sub-active doses of L-NA (1mg/kg, i.p.) and the 5-HT re-uptake inhibitor fluoxetine (2.5mg/kg, i.p.) acted synergistically to increase escape oriented swimming behaviour indicative of an antidepressant-like effect in the test (P<0.05). Co-treatment with the non-selective 5-HT receptor antagonist metergoline (1, 2 and 4mg/kg, i.p.), attenuated the L-NA (20mg/kg)-induced reduction in immobility (P<0.05) and increase in swimming behaviour (P<0.05). Metergoline alone however provoked an increase in immobility (P<0.01) and a reduction in swimming behaviour (P<0.05) in the test. A similar response was obtained following co-treatment with the preferential 5-HT2A receptor antagonist ketanserin (5mg/kg, i.p.) and the 5-HT2C receptor antagonist RO-403440 (5mg/kg, i.p.). Co-treatment with the 5-HT1A receptor antagonist WAY 100635 (0.3mg/kg, i.p.) or the 5-HT1B receptor antagonist GR 127935 (4mg/kg, i.p.) failed to influence the antidepressant-like activity of L-NA. Taken together these data provide further support for a role for 5-HT in the antidepressant-like properties of the NOS inhibitor L-NA in the FST. This work was funded by Health Research Board of Ireland.
BRAINSTEM SEROTONIN TRANSPORTER ABNORMALITIES IN HUMAN IMPULSIVE AGGRESSION CORRELATE WITH IMPAIRED SET-SHIFTING, INCREASED RISK TAKING, AND CHILDHOOD ADVERSITY

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Altered serotonergic neurotransmission plays a major role in the pathophysiology of impulsive aggression (IA). Serotonin (5-HT) transporter (SERT) availability is reported to be reduced in the anterior cingulate (ACC) in IA (Frankle et al. 2005, American Journal of Psychiatry 162(5):915-23) using positron emission tomography (PET). However, this has not been replicated and no studies have compared neurobiological findings with neuropsychological impairments. We therefore aimed to further investigate SERT abnormalities associated with high IA in a population-derived sample, controlling for callous-unemotional (CU) personality traits, using the SERT-selective PET tracer 11C-DASB. Neuropsychological and childhood adversity data were acquired and used to correlate with SERT availability. Healthy drug-free males were identified who scored within the highest (n=10) and lowest (n=12) extremes of impulsivity and aggression (greater than 1.5 SD above or below the population mean, respectively). Both groups were well matched for age, IQ and low CU ratings. All subjects underwent 11C-DASB PET, and SERT availability in multiple brain regions was calculated as binding potential (BPND). Regional SERT BPND values were compared between groups, and correlated with measures of executive function (Tower of London and SET-shifting from the CANTAB test battery; stop signal, IOWA gambling task), and childhood adversity scores. SERT availability was significantly increased (+29.4±9.3%; p=0.001) in the brainstem in high-IA compared to low-IA subjects. We also found a widespread, reduction in SERT across neocortical regions (-2.3±6.5%; p=0.03), but no difference in the ACC. Within the high-IA group, brainstem SERT BPND was significantly (p<0.05) positively correlated with preoperative responding on set-shifting and impaired reward decision making. SERT availability was found to be significantly (p<0.05) positively correlated with the degree of childhood trauma. Our data support the hypothesis that 5-HT function is dysregulated in males with high levels of IA, with SERT substantially increased in brainstem and modestly reduced in neocortex. The correlation with neuropsychological impairment suggests that brainstem 5-HT abnormalities may have a causal role in executive function deficiencies in IA that lead to aggression. The correlation with childhood adversity scores, reported here for the first time, suggests that 5-HT dysregulation in IA may be (at least partially) neurodevelopmental in origin. Our data do not support a previous report of reduced ACC SERT. While acknowledging the need for replication, our novel findings of increased brainstem SERT, and its association with neuropsychological impairment and childhood adversity, significantly extend previous PET findings.

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**MF06**

**MF07**

TESTING THE ROLE OF SEROTONIN IN THE MANAGEMENT OF VALUABLE BUT FINITE RESOURCES

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**Introduction.** Managing valuable but finite resources over the longer-term is an important individual skill, and, as part of a wider group of individuals, is also a cornerstone of social activity. Serotonin has been implicated in decision-making at an individual level and in social contexts. Here, we investigated the effects of reduced serotonin activity on resource management in healthy adults both individually, and as part of a group.

**Methods.** Young, healthy adults were screened to exclude cases of previous or current mood disorder before completing a within-subject, double-blind tryptophan depletion protocol. Participants drank an amino acid drink that either contained the serotonin precursor, tryptophan (n=15; T+ treatment) or did not contain tryptophan (n=19; T- treatment). State positive and negative affect were taken at baseline and +5 hours.

Participants completed 2 resource dilemmas. In the first, 'singleton', game, participants were allowed to harvest monetary amounts from a single resource. Each harvest reduced the size of the resource, which was then replenished at a variable rate. The task was structured such that larger harvests led to rapid depletion of the resource. In the second 'group' game, participants completed a similar game with 3 individuals who shared access to the common resource. These players' behaviour was manipulated in order to determine how tryptophan depletion influenced responses to others' harvesting choices. Sometimes, 1 or 2 players over-harvested (putting the resource under pressure); at other times, 1 or 2 players harvested cautiously (increasing resource size).

**Results.** Total plasma tryptophan was significantly reduced for participants in the T- compared to T+ condition, but state affect was differentially unaffected. In the singleton game, participants who received the T- treatment were significantly more influenced by the size of the current resource when deciding how much to harvest compared to non-depleted controls, and showed a different pattern of integrating the recent fluctuations of resource size when adjusting their harvesting behaviour. In the group game, participants who received the T- treatment over-harvested larger resources when most other players were harvesting cautiously, but harvested cautiously when one other player was harvesting aggressively. Overall, T- participants also made fewer points, and sustained the resource less, in the group game compared to T+ participants.

**Conclusions.** Serotonin activity influences the management of valuable resources owned individually as well as those shared with other individuals. Serotonergic dysfunction may contribute to poor resource management in psychiatric illness and to maladaptive responses in socially inter-dependent contexts. This research was supported by a Medical Research Council award. PIC has been a paid member of advisory boards of Eli Lilly, Servier, Wyeth and Xytis and has been a paid lecturer for Eli Lilly, Servier and Glaxo Smith Kline.
MF08
IS THE INTERACTION BETWEEN LIGHT AND CLONIDINE ON THE PUPIL WAVELENGTH DEPENDENT?
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Pupil diameter at any time reflects the balance between the opposing activities of the sympathetically innervated pupil dilator and the parasympathetically innervated constrictor muscles of the iris. Light and the n2-adrenoceptor agonist clonidine have synergistic constrictor effects on the pupil: light constricts the pupil by activating the parasympathetic output ("pupillary light reflex"), and clonidine by inhibiting the sympathetic outflow [Samuels and Szabadi, 2008, Curr. Neuropsychopharmacol. 6:245-285]. Short wavelength (blue) light is more effective than long wavelength (red/orange) light in evoking the light reflex, due to the stimulation by blue light of melanopsin-containing intrinsically photosensitive retinal ganglion cells that rise to the light reflex pathway [Kawasaki and Kardon, 2007, J. Neuro-Ophthalmol. 27: 195-204]. We compared the effects of clonidine on pupil constriction to blue and orange light stimuli. 16 healthy male volunteers, aged (mean±SEM) 24.9±2.2 years, participated in two sessions (clonidine hydrochloride 0.2 mg or placebo) one week apart, according to a double-blind balanced design. Blue (472 nm) and orange (607 nm) light pulses (30 s), matched for intensity (10, 100, 1000 Cd m-2), were delivered to the right eye; pupil diameter was monitored with an infrared television pupillometer. The maximum constriction during the initial 2 s ("light reflex amplitude") and the mean constriction during the subsequent 28 s ("sustained constriction") were analysed separately. Altemness was assessed using visual analogue scales (VAS), critical flicker fusion frequency (CFF), and the Pupillographic Sleepiness Test to record and analyse pupillary sleepiness waves [Hou et al., 2007, Psychopharmacology 195:41-59]. Heart rate, blood pressure and salivation were also recorded. Data were analysed with ANOVA (significance criterion: p < 0.05). Blue light evoked larger light reflex responses [F(1,15)=79.5] and sustained constriction [F(1,15)=31.4] than orange light. Clonidine had no effect on light reflex amplitude, whereas it enhanced sustained pupil constriction, in equal measure, to both blue and orange light [F(1,15)=9.1]. Clonidine reduced VAS alertness and CFF, and increased pupillary sleepiness waves, consistent with its sedative effects, and reduced blood pressure, heart rate and salivation, consistent with its sympatholytic effects. The interaction between light and clonidine was not wavelength dependent. It was, however, a function of stimulus duration: sustained pupil constriction was sensitive to clonidine while initial constriction ("light reflex amplitude") was impervious to it. This may reflect that the initiation of pupil constriction to light mainly by parasympathetic activity and its maintenance during prolonged stimulation by sympathetic activity. Funded internally (Psychopharmacology Laboratory, University of Nottingham).

MF09
THE IMPACT OF HOUSING CONDITIONS ON BEHAVIOURAL RESPONSES TO CERTAIN PSYCHOTROPIC DRUGS IN THE RAT
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Environmental enrichment (EE) is an animal husbandry practice which involves enhancing an animal’s environment, with the goal of improving animal welfare. Employing physical and social enrichment provides continual sources of dynamic interaction for animals. Despite being a well-established discipline in behavioural science, the consequences of EE on behavioural pharmacological tests have not been extensively examined. The purpose of this study was to examine the consequences of EE (or isolation housing) on a range of behavioural pharmacological tests in the rat. Male SD rats (N=72) were randomly assigned to the 3 housing conditions; IC (isolation) and SC (standard group-housed) were housed singly or in groups of four in standard cages (42 x 25.5 x 20cm), whilst the EE (environmentally enriched) group were housed in groups of four in larger cages (54 x 38 x 19cm) enriched with a variety of wooden, cardboard and plastic toys/objects. After 4 weeks of housing, the pharmacological impact was examined in the following pharmacological 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); Morphine (MOR: 0, 2, 5, 10 mg/kg s.c. 30 min prior to test) on latency in the hot plate test (HPT); Diazepam (DZP: 0, 0.75, 2.5, 5 mg/kg i.p. 30 min prior to test) on anxiety behaviour in the elevated plus maze (EPM). All drugs produced the anticipated effects in their respective tests. One-way ANOVAs revealed that the IC animals showed the most pronounced responsiveness to MOR, DMI and DZP in their respective tests, when compared to SC and EE conditions (p<0.05). A considerable blunting of the dose response effect was observed in the EE group with regards to DMI and DZP, when compared to the other housing conditions. There were no main effects of housing on responses to psychotropic drugs in behavioural tests. There is some evidence of differential dose-responses as a result of housing condition as animals housed in EE appeared to show less sensitivity to the behavioural effects of DZP and DMI than SC and IC controls and IC animals exhibited the clearest dose response effects to doses of DZP, DMI and MOR. Previous research has suggested that housing conditions may alter neurotransmitter levels in the brain, leading to altered sensitivity to psychotropic drugs. Follow-up post-mortem analysis of central neurotransmitter levels will help to interpret these findings. ACKNOWLEDGEMENT: Supported by the Irish Research Council for Science and Technology (IRCSET)

MF10
LATENT INHIBITION IN D1 Dopamine RECEPTOR KNOCK OUT MICE
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Latent inhibition (LI) describes the observation that a previously exposed, inconsequential stimulus is less effective in generating a conditioned response when compared to a novel stimulus. Psychomimetic drugs such as amphetamine have been shown to disrupt LI, a disruption that can be attenuated by haloperidol. In conditions of low initial LI administration of dopamine D2 receptor antagonists such haloperidol can enhance LI. Studies with D2 KO mice have provided evidence amphetamine induced disruptions of LI are not dependent on the D2 receptor. This would suggest a role for other dopamine receptor subtypes in the mediation of amphetamine disrupted LI. The aim of this study was to examine the potential role of the D1 receptor in amphetamine induced disruption of LI using congenic D1 receptor knockout mice (KO). Male and female D1 KO (-/-) and wild-type (+/+) mice were water restricted for seven days. On days 8-13 the mice were trained to lick water from a sipper tube in conditioning chambers. On day 14 the mice were injected i.p. with either amphetamine (2.5mg/kg) or saline vehicle. Twenty minutes after the injection the mice were placed in the chambers and either pre-exposed (PE) to 60 85d tones or left in the chambers for the same amount of time without the stimuli (NPE). On day 15 the mice received the same drug treatments and were placed in the chambers to be conditioned with two pairings of the conditioning stimuli (the 85d tone) and footshock. The mice underwent lick training to re-establish licking behaviour on days 16 and 17 and on the following day LI was tested. For the test sessions the mice were placed in the conditioning chambers and after 90 licks the CS was turned on and remained so until 100 licks had been performed. The time taken to perform licks 81-90 (A) and the time taken to perform licks 90-100 (B) was recorded and used to calculate the suppression ratio using the formula SR=A/(A+B). LI was established in both the wild-type (NPE 0.09±0.001;PE 0.1±0.04) and D1 KO mice (NPE 0.04±0.05;PE 0.13±0.06; P<0.05) saline treated mice. In the wild-type mice, amphetamine treatment disrupted the establishment of LI (NPE 0.05±0.02; PE 0.03±0.06; P=0.05). Amphetamine did not disrupt LI in D1 KO mice (NPE 0.01±0.01; PE 0.10±0.03) and ANOVA with appropriate post hoc analysis) These data suggest a role for the D1 receptor in amphetamine induced disruption of LI, a role that had not been identified by previous pharmacological studies. This work was funded by the Wellcome Trust
IN VIVO CHARACTERISATION OF 5'-AMINO AND AMIDINO-ALKYL NALTIRIDOLE DERIVATIVES AT THE KAPPA-OPIOID RECEPTOR

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Introduction: Selective kappa-opioid receptor (KOP) antagonists are currently being explored as potential treatments for a wide variety of disorders, including cocaine addiction, and mood disorders. However, the standard KOP antagonists, norbinaltorphimine (norBNI) and 5'-guanidinonaltiridole (GNTI), have a very slow onset, and very long duration of action (Carroll et al., 2004, European Journal of Pharmacology, 501; 111–119) which limits their utility for in vivo behavioural assays. The aim of this study was to investigate the KOP antagonist activity in vivo of 5'-Q(2-Aminomethyl) naltiridole (5-AMN) and 5'-Q(2-Methylamidino) butyl naltiridole (5-MABN), previously reported by our group and others, as selective KOP antagonists in vitro, (Jales et al., 2000, Bioorganic & Medicinal Chemistry Letters, 10: 2259-2261; Olmsted et al., 1993, Journal of Medicinal Chemistry, 36: 179). Methods: Antagonist activity was investigated in adult male CD-1 mice using the warm water (50°C) tail withdrawal assay. Animals were group housed, 8 weeks old at start of treatment and randomly assigned to drug-treated or control (0.9% saline w/v) groups (n=4-5 per group). Mice were injected (10ml/kg ip) with 5-AMN, 5-MABN or norBNI all at 1, 3, 5, and 10 mg/kg or saline. Antagonist activity was assessed 1, 3, 7, 14 and 21 days post-treatment against the KOP agonists U50488 (10mg/kg) and U69593 (32 mg/kg). The latency to the first sign of a rapid tail-flick was taken as the behavioural endpoint. A cutoff latency of 15 s was used to prevent tissue damage and the % maximum possible effect calculated [100 × (test latency – control latency) / (15 – control latency)]. Data were analysed by ANOVA and pairwise comparisons by Tukey’s test. Results: The two naltiridole derivatives blocked the antinociceptive effects of KOP agonists but differed in their pharmacokinetic profiles. At 1 day post-treatment, 5-AMN, but not 5-MABN, significantly blocked the antinociceptive effects of both KOP agonists, whereas 5-MABN only showed significant KOP antagonist activity at 3 days post-treatment (all P<0.05, compared to saline control). 5-AMN and 5-MABN were approximately equipotent to norBNI as KOP antagonists. Conclusion: We have shown that modification of naltiridole sidechains creates potent KOP antagonists with differing onset of activity in vivo. We are currently investigating their duration of action in vivo alongside their potential anxiolytic and antidepressant activity. Funding: University of Bath, The Royal Society (SBJ), and NIDA DA07315 (SMH).

A POSITIVE ALLOSTERIC MODULATOR OF NMDA (NRG-1) AMELIORATES AGE-RELATED DEFICITS IN RATS PERFORMING THE IDED SET-SHIFTING TASK

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A decline in cognitive function is associated with aging in humans and other animals. Preventing, slowing or even reversing this decline is a matter of growing interest in the context of our aging society. Tasks dependent upon working memory and attention seem to be particularly vulnerable with increasing age, and reliable performance deficits are seen, for example, in the ID/ED test of attentional flexibility. This task has been successfully adapted for rats: while humans associate one or more aspects of multidimensional visual stimuli with positive feedback, rats readily learn to associate textures or odours with the presence of reward in digging bowls. In a single session, a series of discriminations test acquisition, reversal learning and attentional set-shifting ability. In experiment one, we aimed to demonstrate that there was an age-related deficit on this task. Healthy adult rats were initially tested at 12 months (n=12) and again at 18 months (n=9), and this testing was repeated in a second cohort aged 14 months (n=8). To provide a frame of reference, all appropriate data from past experiments using young rats (3-6 months) was pooled (n=127). In experiment two, eight rats (four of the 18 month olds and four of the 14 month olds) were given the NMDA positive allosteric modulator Org-1 (10mg/kg, ip), and eight were given vehicle injections, once daily for 15 days. A deficit in reversal learning was observed in all rats, even at 12-months old, when compared to young rats. Org-1 significantly improved reversal learning, suggesting an attenuation of the age-related impairment (group*stage F6.84=2.241, p<0.05). It was not possible to draw conclusions about a deficit in set-shifting in these rats because there was no evidence in either experiment that rats had formed an attentional set, and therefore set-shifting could not be confirmed. Aged rats may be impaired in both reversal learning and set-formation (and perhaps also in set-shifting). Modulation of the NMDA receptor may be sufficient to overcome the former but not the latter deficit. The possibilities that impaired reversal learning or prior testing experience affected the aged rats' ability to form attentional set are under investigation. This work was funded by a Royal Society Industry Fellowship to VJB and a BBSRC CASE studentship to EAC, sponsored by MSD Newhouse (BB/F018134/1).

VALIDATION OF AN AIR-PUFF PASSIVE AVOIDANCE PARADIGM TO INVESTIGATE AVERSIVE LEARNING IN RAT MODELS OF CHRONIC PAIN

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Chronic pain is associated with cognitive deficits. Though the neural mechanisms involved remain unknown, there is considerable overlap in brain regions involved in pain and aversion, and so, aversive learning may be affected. Passive avoidance (PA) tests aversive learning in rodents and traditionally pairs aversive foot-shock with the dark compartment of a light-dark arena. This method may, however, be unsuitable for use in animal models of chronic pain, which induce hypersensitivity of the hind-paws. This experiment aimed to validate a PA method using air-puff, and to examine potential alterations in aversive learning in rat models of chronic pain. For the validation experiment, male Sprague-Dawley rats (225g-250g) were divided into air-puff and no air-puff groups. Scopolamine, which inhibits aversive learning, was used as a positive control. Rats were habituated to the PA arena. Air-puff rats received i.p. saline, scopolamine 1mg/kg or scopolamine 3mg/kg 23.5 hours post-habitation. No air-puff rats received saline. Thirty minutes later, rats were placed in the light side of the arena and latency to enter the dark was recorded. They were confined to the dark compartment and air-puff was applied (acquisition). Ninety seconds later, rats were returned to their homecages. No air-puff rats were confined to the dark compartment for 90 seconds, then returned to their homecages. Twenty-four hours later, rats were returned to the light side of the arena and latency to enter the dark was recorded (retention). To examine aversive learning in chronic pain, L5-L6 spinal nerve ligation (SNL) was used to model chronic neuropathic pain and intraplantar-injection of complete Freund’s adjuvant (CFA) was used to model chronic inflammatory pain in rats (175g-200g). PA habituation, acquisition and retention were performed as above, excluding drug treatments. Data analysed by Friedman’s ANOVA followed by Mann-Whitney/Wilcoxon tests (P<0.05). SNL and CFA animals developed characteristic symptoms of chronic pain; allodynia and hyperalgesia. Air-puff produced a significant increase in latency in the dark compartment in the retention test (i.e. PA). This response was dose-dependently reversed by scopolamine, indicating the response was due to learning. Air-puff also produced a significant PA response in both SNL and CFA groups. However, there was no difference between pain groups and their respective controls. These results suggest air-puff can be used as an alternative to footshock to induce a PA response, but aversive learning is not affected in rat models of chronic pain, under these experimental conditions. *Supported by the Irish Higher Education Authority (PRTL4).
MF14

VALIDATION OF LOCALISED VIRAL-MEDIATED GENE MANIPULATION IN THE RODENT PREFRONTAL CORTEX

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The use of viral vectors allows the spatial and temporal control of gene manipulation, creating rodents with restricted genetic modifications that can serve as effective disease models in which the function of the gene can be dissected. Viral-mediated gene manipulation enables targeting of specific brain regions in adult tissues, and thus overcomes the lack of regional specificity and developmental and compensatory effects which limit the usefulness of current constitutive knock-out animals. Recombinant adenovirus-associated viral (rAAV) vectors can transduce non-dividing cell types, such as neurons, efficiently and can maintain gene expression for sustained periods of time allowing behavioural effects of gene manipulation to be monitored closely. rAAV particles expressing enhanced green fluorescent protein (eGFP) under the control of the cytomegalovirus promoter were produced by the University of Pennsylvania vector core. In vitro validation: utility of the viral particles was tested in NG108-15 cells using a range of viral titres over multiple time points; presence of eGFP was used for the detection of infected neurons. In vivo validation: bilateral stereotaxic injections were used to deliver the AAV-eGFP particles or vehicle (PBS/3% sucrose (w/v)) into the prefrontal cortex of male Hooded Lister rats. The rats were allowed to recover from surgery for 1, 3 or 8 weeks (n=3/time point) prior to transcardiac perfusion. Brain sections were evaluated for viral transduction and spread via detection of eGFP expression. Co-staining was performed to identify which types of cells were targeted by the viral particles. In vitro validation of AAV-eGFP confirmed that viral titres between 2x1011gc/ml and 2x107gc/ml were sufficient to generate concentration dependant expression of eGFP in most of the cultured cells within 2-7 days post infection. In vivo use of AAV-eGFP resulted in eGFP positive cells around the area of the needle tract, specifically in the prefrontal cortex at multiple time points following surgery. Several subtypes of cells were transduced by the viral particles. We demonstrate here that the injection of rAAVs at these titres allows for the localised transduction of cells in the prefrontal cortex, and that this can be observed at several time points and in specific cell types. Thus, rAAVs allow targeting of specific brain regions and generation of sustained expression, permitting behavioural testing to be performed. These findings will allow us to use this technique for producing genetically modified animals, to investigate the pathophysiological role of schizophrenia candidate genes in discrete regions of the adult rodent brain. Funding provided by a BBSRC CASE studentship in collaboration with GlaxoSmithKline.

TA01

MALE SEXUAL DYSFUNCTION IN SCHIZOPHRENIA: RELATIONSHIP WITH DRUG TREATMENT, PROLACTIN AND DRD2 GENOTYPE

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Sexual dysfunction induced by antipsychotic drug treatment is under-investigated and under-reported. The underlying mechanisms are unclear and likely to be multifactorial, although effects of prolactin elevation have been implicated. We undertook a study to determine the influence of drug treatment and genetic polymorphisms in two candidate genes with sexual dysfunction in male subjects with remitted schizophrenia, and to assess the possible role of blood prolactin concentrations. 100 male subjects with schizophrenia and meeting criteria for remission were assessed for sexual and erectile dysfunction using the Arizona Sexual Experience Scale (ASEX) and the 5-item version of International Index of Erectile Function (IIEF-5). Subjects were married, living with a sexual partner and receiving antipsychotic drug monotherapy for at least six months. Blood samples were taken for plasma prolactin determination and genotyping of two polymorphisms each of the D2 dopamine receptor (DRD2) and eNOS nitric oxide synthase isoform genes. ANOVA was used for statistical testing; p<0.05 is considered significant. 30 subjects received typical antipsychotic drugs (primarily chlorpromazine and risperidone). Sexual dysfunction determined by ASEX score was significantly greater in the patients receiving typical antipsychotics than those receiving risperidone or clozapine, and threshold criteria for sexual dysfunction and erectile dysfunction were reached significantly greater proportion of subjects on typical drugs (67% and 60%), compared with the atypical drug group (39% and 39%). Prolactin, significantly higher in subjects receiving risperidone compared with those receiving clozapine or typical antipsychotics, was only significantly correlated with sexual dysfunction within the risperidone group. Neither of the eNOS polymorphisms, G894T or T-786C, was significantly associated with sexual or erectile dysfunction. The -141C ins/del, but not Taq1A, polymorphism of the DRD2 gene was significantly associated with sexual dysfunction with the del allele being less frequent in sexual dysfunction subjects. Prolactin was also significantly lower in del allele carriers. Our findings indicate that the older typical antipsychotics are more likely to be associated with sexual dysfunction in men than the atypical drugs, including risperidone and clozapine, despite the higher blood prolactin concentrations associated with risperidone. The pharmacogenetic association with a functional DRD2 polymorphism may, in part, be related to effects on prolactin elevation due to genotype differences in receptor density, although other DRD2 mechanisms may contribute. Certainly factors independent of both prolactin and DRD2 genotype are likely to contribute to the increase in sexual dysfunction in male patients on typical antipsychotic drugs. XRZ was supported by a studentship from Queen's University Belfast.
TA02

BDNF VAL66MET AND ANTIPSYCHOTIC-INDUCED WEIGHT GAIN: A PRELIMINARY ANALYSIS

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Introduction: Antipsychotic-(AP)-induced weight gain and obesity impact negatively on physical health and increase comorbidity (diabetes and cardiovascular disease). Genetic moderators of AP-induced weight gain have been studied extensively, and a variety of candidate genes and polymorphisms, some associated with specific drugs, have now been identified, including the HT2RC receptor gene (Reynolds et al., 2005; Prog Neuropsychopharmacol Biol Psychiatry 29(6):1021-8) and the LEP and LEPR receptor genes (Mueller and Kennedy, 2006; Pharmacogenomics 7(6):863-87). Lane et al. (2006; J Clin Psychopharmacol 26(2):128-34) found an association with the BDNF Val66Met polymorphism and risperidone-induced weight gain. We investigated the BDNF Val66Met and AP induced weight gain in a sample (n=135) of individuals on various APs. Methods: This was a case-control study. Samples were collected from patients of the South London and Maudsley NHS Foundation Trust, some (n=102) by RIO from the Weight Intervention Study (Ohlsen et al., 2004; Psych Bull, 28:164-166), which comprised mainly chronically ill patients; and some from the Genetics and Psychosis (GAP) Study (a first episode psychosis study) (n=33). Inclusion criteria were: age 18-65, diagnosis of psychotic illness, and on continuous antipsychotic treatment for at least 4 weeks. “Cases” were defined by the following criteria: BMI ≥25, and had gained ≥5lb on AP treatment. “Controls” had BMI < 25 and had gained <5lb on APs, and were otherwise matched. DNA was extracted from venous blood using standard protocols, and genotyping was conducted using TaqMan. Results The sample was in Hardy-Weinberg equilibrium. Genotypic and allelic frequencies were within normal limits. Genotype “call rate” was 99.3%, only one patient was not able to be successfully genotyped. On logistic regression (with “caseness” as the dependent variable; gender, ethnicity, diagnosis as covariates), there was no significant association between genotype and AP-induced weight gain (defined by caseness) (P=0.65). When we performed a further logistic regression, using only the subjects from the weight study, who had a longer duration of illness, and of whom over 50% were taking clozapine, we found no significant association between casesness and genotype (P=0.29), but we did find a significant association between casesness and AP medication (P=0.02). Conclusions: We found no association with BDNF Val66Met polymorphism and AP-induced weight gain. However, our sample size was small and unequal (93 cases, 41 controls), and AP treatment was heterogeneous. We plan to address this through collaboration, using a more homogeneous sample in terms of ethnicity and antipsychotic treatment.

TA03

IS LOSS OF GENDER DIMORPHISM A UNIFYING THEME IN SCHIZOPHRENIA FINDINGS? AN MRI TEST OF THE HYPOTHESIS

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Introduction: It is thought that a number of factors may play a role in the aetiology of schizophrenia and that the pathophysiology is likely to involve disturbances of function as a result of aberrant neural development. This is reflected in post mortem and MRI studies which show differences in cerebral structure in individuals with schizophrenia when compared with healthy controls. A number of differing lines of investigation have considered gender differences between schizophrenic patients and healthy controls. These include structural MRI (total brain volume and hemisphere measures), facial asymmetry, and 2D:4D ratio differences in finger length. An overall theme of this body of research can be described as loss of gender dimorphism, possibly relating to the differing mean ages of onset, approximately 28 years in males and 32 years in females, a consistently replicated finding. Although such findings could relate to genetic differences, an alternative hypothesis would relate to possible phases in the developmental trajectory where sex differences could occur. Intra-uterine and the post-natal phase influences would be of interest, particularly if coupled with a model incorporating a phase delay paradigm in development. Methods: In order to test this theoretical model, an existing data-set of brain volumes was studied, including schizophrenic patients and healthy volunteers, with the aim of investigating which areas of the brain show differences in gender dimorphism in structure and laterality in healthy subjects and whether this is lost in the schizophrenic sample. 91 subjects had participated in the study: 45 healthy volunteers and 46 schizophrenics. differences in regional brain volumes and regional lateralisation (measured using structural MRI and analysed using Freesurfer software) between each group were analysed by performing an independent samples t-test to look for gender dimorphism in the fusiform, posterior cingulate and superior parietal cortices when compared with controls, as well as differences in regional lateralisation which may reflect disturbances in neurodevelopment. However a number of regions showed increased dimorphism in the schizophrenia sample. Conclusions: Although three regions in the schizophrenia sample of the four found in the healthy group showed loss of gender dimorphism, additional regions showed gender dimorphism. As far as brain structure is concerned, this data-set did not support the paradigm as a general theme but further study into gender differences using higher resolution may help provide insight into regional differences in morphology.

SB01

ABNORMALITIES IN BRAIN RESPONSES TO SOCIAL INCLUSION AND EXCLUSION IN SCHIZOPHRENIA: AN FMRI STUDY

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Objectives: Research indicates that the orbitofrontal cortex (OF) becomes de-activated in schizophrenia during social exclusion, relative to controls. We aimed to examine whether social inclusion and exclusion impacts brain activity in schizophrenia in the same way. Methods: A social inclusion-exclusion FMRI study was conducted on 26 healthy volunteers and 19 schizophrenia patients. The patients were either untreated at baseline or switched to a new antipsychotic at baseline. The primary outcomes were regional brain activity during social inclusion and exclusion. Results: Social inclusion and exclusion had similar effects on brain activity in healthy controls and schizophrenia patients. During social inclusion, the OFC and bilateral amygdala-hippocampus showed reduced activity relative to controls. During social exclusion, the schizophrenia group showed decreased activity in the OFC, anterior cingulate cortex, and bilateral amygdala-hippocampus, compared to healthy controls. Conclusions: These findings suggest that the neural mechanisms underlying social exclusion are impaired in schizophrenia. Further research is needed to explore the potential role of aberrant neural development in the processing of social stimuli in schizophrenia.
ABSTRACTS

TA04
SEX-SPECIFIC DIFFERENCES IN THE PREVALENCE OF METABOLIC SYNDROME COMPONENTS IN PATIENTS WITH SCHIZOPHRENIA - RESULTS FROM A GERMAN OBSERVATIONAL STUDY

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Introduction: Increased prevalence of metabolic syndrome (MetS) in patients with schizophrenia has been reported by several studies, with diverging results regarding sex-specific differences. In this prospective, observational study we assessed the prevalence of MetS in schizophrenia-patients at baseline and after 3 months of treatment with different antipsychotic medications, and performed a subgroup analysis by sex. Methods: Enrolled were in- and outpatients ≥18 years with a DSM-IV diagnosis of schizophrenia, who were either untreated at baseline or previously treated and switched to a new antipsychotic at baseline. Presence of MetS according to American Heart Association (AHA/NHLB) and National Cholesterol Education Program (NCEP-ATP-III) definitions was determined and Clopper-Pearson 95% confidence intervals (CI) calculated. The analysis comprised patients who had complete metabolic data for both visits and stayed on the medication prescribed at baseline. Multivariable forward selection logistic regressions were used to explore factors associated with MetS (NCEP-ATP-III definition) at both visits, providing p-values and odds ratios (OR). Results: The overall analysis set comprised 476 patients, with 236 (49.6%) males. The mean age was 48.1 years in women and 43.6 years in men. 74 (30.8%) female and 118 (50.0%) male patients were smokers. At baseline, 111 (46.3%) women and 144 (61.0%) men had increased triglyceride values. Numbers at month-3 were 113 (47.1%) and 156 (66.1%), respectively. Decreased HDL-cholesterol values were found in 11 (4.6%) women, 47 (19.9%) men at baseline and in 14 (5.8%) women, 67 (28.4%) men at month-3. MetS-prevalence (AHA/NHLB definition) at baseline was: women: 100 (41.7% CI 35.4;48.2), men: 111 (47.0% CI 40.5;53.6) and at month-3: women: 114 (47.5% CI 41.0;54.0), men: 122 (51.7% CI 45.1;58.2). Respective values for NCEP-ATP-III definition were: Baseline: women: 91 (37.9% CI 31.8;44.4), men: 101 (42.8% CI 36.4;49.4), and month-3: women: 92 (38.3% CI 32.2;44.8), men: 111 (47.0% CI 40.5;53.6). At month-3 the multivariate logistic regression showed a significantly higher risk for men to develop metabolic syndrome (NCEP-ATP-III definition) compared to women 113 (OR female vs. male: 0.56, CI 0.34;0.91, p<0.019). Conclusion: In this German sample of patients with schizophrenia the increase of MetS-prevalence was similar in men and women, if the AHA/NHLB definition was applied, but differed notably according to the NCEP-ATP-III definition. As the main difference between the definitions is that AHA/NHLB includes the use of antihypertensive, anti-diabetic and lipid-lowering medication, women may have received such treatment more often than men during the course of the study. - This study was sponsored by Lilly Deutschland GmbH.

TA05
ABNORMALITIES IN BRAIN RESPONSES TO SOCIAL INCLUSION AND EXCLUSION IN SCHIZOPHRENIA: AN FMRI STUDY

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A basic social human need is to feel accepted and not excluded. There is evidence that patients with schizophrenia are impaired in aspects of social cognition. However, the neural correlates of social impairments in schizophrenia are not well understood. In this study, we examined the neural responses to social inclusion and exclusion in schizophrenia. A control (n=16) and a schizophrenia (n=14) group were scanned using functional magnetic resonance imaging (fMRI) while subjects took part in a social ball passing game with two cartoon animated figures on a screen. During the game, subjects were either “included” (ball being passed to the subject) or “excluded” (ball passed between the two figures). Subjects were led to believe they were playing with real people via a computer network. For image analysis (first level), we implemented an event-related design with two conditions: inclusion and exclusion. For each condition, parameter estimates were taken to two second level analyses: a one-group and a two-group t-test. Within and between groups statistical parametrical maps were thresholded at p < 0.05 whole brain corrected for multiple testing using the SPMS false discovery rate method. In the schizophrenia group, mean values of parameter estimates across voxels within a 10 mm diameter sphere centred at maximum peak coordinates were used for testing correlations with psychopathology measures. During social inclusion controls activated the midbrain and striatum while schizophrenia patients did not show activations. During social exclusion the schizophrenia group showed deactivation of the orbitofrontal cortex (OFC) and bilateral amygdala-hippocampus; these regions showed reduced activation relative to controls. Notably, in schizophrenia, decreased activation in the OFC during exclusion correlated with increased severity of negative symptoms (r=-0.621, p=0.018). Results suggest a trend during social inclusion for schizophrenia patients not experiencing social inclusion as rewarding as controls. During exclusion, the abnormal pattern of brain activity in schizophrenia suggest patients were not processing information as controls; this may be linked to impairment in dealing with stressful situations, which in turn could lead to social withdrawal. Supporting this hypothesis, we found a negative correlation between negative symptoms (which includes social withdrawal) and brain activity during social exclusion, in the OFC. The OFC has been previously implicated in the processing of social stimuli (Fridh and Wollpert, 2003, Oxford press). Abnormalities in the processing of social stimuli in the OFC of patients with schizophrenia has been related to a dopamine dysregulation (Brunet-Gouet and Decety, 2006, Psychiatry Research Neuroimaging, 148, 75-92).
ASSESSMENT OF NEONATAL VENTRAL HIPPOCAMPAL LESIONED GERBILS AS A METHOD TO EVALUATE THE THERAPEUTIC POTENTIAL OF NK3 RECEPTOR ANTAGONISTS

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Selective tachykinin NK3 receptor antagonism is a novel pharmacological strategy to treat both positive symptoms and cognitive impairment associated with schizophrenia. The neonatal ventral hippocampal (NVH) lesion in the rat is a well established neurodevelopmental animal model showing behavioural abnormalities thought to simulate some aspects of positive and negative symptoms as well as cognitive deficits classically observed in schizophrenic patients. Since NK3 receptor pharmacology is similar between human and gerbil, but differs in rat, the aim of this study was to set up and pharmacologically validate NVH lesions in gerbils to provide a disease-related model for the assessment of NK3 selective antagonists. Surgery was performed on postnatal day 14 in a) sham-non operated gerbils; b) sham-operated gerbils infused with aCSF; and c) lesioned gerbils infused with the neurotoxic agent, ibotenic acid, into the ventral hippocampus. Effects of the NVH lesion were assessed without pharmacological treatment in a locomotor activity (LMA) test, in the prepulse inhibition (PPI) of startle reflex test and on spontaneous alternation in a Y-maze, both at pre-puberty (postnatal day 45) and post-puberty (postnatal day 90). At post-puberty, the effects of acute treatment with the NK3 selective antagonist SB222200 (10, 30 mg/kg i.p.), the typical antipsychotic haloperidol (0.1, 0.3 mg/kg p.o.) and the atypical antipsychotics olanzapine (10, 30 mg/kg p.o.), risperidone (0.3, 3 mg/kg p.o.) and clozapine (3, 10 mg/kg p.o.) were assessed on LMA. The NVH lesioned gerbils exhibited a highly significant and robust hyperactivity over time that was reversed by SB222200, olanzapine and risperidone, but not by haloperidol or clozapine. In contrast to the rat, deficits in PPI were not apparent. A deficit in spontaneous alternation in the Y-maze was observed which is indicative of impaired working memory and was reversed by the selective NK3 antagonist SB22200. Magnetic resonance imaging was undertaken in order to collect anatomical images to identify the extent of the lesions and to match these with observed behaviour. In summary, the atypical antipsychotics olanzapine and risperidone reversed the highly significant and long lasting lesion-induced hyperlocomotion. Furthermore, the NK3 antagonist SB222200 normalized, probably indirectly via modulation of the dopaminergic system, hyperlocomotion as well as working memory deficits in the Y-maze. In conclusion, the NVH lesion in the gerbil provides new insights concerning the experimental method itself and also explores the role of neurokinin receptor antagonists as potential treatments for schizophrenia

RISPERIDONE, BUT NOT HALOPERIDOL REVERSES THE OBJECT MEMORY DEFICITS INDUCED BY NEONATAL PHENCYCLIDINE IN ADULT RATS

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Introduction: Early postnatal treatment of rats with phencyclidine (PCP) on postnatal days (PND) 7, 9 and 11 has been proposed as a neurodevelopmental model of schizophrenia (Wang et al., 2001, Neuroscience, 107: 535–50). Aim: The aim of the present study was to assess whether the episodic memory deficits produced by neonatal PCP treatment in male and female rats in the novel object recognition paradigm (NOR) can be reversed by either typical (haloperidol) or atypical (risperidone) antipsychotics. Methods: 24 male and 24 female hooded-Lister rats received subcutaneous injections of either vehicle (0.9% saline) or PCP (10 mg/kg) on PNDs 7, 9 and 11, with the day of parturition day 0. On the test day, adult rats were injected acutely with either haloperidol (0.05 mg/kg, i.p.) or risperidone (0.2 mg/kg, i.p.) and tested for object recognition memory deficits using the NOR paradigm (Grayson et al., 2007, Behav Brain Res 184: 31-38). Results were expressed as mean ± SEM and analyzed by ANOVA followed by post-hoc Dunnett’s-test. Results: In both males and females, there was no significant difference in exploration time (s) of the two familiar objects in the acquisition trial in any group. In males, in the retention trial, vehicle treated rats spent significantly (p < 0.001) more time exploring the novel compared to the familiar object, an effect that was abolished in the group treated with 10 mg/kg PCP alone and in combination with acute haloperidol treatment (0.05 mg/kg). However, PCP treated rats that received acute risperidone treatment (0.2 mg/kg) spent significantly (p<0.05) more time exploring the novel compared to the familiar object. In females, in the retention trial, vehicle treated rats spent significantly (p < 0.001) more time exploring the novel compared to the familiar object, an effect that was abolished in the group treated with 10 mg/kg PCP and acute haloperidol (0.05 mg/kg). However, PCP treated rats that received acute risperidone (0.2 mg/kg) spent significantly (p<0.05) more time exploring the novel compared to the familiar object. Risperidone-induced hyperactivity at adulthood are reversed by risperidone but not by haloperidol in both male and female rats. This supports the validity of this model for investigation of cognitive deficits of relevance to schizophrenia. Funding source: b-neuro.

ATYPICAL ANTIPSYCHOTIC RISPERIDONE REVERSES THE RECOGNITION MEMORY DEFICITS INDUCED BY POST-WEANING SOCIAL ISOLATION IN RATS

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Rearing 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. Risperidone is an atypical antipsychotic with affinity at a range of receptors, particularly the serotonin 5-HT2A/C and dopamine D2 receptors, which is currently used in the treatment of schizophrenia. This study evaluated the ability of risperidone to reverse the behavioural deficits induced by post-weaning social isolation of rat pups to further test the predictive validity of this model. Forty-five male Lister-hooded rats obtained immediately after weaning on postnatal day (PND) 22-24 were either housed in groups of 3-4 (n=16) or singly (n=29) for a period of 4 weeks. During this time socially isolated subjects received minimal handling but maintained visual, auditory and olfactory interaction with littermates. On PND 51 novel cage induced locomotor activity (LMA) was assessed and used to subdivide rats into balanced groups based on activity. On PND’s 58, 59, 65 and 72 rats received either vehicle (1 mL/kg; i.p.) or risperidone (0.2 mg/kg or 0.5 mg/kg; i.p.) 30 minutes prior to recording LMA, novel object recognition (NOR), prepulse inhibition (PPI) of startle reflex test and on spontaneous alternation in a Y-maze, both at pre-puberty (postnatal day 45) and post-puberty (postnatal day 90). At post-puberty, the effects of acute treatment with the NK3 selective antagonist SB222200 (10, 30 mg/kg i.p.), the typical antipsychotic haloperidol (0.1, 0.3 mg/kg p.o.) and the atypical antipsychotics olanzapine (10, 30 mg/kg p.o.), risperidone (0.3, 3 mg/kg p.o.) and clozapine (3, 10 mg/kg p.o.) were assessed on LMA. The NVH lesioned gerbils exhibited a highly significant and robust hyperactivity over time that was reversed by SB222200, olanzapine and risperidone, but not by haloperidol or clozapine. In contrast to the rat, deficits in PPI were not apparent. A deficit in spontaneous alternation in the Y-maze was observed which is indicative of impaired working memory and was reversed by the selective NK3 antagonist SB22200. Magnetic resonance imaging was undertaken in order to collect anatomical images to identify the extent of the lesions and to match these with observed behaviour. In summary, the atypical antipsychotics olanzapine and risperidone reversed the highly significant and long lasting lesion-induced hyperlocomotion. Furthermore, the NK3 antagonist SB222200 normalized, probably indirectly via modulation of the dopaminergic system, hyperlocomotion as well as working memory deficits in the Y-maze. In conclusion, the NVH lesion in the gerbil provides new insights concerning the experimental method itself and also explores the role of neurokinin receptor antagonists as potential treatments for schizophrenia
TA09

**INFLUENCE OF MEPARFYNOX ON PREPULSE INHIBITION [PPI] AND NEUROPLASTICITY DEFICITS IN ISOLATION REARED WISTAR RATS**

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Previously, we demonstrated Meparfnol, an anxiolytic withdrawn from clinical use by the FDA Drug Efficacy Study Implementation Program (1968-1974), to significantly enhance prepulse inhibition of startle, a non-declarative form of memory, but to be without any significant effect on water maze spatial learning, a declarative form of memory, in C57Bl/6 male mice. Given that prepulse inhibition deficits are a behavioural feature of schizophrenia, we determined the influence of chronic meparfnol administration on the prepulse inhibition deficits in rats that are associated with isolation rearing, an animal model emulating many of the characteristic features of this mental illness. We also determined if these behavioural deficits could be correlated with change in neuroplastic status, as evidenced by the levels of postsynaptic density protein-95 (PSD-95), a marker of synapse integrity. Male Wistar rats were housed singly in non soft bottom cages from post natal day [PND] 25, treated with meparfnol (50 mg/kg i.p.; Sigma-Aldrich, Inc., UK) from PND 72 to 79 and assessed for PPI deficits, in a drug free state, on PND 80. The animals were then killed, and the prefrontal cortex isolated. The tissue was homogenised in homogenisation buffer and the proteins separated on 10 % SDS polyacrylamide gels. The separated proteins were transferred to nitrocellulose and probed with anti-PSD-95 (Cell-Signalling Technology, Inc, USA), washed and incubated with goat anti-rabbit (Sigma-Aldrich, Inc., UK) conjugated to HRP enzyme. The resulting immunostained bands were quantified by densitometry using ImageJ analysis software (http://rsb.info.nih.gov/jj/docs/index.html). Rats reared in isolation exhibited significant PPI deficits (Social vs Isolation; F[1,60]=5.2; P=0.02) and these could be reversed by chronic treatment with meparfnol (Isolation vs Drug-treated; F[1, 76]=0.78; P=0.38). Analysis of PSD-95 protein expression in tissue derived from the prefrontal cortex of rats reared in isolation revealed significant deficits in this synaptic protein marker (Social vs Isolation; P=0.04, Student t-test) and these were reversed following chronic meparfnol treatment (Isolation vs Drug-treated; P=0.69, Student t-test). These studies demonstrate chronic meparfnol treatment to significantly ameliorate behavioural and neuroplastic deficits in Wistar rats reared in isolation, suggesting the possibility that this drug may have antipsychotic potential. This study was supported by Enterprise Ireland (PC/2008/0334).

TA10

**CHANGES IN EXTRACELLULAR AMINO ACIDS IN THE FRONTAL CORTEX OF ISOLATION-REARED ANIMALS PERFORMING A NOVEL OBJECT DISCRIMINATION TASK: A COMBINED IN VIVO MICRODIALYSIS AND BEHAVIOURAL STUDY**

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Postweaning, social isolation of rat pups is an environmental animal model of schizophrenia which is consistently used in laboratories to mimic the neurodevelopmental underpinnings of psychosis. Social isolation produces irreversible alterations in both behaviour and neurotransmitters in resultant adult rats, however few studies have examined changes in glutamategic function. The present study aimed to identify changes in a broad spectrum of extracellular amino acids in the medial prefrontal cortex (mPFCx) – a region centrally implicated in schizophrenia – of isolation-reared rats by in vivo microdialysis. Furthermore, measurements of extracellular amino acids were taken whilst animals were performing an adapted novel object discrimination task to evaluate any functional relationship. Male Lister-Hooded rats were weaned on postnatal day (PND) 22-25 and were either group-housed (3-4 per cage; n=9) or socially-isolated (n=8) for a period of 5 weeks during which they received minimal handling but maintained visual, auditory and olfactory interaction with littermates. Locomotor activity was measured on PND 60. On PND 67, rats underwent stereotactic surgery under isoflurane anaesthesia to implant a guide cannula in the mPFCx (AP = + 2.2 mm, ML = ±0.2 mm DV = -1.8 mm from Bregma). Following a 7 day recovery period, a 4 mm, commercially available, concentric microdialysis probe was inserted into the guide cannula and (aCSF) dialysate samples were collected 18 h later (flow rate = 2 µl/min, time/sample = 20 min). Following the collection of 5 basal samples, 2 identical objects were presented to the rats and the time spent exploring each was scored manually for 5 min. Two hours later, one of the objects was replaced with a novel object and exploration times were scored for 5 min. One hour later, tetrodotoxin was infused into brain and samples were collected for a further 1 h. Samples were snap frozen and subsequently measured by HPLC coupled with fluorescence detection. Basal levels of amino acids (nM) were calculated as mean ± SEM, and time-course data as a % of baseline mean ± SEM. Social isolation induced a robust deficit in novel object discrimination compared to group-housing (Discrimination index (novel-familiar-total exploration); isolate 0.50 ± 0.03, group 0.74 ± 0.02; p<0.0001, Student’s t-test). Significant increases in extracellular basal levels of GABA, L-serine, tyrosine, arginine (all p≤0.05), glutamate, aspartate, citrulline (all p≤0.01), glycine, alanine and taurine (all p≤0.001 Student’s t-test) were identified in the isolates compared to group-housed animals. During the behaviour there were significant differences in the time-course of glutamate (p≤0.01), L-serine, D-serine, PEA, taurine (p≤0.05) and arginine (p<0.001 by 2-way ANOVA), but these were identical in isolation-reared and group-housed rats. Findings from the present study highlight a prominent difference in the baseline extracellular amino acid profile of isolation-reared rats compared to group-housed conspecifics. Furthermore, it appears that changes in the activity of amino acids, including glutamate and serine, in the mPFCx may contribute to performance in the novel object discrimination task. Whether differential release of these amino acids contributes to the deficit in object recognition induced by isolation rearing remains to be addressed in future studies. This work was supported financially by the BBRC and the University of Nottingham.
TA11

CAN COMBINING TWO DEVELOPMENTAL MODELS OF SCHIZOPHRENIA IN THE RAT PRODUCE A MODEL WITH GREATER TRANSLATIONAL AND PREDICTIVE RELEVANCE?

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The heterogeneous symptoms of schizophrenia make it difficult to treat and model in animals. The current study combines two developmental models of schizophrenia: administration of the anti-mitotic agent methylazoxymethanol (MAM), prenatally on gestational day 17 (GD17) to pregnant dams, and subsequently rearing rat pups in social isolation. The objective was to determine whether combining these interventions produces more robust behavioural and neurological deficits with greater translational and predictive relevance than they do alone. Twelve pregnant Lister-Hooded rats were dams were administered either MAM (28mg/kg i.p.) or vehicle on GD17. From the resulting litters, 30 male pups were weaned on post-natal day 22-24 and housed in groups or isolation, resulting in 4 treatment groups: group-housed controls (n=6), isolate controls (n=8), group-housed MAM-treated (n=8), and isolate MAM-treated (n=8). Six weeks post-weaning, rats were monitored in a battery of behavioural tests to assess locomotor activity (LMA), novel object discrimination (NOD), prepulse inhibition (PPI) of acoustic startle, and a conditioned emotional response (CER). Following these tests, total brain mass from each rat was measured, and hippocampal volumes were estimated from cortical slices. Neither MAM nor isolation, alone or combined in LMA in a novel open field. During the NOD task, all group-housed rats significantly differed from normative data and familiar rats in the second choice trial, whereas isolation-reared rats (irrespective of MAM treatment) both explored objects equally (GH-Con and GH-MAM: p>0.01, Iso-Con and Iso-MAM: p>0.05 Bonferroni post-hoc following 2-way ANOVA). During CER, isolation-reared rats showed significantly less freezing than group-housed counterparts (irrespective of MAM treatment) 24h and 48h post-exposure to the conditioning chamber (main effect of treatment p<0.001, 2-way ANOVA). Isolation rearing and MAM administration alone had no effect on PPI but in combination, both reduced PPI (p<0.05) compared with both controls and MAM alone. Hippocampal size:total brain mass ratio was also decreased in MAM-treated rats (main effect of drug p=0.0102; 2-way ANOVA). Prenatal MAM treatment and isolation rearing of rat pups both produce behavioural and anatomical deficits in adult rats, but combined treatment may exacerbate some traits. In conclusion combining prenatal MAM treatment with isolation rearing may be a robust and useful preclinical model of schizophrenia. This research was funded by the BBSRC.

TA12

MODAFINIL REVERSES PCP-INDUCED DEFICITS IN COGNITIVE FLEXIBILITY

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At present there are no effective therapies for the treatment of the cognitive deficits seen in schizophrenia. Subchronic treatment with Phencyclidine (PCP) produces cognitive deficits, alterations in brain function and neurochemistry in rats akin to those seen in schizophrenic patients (Pratt et al., 2008. Br.J.Phamacol. 153:S465-S470). To further validate this translational model as a model of the cognitive inflexibility observed in schizophrenia here we investigate the ability of modafinil, a drug shown to reverse this deficit in schizophrenic patients (Turner et al., 2004. Neuropsychopharmacology. 29:1363-1373), to reverse the PCP-induced deficits in an attentional set-shifting task (ASST). Male Lister Hooded rats received either subchronic vehicle (saline, i.p.) or PCP (2.5mg/kg, i.p, 1 x daily for 5 days). 72 hours after the final treatment animals were tested in the ASST as previously described (Egerot et al., 2005. Psychopharmacol. 179:77-84). 30 minutes prior to behavioural testing animals received either acute Modafinil (64 mg/kg, i.p.) or vehicle (5% methylcellulose). Acute treatment was repeated 30 minutes prior to the fourth discrimination in the ASST due to the short half-life of modafinil. Data was analysed by Mann-Whitney U-test or t-test, Bonferroni corrected as appropriate. Significance was set at p<0.05 throughout. Subchronic PCP treatment impaired the ability of rats to switch attentional-set, as reflected by a significantly increased extradimensional/intradimensional (ED/ID) set-shifting ratio in PCP-treated animals relative to controls. Acute modafinil treatment reversed this set-shifting deficit as the ED/ID ratio in PCP-treated animals given acute modafinil was significantly lower than that of PCP-treated animals given vehicle but was not different from controls. In addition, subchronic PCP-treatment induced a deficit in reversal-learning (Rev3). This deficit was not reversed by modafinil. These results show that modafinil modulates distinct cognitive domains in the ASST and further validates the subchronic PCP model as a translational model to identify compounds that target the unmet therapeutic need in schizophrenia. Funding for this work was provided by BBSRC.

TA13

SCHIZOPHRENIA-LIKE HYPOFREQUENCY AND SLEEP REDUCTIONS IN DISC1 TRANSGENIC MICE

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Schizophrenia is a chronic and disabling mental disorder affecting ~1% of the population. Apart from positive and negative symptoms, patients develop severe cognitive deficits as a progression of the disorder, paralleled in 80% by an overt sleep reduction with increased nocturnal awakenings (Monti & Monti, 2005, Int. Rev. Psychiat. 17:247) and altered EEG, especially in dorsolateral prefrontal cortex (Farzan et al., 2009, Neuropsychopharmacol 34:1543). Such anomalies remain elusive in existing animal models; here, we examined the existence of such phenotypes (p<0.05) in 2-month-old mice. Disc1 transgenic mice. Disrupted-in-Schizophrenia (DISC1) transgenic mice were maintained on a mixed C57BL/6 x CBA background (Shen et al., 2008, J. Neurosci. 28:10893). They were of mixed gender, genotype (WT n=6; DISC1 +/- n=7; DISC1 +/- n=6) and aged 6 months. Epidural gold electrodes were surgically implanted above prefrontal cortex and hippocampus using stereotaxic coordinates. For recording, animals were placed in home-cage observation chambers (PhenoTyper) for 4 days. Then, wireless microchips (Neurologger) were connected to the head-stage and EEG was recorded continuously for at least 24h. Data were downloaded to PC, transformed into txt format, fast fourier transformed for spectral power and vigilance staged using SleepSign. Circadian activity was determined using the in-house software Mmini. Parametric states were used for genotype differentiation. Overall, both DISC1 transgenic groups showed normal ambulatory activity and no anomaly in circadian rhythms. Also, there was no difference in habituation to the novel environment. During the light cycle (sleep phase), DISC1+/+ mice showed increased wakefulness (t=1.18; p=0.05) at the expense of non-REM sleep (T=2, p=0.04) compared with WT; REM did not change. Furthermore, the number of nocturnal awakenings and sleep latency was enhanced(not significant) compared with WT controls. During the dark cycle (wake phase of mice), DISC1 mice displayed a reduction of spectral power for higher frequency bands (beta and gamma (F=2.4, p=0.001)), which was specific to the dorsomedial prefrontal recording site, but was not observed at hippocampal recording sites. It occurred during all vigilance stages, but with higher prominence during wakefulness. Collectively, our DISC1 mice present with an interesting phenotype in terms of physiology, which mirrors symptoms of schizophrenia. Sleep reduction is mainly ascribed to stage 2 and 4 slow-wave sleep in patients, which corresponds to non-REM sleep in our model. The observed hypofrontality also is reminiscent of gamma-spectral reduction in power observed in patient cohorts, but was observed here in a home-cage setting without sensory challenge. Nevertheless, it coincided with cognitive phenotypes measured as a reduction in social memory (see accompanying abstract, Riedel et al.). Supported by TMR1 (NS_AU_133).
Schizophrenia is a chronic and disabling mental disorder affecting ~1% of the population. Although diagnosed by the occurrence of positive and negative symptoms, it is now established that cognitive decline precedes the development of these classical parameters. Part of the MATRICS initiative to establish cognition as a primary treatment target in schizophrenia is therefore tests for social cognition and attention, both of which are impaired in patients (Young et al., 2009, Pharmacol. & Ther. 122:150). Especially social recognition deficits have been ascribed to prefrontal deficiency (Yamada et al., 2009, Eur. Arch. Psychiat. Clin. Neurosci. 259:227) and we reasoned these to be similarly existent in our DISC1 transgenic model. Disrupted-in-Schizophrenia (DISC1) transgenic mice aged 4-6 months were maintained on a mixed C57BL/6 x CBA background (Shen et al., 2008, J. Neurosci. 28:10893). They were of mixed gender and genotype. Pre-pulse inhibition (PPI) of startle responding was recorded after three habituation sessions. During test, mice were exposed to 120db startle pulses and responses were compared with pre-pulse (72-82dB) and startle pulse combinations, and reductions in startle amplitude were measured as dependent variable. Social cognition was video recorded (Ethovision) in a three chamber arena with habituation followed by sociability (stranger 1 confined to chamber in chamber 1) and social memory (stranger 1 as before, stranger 2 in opposite chamber) with 5 minute intervals. Control mice prefer the unknown mouse in each phase and show strong spatial bias and interactions in the zone close to the strangers. Parametric statistics were applied. We observed a deficit in startle responses to 90-120db tones (all t’s>2.8, p’s<0.05; WT; n=12; DISC1+/+ n=12), but not at ≤80db. Similarly, PPI was impaired in DISC1 mice relative to WT controls at all pre-pulse intensities (t’s>2.5, p’s<0.05). Social exploration of stranger 1 was not different between genotypes (WT n=14, DISC1+/- n=18, DISC1+/+ n=18) but a clear impairment in social recognition was obtained in homozygous (t=1.7, p=0.1 between stranger 1 and 2), but not heterozygous DISC1 mice or WT (t≤2.5, p’s>0.05). These phenotypes are congruent with cognitive deficits that are characteristic features of schizophrenia. Both recognition memory and attentional deficits have been directly linked with prefrontal cortex dysfunction (Campella & Guirat, 2009, Clin. Neurophysiol. 39:31) and are thus likely connected to the observed reduction in gamma frequency power in DISC1 mice (see accompanying abstract, Platt et al.). Our mouse over-expressing mutated DISC1 thus presents the first preclinical schizophrenia model with a hypofrontal physiological and behavioural anomaly. However, the exact cellular correlates for these dysfunctions remain to be investigated. Parts of this project were funded by TMRI (NS_AU_133).

A large number of risk genes have been associated with schizophrenia; these include DTNBP1, DISC1 and NRG1. Although genetic factors are established, neuregulin 1 (NRG1) being one of the genes associated most consistently with schizophrenia, contribution from early environmental factors is also indicated. Viral infection during pregnancy has been associated with increased risk for schizophrenia in the offspring. Polyribosinosinic–polycytidylic acid (PolyI: C) is a known immune system activator. PolyI: C mimics viral infection by activating the toll-like receptor 3 signalling pathway. Behavioural abnormalities related to schizophrenia have been described in the offspring of pregnant dams treated with PolyI: C. Serum cytokine levels are elevated in mice following prenatal PolyI: C treatment. Neuregulin heterozygous knockout and wildtype breeding pairs (on a C57BL6 background) were generated. Pregnancy was confirmed by the presence of a vaginal plug and was considered gestation day 0 (GD0). Pregnant dams on GD 9 received a single injection (5mg/kg i.p.) of PolyI: C or vehicle. Three hours after either PolyI: C or vehicle injection trunk blood was collected. Serum cytokines were analysed using a multiplex cytokine assay As expected, two-way ANOVA with main factors of genotype and treatment demonstrated PolyI: C-induced increase in maternal serum cytokine levels. Cytokine levels were increased [IL-6: F(2,5)= 10.42, P<0.001, IL-10 F(1,4)= 46.05, P<0.001, TNF alpha F(1,25)=15.27, P<0.001]; this effect did not differ between the genotypes. Maternal administration of PolyI: C led to a marked increase in serum protein levels of IL10, TNFa, mKC and IL-6 on GD9 relative to vehicle treated controls. These increases indicate that PolyI: C is activating the maternal immune system. These effects do not differ between the genotypes which supports ongoing studies of behavioural phenotypes in offspring as a putative model of gene × environment interaction in schizophrenia. These studies were supported by Science Foundation Ireland (07/IN.1/I960).

**TA16**

**A MODIFIED HANGING-WIRE TEST IN MICE AS AN IN VIVO HIGH-THROUGHPUT SCREENING MODEL FOR DRUG-INDUCED MOTOR IMPAIRMENT**

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In rodents, disturbance of motor coordination is often determined using a rotarod. A more challenging test however for mice to perform seems to be the hanging-wire test (HWT). The mice are placed with their forepaws onto a metal wire 25 cm above the floor. The primary measure used is the latency to fall off the wire. Here, the HWT is evaluated as a high-throughput screening model using mouse-population determined cut-off points. The cut-off approach is intended to lead to small group sizes (n=5) for testing drug effects. In the acute test, mice were trained 4 times prior to drug treatment, after which 5 post-drug trials were performed (in pairs at 15-min intervals). For an impairment-reversal test, after 4 training trials, a challenge drug (e.g. PCP) was given followed by 4 trials to determine the impairment over 30 min. Then, the vehicle or test drug can be given followed by 8 post-drug trials to evaluate the potential reversal effect for another 60 min. Initial vehicle studies revealed that some mice jumped down from the wire. By adding a 1-cm layer of water below the wire this alternative behavior to hanging on the wire for a maximum of 30 sec could be minimized. As a result, the individual cut-off of 6 sec without water for the normalized latency to fall, increased to 17 sec in the modified HWT with water below the wire. Various drugs including PCP, scopolamine and d-amphetamine were tested acutely leading to rather high ED-50 values for motor impairment of 1.26, 0.36 and 7.94 mg/kg substitutively respectively. For the reversal study, PCP (5 mg/kg) was selected in order to determine the potential of this approach with 4 extra sessions. This dose of PCP is known to induce both hyperlocomotion and motor coordination problems. We hope that the addition of the HWT can help to discriminate between hyper-locomotor and motor impairment effects of NMDA-antagonists like PCP. In conclusion, the modified HWT in mice can be used as a high-throughput model to determine both potential motor function changes with new drugs as well as reversal properties after drug-induced disruption like for example with PCP.
TB01
IDENTIFICATION OF CAPTODIAMINE AS A PUTATIVE ANTIDEPRESSANT
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Previously, we have shown that chronic treatment with captodiamine, formerly used in clinical practice, to significantly reduce time spent immobile in the forced swim test [FST], a paradigmatic behaviour commonly used to assess antidepressant efficacy. We have also shown captodiamine to have significant affinity for the D3 dopamine receptor, the D1 receptor and the 5-HT2c receptor. The aim of the current study was to determine the agonist/antagonist actions of captodiamine at each of these receptors. The action of captodiamine at the D1 receptor was determined by administration of ritracloza (5mg/kg, i.p.); a sigma 1 receptor antagonist, to C57Bl/6 mice and measuring apomorphine-induced rotation (aPom). Captodiamine at 10μM and 100μM induced (10μM) increases in intracellular calcium concentration as measured using a fluorescence-based confocal microscopy assay. Using the above procedures, we observed administration of ritracloza to reverse the decreased immobility induced by captodiamine in the FST (vehicle vs ritracloza/captodiamine-treated; p=0.7; Student-test). In a single experiment it was found that captodiamine, similar to other D3 agonists, attenuated EFS induced relaxation in the rat pylorus. Finally, captodiamine, at doses of 1μM, 10μM and 100μM, was found to significantly inhibit 5-HT-induced Ca2+ release in HEK 293T cells over-expressing the 5-HT2c receptor (10μM 5-HT [control] vs 10μM 5-HT + captodiamine; P=0.0131; One-way Anova, n=3). Collectively, these findings indicate captodiamine to exert agonist actions at the D1 receptor and an antagonist action at the 5-HT2c receptor. Preliminary results suggest agonist action at the D3 receptor, however further studies are required. As both 5HT2c receptor antagonism and D1 receptor agonism have separately been demonstrated to decrease immobility time in the FST, the findings reported here support captodiamine to be a potential antidepressant. This work was supported by Enterprise Ireland and the HEA PRTLI cycle 4.

TB02
PHARMACOLOGICAL AND PSYCHOLOGICAL INTERVENTION STRATEGIES FOR DEPRESSION: EVIDENCE FOR INTERFERENCE EFFECTS USING A BIOMARKER MODEL
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Introduction. Anxiety and depression are associated with a tendency to prioritise negative information. The therapeutic efficacy of both the pharmacological and psychological treatments of these emotional disorders may be mediated by their ability to reduce these negative processing biases. Interestingly, neuroimaging studies suggest that pharmacological and psychological interventions alter distinct aspects of a distributed emotional processing system suggesting that, when combined, the effects of the two treatments may either combine synergistically or interfere with one another. We tested these competing hypotheses by assessing the interaction between the antidepressant medication citalopram and a cognitive training regime on behavioural measures of emotional processing and subjective response to both mood induction and social stress. Methods. 62 healthy participants were randomly assigned to one of four treatment groups. The pharmacological intervention was seven days of citalopram or placebo. the psychological intervention was seven days of positive attentional bias training (a cognitive task designed to induce a positive bias in attention to emotional information) vs. a neutral version of the task. A factorial design was employed allowing assessment of the individual interventions and their combination. The effects of the interventions were assessed on day seven using behavioural measures of processing bias and subjective mood response as measured with the PANAS scale to a Venet mood induction and social failure stress task. Results. A clear valence specific interference effect was seen in emotional memory [F(1,58)=3.07, p=0.028]; both cognitive training [t(29)=2.7, p=0.01] and citalopram [t(29)=3.5, p=0.001] reduced recognition memory for negative words when administered on their own. However, the combination of drug and cognitive training caused no reduction compared to placebo treatment [t(30)=0.99, p=0.32]. This memory effect seemed to arise as a consequence of the interventions altering the encoding of the information as the same interaction was found in reaction time during initial processing [F(1,58)=4.8, p=0.03]. Interestingly the treatments seemed to have independent rather than interfering effects on subjective mood; citalopram prevented an increase in negative mood over the course of the mood induction [F(1,57)=6.0, p=0.02], whereas positive training tended to produce the same effect over the social failure task [F(1,57)=3.9, p=0.054]. Conclusion. We found no evidence of synergy between pharmacological and psychological interventions on measures of either cognition or mood. When these interventions did interact this was to produce an interference effect. These findings may account for the difficulty in finding beneficial effect when drug and cognitive treatments are combined in clinical situations.

TB03
BEHAVIOURAL DEPRESSION AND THE ROLE OF MEDIAN RAPHE NUCLEUS NMDA RECEPTORS
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Introduction: Exposure to uncontrollable stressors leads to behavioural and neurochemical changes, which have been associated to mal functioning of the Median Raphe Nucleus (MrN)-Dorsal Hippocampus (DH) serotonergic pathway. These deficits can be attenuated by intra-hippocampal injections of NMDA antagonists or 5-HT1a agonists. Activation of MrN NMDA receptors (NMDAr) increases serotonin release in both MrN and DH. In this study we investigated whether activation of MrN NMDAr could prevent and/or attenuate the effects of previous exposure to forced swim. Methods: Male Wistar rats with cannulas aimed to the MrN were forced to swim for fifteen minutes (Pre-test, PT) and tested twenty four hours later. All animals received two intra-Mrn injections (0.2μl each) of saline (Sal), AP7 and/or NMDA (five minutes interval), administered as follows: Sal+Sal, Sal+NMDA (1nmol), AP7+Sal (3nmol) and AP7+NMDA. The injections were given immediately after or before PT or twenty four hours after. In control groups rats received the treatment twenty four hours or five minutes before test. Latency to display immobility (Lat) and total time spent immobile (TSI) were registered and analyzed by one-way ANOVA followed by Duncan for each experimental protocol. Results: When administered after PT, NMDA increased LAT (185.7±27.3; F(3,43)=5.5; p=0.05) and decreased TSI (154.2±17.4; F(3,43)=6.5; p=0.05) when compared to control group (Sal+Sal: Lat=43.8±8.9; TSI=214.8±21.6). AP7 antagonized this effect on Lat when given before PT (P<0.05). NMDA induced significant increase in TSI (88.2±24.1). On the other hand, AP7 blocked NMDA effects (P<0.05) and decreased TSI (154.2±17.4) when given alone. When given before PT, only AP7 increased LAT (106.1±56; F(3,27)=2.7; p=0.05) and reduced TSI (93.6±12.7; F(3,27)=3.0; p=0.05) in comparison to saline (Lat=52.1±9.5; TSI=176.3±15.4) and NMDA (Lat=65.6±11.7; TSI=160.7±10.1) treated rats. In previously stressed rats treatment with AP7 (101.9±6.5) and AP7+NMDA (80.3±9.4) increased LAT (F(3,30)=4.7; p<0.05) when compared to saline (52.1±9.5) treated animals, while NMDA (65.6±11.7) alone did not. AP7 (P<0.05) and NMDA (P<0.05) significantly reduced TSI (F(3,30)=5.4; p<0.05) when compared to control group (168±19.3) and NMDA treated rats (160.7±10.1). No effects of drugs were observed when treatment was given twenty four hours (LAT: F(3,19)=4.0; p=0.05; TSI: F(3,19)=2.9; p=0.05) in non-stressed rats. Conclusions: Our data suggest that both activation and blockade of MrN NMDAr facilitate the behavioural adaptation to an uncontrollable stressor. The mechanisms underlying such adaptation could be related to intrinsic mechanisms within the MrN, involving serotonin release as supported by physiological studies. Affiliation: none. Financial Support: CAPES, CNPq e FAPESP.
TB04

ANTIDEPRESSANT TREATMENT DECREASES NEURAL RESPONSES TO NEGATIVE SELF-REFERENTIAL WORDS IN SUBJECTS WITH HIGH NEUROTICISM

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Introduction: Neuroticism is a personality trait linked to increased vulnerability to psychopathology and to biases in the processing of emotional stimuli, such as self-referential words. Neuroimaging studies have identified a fronto-parietal network of areas underlying these cognitive biases (Chan SW et al., 2008. Neuropsychologia 46(12):2996-903). Moreover, short-term antidepressant administration has been shown to modify neural activation in similar circuits in healthy volunteers (Norbury R et al., 2008. Mol Psychiatry 13(11):1011-20). The aim of our study was to investigate whether short-term antidepressant administration would normalise these abnormalities in subjects with a personality profile at risk for psychopathology. Methods: Never-depressed highly neurotic subjects (n=29), who scored above 16/24 on the neuroticism scale of the Eysenck Personality Questionnaire, 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 functional MRI data were acquired using a rapid event-related design while subjects performed a word categorization task, with personality self-descriptors appearing on the screen for 500ms. During the same session resting brain blood perfusion levels were acquired using Arterial Spin Labeling. The effects of citalopram on BOLD response to positive, negative and control words were examined using an analysis of covariance model with cerebral perfusion as a voxel-wise covariate of no interest with cluster-based thresholding of Z=2.3 and a corrected spatial extent of p<0.05. Results: Whole brain analysis revealed a significant group x word valence interaction (negative vs.control words ) in a single cluster including parts of the dACC (BA 32), right Orbitofrontal Cortex (BA11) and right Caudate (voxels=565; Z= 3.41; x,y,=40, 0, 16) – areas previously implicated in the processing and regulation of emotional stimuli. Post hoc analyses revealed that this effect was driven a decreased response to negative self-descriptors in the citalopram treated subject. Importantly, these effects were present despite the absence of any significant between-group differences in mood or behavioural performance. Conclusions: Short term citalopram treatment in subjects with a vulnerable personality phenotype modulates the response to personality characteristics in brain areas previously related to high neuroticism and involved in self-referential processing. In particular, citalopram could decrease the self-related relevance of negative descriptors in high neurotic subjects. This effect suggests that antidepressants may act by modifying specific neural dysfunctions correlated to negative biases in the processing of emotional information. Further investigations are needed to verify whether the similar effects are seen in clinical populations. Study supported by MRC grant.

TB05

NICOTINE REVERSES ANHEDONIC-LIKE RESPONSE AND COGNITIVE IMPAIRMENT IN THE RAT CHRONIC MILD STRESS MODEL OF DEPRESSION: COMPARISON WITH SERTRALINE

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Smoking rates among depressed individuals is higher than among healthy subjects, and nicotine alleviates depressive symptoms. In rodents, nicotine induces antidepresant-like effects in the forced swim test and the learned helplessness paradigm. Clinical depression is associated with anhedonia (reduced ability to experience pleasure) and impaired cognition. In rats, chronic mild stress (CMS) induces an anhedonic-like state, as measured by decreased intake of a sucrose solution, as well as impaired performance in the spontaneous alternation (SAB) test, used to assess working memory function. Here, we examine the effect of chronic nicotine (0.4 mg/kg/day), the antidepressant sertraline (5 mg/kg/day), and the combined treatment with nicotine and sertraline, on CMS-induced reduction in sucrose intake and impairment in SAB test performance in male Wistar rats. A two-stage study design was employed. Stage I: 3-weeks stress period without drug treatment; Stage II: 6-weeks stress + drug treatment (veh+veh, nic+veh, veh+sertr, or nic+sertr). The effect of CMS was assessed using the sucrose test with measurements taken weekly. Similarly, rats in the non-stressed control group were randomly assigned to each of these four treatments. SAB testing was performed at Week 9. The CMS consisted of consecutive 10-14 hour period with the following stressors: Wetter (water in cage); 45° cage tilting; grouping; stroboscopic light; intermittent lighting; food deprivation; water deprivation; food+water deprivation; no stress. Sucrose intake was analysed by a three-way repeated measures analysis of covariance (RM ANCOVA), with Stress and Treatment as independent factors, Time (Week 3 and Week 9) as the repeated factor, and baseline sucrose intake as covariate. Effect of treatment on alternation ratio in the SAB test was analysed by two-way ANOVA with Stress and Treatment as independent factors. ANCOVA/ANOVA was followed by Planned Comparisons of the predicted means. Nicotine and sertraline both showed a significant and equally efficacious reversal of the CMS-induced decrease in sucrose intake (p<0.001). Similarly, the combined nicotine+sertraline treatment significantly reversed the decreased sucrose intake; however, no additive or synergistic effects of the combination was observed with the doses tested. In the SAB test, nicotine (p<0.01), but not sertraline or nicotine+sertraline, reversed the CMS-induced impaired performance. These results show that the effect of nicotine on a CMS-induced anhedonic-like state in rats is similar to that of a standard antidepressant drug. Moreover, the data suggests that nicotine alleviates working memory disturbance induced by CMS. A treatment strategy involving the targeting of nicotinic acetylcholine receptors may prove beneficial for emotional and cognitive disturbances associated with depression. This work was funded by NeuroSearch A/S, Denmark and the Danish Ministry of Science, Technology and Innovation.

TB06

TREATMENT RESISTANT DEPRESSION AND THE CAR (CORTISOL AWAKENING RESPONSE)

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Introduction: Hypothalamic-Pituitary-Adrenal (HPA) axis dysfunction is found in some patients with depression. There is preliminary evidence that it is especially prevalent in patients with Treatment Resistant Depression (TRD). A naturalistic measure of HPA axis activity is the Cortisol Awakening Response (CAR); CAR has not been measured in TRD so far. Methods: 27 patients (22 females and 5 males) with a primary diagnosis of unipolar TRD were recruited from a tertiary inpatient unit, all of whom were resistant to at least one prior antidepressant, along with 33 healthy controls matched for age, gender, weight/BMI and menstrual history. Salivary cortisol was measured at 0, 15, 30, 45, 60, 90 minutes following awakening over two consecutive days. The outcome variables used to assess the CAR were: a) mean cortisol levels at each timepoint over the two days; and b) total post-awakening cortisol output calculated using the area under the curve (AUC). Results: Patients were highly treatment resistant, having failed a mean of 4 prior antidepressants and 10 treatments in total. An independent t-test was used for statistical comparisons. There was no significant difference in the mean (+SD) awakening cortisol value between patients (14.3±6.7 nmol/l) and controls (11.6±5.1 nmol/l; p=0.09). However, all subsequent values were higher in patients: 15 minutes - 16.6±6.6 vs 13.3±5.0 nmol/l, (p=0.03); 30 minutes - 18.4±6.6 vs 14.7±6.3 nmol/l (p=0.04); 45 minutes - 17.5±6.7 vs 13.6±6.7 nmol/l (p=0.04); 60 minutes - 15.6±6.7 vs 11.6±5.4 nmol/l, (p=0.02); and 90 minutes - 14.0±6.5 vs 8.9±4.0 nmol/l, (p=0.002). The AUC was higher in patients both on Day 1 (1596±412 vs 1108±444 nmol/lh, p=0.007) and Day 2 (1451±498 vs 1096±567 nmol/lh, p<0.02). Conclusions: There is a heightened CAR in TRD, a previously unreported finding. TRD probably represents a biologically severe form of depression characterised by raised HPA activity. Raised HPA activity has potentially important implications in the aetiology and treatment of TRD.
THE SALIVARY RATIO OF CORTISOL/DHEA IN TREATMENT-RESISTANT UNIPOLAR DEPRESSION

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Introduction: Although a hyperactive hypothalamic-pituitary-adrenal axis (HPA axis) has been described in more severe forms of depression it has been hypothesised that as the adrenal steroid dehydroepiandrosterone (DHEA) may counteract the effects of cortisol in the brain, a true measure of the “net” effect of cortisol is better obtained by calculating the ratio of cortisol to DHEA. In a preliminary study using single 0900h plasma samples, we recently found the cortisol/DHEA ratio predicts the response to treatment in patients with treatment resistant depression (TRD). However, the cortisol/DHEA ratio in saliva may represent a more valid and accessible measure, and has yet to be studied in TRD. Methods: We recruited 20 patients with treatment resistant unipolar depression who were resistant to at least one prior antidepressant (with a mean of 4 prior failed antidepressant and 10 failed total treatments) and still significantly depressed; and 30 healthy controls matched for age, gender, weight, body mass index and menstrual 0800h, 1200h and 2200h over 4 days within the same week. Collection of saliva was done via the drooling method to avoid interference in DHEA assays. Results: The mean ratio of cortisol/DHEA did not differ between patients and controls at any time point. Similarly mean DHEA did not differ between the two groups at any time points. Mean cortisol in patients was higher (p <0.01) compared to controls only at 2200h Conclusions: The salivary cortisol/DHEA ratio was not appreciably altered in this sample of patients with severe unipolar TRD, although there was some evidence raised cortisol levels. However, given the previous suggestion that changes of the ratio in plasma may predict response to treatment, further similar work on the utility of the salivary cortisol/DHEA ratio is indicated.

CYTOKINE PROFILE IN TREATMENT-RESISTANT DEPRESSION

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Abstract There are studies that major depression is accompanied by an immune response with an increased production of pro-inflammatory cytokines, such as interleukin 1(1L-1), IL-6 and Tumor necrosis factor (TNF-α). Aims of the study were to determine serum levels of interleukins (IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10), interferon-gamma (IFN-γ), TNF-α, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and monoclonal chemotactic protein-1 (MCP-1) in subjects with treatment-resistant depression, and to assess their relationships with the psychopathological dimensions. Methods: Twenty-one subjects with treatment-resistant in patients with depression (TRD) and twenty-one age, gender and BMI matched healthy controls (HC) were recruited from the Affective Disorders Unit, Bethlem Royal Hospital. Biochip array technology was used for quantification of cytokines serum concentrations in samples. The psychopathology was assessed by the Hamilton Depression Scores (HAM-D), BECK depression questionnaire (BECK), Beck Anxiety Inventory (BAI) during the first week of admission and before discharge. Furthermore, patients were evaluated weekly using the BECK. Responders were considered those who reduced their HAMD baseline scores by 50%. Results. No normalisation of cytokines were used. IL-6 serum levels were significantly higher in patients than in controls (HC=0.18 ±0.08, TRD=0.44 ± 0.07, p=0.02); a similar trend for MCP-1 (HC=2.27 ± 0.05, TRD=2.21 ±0.05, p=0.09) was also observed. Treatment nonresponders (TRD-NR) had decreased levels of IL-6 (TRD-NR=0.14, vs TRD=0.47, p=0.05), but increased levels of IL-1α (TRD-NR=0.07, vs TRD=0.05, p=0.02). Both Log IL-2 and Log EGF had a trend positive correlation with depressive symptomatology as assessed by BECK (Log IL-2 P=0.48, p=0.09; Log EGF P=0.43, p=0.08). Discussion. Our data support the hypothesis that immune system alterations are involved in the multifactorial pathogenesis of depression. Cytokines, and more consistently IL-1α, may represent markers of the immunological activation in a subgroup of depressed patients. Finally IL-2 and EGF seem to be associated with psychopathology. Conclusion. These results suggest that: (1) major depression and TRD are accompanied by an activation of the monocytic arm of cell-mediated immunity; (2) the latter may be related to the immune an acute phase response in major depression; and (3) activation of inflammatory response may be a marker for unresponsiveness to antidepressive treatment. Livia Carvalho is funded by the NARSAD and ECNP Young Investigators Award. This research has been funded by the UK Medical Research Council, the South London and Maudsley NHS Foundation Trust & Institute of Psychiatry NIHR Biomedical Research Centre for Mental Health, Biomedical Research Centre and the Commission of European Communities 7th Framework Programme Collaborative Project Grant Agreement n°22963 (Mood Inflame).

DEPRESSION: BASELINE MEASURES AND SINGLE CASE REPORT

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Introduction: Augmentation of an antidepressant with an antipsychotic is one of the management strategies recommended by NICE (NICE clinical guideline 90 Depression: the treatment and management of depression in adults) when patients with depression have an inadequate response to initial treatment. The aim of this study was to evaluate efficacy of prolonged release quetiapine fumarate (quetiapine XL) + antidepressant (AD) and quetiapine XL monotherapy versus lithium+AD in patients with treatment-resistant MDD (Stage I and II, non responders to one or two antidepressants) and MADRS score ≥25. Methods A 6-week, randomised open-label, rater-blinded study, in patients with treatment-resistant MDD and MADRS score ≥25. Patients received quetiapine XL (300mg/day)+AD (SSRIs/venlafaxine) or monotherapy quetiapine XL (300mg/day), or lithium (0.6-1.0mmol/L)+AD. Primary efficacy variable: Non-inferiority of quetiapine XL+AD or quetiapine XL monotherapy versus lithium+AD was evaluated (pre-specified non-inferiority limit: 3 MADRS points; per-protocol population). Change from baseline at Week 6 in MADRS score was also evaluated. If non-inferiority was demonstrated, superiority testing was performed (modified ITT population).

Results A total of 688 patients were randomised. Quetiapine XL+AD and quetiapine XL monotherapy were not inferior to lithium+AD. Non-inferiority was also demonstrated for quetiapine XL+AD in patients with 1 and 2 treatment failures and for quetiapine XL monotherapy in patients with 2 treatment failures. Quetiapine XL+AD was significantly more effective than lithium+AD (p<0.05) in MADRS change from baseline (analysis discounting multiplicity); significance was observed from Day 4 (p<0.01) onwards. Superiority testing of primary efficacy variable showed no significant difference between quetiapine XL monotherapy and lithium+AD. Conclusions Quetiapine XL+ongoing AD and quetiapine XL monotherapy were non-inferior to lithium+ongoing AD in patients with treatment-resistant MDD. There was also an early efficacy advantage (MADRS scale) for quetiapine XL augmentation compared with lithium augmentation of SSRIs/venlafaxine treatment and in a post-hoc endpoint analysis significant superiority of quetiapine XL+AD compared with lithium+AD. Results of this study demonstrate that augmentation of SSRIs/venlafaxine with quetiapine may be another treatment option for patients with depression who fail to respond to initial treatment.
TB10

NEUROPSYCHOLOGICAL CHARACTERISTICS OF PATIENTS UNDERGOING DEEP BRAIN STIMULATION FOR TREATMENT RESISTANT DEPRESSION: BASELINE MEASURES AND SINGLE CASE REPORT

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Patients with chronic and treatment refractory depression are profoundly disabled. Here we report the neuropsychological characteristics of patients selected for a trial of deep brain stimulation of the sub-genual cingulated, ventral capsule and nucleus accumbens. The Wechsler adult intelligence scale-III (WAIS-III), Conner's continuous performance test (CPT-II), Trail making test (TMT), Delis-Kaplan executive functions system (DKEFS) sub-tests, Stroop, Emotional Stroop, Brixton and Hayling Tests, and Ekman faces were measured at the start and end of study. We enrolled eight severely depressed, disabled patients, as confirmed by clinical scales, with average intelligence (full scale IQ 93). The group's Wechsler Adult Intelligence Scale Perceptual Organisation Index, Processing Speed Index and Working Memory Index were all significantly lower than Verbal Comprehension Index (p<0.05), suggesting reduced ability compared with their level of crystallized intellect. Visuo-spatial memory was significantly lower than auditory memory [79±95, t(7)=4.13, p=.004]. Most patients performed below average on tests of attention and working memory though two performed within the average range on tests of attention and above average on the tests of working memory. Two patients demonstrated executive difficulties on the Stroop task. Profound performance deficits were observed in colour-interference, indicative of inhibition and cognitive flexibility impairments. For the emotional Stroop, no differences in physical threat were found; all but one patient were slower for recognition of social threat (p<.008). Recognition of emotion in unmorphed Ekman faces was not impaired. The HAM-D psychomotor retardation sub-scale correlated with trails A (p=0.01) but not trails B. Five patients showed impairments on both Hayling and Brixton tests. Two patients were unable to complete all tests. One patient to complete the treatment cycle showed marked improvement on neuropsychological measures (DKEFS, CPT, WAIS-III, TMT, Hayling), despite a lack of treatment response. This improvement in test scores was associated with an enhancement in performance on a measure of effort for cognitive testing, i.e. they were more engaged with the assessment at follow up compared with preoperatively. As a group these patients are impaired in a number of neuropsychological domains, although two out of eight were entirely within normative values across all tests. One patient examined at the end of the clinical trial, showed an improvement in scores with no evidence of any worsening of cognitive function or cognitive impairment - which speaks to the safety of the procedure. We are grateful to Friends of Frenchay Hospital for equipment donation and North Bristol NHS Trust for other financial support.

TB11

THE CLINICAL CHARACTERISTICS OF PATIENTS WITH TREATMENT RESISTANT DEPRESSION REFERRED FOR DEEP BRAIN STIMULATION

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About 10% of patients with major depressive disorder do not respond to resolute pharmacotherapy. Here we report the clinical characteristics of patients selected for a trial of deep brain stimulation of the subgenual cingulate and the ventral capsule/nucleus accumbens for treatment resistant depression (TRD) highlighting the sequence of failed psychopharmacological interventions and comparing them with other TRD patients. Clinical and treatment data were collected prospectively on three groups of patients with unipol lar TRD and compared. Group 1: 8 patients who had DBS; group 2: 7 patients who were selectable for DBS but did not have it; group 3: 53 patients with TRD referred over the same period who were not selectable. We also compared these data with data collected 20 years previously in TRD patients referred for ablative neurosurgery. When compared with group 3, patients suitable or selected for DBS were significantly different. They were younger (48 v 57 years), had been in the current episode for longer (94 v 35.5 months), were more severely depressed (MADRS= 39 v 30, HAMD17= 28 v 20), had attempted suicide (54% v 17%), had more comorbid anxiety disorders (93% v 55%) and had received more treatments other than SSRIs, tricyclic antidepressants, benzodiazepines and antipsychotics. At the time of surgery patients had been in the current episode for an average of 140 months, an average MADRS score of 39, HAMD of 26, GAF of 31, were at the 99th centile of GSI (SCL-90), had taken an average of 12 psychotropic drugs alone and in combination, and had received an average of 52 ECT treatments each. Demographically, patients referred for DBS in 2006-7 were similar to patients referred for ablative neurosurgery in 1988-1989. Treatments received were broadly similar, however significantly fewer people had received ECT in the current sample (68% v 100%, p=0.0001). Patients who have entered our DBS trial are severely and chronically ill. Compared with a group referred for pharmacological intervention they are younger, have been in the current episode for longer, have had more treatments and have more axis I diagnoses. They are similar to patients referred for functional neurosurgery in the late 1980s, although ECT is now used less. We thank the friends of Frenchay hospital for donating equipment for this trial and North Bristol NHS Trusts for financial support.

TB12

BLOOD FLOW CHANGES DURING DEEP BRAIN STIMULATION FOR TREATMENT RESISTANT DEPRESSION: A PET STUDY

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Deep brain stimulation is emerging as a possible treatment for severe and chronic treatment resistant depression. DBS in two brain areas has been reported as having potentially beneficial effects. The areas are the subgenual cingulate (SGC) and the ventral anterior capi/ nucleus accumbens (VACNAc). Here we report preliminary data on stimulation in both sites, showing the pattern of decreased perfusion on a priori selected areas. Eight patients have entered a randomised trial of DBS where patients start on bilateral SGC or bilateral VACNAC stimulation and switch to the alternate site if there has been no remission. H215O PET scans are carried out at the Wolfson Molecular Imaging Centre, University of Manchester at baseline and after chronic (at least 4 months) stimulation in a specific area. Scans were processed using SPMS (8mm smooth) and MarsBAR to select specific a priori selected regions of interest (in stereotactic co-ordinates/volumes) to test hypothesis about the distal effects of stimulation. The statistical threshold was set at p<0.005. We report results in up to 4 people per group who have had DBS and PET scans which allow comparisons. Significant decreases in perfusion were seen in the stimulated areas. No increases were seen in any of the brain volumes reported below. Chronic stimulation statistically significantly decreased perfusion in the following: SGC Stimulation: Right Inferior Orbitofrontal (p=0.002), Left Inferior Orbitofrontal (p=0.0009), Right Middle Frontal (p=0.002) and Left Middle Frontal (p=0.0006). VACNAC stimulation: Right Caudate (p=0.00001) and Left Caudate (0.002). Amygdalae, cerebelum, dorsal anterior cingulate, hippocampi, hypothalamus, pallida, thalami had non significant decreases. We have demonstrated that chronic stimulation of SGC or VACNAC produces distal changes in perfusion. According to current anatomical knowledge some of these effects have to be indirect/multisynaptic and clearly influence different pharmacological systems. We are grateful to Friends of Frenchay hospital for donation of equipment in this trial and to the North Bristol NHS Trust for other financial support.
TB13

DEEP BRAIN STIMULATION IN THE SUBGENUAL CINGULATE ALTERS REM SLEEP IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION

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In Bristol, we are carrying out a pilot trial of deep brain stimulation (DBS) in treatment resistant depression (TRD) and studying its effects on objective sleep. Sleep disturbance is a common, distressing, and poorly treated symptom of TRD. In particular, REM sleep is known to be altered in major depressive episodes, and most antidepressant drugs, MAOIs, SSRIs, TCAs, SNRIs suppress REM sleep in depressed patients. Here we present sleep data for all patients at baseline and during the first treatment phase (n=8), this being their first exposure to DBS. Patients have bilateral implantation of electrodes in the subgenual cingulate (SGC) and ventral anterior capsule nucleus acumens (VACNac). Patients are randomised to continuous bilateral stimulation in one of the areas alone for a period of at least 4 months, after which stimulation can be switched to the second target, and they continue with their individual antidepressant regime during treatment. Before and during DBS stimulation periods sleep recordings are carried out at regular intervals. At baseline REM sleep suppression was evident in 6 of our patients due to their antidepressant medication (2 receiving MAOIs, 2 TCAs, 2 SNRIs), with 2 patients, (1 trazodone, 1 trimipramine) displaying no REM suppression at baseline. In patients receiving SGC stimulation first (n=4) all exhibited REM suppression at baseline. During the first week of stimulation they had a consistent increase in average REM sleep time (from 22min at baseline to 117min) and shortening of REM latency (from 209min to 114min). These values returned to baseline levels with chronic stimulation (REM min 26; REM latency; 177min). This change in REM was not apparent in those receiving VACNac stimulation first. These data suggest that acute SGC stimulation consistently increases REM sleep that has previously been suppressed by antidepressants. Since this effect was not seen during chronic stimulation, this suggests adaptation. To our knowledge this is the first study that shows higher cortical areas (such as SGC) may influence REM sleep. DBS in Parkinson’s disease has been reported to increase REM sleep when stimulating the pedunculopontine nucleus (Lim et al, 2009) (these patients were not receiving antidepressants) however this is a subcortical structure well known to be crucial for the generation of REM sleep. We will discuss potential anatomical and pharmacological mechanisms for our finding. We are grateful to Friends of Frenchay hospital who donated DBS equipment and to North Bristol NHS Trust R&D for other financial support.

TB14

COMPARISON OF OLANZAPINE AND VALPROATE OVER 12 MONTHS OF TREATMENT IN THE EMBLEM STUDY

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The EMBLEM observational study has previously supported the results of a 3-week RCT which suggests that olanzapine monotherapy is more effective than valproate monotherapy in the treatment of acute mania (Novick et al., 2009, Pharmacopsychiatry 42:145–152). The current post-hoc analysis assesses 12-month outcomes of the same EMBLEM patient population. EMBLEM (European Mania in Bipolar Evaluation of Medication) was a 2-year, prospective, observational study of health outcomes associated with treatment of mania. Severity of illness was assessed at baseline and 12 months using the CGI-BP overall bipolar illness, CGI-BP mania and CGI-BP depression. 621 EMBLEM patients were analysed (n=107 valproate, n=514 olanzapine). Mean modal dose was 15.9 (sd=8.1, range 2.5-60.0) and 94.7 (sd=40.2, range 250.0-2000.0) for olanzapine and valproate-treated patients respectively. At baseline, psychosis was present in 50.6% of olanzapine-treated patients and 24.3% of valproate-treated patients (p<0.001). 49% of both treatment groups were completers over 12 months. Both treatment groups improved from baseline to 12-months in mean CGI-BP overall illness, mania and depression ratings, with significantly greater mean improvement in CGI-BP overall in the olanzapine compared with the valproate group (LSM=-0.224, 95%CI=-0.222-0.426, p=0.030) using linear mixed modelling to adjust for baseline differences. There were no significant differences in symptomatic remission, recovery or relapse between treatment groups. EMBLEM patients without psychosis treated with olanzapine had significantly greater mean improvement in CGI-BP overall (LSM=-0.325, 95%CI=-0.197-0.554, p=0.005) and CGI-BP mania (LSM=-0.269, 95%CI=-0.043-0.495, p=0.020) compared to the valproate-treated group. Patients with psychosis treated with olanzapine did not differ in treatment outcomes from those treated with valproate. EMBLEM patients treated with olanzapine experienced significantly greater weight gain than patients treated with valproate, although there was no significant difference in the number of patients with >7% weight gain between groups. There was a significantly greater incidence of treatment-emergent Parkinsonism and gastrointestinal adverse events in EMBLEM patients treated with olanzapine and of memory loss/concentration difficulties and insomnia in patients treated with valproate. The results of this post-hoc analysis suggest that olanzapine monotherapy may be more effective than valproate monotherapy in overall bipolar improvement over 12 months of treatment. For non-psychotic patients, olanzapine monotherapy may be more effective than valproate monotherapy in both overall bipolar illness and mania improvement however; the EMBLEM results also indicate that in clinical practice, physicians tended to prescribe olanzapine for patients with psychotic mania and valproate for non-psychotic mania. Observational studies can examine the effectiveness of interventions in routine care, providing complementary information to RCTs. The EMBLEM study was sponsored by Eli Lilly and Company Limited.
TB15

THE EFFECTS OF QUETIAPINE ON RISKY DECISION-MAKING

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Psychiatric illnesses, including bipolar disorder, frequently involve problems with risky decision-making that might reflect underlying pathophysiology and influence clinical outcome. One possible mechanism for such effects is altered attention towards, and processing of, reward-related cues when selecting between actions with motivationally significant outcomes. Previous experiments suggest such processing is influenced by the activity of neuromodulators such as dopamine and serotonin (Pessiglione et al., 2007; Rogers et al., 2003). Quetiapine is an atypical antipsychotic drug with pharmacological actions that include noradrenergic reuptake inhibition and antagonism at both dopaminergic D2 and serotonergic 5-HT2A receptors. In this experiment, we investigated the effects of one-week quetiapine administration on the processing of reinforcement cues when making risky decisions in healthy adult volunteers. Twenty healthy volunteers were randomly allocated to receive 150mg quetiapine XL (titrated over three nights in 50mg steps) for seven nights. Twenty-one age-, sex-, and IQ- matched control volunteers received a matched placebo substance with sham titration. On the eighth day, all participants completed a risky decision-making task that involved a series of choices between two simultaneously presented gambles that differed in the magnitude of their possible gains, the magnitude of their possible losses, and the probabilities with which these outcomes were delivered. This task also assessed non-normative shifts between risk-averse choices for gambles involving equivalent gains to risk-seeking choices for gambles involving equivalent losses, i.e. the 'reflection effect'. The two groups were well matched in terms of baseline mood and personality characteristics and there were no effects of quetiapine on state affect or anxiety (all p>0.1). However, those participants who received quetiapine showed reduced discrimination between small and large gains, F(1,37)=6.442, p=0.015, and between small and large losses, F(1,37)=6.959, p=0.012, when choosing between risky actions. Deliberation times for these choices were unaltered. One-week quetiapine administration also had no significant effect on non-normative shifts between risk-averse and risk-seeking choices, reflection effect, F<1. These findings suggest that one-week quetiapine administration alters the processing of reinforcement signals during risky decision-making by reducing sensitivity to differences in gains and differences in losses when selecting between options. Our results complement previous demonstrations that manipulation of tryptophan (Murphy et al., 2009; Rogers et al., 2003) and tyrosine activity (Scarna et al., 2005) alters processing of reinforcement cues during risky decision-making. These effects are consistent with quetiapine's actions at monoamine and catecholamine sites and its efficacy in the treatment of bipolar disorder. PLR is supported by an MRC studentship.

TB16

THE USE OF LITHIUM TO ENABLE THE INITIATION OF CLOzapINE THERAPY IN A PATIENT WITH PRE-EXISTING NEUTROPENIA

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Clozapine is licensed in the UK for treatment resistant schizophrenia. Agranulocytosis is however a potentially lethal side effect. Leukocytosis is a common finding in patients taking lithium, and this side effect has been used to advantage to raise the white cell count in patients whose baseline count is too low to allow the initiation of clozapine.(Paton C., Esop R.,Managing clozapine-induced neutropenia with clozapine. 2005, Psychiatric Bulletin. 29, 186-188.) Lithium has also shown to be effective in raising the white cell count in patients who develop clozapine-induced neutropenia, thereby enabling the drug to be reintroduced.(Silverstone P H., Prevention of clozapine-induced neutropenia by pre-treatment with lithium. 1998 Journal of Clinical Psychopharmacology, 18(1), 86-88) We present a case of a twenty four year old Caucasian male with pre-existing neutropenia where the use of lithium enabled the initiation of clozapine. CASE REPORT At around the age of 18, his parents noticed a change in his behaviour. He became more withdrawn, suspicious, and struggled with tasks which required organisation. Features of a psychotic illness in the form of delusions and hallucinations emerged a year later. He achieved only partial remission on a variety of antipsychotics at maximum licensed doses. In addition, he and his family received psychosocial interventions. As he fulfilled the criteria for treatment resistant schizophrenia, clozapine was considered. However, repeated full blood counts revealed neutropenia. He agreed to start on lithium in a bid to raise his white cell count, and the neutrophil count increased to 2.8 thereby enabling him to be commenced on clozapine. Both his positive as well as his negative symptoms improved. Apart from hypothyroidism which he developed as a result of lithium therapy, he tolerated both medications well. DISCUSSION Our case highlights that pre-treatment with lithium can be used in patients whose neutrophil counts are too low to enable the initiation of clozapine. We attribute the improvement in his mental state to clozapine rather than to lithium as he had no significant affective symptoms during his illness.

TB17

ANNUAL COST OF MANAGING BIPOLAR DISORDER TO THE UK HEALTHCARE SYSTEM

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Introduction: Bipolar disorder is associated with significant impairment in personal and social functioning and places a substantial burden on society (NICE CG38, 2006). Das Gupta and Guest (2002) estimated an annual social and economic cost of approximately £2 billion in the UK with 10% of this attributable to National Health Service (NHS) resource use, of which 15% was attributable to hospital admissions. However, these cost estimates are based on data collected over ten years ago, and a number of guidelines (e.g. NICE bipolar guidelines, 2006; Quality Outcomes Framework, 2006) have since been introduced that may impact on the diagnosis and management of bipolar disorder, and consequently, the cost of managing this condition. The aim of this study was to estimate the annual cost associated with managing bipolar disorder to the UK NHS. Methods: A retrospective observational study was conducted to quantify the annual cost of resource use associated with managing bipolar disorder in the UK. Primary care resource use was estimated using the IMS Disease Analyzer, a nationally representative sample of GP practices. Two published sources of data from the NHS Information Centre were used to assess resource use in secondary care and in outpatient and community mental health. The number of bed days and day attendances for patients hospitalised were obtained from the Hospital Episode Statistics (HES). This was supplemented with Mental Health Minimum Dataset (MHMDS) to quantify outpatient and community mental health face-to-face contacts. Resource use was examined between 01 April 2007 and 31 March 2008. This period was selected as the most recent period in which to allow data from different sources to be aligned. All resource use was projected to national levels. Costs were based on National Schedule of Reference Costs 2008-2009, Unit Costs of Health and Social Care (PSSRU), 2009, NICE Guideline 38 2006 (inflated) and the Monthly Index of Medical Specialties (MIMS), January 2010. Results: The annual cost of bipolar disorder to the NHS was estimated to be £342 million at 2009/2010 prices, of which hospitalisations (admissions and day care) accounted for £207 million (60%), outpatient and community mental health contributed £91 million (27%), and medication contributed £25 million (7%) of the overall direct costs of care. Conclusions The annual cost of managing bipolar disorder is a significant challenge to the NHS. Therapeutic strategies that optimise community-based management, early relapse detection, prevention of recurrence and hospitalisation could reduce the economic burden of this illness. Topic keyword: Affective disorders Sources of financial support: This study was funded and conducted by AstraZeneca Luton, UK.
**TC01**

**EFFECTS OF D-AMPHETAMINE ON THE BEHAVIOUR OF NK1r+/+ AND NK1r−/− MICE IN THE 5 CHOICE SERIAL REACTION TIME TASK**

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The neuropeptide 1 knock-out (NK1r−/−) mouse is a model of attention deficit hyperactivity disorder (ADHD). We have previously reported that NK1r−/− mice exhibit hyperactivity, which is prevented by d-amphetamine (d-AMP) or methylphenidate. These psychostimulants are first-line treatments for ADHD. Furthermore, polymorphisms in the human NK1R gene, TACR1, have been found in the DNA of ADHD patients (Yan et al., 2010, J Psychopharmacol, 24, 27-38). Additional core features are impulsivity, and inattentiveness, which are evident in NK1r−/− mice when they are tested in the 5 Choice serial reaction time task (5-CSRTT, this meeting). Here we explored whether these cognitive deficits are prevented by d-AMP. Mice were trained to criterion in the 5-CSRTT as described in Oliver et al. (2009, Psychopharmacology, 204, 679-692) and Yan et al. (this meeting). They were then tested with a long inter-trial interval (LITI, 7s) followed by a variable ITI (VITI: 2, 5, 10 and 15 s). All animals were given an i.p injection of saline or d-AMP (0.3 or 1 mg/kg) or no injection (NI). The sequence of these four test conditions was randomised, with each being tested once in every mouse at weekly intervals. Perseveration in wildtype mice, tested in the LITI, was reduced by either saline or d-AMP. By contrast, perseveration was increased in NK1r−/− mice after saline injection but not following injection of d-AMP (1 mg/kg) (treatment×genotype interaction: F(2,145.4)=4.831, P<0.05). When tested in the VITI, both omissions (F(1,21)=7.676, P<0.05) and perseveration (F(1,21)=6.501, P<0.05) were greater in untreated NK1r−/− mice than wildtypes, but there was no genotypic difference after d-AMP. Overall, premature responding was increased, rather than reduced, by d-AMP, especially in NK1r−/− mice. Perseveration, which is common in ADHD patients, was greater in NK1r−/− mice and exacerbated by a saline injection but prevented by d-amphetamine. These findings support our proposal that NK1r−/− mice are a model of this disorder. However, neither premature responses (an index of impulsivity) nor omissions (an index of inattentiveness) were reduced by this drug. The specific effects of amphetamine, with respect to these different elements of cognitive performance, and their vulnerability to experimental parameters, should be taken into account when investigating the effects of this drug on behaviour. This work was supported by the MRC.

**TC02**

**BEHAVIOUR OF NK1r+/+ AND NK1r−/− MICE IN THE 5-CHOICE SERIAL REACTION TIME TASK**

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Mice that lack functional substance P-prefering NK1 receptors (NK1r−/−) are a model of Attention Deficit Hyperactivity Disorder (ADHD) as evidenced by their hyperactivity and impaired regulation of monoamine transmission in cortical-stratial regions (see Yan et al, 2009, Neuropharmacology, 57: 627-635). Here, we used the 5-Choice Serial Reaction Time Task (5-CSRTT) to investigate whether these mutants also display inattentiveness and impulsivity, which are further core features of this disorder. Male NK1r+/+ and NK1r−/− mice (129/Sv X C57BL/6 crossed with an outbred Mf1 strain) were trained in the 5-CSRTT (as described in Oliver et al, 2009, Psychopharmacology, 204: 679-692). They were then tested with a long inter-trial interval session (LITI, ITI increased to 7s) and a variable ITI session (VITI, ITI = 2-15s). These tests impose different demands on attentiveness and response control. Both NK1r+/+ and NK1r−/− mice passed the 5-CSRTT training and reached the baseline for testing. The performance of the two genotypes did not differ at baseline, except for a small increase (+17%) in latency to collect the food reward after a correct response in NK1r−/− mice compared with the wildtypes (post hoc LSD test: P = 0.001). In the LITI test, % omission was greater in NK1r−/− than in NK1r+/+ mice (LSD: P = 0.05) as the mutants made more omission errors than they did at baseline, compared with the wildtypes (LSD: P = 0.01). The LITI test also increased premature responding of the animals (F(1, 44) = 53.5, P = 0.001) but the increase did not differ between genotypes. Finally, during the VITI test, NK1r−/− mice perseverated more than the wildtypes (LSD: P = 0.030). In the VITI test, % omission, premature responding and latency to make a correct response were all greater in NK1r−/− than in NK1r+/+ mice (LSD: P < 0.05 or less). This suggested a greater deterioration of the performance of the mutants from baseline, compared with the wildtypes. NK1r−/− mice learned the 5-CSRTT to the same criteria as the wildtypes. However, by increasing the task difficulty with the LITI and VITI schedules, inattentiveness and poor response control emerged in the mutants. These behavioural deficits consolidate NK1r−/− mice as a model of ADHD. [This work was sponsored by the Medical Research Council]

**TC03**

**ENHANCED DOPAMINE AVAILABILITY AND RESPONSE READINESS, THE INFLUENCE OF 3 DOESES OF METHYLPHENIDATE ON CONTINGENT NEGATIVE VARIATION IN THE EEG OF HEALTHY VOLUNTEERS**

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The basal ganglia play an important role in motor control. It is dependent on dopaminergic input. Preparation of a motor response has been associated with dopamine release in the basal ganglia. Response readiness may therefore serve as a pharmacodynamic marker of dopamine activity. Response readiness can be measured using the contingent negative variation (CNV) amplitude. CNV is a slow negative shift in the electroencephalogram. It is evoked by a paradigm in which a warning stimulus (S1) signals the occurrence of the imperative stimulus (S2) 4 seconds later, to which the participant has to respond. The present study examined the utility of response readiness as a marker of dopamine activity. CNV was measured in healthy volunteers after administration of placebo or 10, 20 or 40 mg of methylphenidate, a catecholamine re-uptake blocker which enhances primarily the synaptic concentration of dopamine and also noradrenaline. In addition, participants filled out two VAS scales measuring subjective feelings: POMS and Bond & Lader. Data were analyzed by an analysis of covariance model for crossover designs with terms for treatment order and pre-dose baseline values as covariate. Responses to S2 were significantly faster after 40 mg of methylphenidate. To a smaller extent, faster responses were also observed after 10 and 20 mg of methylphenidate. CNV amplitude was significantly larger one hour after 40 mg of methylphenidate. The subjective measures revealed that participants felt more alert after 40 mg of methylphenidate and more vigorous after all doses of methylphenidate. These preliminary results suggest that response readiness measured by the CNV paradigm seems consistent with dose-dependent increase after methylphenidate. Furthermore, this might indicate that increased dopamine activity can improve response readiness. The observed methylphenidate effects on subjectively experienced effects seem to be consistent with that. This study was sponsored by F. Hoffmann La-Roche Ltd, Basel, Switzerland.
**TC04**

**DISTINCT EFFECTS OF METHYLPHENIDATE IN THE PREFRONTAL CORTEX ASSOCIATED WITH ATTENTIONAL CAPTURE AND RESPONSE INHIBITION**

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Methylphenidate (MPH) can improve inhibitory control in stop signal tasks (SSTs). While the mechanism for this effect is unknown, the right inferior frontal gyrus (rIFG) has been linked with inhibition (Rubia et al, 2003, NeuroImage, 20, 351-358). Yet, the rIFG is also recruited during attentional capture (Hamshire, et al, 2010, NeuroImage, 50, 1313-1319; Sharp, et al, 2010, Proceedings of the National Academy of Sciences, In Press). We assessed effects of MPH (40mg) on two SSTs. One similar to previous versions (Rubia, et al, 2003, NeuroImage, 20, 351-358). In a second task, we attempted to separate the contribution of attentional capture. A double-blind placebo-controlled crossover design was used. 16 healthy males performed the SST and a modified SST (mSST) during fMRI scanning 1.5h after dosing; the latter including continue trials matched perceptually and in frequency to stop trials but not requiring stopping. Images were acquired on a 3T GE HDs System. Standard pre-processing and analysis were conducted (SPM5). Statistical significance was defined following correction for multiple comparisons (p<0.05) for the whole brain or the bilateral IFG region of interest. Compared to placebo, MPH reduced activation in the rIFG during successful stop>go on the SST (BA47, x=-44,y=-28,z=-2; 350 voxels; Z=4.8; p<0.001) and mSST (BA47; 32, 26, -14; 101 voxels; Z=4.05; p<0.04 using SVC) consistent with the hypothesis. To assess attentional capture effects of the continue trials, we contrasted continue>go. MPH reduced activation in the orbital aspect of the rIFG (BA38; 30, 20, -22; 41 voxels; Z=4.38; p<0.02 using SVC). For stop trials, controlling for attentional capture (stop>continue), methylphenidate did not attenuate the activation of the IFG. A connectivity analysis was performed using the orbital IFG (BA38) and rIFG (BA47) as seed regions in a separate group of 16 volunteers scanned at rest. The orbital rIFG (BA38) region was functionally coupled to inferior brain regions implicated in the ventral attentional network (Corbetta, et al, 2002, Journal of Cognitive Neuroscience, 14, 508-523). rIFG (BA47) activity was correlated with overlapping inferior regions as well as regions commonly linked to response inhibition, including the preSMA (BA32; -5, 16, 50) and sub-thalamic nucleus (-4, -16, 2). Overall, these findings suggest that MPH effects on rIFG activity during the SST cannot be unequivocally attributed to inhibition, but to a joint effect on inhibition and attentional capture. This project was funded by departmental funds of the Department of Neuroimaging; Institute of Psychiatry at King's College London.

**TC05**

**POSITIVE EFFECTS OF RED BULL® ENERGY DRINK ON DRIVING PERFORMANCE DURING PROLONGED DRIVING**

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Introduction: Prolonged highway driving can be affected by sleepiness. During driving, performance progressively gets worse. It is therefore advised to have a 15-minute break after every two hours of continuous highway driving. The purpose of this study was to examine the effects of Red Bull® Energy Drink versus placebo. Methods: 24 healthy volunteers participated in this double-blind placebo controlled crossover study. After 2 hours of driving in the STSIM driving simulator subjects had a 15-minute break in which they consumed Red Bull® Energy Drink (250 ml) or placebo (Red Bull® Energy Drink without the following functional ingredients: caffeine, taurine, glucuronolactone, B vitamins (niacin, pantothenic acid, vitamin B6, vitamin B12 and inositol) before driving 2 additional hours. A third condition comprised 4 hours of uninterrupted driving. Primary parameter of the highway driving simulator test was the Standard Deviation of Lateral Position (SLDP), i.e. the weaving of the car. Secondary parameters included the standard deviation of Speed, subjective driving quality, driving style, mental effort to perform the test, and subjective sleepiness. Data were analyzed using SPSS, ANOVA for repeated measures. Paired comparisons were made for each hour of driving. Effects were regarded as significant if p<0.05. Results: In the first two hours, no significant differences between the treatments were observed on any parameter. Relative to placebo, Red Bull® Energy Drink significantly improved driving: SLDP values were significantly reduced during the 3rd (p=0.046) and 4th hour of driving (p=0.011). During the 3rd hours, Red Bull® Energy Drink significantly reduced the standard deviation of Speed (p=0.004). In line, for the 3rd hour of driving after consumption of Red Bull® Energy Drink subjects reported significantly improved driving quality (p=0.0001) and reduced mental effort to perform the test (p=0.024). During both the 3rd and 4th hour of driving, subjective sleepiness was significantly less pronounced after Red Bull® Energy Drink when compared to placebo (p=0.001 and p=0.009, respectively). When compared to placebo, in the 3rd hour of driving after consumption of Red Bull® Energy Drink, subjects rated their driving as significantly more comfortable (p<0.004, predictable (p<0.001), relaxed (p<0.011), responsible (p<0.0001), and safe (p<0.002). Relative to prolonged driving, the effects of Red Bull® Energy Drink were significant for each parameter during both the 3rd and 4th hour of driving, except for mental effort during the 4th hour of driving. Conclusion: Red Bull® Energy Drink significantly improves driving performance during prolonged driving. Acknowledgment: the study was registered at www.clinicaltrials.gov, trial identifier: NCT01007877. The study was financially supported by Red Bull GmbH.

**TD01**

**PREVIOUS COCAINE USE DECREASES PRESYNAPTIC LIMBIC DOPAMINERGIC FUNCTION: A [18F]-DOPA PET STUDY**

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Introduction: Cocaine acts to increase synaptic dopamine levels by blocking the dopamine transporter. Chronic cocaine users show marked decreases in baseline limbic striatal dopamine levels (Martinez et al., 2009, Am J Psychiatry,166:1170–1177) and amphetamine induced limbic dopamine release (Martinez et al., 2007, Am J Psychiatry 164:622–629). Decreases in striatal dopamine synthesis have also been noted in cocaine dependent volunteers which is also reduced in cocaine dependent volunteers who have been abstinent from cocaine for between 15 and 30 days (Wu et al., 1997, Neuropsychopharmacology, 17, 402–409). Decreases in striatal dopamine synthesis have been postulated to act as a risk factor for cocaine craving and relapse (Dackis and Gold, 1985, Neurosci Biobehav Rev, 9, 469-477) however no studies have investigated the effect of recreational cocaine use on presynaptic striatal dopamine function over the long term. We therefore examined the effects of previous infrequent recreational cocaine use on limbic [18F]-DOPA binding. Methods 8 healthy volunteers (2 females, mean age 26 years (+3) who had previously used cocaine recreationally at least once, but had not used in six months prior to imaging, were compared to 41 healthy volunteers (21 females, mean age 37 years (+14)) who had never used cocaine. Each volunteer underwent high resolution [18F]-DOPA PET to determine presynaptic dopamine function. All scans were head movement corrected 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. The effect of previous cocaine use on [18F]-DOPA Ki values was determined using a multivariate ANOVA with age included as a covariate. Results A history of any previous cocaine use was associated with significantly lower right (F(1,41)=8.0, p<0.007) and left (F(1,41)=5.1, p<0.03) limbic Ki values. Mean right and left limbic Ki values (/min) for the cocaine group were 0.0129 and 0.0142 and for the non-use group were 0.0143 and 0.0150 respectively. Conclusions These results show that previous infrequent recreational cocaine use is associated with lower bilateral presynaptic limbic striatal dopamine function. This is the first time that these decreases, measured by [18F]-DOPA PET, have been reported after recreational cocaine use and implies that even infrequent recreational cocaine use may produce long term decreases in limbic striatal dopaminergic function.
SUBSTANCE USE AND REGIONAL GREY MATTER VOLUME IN INDIVIDUALS AT HIGH RISK OF PSYCHOSIS

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Introduction: Individuals with attenuated symptoms of psychosis (at risk mental state – ARMS) are at greatly increased risk of developing a psychotic illness. Psychosis risk and subsequent transition are both associated with regionally reduced cortical grey matter volume. There has been considerable interest in the interaction between psychosis risk and substance use. In this study we investigate the relationship between alcohol, cannabis and nicotine use with grey matter volume in ARMS subjects and healthy volunteers.

Methods: Twenty seven ARMS subjects and 27 healthy volunteers took part in the study. All subjects completed a face to face interview, in which demographic details and information about their recent drug and alcohol use was obtained. All subjects underwent volumetric MRI imaging (IR-SPGR) on a 3T scanner (GE) at the Institute of Psychiatry, London. Images were segmented into grey matter, white matter and CSF using SPM-5. The relationship between regional grey matter volume and cannabis use, smoking, and alcohol use in controls and ARMS subjects was analysed using a GLM implemented in FMRIB Software Library (FSL). Any regions showing a significant relationship with drug was analysed using a separate GLM to determine whether there was any group difference in this relationship. Results: Alcohol use was associated with reduced grey matter volume in cerebellum, right insula, bilateral temporal poles, and medial prefrontal cortex. It was also associated with increased grey matter in posterior cingulate and left superior temporal cortex. Cannabis use was associated with reduced grey matter in prefrontal cortex, and increased grey matter volume in superior temporal cortex. These relationships did not differ between ARMS subjects and controls. Nicotine use was not associated with any differences in grey matter volume. Conclusions: Our data suggest that alcohol and cannabis use, but not nicotine use are associated with significant alterations in regional grey matter volume. However, there was no evidence that substance use is associated with more marked changes in grey matter volume in subjects at high risk of psychosis than in healthy volunteers.

IMPACT OF SYSTEMIC GHRELIN AND COCAINE ON INTRACRANIAL SELF-STIMULATION IN THE ADULT RAT

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Introduction Food restriction (FR) augments the behavioral and reinforcing effects of psychostimulants such as cocaine and amphetamine. The precise mechanisms by which FR exerts these effects is unknown, but may possibly be related to the effects of FR on plasma ghrelin (GHR) levels. GHR is a 28 amino acid peptide secreted peripherally by the gut and is the only gut hormone known to stimulate food intake. FR increases GHR levels whereas feeding reduces plasma GHR. Additionally, GHR receptors can be found in reward centers of the brain such as on ventral tegmental dopamine neurons and systemic injections of GHR increase dopamine levels within the shell region of the nucleus accumbens. Thus the CNS GHR system appears well positioned to facilitate reinforcement. Psychostimulants induce locomotion and augment reward-seeking behavior. Recent studies have examined the effects of GHR on locomotion when paired with cocaine and report its augmenting effect and have shown that GHR can augment cocaine-induced conditioned place preference. Method and Results: To further assess the impact of GHR on brain reinforcement systems, the present study used two procedures in which rats lever press to deliver intracranial electrical stimulation of the lateral hypothalamus (ICSS). In the first experiment, rats were required to exert greater effort on a progressive ratio schedule in order to earn ICSS. Systemic GHR (5 nmol, IP) suppressed break point ratios (from baseline) by 31%, whereas cocaine at doses of 1.25 and 5.0 mg/kg (IP) increased break point ratios by 54% and 272%, respectively. Admniters of 5 nmol GHR and cocaine resulted in lower breakpoint ratios than expected from cocaine alone. In a second study, we assessed the impact of GHR at doses of 5, 10 and 30 nmol (IP) using a rate-frequency procedure in which ICSS intensity is held constant while frequency is systematically varied across 15 half-log steps. In this paradigm, GHR suppressed the maximal rates of ICSS responding and suppressed the threshold frequency of stimulation. In contrast, cocaine at 2.5 and 5.0 mg/kg shifted the rate-frequency curve to the left. Conclusion: Taken together, these observations suggest that in the ICSS paradigm, GHR acts to inhibit reinforcement.

SIMULTANEOUS POLYSUBSTANCE USE AND SEROTONIN TRANSPORTER AND 2A RECEPTOR BINDING AMONG HUMAN MDMA AND HALLUCINOGEN USERS

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Background and aims: The recreational drug ecstasy or MDMA (3,4-methylenedioxy-n-methamphetamine) is a potent releaser and reuptake inhibitor of the synaptic vesicle monoamine transporter (SVT) and the serotonin transporter (SERT). MDMA use is associated with reduced grey matter volume in cerebellum, right insula, bilateral temporal poles, and medial prefrontal cortex. MDMA use is also associated with increased grey matter in posterior cingulate and left superior temporal cortex. Cocaine use was associated with reduced grey matter in prefrontal cortex, and increased grey matter volume in superior temporal cortex. These relationships did not differ between ARMS subjects and controls.

Methods: Twenty seven ARMS subjects and 27 healthy volunteers took part in the study. All subjects completed a face to face interview, in which demographic details and information about their recent drug and alcohol use was obtained. All subjects underwent volumetric MRI imaging (IR-SPGR) on a 3T scanner (GE) at the Institute of Psychiatry, London. Images were segmented into grey matter, white matter and CSF using SPM-5. The relationship between regional grey matter volume and cannabis use, smoking, and alcohol use in controls and ARMS subjects was analysed using a GLM implemented in FMRIB Software Library (FSL). Any regions showing a significant relationship with drug was analysed using a separate GLM to determine whether there was any group difference in this relationship. Results: Alcohol use was associated with reduced grey matter volume in cerebellum, right insula, bilateral temporal poles, and medial prefrontal cortex. It was also associated with increased grey matter in posterior cingulate and left superior temporal cortex. Cannabis use was associated with reduced grey matter in prefrontal cortex, and increased grey matter volume in superior temporal cortex. These relationships did not differ between ARMS subjects and controls. Nicotine use was not associated with any differences in grey matter volume. Conclusions: Our data suggest that alcohol and cannabis use, but not nicotine use are associated with significant alterations in regional grey matter volume. However, there was no evidence that substance use is associated with more marked changes in grey matter volume in subjects at high risk of psychosis than in healthy volunteers.
**TD05**

**REDUCED DORSAL PREFRONTAL GRAY MATTER FOLLOWING CHRONIC KETAMINE USE**

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Background: ketamine’s use as a recreational drug is spreading rapidly among young people all over the world. Epidemiological studies have shown a link between chronic ketamine use and cognitive impairments, bladder dysfunction and ketamine-related death. To date, little is known about the long-term effects of ketamine use on brain structure and function. Methods: We used voxel based morphometry in conjunction with statistical parametric mapping on the structural magnetic resonance images of ketamine-dependent (n = 41) and drug-naive control individuals (n = 44) to assess differences between the two groups in gray matter volume. Results: We observed significant decreases in gray matter volume in bilateral frontal cortex (left superior frontal gyrus and right middle frontal gyrus) of ketamine users in comparison to controls (p < 0.05 corrected for multiple comparisons at cluster-level). Duration of ketamine use was negatively correlated with gray matter volume in bilateral (right: Pearson Correlation = -0.402, p = 0.009; left: Pearson Correlation = -0.395, p = 0.011) frontal cortex while the estimated total lifetime ketamine consumption was negatively correlated with gray matter volume in left superior frontal cortex (Pearson Correlation = -0.366, p = 0.019). Conclusions: We have demonstrated a reduction in frontal gray matter volume in patients following chronic ketamine use. The link between frontal gray matter attenuation and the duration of ketamine use and cumulative doses of ketamine perhaps suggests a dose-dependent effect of long-term use of the drug. Our results have important implications for the clinical problems that are likely to emerge with the growing leisure use of ketamine and are relevant too to the status of the drug as a model for schizophrenia. This work was supported by grants from the National Key Technology R&D Program in the 11th Five-Year Plan of China [2007BAI07B01], Natural Science Foundation of China [30971050, 30870893, 30900486] and National Key Basic Research and Development Program (973) [2006CB500808, 2007CB512301]. Paul C Fletcher is supported by the Bernard Wolfe Health Neuroscience fund and by the Wellcome Trust. Yanhui Liao is supported by a fellowship from the China Scholarship Council and by Professor Trevor W Robbins to study at University of Cambridge, Behavioural and Clinical Neuroscience Institute.

**TD06**

**ASSOCIATION BETWEEN THE EXCITATORY AMINO ACID TRANSPORTER 2 GENE POLYMORPHISM AND METHAMPHETAMINE DEPENDENCE**

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Research strongly implicates the glutamatergic system in the etiology of drug dependence. Changes in EAAT2 protein expression have, for example, been reported after exposure to methamphetamine (METH) (Shira et al, 1996, Psychiat. Clin. Neurosci., 50, 161-164) and cocaine Knackstedt et al, 2010, Biol. Psychiat., 67, 81-84). Polymporphisms of the EAAT2 gene (SLC1A2) have been associated with schizophrenia (Deng et al, 2004, BMC Psychiatry, 4, 1-6), some positive symptoms of which are similar to those occurring in METH dependence. The aim of this study was to investigate the association of EAAT2 gene polymorphisms with METH dependence. One hundred METH-dependent subjects, meeting DSM-IV criteria for amphetamine-like dependence, and 102 ethnically-matched healthy subjects were recruited and written informed consent was obtained from all participants. All subjects were genotyped for two EAAT2 single nucleotide polymorphisms (SNP2: rs4755404 and SNP6: rs1885343) from blood using PCR methods. The genotype and allele frequencies were analyzed using Chi2 test. The polymorphisms for both the control and drug-dependent groups were in Hardy-Weinberg equilibrium (P = 0.05). There was a significant difference between the groups in genotype (P = 0.024) but not in allele frequencies (P = 0.159) in SNP6. Additionally, a significant excess of G/G genotype versus A allele carriers was also observed in SNP6 in METH-dependent subjects compared to the control group (P = 0.010). There were no significant differences in either genotype (P = 0.198) or allele (P = 0.611) frequencies in SNP2, although there was a non-significant trend (P = 0.077) to a greater frequency of the CC genotype in METH dependence. Furthermore, a significant haplotype association (P = 0.021) of SNP6-SNP2 was detected, in which the frequency of the A-G haplotype in METH dependence (16.0%) was lower than in controls (25.3%). The results show a significant association between an EAAT2 gene polymorphism and METH dependence. These findings parallel a previous report that found association of the EAAT2 polymorphism with schizophrenia (Deng et al, 2004). Moreover, genetic variation of the EAAT2 gene has been reported to confer vulnerability to risk-taking behavior in alcoholics (Sander et al, 2000, Psychiat Genet., 10, 103-107). Our findings suggest that absence of the A allele of rs1885343 of the EAAT2 gene may confer vulnerability to a risk factor for METH dependence. This study was supported by grants from the Thailand Research Fund (TRF) and Commission on Higher Education (CHE), and PMI2 Connect Research Co-Operation Award, British Council UK. WK was supported by the Strategic Scholarships for Frontier Research Network (SSFRN) PhD studentship from CHE, Thailand.

**TD07**

**MOLECULAR MECHANISMS UNDERLYING CORTICOSTERONE SELF-ADMINISTRATION AND ITS IMPACTS ON SPATIAL AND RECOGNITION MEMORY IN MICE**

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Corticosterone (CORT) the main glucocorticoid in rodents has been shown to facilitate acquisition and reinstatement of addictive drugs. Limited research was carried out to address whether corticosterone is rewarding. In two experiments, rats self-administered corticosterone in particular when they received high doses of corticosterone which produced a stress like corticosterone plasma level. Previously, we showed that mice also self-administered corticosterone. C57BL/6J male mice were tested for corticosterone preference using a two-bottle choice test and a flavour (inosine monophosphate, IMP) to help discriminating the hormone which is tasteless. They had the choice between IMP versus water (control group), unflavoured corticosterone versus water, unflavoured corticosterone versus IMP, IMP-flavoured corticosterone versus water, or 1% ethanol (the vehicle for corticosterone) versus water. Mice self-administered unflavoured corticosterone over a 3-week period (acquisition) and these corticosterone-dependent mice exhibited the same appetite for the hormone after a withdrawal period (relapse), and in a later phase (switching) when the aversive IMP-flavoured solutions were exchanged for unflavoured ones. Corticosterone dependent mice showed no memory impairment in the spatial alternation test. Mice which self-administered high doses of unflavoured corticosterone (versus IMP), before switching, had impaired recognition memory. However, the molecular mechanisms underlying reward associated corticosterone self-administration and its impacts on learning and memory process in corticosterone dependent mice are not known. Here, we measured the levels of a number of proteins known to play a role in addiction, neuroplasticity and cognition using Western immunoblotting, in the frontal cortex and hippocampus, two brain regions critical for cognition. They include synaptophysin, a marker of synaptic density, and components of the brain derived neurotrophic factor (BDNF) signalling pathway: BDNF, its receptor, TrkB, and its upstream modulator active Erk1/2. Data were analysed by one way ANOVA followed by planned comparisons and results showed low ERK2 activity in the hippocampus (P < 0.05) and the frontal cortex (P < 0.05) of mice which had a choice between unflavoured corticosterone versus IMP and IMP-flavoured corticosterone versus water, respectively, as compared to the control. However, there was no difference in synaptophysin levels between groups. In conclusion, the data show that the development and maintenance of corticosterone self-administration is associated with a reduced activity of the ERK1/2 signalling pathway, consistent with its involvement in addiction. Reduced ERK1/2 signalling has been linked to impaired cognition and could contribute to the memory deficits seen in corticosterone-dependent mice. Funded by Egyptian Ministry of Higher Education
THE ADMINISTRATION OF PSILOCYBIN TO HEALTHY HALLUCINOGEN-EXPERIENCED VOLUNTEERS IN A MOCK-FMRI ENVIRONMENT: A PRELIMINARY INVESTIGATION OF TOLERABILITY

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Introduction: This study sought to assess the tolerability of intravenously administered psilocybin in healthy, hallucinogen-experienced volunteers in a mock-magnetic resonance imaging environment as a preliminary stage to a controlled investigation using functional magnetic resonance imaging (fMRI) to explore the effects of psilocybin on cerebral blood flow and activity. Methods: Nine healthy, hallucinogen-experienced volunteers participated in this study. Three subjects received 1.5mg and six subjects received 2mg psilocybin (intravenous preparation) in an open-label design. Real-time subjective ratings were taken every minute and measures of heart rate and blood pressure were taken continuously five minutes before and twenty minutes after a sixty second infusion of psilocybin. Drug effects were rated on a 0-10 basis with zero representing “no drug effects” and ten “extremely intense drug effects”. Results: Both doses of psilocybin were psychologically and physiologically well tolerated by all of the volunteers. The 2mg dose produced stronger subjective effects (range of drug effects ratings = 5 to 8.5/10) than 1.5 mg (range of drug effects ratings = 3 to 8/10), with a faster onset (peaking 3min post end of infusion at 2mg and 6mins at 1.5mg) and longer duration of effects (F = 10.3, df = 1, p = 0.005). No acute or subacute adverse phenomena were reported or observed. All subjects expressed an opinion that the drug experience would be tolerable in a real MR scanner. Conclusions: With appropriate care, this study supports the viability of functional magnetic resonance imaging work with psilocybin. Funding: This study was funded by the Beckley Foundation and the Neuropsychoanalysis Foundation.

INSTABILITY OF THE ILLICIT PSYCHOSTIMULANT MARKET LEADS TO THE RISE OF "LEGAL HIGHS" IN THE NETHERLANDS

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The Drug Information and Monitoring System (DIMS) in The Netherlands monitors trends and new substances circulating on the drug market from the perspective of health care (Vogels, et al., 2009, Addiction 104:2057-66). Our aim was to investigate whether a recent instability of the psychostimulant market has led to the introduction of new substances or trends and their possible health risks. We analyzed all synthetic psychostimulants with gas chromatography and mass spectrometry. We also compared DIMS findings during 2008 and 2009 with those of The Netherlands Forensic Institute (NFI) during both years. The NFI receives drug samples obtained from police seizures. We gathered acute subjective effects of two highly prevalent new substances from users through the DIMS network. We confirmed the instability of the ecstasy and the speed markets in the The Netherlands, showing a substantial decrease of ecstasy tablets containing MDMA (3,4-methylenedioxymethylamphetamine) and a decrease in amphetamine in powders sold as “speed”. In addition, two new designer drugs were detected increasing significantly during the decline of the ecstasy and speed markets: mephedrone and 4-fluoroamphetamine. Whereas mephedrone was sold as “ecstasy” in tablet form, 4-fluoroamphetamine substituted for amphetamine on the “speed” market in powder form. We gathered information on the acute subjective effects of both substances from more than 100 drug users. Effects of both drugs were considered positive, but they also seemed to evoke rather unpleasant side-effects: mephedrone, as opposed to MDMA, induced strong feelings of craving and 4-fluoroamphetamine caused excessive intranasal burning, nosebleeds and headaches when snorted. Both pure mephedrone and 4-fluoroamphetamine are directly sold through the internet. Both substances are not legislated in most EU countries, therefore they are tentatively referred to as “legal highs”. Since the list of these kind of drugs grows longer each year, the scientific community has trouble keeping up with experimental research on these chemicals. Dating further research, our findings are suggestive for both substances to be a cause for health concern, especially if the synthetic psychostimulant market situation remains unstable and the availability of these “legal highs” remains uncontrolled. This research was financially supported by the Dutch Ministry of Health, Welfare and Sport.

AGE RELATED EFFECTS OF ACUTE EXPOSURE TO Δ9-TETRAHYDROCANNABINOL ON GLUCOSE UPTAKE - A SEMI QUANTITATIVE [14C] 2-DEOXYGLUCOSE AUTORADIOGRAPHY STUDY

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Cannabis is the most commonly used illicit drug worldwide with a particularly high prevalence rate amongst adolescents. Throughout adolescence the brain undergoes sequential maturation commencing in areas of the brain involved with basic functions, with areas involved in executive function and attention e.g. prefrontal cortex (PFC) being last to mature (Thompson & Nelson 2001 American Psychologist 51(1):5-15).There is increasing evidence of age-related susceptibility to the deleterious effects of cannabis as early onset of use may increase vulnerability to the adverse consequences and lead to more severe sequelae than recreational use in adulthood (Pope et al. 2003 Drug Alcohol Depend 69:303–310). The aim of the present study was to determine (I) whether there are age-related differences in baseline levels of regional brain activity (II) whether acute exposure to Δ9-tetrahydrocannabinol (Δ9-THC), the principal psychoactive constituent of Cannabis sativa, results in differential effects on neural activity in discrete brain regions in peripubertal rats compared to adult rats. Cerebral glucose uptake (73 brain regions) was determined in Lister-hooded male rats aged either 35 or 70 days (n=20/gp) following acute i.p. administration of Δ9-THC. Differences in glucose uptake (73 brain regions) were determined between peripubertal and adult rats suggestive of maturation and/or use of brain areas. Additionally, in some areas peripubertal animals were shown to be more sensitive to Δ9-THC which may underlie differential liability to the deleterious effects of cannabinoids. Parallel studies are underway to investigate the ontogeny of functional cannabinoid receptors in the rat from birth to adulthood. Supported by an IMB capacity building award.
CANNABIDIOL WEAKENS THE APPETITIVE EFFECTS OF DELTA-9-TETRAHYDROCANNABINOL: A NATURALISTIC STUDY OF CANNABIS SMOKERS

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Introduction: The concentration of the main psychoactive ingredient in cannabis, Δ9-tetrahydrocannabinol (THC), is increasing in street cannabis worldwide, along with cases of cannabis dependence. Cannabidiol, the second most abundant cannabinoid in street cannabis, appears to have pharmacologically and behaviourally opposing effects to THC when administered in the laboratory, and in contrast to THC, levels of cannabidiol in street cannabis are decreasing. It has not been investigated how the ratio of these cannabinoids may affect the appetitive/reinforcing effects of cannabis in humans. Method: Ninety-four cannabis users were tested 7 days apart, once while non-intoxicated and once while acutely under the influence of their own chosen smoked cannabis on dependence-related measures. A sample of the cannabis smoked was collected from each user and analysed for levels of cannabinoids. CBD:THC ratios in the cannabis were calculated, and individuals in the top and bottom tertiles were compared on indices of the reinforcing effects of drugs, explicit liking and implicit attentional bias to drug stimuli. Results: When intoxicated, smokers of low CBD:THC strains of cannabis showed increased attentional bias to drug and food stimuli compared with smokers of high CBD:THC strains (F(1,57)=5.63, p=0.021). On both test days, individuals smoking higher CBD:THC strains also reported a lower liking of cannabis stimuli (F(1,59)=12.44, p=0.001). Conclusions: These findings suggest that CBD possibly has potential as a treatment for cannabis dependence and obesity. It also appears that there is a potentially higher risk for dependence associated with smoking low CBD strains of cannabis such as ‘skunk’ or ‘sinsemilla’, and users should be made aware of this and encouraged to use strains containing higher levels of CBD. This study was funded by a grant from the Medical Research Council (UK).

IN SMOKED CANNABIS, CANNABIDIOL ATTENUATES THE ACUTE MEMORY IMPAIRING EFFECTS OF DELTA-9-TETRAHYDROCANNABINOL (THC)

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The two main constituents of cannabis, cannabidiol (CBD) and delta 9-tetrahydrocannabinol (THC) have opposing effects both pharmacologically and behaviourally when administered in the laboratory. Although street cannabis is known to contain varying levels of each cannabinoid, no research has yet examined how this impacts upon the acute effects of the drug in naturalistic settings and so this study aimed to determine these impacts. 134 cannabis users were tested 7 days apart, once while non-intoxicated and once while acutely intoxicated by their own chosen smoked cannabis, on measures of memory and psychotomimetic symptoms. Using an unprecedented methodology, a sample of cannabis (as well as saliva) was collected from each user and analysed for levels of cannabinoids. On the basis of highest and lowest CBD content of cannabis, two groups of individuals were directly compared. The low CBD group (n=22) did not differ from the high CBD group (n=22) in delta 9-THC content of smoked cannabis, years in education, psychosis proneness, age at which cannabis was first used or frequency of cannabis use per month. However, the high CBD group exhibited higher premorbid verbal IQ and reported using less units alcohol per session. When non-intoxicated, the groups did not differ in number of items recalled on a prose recall task. However, when intoxicated the low CBD group recalled fewer items of prose, both immediately (p=0.002) and after a 30 minute delay (p=0.001). CBD content did not affect psychotomimetic symptoms, which were elevated in both groups when intoxicated. The antagonistic effects of CBD at the CB1 receptor are probably responsible for its profile in smoked cannabis, attenuating the memory impairing effects of THC. In terms of harm reduction, users should be made aware of the higher risk of memory impairment associated with smoking low CBD strains of cannabis like ‘skunk’ and encouraged to use strains containing higher levels of CBD.

IN HEALTHY SUBJECTS CANNABIDIOL INHIBITS Δ9-TETRAHYDROCANNABINOL INDUCED ACUTE PSYCHOSIS AND TACHYCARDIA VIA A NON-PHARMACOKINETIC MECHANISM

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Introduction The pro-psychotic properties of cannabis are attributable to Δ9-tetrahydrocannabinol (THC) (Murray et al. 2007 Nat Rev Neurosci 8,885-95). Another plant-derived molecule, cannabidiol (CBD) displays anti-psychotic properties in animal models and in humans (Zuardi et al. 2006 Brazilian journal of medical and biological research 39,421-29). In the UK, new forms of cannabis (sinsemilla), which contain high concentrations of THC but negligible concentrations of CBD, now dominate the illicit cannabis market and there is concern that sinsemilla might be more hazardous for mental health than traditional cannabis (Hall 2006 Lancet 367,193-195; Potter et al. 2008 Journal of forensic sciences 53,90-94). Although evidence for this is sparse, some have speculated that it is the absence of CBD, rather than rising concentrations of THC, which is important (Smith 2005 Addiction 100,1558-60). Animal work and early human studies suggested that CBD could antagonise some of the pharmacological effects of THC (Pertwee 2007 British journal of pharmacology 153,199-215). However, what remains unknown is whether CBD inhibits the pro-psychotic effects of THC. Here, using intravenous preparations and standard rating scales we tested the effect of CBD on THC-psychosis. It was hypothesized that THC-elicted positive psychotic symptoms, would be less under CBD than placebo conditions. Design A within-subjects, placebo-controlled, double-blind investigation of whether intravenous (IV) CBD attenuates the acute psychotic reaction elicited by IV THC. Methods Healthy subjects (n=6) attended for 2 experimental sessions at least 2 weeks apart. ‘Pre-Treatments’, IV CBD (5mg) or placebo, were administered intravenously immediately prior to IV THC (1.25mg). Positive psychotic symptoms were assessed at baseline and at 30 minutes post-THC, by an independent psychiatrist using the PANSS rating scale (5-factor version). Previous studies have shown that THC-elicted psychosis peaks at 30 minutes post-injection. Non-parametric statistical tests were used to compare PANSS positive scores. Results The major finding was that, at 30 minutes post-dosing, THC-elicted PANSS positive symptoms were significantly lower under CBD compared to placebo conditions (z=-2.3, p=0.05). Plasma concentrations of THC were numerically higher under the CBD versus the placebo arm, but differences did not reach significance. Summary The finding that ‘a mixture’ of CBD and THC is less psychotomimetic than an equivalent dose of THC on its own suggests that CBD ‘protects’ against THC-induced psychosis. The results are consistent with recent epidemiological work which has indicated that the absence of CBD in sinsemilla might be an important factor underlying psychotogenicity (Morgan & Curran 2008 Br J Psychiatry 192,306-307; Di Forti et al. 2009 Br J Psychiatry 195,488-491). The effect of THC on heart rate is mediated directly on the vagus n. via CB1 receptors. This suggests that the effect of CBD on THC-psychosis might similarly be mediated via CB1. funding: MRC
TD14

DO REGULAR CANNABIS USE AND POSITIVE SCHIZOTYPAL PERSONALITY TRAITS IMPACT ON NORMAL LATENT INHIBITION FUNCTIONING?

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Background & Aims Latent inhibition (LI) refers to the slower learning of an association between a conditioned stimulus (CS) and the unconditioned stimulus (UCS) when pre-exposed to the CS without any other consequence. LI is measured as the difference in the efficacy of conditioning between the pre-exposed (PE) and non pre-exposed (NPE) groups. LI is impaired in schizophrenia, amongst high schizotypal scorers and in amphetamine-treated rats (Serra et al., 2001). The aim of this study was to explore the link between regular cannabis use on behavioural (i.e. deficits in selective attention) and trait outcomes (i.e. schizotypal scores) linked to psychosis using a non clinical sample. Specifically, it was hypothesised that cannabis users would show impaired LI by comparison with non-users.

Method 40 participants (20 regular cannabis users and 20 non-cannabis users, mean age = 30) were randomly allocated to the pre-exposed (PE) and non pre-exposed (NPE) conditions of the LI task. All participants completed the Schizotypal Personality Questionnaire (SPQ-B; Raine., 1991). Results & Discussion The preliminary ANOVA revealed a statistically significant main effect of cannabis use on LI, F (1, 36) = 10.3, p = 0.003; LI was abolished in the cannabis group with no difference found between the scores in the PE versus the NPE condition. However, normal LI was not found in the non cannabis group; they took less time overall in the PE condition than in the NPE condition. Therefore, a secondary ANOVA was conducted to elucidate these findings and revealed a statistically significant difference between NPE and PE groups for the SPQ total (p = 0.018) and the subscale disorganised thinking (p = 0.004). People in the PE condition exhibited twice as many psychotic-like traits overall and significantly more for disorganised thinking. This finding ties in with existing research correlating disorganised thinking with greater attentional deficits seen in patients with schizophrenia (Baxter and Liddle, 1998). Further to this, this effect of schizotypy in the PE condition for the LI task was stronger for cannabis users versus non users. These findings indicate that, even in relatively small groups, there seems to be some effect of cannabis use and schizotypal personality traits on normal LI functioning. LI is a sensitive task which could be utilised to highlight early selective attention deficits in cannabis users.

TD15

VERBAL LEARNING AND MEMORY IN ADOLESCENT CANNABIS AND ALCOHOL USERS

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Introduction: Deficits in verbal learning and memory are frequently observed in adult cannabis users and there are growing concerns that the adolescent brain may be more vulnerable to the adverse cognitive effects of exposure to cannabis. Adolescent cannabis users also tend to consume more alcohol than non-users, raising questions about the specificity of drug effects. This issue was investigated by comparing verbal learning and memory in adolescent cannabis users, alcohol users and non-users of either substance. Methods: Subjects (n=181; 52 cannabis users (mean 2.4 years of use, currently 14 days/month, median abstinence 20.3 hours), 67 alcohol users (mean 1.33 years of use, currently 5 days/month), 62 controls) were recruited from school cohorts in the Wollongong Youth Study and the general community. Groups were matched on age (range 16-20, mean 18.3, SD=0.46), years of education and premorbid intellectual functioning. Cannabis and alcohol groups were matched for alcohol consumption. Subjects completed the Rey Auditory Verbal Learning Test and premorbid measures of verbal ability were obtained from entry to high school (age 12). Results: Adolescent cannabis users learned fewer words across the five learning trials (F(2,177)=5.99, p<0.01), recalled significantly fewer words in total (F(2,176)=10.57, p<0.001), after interference (γ2(2)=8.07, p<0.05) and a delay (γ2(2)=15.44, p<0.001), and recognised fewer words from a less well-learned list (F(2,178)=4.66, P<.05) than both alcohol users and controls. Effects remained significant after controlling for alcohol consumption, other substance use, pre-morbid intellectual ability and psychological symptoms. Memory performance worsened as a function of quantity, frequency, duration and age of onset of cannabis use. Quantity of cannabis used per month and age of onset of regular cannabis use were significant predictors of memory performance in a regression model (p<0.001) and accounted for 31.5% of the variance in words recalled. Alcohol use and premorbid intellectual ability accounted for very little of the variance (2.4% and 0.2% respectively). Alcohol users did not differ from controls and no gender effects were found. Conclusions: Verbal learning and memory deficits appear to be specific to cannabis but not alcohol exposure during adolescence. Impairment increased as a function of quantity, frequency, duration and age of onset of cannabis use. Relative to their age-matched counterparts, adolescent cannabis users demonstrated similar memory deficits to those reported in adult long-term heavy users, despite relatively brief exposure to cannabis. The results indicate that cannabis adversely affects the developing brain and reinforce concerns regarding the impact of early exposure. This research was supported by grants from the National Health and Medical Research Council of Australia (Grant 514604) and the Australian Research Council (Grants LP0453853, DP0878925). Yucel is supported by a National Health and Medical Research Council Clinical Career Development Award (Grant 509345). Lubman is supported by the Colonial Foundation.
ABSTRACTS

TD16

REFLECTION IMPULSIVITY IN ADOLESCENT CANNABIS USERS

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Introduction: Heavy cannabis users seem to develop in the prefrontal cortex) showed certain genes to be associated with impulsivity and others with compulsivity, suggesting independent genetic bases for both traits that can contribute to understanding of the genetic basis of impulsivity and its relationship with addiction disorders. Supported by EU FP6 project "IMAGEN"
TE01
FOS EXPRESSION IN THE PREFRONTAL CORTEX AND NUCLEUS ACCUMBENS SHELL IN THE RAT BRAIN FOLLOWING EXPOSURE TO A RETROSPECTIVE TIMING TASK

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It has been proposed that the dorsal striatum and the prefrontal cortex play a pivotal role in interval timing [Matell and Meck, 2004, Cog Brain Res 21:139-170]. We examined whether performance of a temporal discrimination task is associated with increased neuronal activity in the striatum and prefrontal cortex, as revealed by Fos expression, a marker for neuronal activation [Herdegen and Leah, 1998, Brain Res Rev 28:370-490]. Twelve rats were trained on a discrete-trials psychophysical procedure (DTPP) in which a light (22 cd m-2) was presented for a variable time, t (2.5-47.5 s), after which levers A and B were presented. A response on A was reinforced if t<25 s, and a response on B if t>25 s. Twelve rats were trained on a control task, the light intensity discrimination procedure (LIDP), in which a light of variable intensity, i (3.6-128.5 cd.m-2) was presented for 25 s. A response on A was reinforced if i<22 cd.m-2, and a response on B if i>22 cd.m-2. Training continued for 60 sessions. Ninety minutes after the final session, the rats were perfused with fixative and their brains sectioned coronally at 40 μm. Sections were labelled for Fos [Bortlikova et al., 2006, Psychopharmac 185:188-200]. Behavioural data were analysed using a two-parameter logistic equation and measures of the central tendency of discrimination (indifference point: t50 [DTPP], i50 [LIDP]) and discriminative precision (Weber fraction) were derived [Al-Zahrani et al., 1996, Psychopharmac 123:103-110]. Performance on the DTPP and LIDP was similar to that reported previously [Hampson et al., 2010, Behav Pharmacol 21:11-21]. In both schedules, proportional choice of lever B increased as a function of stimulus duration or intensity and was well described by the logistic equation (r2>0.9). In the DTPP, t50 was 27.5±2.34 s (mean±SEM); the Weber Fraction was 0.62±0.08. In the LIDP, i50 was 20.6±2.7 cd.m-2; the Weber Fraction was 1.76±0.57. Multivariate ANOVA revealed that Fos expression in the orbital prefrontal cortex (OPFC) [F(1,20)=4.8, P=0.05] and nucleus accumbens shell (AcbS) [F(1,20)=4.1, P=0.05] was significantly higher in the rats exposed to the DTTP than in those exposed to the LIDP, indicating greater neuronal activation in these areas during the DTPP. Fos expression in the dorsal striatum did not differ between the groups. These results support the notion that the OPFC and the AcbSs are involved in temporal discrimination. However they provide no evidence for an involvement of the dorsal striatum in this behaviour. Supported by the BBSRC.

TE02
INVolVEMENT OF THE ORBITAL PREFRONTAL CORTEX AND NUCLEUS ACCUMBENS CORE IN INTER-TEMPORAL CHOICE: EVIDENCE FROM FOS EXPRESSION

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Lesions of the orbital prefrontal cortex (OPFC) and nucleus accumbens core (AcbC) can disrupt performance in inter-temporal choice tasks, possibly by increasing the organism’s sensitivity to delay of reinforcement (delay discounting) [Cardinal et al., 2001, Science 292:2499-2501; Kheramin et al., 2002, Psychopharmacology, 165:9-17; Winstanley et al., 2004, J Neurosci, 24:4718-4722; Bezzina et al., 2007, Psychopharmacology, 195:71-84; da Costa Araújo et al., 2009, Behav Brain Res 202:272-277]. We examined whether exposure to an inter-temporal choice task (adjusting-delay schedule) would induce neuronal activation in these areas, as indicated by enhanced expression of the Fos protein, a marker for neuronal activation [Herdegen and Leah, 1998, Brain Res Rev 28:370-490]. Twelve rats were trained to press levers A and B under an adjusting-delay schedule [Mazur, 1996, J Exp Anal Behav, 66:63-73] in which a response on A delivered 50 μl of a sucrose reinforcer after 2 or 18 s, whereas a response on B delivered the same reinforcer after a delay that was adjusted in accordance with the rat’s choices. Another twelve rats were trained under a similar schedule in which a response on A delivered a reinforcer of size 20 or 180 μl, whereas a response on B delivered a reinforcer whose size was adjusted in accordance with the rat’s choices. A third group underwent training on a schedule that did not entail delay of reinforcement. A control group underwent food restriction without behavioural training. The rats were killed 90 min after the final (70th) training session for immunohistochemical staining of 40-micron coronal brain sections. Fos expression in the OPFC and AcbC in the experimental groups was compared with that in the control group (ANOVA, Dunnett’s test; criterion p<0.05). Significantly higher levels of Fos expression (counts.mm-2, mean±SEM) were seen in the OPFC of rats exposed to the adjusting-delay (386±18) and adjusting-magnitude (284±14) schedules than in the control group (165±14). Significantly higher levels were seen in the AcbC of rats exposed to the adjusting-delay (166±18), but not the adjusting-magnitude schedule (104±10), compared to the control group (81±11). The results suggest that exposure to the adjusting-delay schedule produced neuronal activation in both the OPFC and AcbC, whereas exposure to the adjusting-magnitude schedule produced activation in the OPFC but not the AcbC. The results are consistent with previous findings implicating both the AcbC and the OPFC in delay discounting, and the OPFC in sensitivity to reinforcer size [references: see above]. Supported by the Wellcome Trust.
TE03

THE EFFECT OF DESTRUCTION OF LATERAL HYPOthalamic ORExinergic NeURones ON ProGRESSIVE RATIO SCHEDULE PERFORMANCE: EVIDENCE FOR AN EFFECT ON MOTOR PERFORMANCE

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The orexins are hypothalamic neuropeptides that have been implicated in feeding, reward processing, addiction and the sleep/wakefulness cycle. It has been suggested that a sub-population of orexinergic neurones whose somata lie in the lateral hypothalamic area (LHA) have a specific role in regulating the reinforcing efficacy of food and drugs [Harris and Aston-Jones, 2007, Trends Neurosci 29:571-577]. We examined the effect of destruction of LHA orexinergic neurones on performance on the progressive-ratio (PR) reinforcement schedule, in which the response requirement increases progressively for successive reinforcers. The data were analysed using a mathematical model which yields a quantitative index of reinforcer value and dissociates effects of interventions on motor and motivational processes [Killeen, 1994, Behav. Brain Sci. 17:105-172]. According to this model, response rate, R, is related to ratio size, N, according to a bitonic function R=[1-(1-B)/N]/δ-N/a. The peak of the function (1/B: maximum response rate) is regarded as an index of motor performance, whereas the slope of the descending limb reflects the incentive value of the reinforcer, a (slope=1/a) [Bezzina et al., 2008, Psychopharmacology, 197:339-350].

Thirty-six female Wistar rats were trained to steady state (110 sessions) under a PR schedule using food-pellet reinforcement. They received bilateral injections of conjugated orexin-saporin (OX-SAP) into the LHA (15ng in 0.3ul) (n=14), or sham lesions (n=16). After surgery they were trained for a further 40 sessions. Killeen’s equation was fitted to the data from each rat and the parameters derived for successive blocks of 10 sessions. Data were analysed by ANOVA (group x block), followed by multiple comparisons between groups within blocks. Orexin-positive neurones were identified immunohistochemically from 40-micron coronal sections through the LHA. The OX-SAP lesion reduced response rate compared to the sham-lesioned group. The ‘incentive-value’ parameter, a, was not significantly altered by the lesion. However, peak response rate was reduced in the lesioned group, reflected in significant increases in δ (mean±SEM post-surgical changes in δ [s] in the four post-surgical blocks: sham-lesioned group, -0.04±0.05, 0.06±0.04, -0.09±0.03, 0.09±0.05; OX-SAP-lesioned group, -0.10±0.05, -0.19±0.09*, -0.09±0.08*, -0.09±0.07*; P<0.05). The number of orexin-positive neurones in the LHA of the lesioned group was reduced by 45.8% compared to the sham-lesioned group (P<0.001). The results indicate that partial depletion of LHA orexinergic neurones disrupted food-reinforced responding on the PR schedule. This disruption was not caused by a change in the incentive value of the reinforcer, but by a change in non-motivational processes encapsulated in δ. Funded by the University of Nottingham.

TE04

PAIRWISE DISCRIMINATION FOLLOWED BY REVERSAL IN C57BL/6J USING MOUSE TOUCHSCREEN OPERANT BOXES

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Touchscreen technology allows the assessment of multiple cognitive abilities in an experimenter-independent fashion, and denotes a significant step forward for translational research in that human cognitive tests can be back-translated for use in preclinical species, and vice versa, whilst still exploring the same underlying neurobiological pathways. Here, in a beta test of novel mouse touchscreen technology with Campden Instruments Ltd, we report the acquisition by C57BL/6J mice (n=12) of a pairwise discrimination paradigm, whereby the animals were trained to discriminate between two visual stimuli (“marble” and “fan”) displayed on the touchscreen. Mice were counterbalanced, such that half the mice had the “marble” whilst the other half had the “fan” as the correct stimulus. A nosepoke to the correct stimulus was paired with a liquid reinforcer, whereas a nosepoke to the incorrect stimulus resulted in a 5 sec timeout (house light on) and a repeat of that same trial under a correction procedure. All mice were presented with 1 session per day comprising a maximum of 30 trials or 1 hour test (whichever was the shortest), until a performance criterion of 70% correct for 2 consecutive days had been reached. The acquisition curve revealed that mice performance was different from chance after 7 days (student’s t test: p<0.01). However detailed analysis (2 way ANOVA time x cue) showed that the two visual stimuli used were not of equal salience; specifically, the mice had a bias towards the “marble” stimulus. Such a finding has the potential to confound any subsequent reversal data as a shift from “fan” to “marble” could be perceived as being significantly more difficult than a shift in the opposite direction. Consequently, we assessed different pairs of visual stimuli in order to identify a suitable equal-salient pair for subsequent use. Having identified a visual pairing of equal salience, namely “flash” and “wheel”, the acquisition and reversal performance of the mice was re-assessed. Mice achieved criterion performance in 3 days (student’s t test: p<0.01). At the reversal stage, all mice perseverated to the previously correct stimulus (Student’s t test shows % trial correct significantly different from chance performance, p<0.01), prior to acquiring the reversal discrimination in 7 days. In conclusion, touchscreen technology is an increasingly useful and widespread tool with the scope to assess many cognition domains in the rodent in a high throughput and translational manner. The present data support this view but highlight the importance of ensuring task performance is critically reviewed to minimise confounds in data interpretation.

TE05

DIFFERENTIAL EFFECTS OF PREE- AND INFRA-LIMBIC DOPAMINE DEPLETION ON TRANCE CONDITIONING MEASURED IN A CER PROCEDURE

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Introduction: Lesion studies suggest that, consistent with known projections from hippocampus, medial prefrontal cortex (mPFC) is part of the network necessary for trace fear conditioning. Moreover, single neuron recordings have shown increased and decreased activity in prelimbic and infralimbic cortex during conditioning with a 20s trace interval (Gilmartin and McEchron, 2005, Behavioral Neuroscience, 119, 1469-1510). However, the role of key neuromodulators within mPFC and the extent to which its projection to infralimbic and subiculum regions are differentially involved in the processes necessary to bridge conditioning over a trace interval are not yet established. Here we examined the effect of dopamine (DA) depletion in prelimbic and infralimbic cortex on trace conditioning in a fear conditioned emotional response (CER) procedure. Methods: 6-hydroxydopamine was used to lesion DA terminals within prelimbic and infralimbic cortex. After a minimum of 1 week to recover, rats were water deprived and placed to drink in their allocated conditioning boxes for a total of 5 days. Trace conditioning was subsequently measured in a threat-motivated CER procedure to test suppression to a light conditioned stimulus that had previously been paired with footshock (unconditioned stimulus) at either a 10 or 30s trace interval on each of 2 conditioning trials. Over the subsequent two days, trace conditioning was followed byreshaping and then a test session, to re-establish drinking and to determine the levels of conditioned fear in the different groups, respectively. Results: 6-hydroxydopamine produced differential depletion of DA in prelimbic and infralimbic cortex depending on the site of injection; the pretrial lesion was anatomically selective whereas the infralimbic lesion produced DA depletion in both subregions of mPFC. T-tests showed no differences in the level of conditioning at the 10 and 30s trace intervals in sham- and infralimbic- lesioned animals. However, the pretrial-lesioned group showed a clear trace effect as there was less conditioning at the 30s compared to the 10s interval (p<0.05). Conclusions: At 10 and 30s, the trace intervals used in the present study resulted in little conditioning in sham- and infralimbic-lesioned groups. By contrast, in pretrial cortex the effect of DA depletion was to accentuate the difference in conditioning supported at the 10 and 30s trace intervals. Thus, consistent with the results of single neuron recordings which suggest that activity in pretrial neuromodulators mediates bridging over a trace interval (Gilmartin and McEchron, 2005, Behavioral Neuroscience, 119, 1469-1510), the present findings point to the role of DA as a neuromodulator of trace conditioning in pretrial cortex. This work was supported by the Wellcome Trust (ref. 082940) and part supported by BAP in vivo training funds.
Introduction: Patients with schizophrenia exhibit poor working memory performance. While there are large discrepancies in the definition of working memory used form study to study, the NIH-funded MATRICS initiative recommended that the span capacity domain of working memory be assessed when assessing the efficacy of a putative therapeutic for FDA approval. The radial arm maze (RAM) can be used to assess spatial span capacity, although protocol differences have limited its use. We have used an automated 12-arm RAM in mice with only a 1 s delay between choices to counter simple strategy formation, and where only two never-baited arms are used to assess reference memory. We hypothesized that span capacity (number of baited arm entries prior to a repeat entry) and reference memory (entries into never-baited arms) would be pharmacologically dissociable and that working memory span capacity performance would not be confounded by strategy formation. Methods: We trained C57BL/6N mice (n=12) to perform a win-shift strategy in the RAM. Strategy use was measured using a spatial coefficient of variation analysis based on arm choices. Stable performance (no effect of day over four consecutive days for any measure), was challenged with a) scopolamine (0.1, 0.3, and 1 mg/kg) and b) bromocriptine (0.1, 1, and 10 mg/kg) in a cross-over design, with a 1-week washout period between drug challenges. Data were analyzed using a repeated measures one-way ANOVA. Results: Span capacity increased in mice as training continued (F(18,198)=2.2.3, p<0.005), while strategy usage decreased (F(18,198)=2.3, p<0.005). Scopolamine increased reference memory errors during stable performance (F(3,33)=5.1, p<0.005) but span capacity was unaffected. Bromocriptine increased span capacity (F(3,33)=3.2, p<0.05), without affecting reference memory errors. Conclusion: Mice readily achieved maximal performance in the 12-arm RAM with training, while their use of strategies diminished. We observed a double dissociation of working memory span and reference memory performance measures in our drug challenges. Scopolamine impaired reference memory while not affecting spatial span capacity, an effect that is consistent with human testing. Bromocriptine, however, improved span capacity in mice without affecting reference memory, again consistent with human performance. These data confirm that working memory span capacity can be measured in mice and reveal drug effects that are consistent with reported effects in humans. This task may therefore prove useful in developing animal models of deficient working memory span capacity as well as assessing putative treatments. These studies were funded by R21-MH085221 and a NARSAD Young Investigators Award (JWY)
TE09

INVESTIGATION OF THE ROLE OF CATECHOL-O-METHYLTRANSFERASE (COMT) ON HIPPOCAMPUS-DEPENDENT BEHAVIOUR

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Catechol-o-methyltransferase (COMT) metabolises catechol-containing compounds and may be genetically associated with schizophrenia and obsessive compulsive disorder. In the hippocampus, COMT expression is abundant (Matsumoto M et al, 2003. Neurosci, 116(1):127-37) and inhibition of COMT alters dopamine metabolism (Laatikainen LM et al, 2009. J Psychopharmac 23(suppl):A17), suggesting a functional role for hippocampal COMT. The present study examined the acute effects of a centrally-acting COMT inhibitor, tolcapone, on hippocampus-dependent behaviour in rats. Twenty-four age-matched male Lister-Hooded rats (209-263g) were food deprived and habituated to the T-maze. Once all the animals were running freely and consuming the food rewards (Noyes sucrose pellets), rats were trained on the delayed rewarded alternation (spatial working memory, non-matching to place) task for approximately two weeks (Rawlins JNP&Olton DS, 1982. Behav Brain Res, 5(4): 331-358). Delays of 30 sec and 600 sec between the sample and choice runs were compared. On the day of testing, rats were either treated with a single intraperitoneal dose of tolcapone (30mg/kg) or vehicle, or merely handled (no injection controls). Each rat received forty choice trials on the testing day. The number of 30 sec and 600 sec delay trials, as well as the number of times each goal arm contained the reward, were balanced across each block of 20 choice trials. Performance data across forty trials were analysed using repeated measures ANOVAs with LSD post-hoc tests. A two-way ANOVA on test day performance revealed a significant group*delay interaction (F(2,21)=4.77; p=0.02) and a significant main effect of delay (F(1,21)=12.05, p<0.001). LSD post-hoc tests demonstrated that tolcapone-treated rats performed significantly better than vehicle-treated rats on the 30sec delay task (p=0.001).

However, it is also notable that there was a trend for the vehicle-injected rats to perform worse than the no injection controls (p=0.06). These data are consistent with a significant memory-enhancing effect of the COMT inhibitor tolcapone on a hippocampus-dependent behavioural task, although further experiments are required to identify the underlying basis of this effect. This is in accordance with studies suggesting a role for dopamine in hippocampus-dependent learning and memory (O’Carroll C et al, 2006. Learn Mem, 13(6):769-90) and extends the evidence that COMT inhibition can improve other domains of attention and memory. This research was supported by a MRC Project Grant, and PhD studentship (LML).

TE10

SEROTONIN 2C RECEPTOR ANTAGONISM HAS DIFFERENTIAL EFFECTS ON COMPONENTS OF A SPATIAL REVERSAL LEARNING TASK IN MICE

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Reversal learning requires the ability to both dissociate associations of positive (perseverance) and negative (learned non-reward) valence. These two processes can be separated by providing a novel response option replacing either the previously correct or incorrect response option. This method has been used to investigate the role of 5-HT1 and OFC in primate visual reversal learning (Clarke et al. 2007, Cerebral Cortex, 17, 18-27) and rat somatosensory and olfactory reversal learning (Tait and Brown 2008; Ann. N.Y. Acad. Sci. 1121, 407-420). Here we use a novel maze-based egocentric spatial reversal learning task to differentiate manipulations of learned non-reward and perseverance in mice treated with the 5-HT2C antagonist SB242084. Seventy-two C57BL6J male mice were trained in a two-choice egocentric spatial discrimination task, where a response in one of two available directions was rewarded. After reaching criterion, mice were treated with either 0.5 mg/kg SB242084 or saline (s.c.) and assigned to one of three conditions; (1) Full reversal, where the previously correct direction became incorrect, and the previously incorrect direction became correct; (2) Perseverance, where the previously correct direction became incorrect, and the previously incorrect direction was replaced by a novel correct direction; (3) Learned non-reward, where the previously incorrect direction became correct, and the previously correct direction was replaced by a novel incorrect direction. The effects of SB242084 on total trials to criterion was analysed by two-way ANOVA. SB242084 had opposite effect on perseverance and learned non-reward. There was a significant overall drug × condition interaction on trials to criterion (F(2,61) = 5.6, p = .05). SB242084 had no significant effects on trials to criterion in the full reversal condition (F(1,19) = 1.8, ns). However, SB242084 significantly decreased trials to criterion in the perseverance condition (F(1,20) = 4.5, p < .05), while significantly increasing trials to criterion in the learned non-reward condition (F(1,22) = 4.4, p < .05). 5-HT2C antagonism through SB242084 had opposite effects on trials to criterion in the perseverance and learned non-reward conditions. SB242084 decreased trials to criterion in the perseverance condition, while increasing trials to criterion in the learned non-reward condition. These results display clear resemblance to OFC lesioned rats in a similar bowl-digging procedure (Tait and Brown 2008). Additionally, the opposing effects of 5HT2C antagonism on perseverance and learned non-reward results in no apparent overall effects on spatial reversal learning in this task. Thanks to BBSRC and Eli Lilly for support.

TE11

PRENATAL CHRONIC MILD STRESS: IMPACT ON LOCOMOTOR ACTIVITY, ANXIETY-LIKE BEHAVIOUR AND COGNITIVE FUNCTION IN MICE OFFSPRING

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Introduction: In utero exposure to stress is thought to disrupt the development of the central nervous system, increasing vulnerability to mental disorders into adulthood. We aimed to examine the impact of prenatal chronic mild stress (CMS) applied either throughout gestation or in the final week of gestation (when the brain most develop), on the offspring’s behaviour at weaning (adolescence) and in early adulthood (7 weeks old). Method: Eight week-old B6D2F1 female mice were randomly divided into stress and control groups after being mated. The CMS procedure involves the sequential application of mild stressors such as confinement, paired housing, cage tilt (30°), and was applied to the stress group from gestation day 14 (experiment 1) or from 2 ± 1 day after mating (experiment 2) until parturition. The control females were left undisturbed. The offspring males and females underwent open field testing (OFT) at weaning and a battery of tests (OFT, novel object recognition and contextual fear conditioning) at age 42-50 days old, to assess locomotor activity, exploratory and anxiety-like behaviour, and cognitive function. Differences between groups were analysed by using ANOVA. Results: Prenatal CMS did not significantly alter OFT behaviour at weaning, but reduced locomotor activity at adulthood in experiment 1, regardless of gender (p<0.05). In experiment 2, there was a significant prenatal stress × sex interaction effect (p<0.05) with prenatally stressed males exhibiting reduction in locomotor activity, whilst prenatally stressed females showed higher locomotion compared to nonprenatally-stressed females. Female mice which were prenatally stressed during the last week of gestation also showed a reduction in anxiety-like behaviour (p<0.05), but this effect disappeared when mice were prenatally-stressed throughout gestation. In addition, CMS applied during the last week of gestation was sufficient to alter object recognition in males and females (p<0.01), but facilitated acquisition (p<0.05) of contextual fear in male only. Conclusions: These findings demonstrate that in utero exposure to CMS affects the behaviour of the offspring as a function of the gestation period where it is applied and in age- and gender-dependent manner, which supports the hypothesis that prenatal stress induces disruptions of the offspring’s central nervous development. Funded by the Malaysian Ministry of Higher Education.
A68 ABSTRACTS

TE12

REVERSAL OF VESICULAR GLUTAMATE TRANSPORTER 1 (VGLUT1) LENTIVIRAL SHORT HAIRPIN RNA (SHRNA) VECTOR-INDUCED COGNITIVE DEFICITS BY A 5-HT6 RECEPTOR ANTAGONIST

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Glutamate uptake into synaptic vesicles for exocytotic release occurs via VGlut1-3 transport proteins. Of these, VGlut1 is most abundant in the cortex and hippocampus, and its expression decreases in schizophrenia (Eastwood & Harrison 2005 Schiz Res 73 159). We have previously shown that intra-hippocampal administration of a lentiviral shRNA vector targeting VGlut1 induces selective cognitive impairments in novel object discrimination (NOD) and Morris water maze (WM) tasks (King et al 2009 J Psychopharmacol 23S A19), and attenuates glutamate eflux during in vivo microdialysis and microsensor studies (Qin et al 2010; FENS, Amsterdam). The present study examined the brains of shRNA-treated mice for microglial activation (Cd11b immunohistochemistry; IHC), and assessed the ability of a 5-HT6 receptor antagonist to overcome shRNA-induced NOD and WM deficits. Male C56Bl6J mice (22-26g; Charles River UK) underwent a 1h locomotor activity test on d1 of the experiment to allow balanced allocation to control or VGlut1 groups. On d2 or 3 they received bilateral injections of scrambled control or VGlut1 targeting lentiviral virions (King et al 2009 J Psychopharmacol 23S A19) into the dorsal hippocampus under isoflurane anaesthesia. Perfuse-fixed brains of six mice were collected on d12 for IHC with monoclonal rat anti mouse Cd11b primary (AbD serotec) and polyclonal rabbit anti rat secondary (Dako) antibodies. Remaining mice received vehicle or SB-399885 (Tocris) 20mg/kg i.p. 30min prior to NOD (d12) and WM (d16-19) testing (n=8/group). IHC revealed no major inflammatory response to lentiviral shRNA delivery. In controls and VGlut1 knockdowns Cd11b staining was confined to the needle tract, with no obvious lesion at the tip and no evidence of any cellular reaction >30μm from the centre of the tract. All mice demonstrated comparable performance during NOD and WM acquisition. Discrimination was impaired in VGlut1 knockdowns (P=0.6198, whereas control P=0.0427; Student’s paired t-test) and reversed by SB-399885 (P=0.016). This compound failed to normalise WM probe performance at the 20mg/kg dose level. Intra-hippocampal administration of a VGlut1 targeting shRNA lentiviral vector significantly impaired memory retention in hippocampal-dependent cognitive tasks, without causing any major inflammatory response. The 5-HT6 receptor antagonist SB-399885 reversed the NOD deficit in this preliminary single dose level study. The AGLAEAP project is funded by the European Commission 6th Framework for Research & Development.

TE13

FUTURE EVENT SIMULATION IMPROVES ALCOHOL-INDUCED PROSPECTIVE MEMORY IMPAIRMENTS

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Background: Whilst alcohol’s acute amnesic qualities on retrospective memory are well established, little is known of the way in which it may affect prospective memory – remembering to do something in the future. In addition, no study to date has explored how future event simulation at encoding (imagining scenarios of future action completion) impacts on subsequent prospective memory. We therefore aimed to determine the acute effects of alcohol on prospective memory through the use of a laboratory measure designed to mimic prospective memory tasks encountered in everyday life (virtual week). We also aimed to investigate the role of the event simulation in prospective memory processes and the resulting prospective task completion in both alcohol and placebo conditions. Methods: Using a double-blind independent groups design, 40 healthy volunteers were administered alcohol (0.6 g/kg) or matched placebo. Participants carried out the ‘virtual week’ task with a within task manipulation of simulation versus no simulation. In a further study, 32 healthy volunteers were administered alcohol (0.6 g/kg) or matched placebo and carried out the ‘virtual week’ task. Each day of the virtual week alternated between recent and remote contexts. Future event simulation was again manipulated within task. Episodic memory and executive function were indexed during both studies through the use of a source memory task and the Tower of London task, respectively. Results: In both studies, alcohol was found to produce global impairments across all prospective memory tasks during ‘virtual week’ (p = 0.002 and p = 0.02, studies 1 and 2 respectively). In study 1, future event simulation showed a tendency to improve prospective memory deficits induced by acute alcohol in event-based prospective memory tasks, which rely on external cues in the environment. Study 2 showed that prospective memory deficits induced by acute alcohol were significantly improved following alcohol exposure (p = 0.02). A tendency for better prospective memory performance on event-based tasks was also found within a recent context, irrespective of group. Conclusions: Our findings support the idea that alcohol can compromise prospective memory processes in everyday life. We provide the first evidence that future event simulation can overcome alcohol-induced deficits in event-based prospective memory tasks. Our findings have important clinical implications for the rehabilitation of chronic alcohol abusers, where future event simulation could potentially be used as a therapy adjunct. This study was funded by the UK Alcohol and Education Research Council (AERC).

TE14

THE ROLE OF THE MUSCARINIC AND SEROTONERGIC SYSTEM IN LEARNED IRRELEVANCE USING A WITHIN-SUBJECT DESIGN SUITABLE FOR EEG

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Learned irrelevance (Lirr) refers to a reduction in associative learning after pre-exposure of the conditioned (CS) and unconditional stimulus (US) in a non-contingent fashion. It reflects the ability of normal individuals to ignore inconsequential stimuli, i.e., to filter out irrelevant information from sensory and (pre)attentive information processing. In acute schizophrenia, this ability is compromised, resulting in sensory overload and disrupted Lirr. Although it is generally assumed that the neurochemistry of acute schizophrenia involves an excess of dopaminergic neurotransmission, it appears that other neurotransmitter systems such as the muscarinic and serotonergic system are involved as well. For example, the pharmacological profile of atypical antipsychotics, which possess a better efficacy as compared to first-generation drugs, has been suggested to partly consist of M1 muscarinic agonistic and 5-HT2A antagonistic effects. Therefore the goal of the current study was to investigate the role of biperiden, a selective muscarinic M1 antagonist, and acute tryptophan depletion (ATD), which is presumed to lower serotonergic neurotransmission, on Lirr in normal healthy volunteers. An initial data analysis has indicated that both BIP (F(1,14)=0.027, ns) and ATD (F(1,14)=1.362, ns) did not affect Lirr; however, BIP did prolong reaction times (F(1,14)=8.797, P<0.05). In a verbal word learning task which was also used in the same study, both BIP (F(1,16)=5.605, P<0.05) and ATD (F(1,16)=13.706, P<0.01) were found to impair delayed recall. Thus, the disruption in Lirr seen in acute schizophrenia is not likely to be mediated by the muscarinic M1 receptor or the serotonin system. In contrast, both the muscarinic M1 receptor and the serotonin system appear to be implicated in verbal memory. Funding was provided by the Dutch Alzheimer Research Foundation (ISAO).
THE SLEEP DEPRIVATION MODEL OF COGNITIVE IMPAIRMENT AND THE EFFECTS OF THE PRO-COGNITIVE DRUG, DONEPEZIL

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A central problem in research into pharmaco-cognitively-induced cognitive enhancement is that baseline performance in healthy volunteers is often relatively high and therefore insensitive to further improvement. Thus, the challenge is to find effective models of cognitive impairment that can be used to screen for efficacy of potential pro-cognitive compounds. Here, we report data from a study in which 30 healthy volunteers were administered either a 5mg daily dose of the acetylcholinesterase inhibitor donepezil or placebo for 14-17 days, then underwent either 24 hours sleep deprivation or a normal night of sleep, and were subsequently tested on a battery of CANTAB cognitive tasks designed to measure different components of memory and executive function. Sleep deprivation selectively impairs memory performance on several tasks, including pattern recognition (accuracy $p = 0.06$; latency $p = 0.03$) N-back (verbal working memory - N=0 $p=0.028$; N=1 $p=0.001$; N=2 $p=0.019$) and long-term word recognition ($p < 0.001$). In contrast, performance on other components of executive function, including reward-related decision-making, planning, attentional set-shifting and spatial working memory, was unimpaired ($p$ values all $> 0.15$). Treatment with donepezil had no effect on any of the tasks ($p$ values all $> 0.15$). The results confirm that 24 hours of sleep deprivation is an effective method for inducing a selective, transient impairment in memory performance, but that this impairment is not reversible by an established pro-cognitive drug targeting the cholinergic system. The findings question the sensitivity of the sleep deprivation model in identifying the pro-cognitive potential of candidate cognitive enhancing drugs.

PROGRESSIVE RATIO RESPONDING IN AN OBESE MOUSE MODEL: EFFECTS OF FENFLURAMINE

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Introduction The progressive ratio schedule of operant responding is a well-validated task for assessing the rewarding aspects of abused drugs and natural rewards including food. Interestingly, progressive ratio paradigms have mainly been neglected in the field of animal research in obesity. Among the most widely studied mouse models of obesity is the leptin-deficient ob/ob mouse, characterised by hyperphagia and obesity. To date there are no studies on the behaviour of these mice in progressive ratio responding, thus we sought to validate the utility of the progressive ratio paradigm in obese mice and demonstrate its sensitivity to an anorectic drug challenge. Methods Male ob/ob mice (n=8) and their lean controls (n=8) were food restricted to 85% of their free-feeding body weight and trained to respond by nosepoke for sucrose rewards in an operant chamber. Animals were then tested in fixed ratio (FR) paradigms with response demands of 1, 3, 6 and 9, with two daily sessions on five consecutive days in each FR-step. Subsequently response behaviour was assessed in a linear (increment: 3n+3) and a progressive ratio schedule (FR), with one daily session for 16 consecutive days, followed by testing in an exponential (increment: 5*2n-5) FR schedule. After eight days of baseline testing in the exponential PR-task, fenfluramine (5-10 mg/kg; i.p.) was administered in a double crossover design. Results Obese animals showed equal FR-acquisition and -responding for ratios 1 and 3, but displayed lower responding in ratios 6 and 9 compared to the lean control group. Interestingly, obese animals showed equal motivation to respond in linear and exponential PR schedules compared to lean controls. Fenfluramine (5-10mg/kg) dose-dependently induced an anorectic effect in both genotypes [overall effect of drug: $p=0.056$ (5mg/kg) and $p=0.001$ (10mg/kg)] and reduced PR responding significantly. Conclusions This study, for the first time, describes motivational food intake in a progressive ratio paradigm in ob/ob mice. Despite their increased body weight and low locomotor activity ob/ob mice were equally able and motivated to learn the operant task. Leptin deficiency did not alter appetitive learning or motivation in the progressive ratio. The utility and sensitivity of the progressive ratio operant task for studies on motivational food intake was demonstrated by a challenge with the anorectic agent fenfluramine. Acknowledgements The work described herein was supported by Enterprise Ireland under Grant Number CC20080001. JFC and TGD are also supported in part by Science Foundation Ireland in the form of a centre grant (Alimentary Pharmacobiological Centre).

RELATIONSHIP BETWEEN OBSESSIVE & COMPULSIVE BINGE-EATING BEHAVIOUR AND DIMENSIONS OF IMPULSIVITY IN AN OVERWEIGHT AND OBESE POPULATION

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Background: Behavioural and personality traits such as binge eating and impulsivity have been linked to clinical obesity. The aim of this study was to assess 1) the relationship between sub-scales of binge-eating behaviour and impulsivity and 2) their relationship to BMI in overweight and obese participants. Methods: The sample consisted of 188 (133M, 55F) otherwise healthy overweight and obese participants (no history of physical or psychiatric illness, aged 18-60, BMI >25kg/m2). All completed the Binge eating scale (BES), Yale Brown Obsessive Compulsive Scale modified for binge eating (Y-BOCS-BE) and the Barratt Impulsiveness Scale version 11 (BIS-11). Additionally, height and weight was recorded in order to calculate BMI. Results: Spearman’s correlations indicated that all three sub-scales (attentional, motor and non-planning impulsivity) of BIS-11 were significantly, but weakly, correlated with total score of the BES (r=0.20-0.29, all p’s <0.01). All sub-scales of the BIS-11 were also weakly correlated with total score and the sub-scales of Y-BOCS-BE (r=0.20-0.37, all p’s <0.01). Y-BOCS-BE and BES total scores exhibit a high correlation (r=0.71, p<0.0001). BMI was moderately correlated with BES total score (r=0.41, p<0.0001). BMI was also weakly correlated with total score and the obsessive and compulsive sub-scales of Y-BOCS-BE (r=0.19-0.28, all p’s <0.01). Obese participants scored significantly higher on the BES when compared to overweight participants (p<0.0001). Discussion: The current investigation indicates a link between obsessive and compulsive binge eating behaviour and dimensions of impulsivity in a local community sample of overweight and obese participants. The reported relationship between BMI and binge eating behaviour suggests that some individuals with impulsive traits may present with increased obsessive and compulsive binge eating behaviour, which in turn may increase their risk of developing obesity. These results indicate that specific eating behaviours and psychological traits may provide important therapeutic targets in the development of novel centrally acting anti-obesity drugs.
TF03

EFFECTS OF THE \( \mu \)-OPIOID RECEPTOR INVERSE AGONIST GSK1521498 ON EATING BEHAVIOUR IN OVERWEIGHT AND OBESE SUBJECTS

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Background: Endogenous opioids acting on central \( \mu \)-opioid receptors (MORs) play a critical role in neural mechanisms of appetite control, particularly in hedonic and consummatory aspects of eating. GSK1521498 is a MOR ligand under development for the treatment of obesity. In this study, we examine the effects of GSK1521498 using experimental models that may be predictive of anti-obesity efficacy, namely, i) a hedonic taste preference test (subjective rating of sweetened dairy products, with varying fat and sucrose content), and ii) an ad libitum food intake paradigm (with snack items categorized according to their sugar and fat content) in obese and overweight volunteers. Method: The study adopted a double-blind placebo controlled cross-over design in which the effects of a single dose of GSK1521498 (25mg) and placebo were examined in 20 otherwise healthy overweight or obese male subjects (BMI range 25-35 kg/m2). Results: Treatment comparisons of change from baselines in the hedonic taste preference scores and energy intake from the ad libitum snacking were performed separately using a mixed model ANCOVA. GSK1521498 significantly reduced hedonic ratings of sugar and fat at, i) all levels of fat and sugar content (p<0.0028), ii) the highest levels of fat (38.9%; p=0.0207, 19.1%; p=0.0398) and iii) the highest level of sugar (32%; p=0.0155). Furthermore, GSK1521498 reduced caloric intake by 27% for all categories of fat and sugar (p=0.0199) and by 39% for the high fat and high sugar category (p=0.0167). Discussion: These findings are consistent with the literature implicating MORs in hedonic and consummatory aspects of eating behaviour and provide encouraging preliminary evidence that GSK1521498 can selectively reduce caloric intake attributable to foods with high fat and/or high sucrose concentrations. This proximal effect on eating behaviour is a necessary condition for GSK1521498 to elicit longer-term effects on body weight and may provide a viable treatment option for obesity and related eating disorders.

TF04

APPETITE SUPPRESSING EFFECTS OF ECSTASY (MDMA) IN THE WEEK FOLLOWING USE

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There is evidence that MDMA/ecstasy acutely suppresses appetite (Vollenweider et al, 1998) and that users are very much aware of this effect (Curran and Robjant, 2006). However, data on appetite effects of MDMA is very limited and little is known about the detail of such effects in regular users of the drug. In the current study we explored eating patterns in 40 young clubbers: 20 who regularly used ecstasy and 20 who used alcohol on nights out. All participants were asked to keep a daily eating diary for two days in total, noting everything that was eaten and drunk during each meal, time and place of eating and enjoyment of eating at each meal/eating occasion. For these two weeks, one week consisted of eating reports for 7 days after a night-out in which they used their drug of choice (ecstasy or alcohol), and one week when they did not; with the order of diary completion counterbalanced. On completion, diaries were scored blind and total calories per day worked out for each of the 14 days, for each participant. Daily scores for numbers of eating occasions, meal sizes and food enjoyment were also evaluated. A preliminary split-plot ANOVA for average daily calorie intake across the week revealed a significant interaction effect (F(1,35) = 12.98, p = 0.001); with no change in calorie intake for the alcohol group ‘on’ or ‘off’ drug, but a significant fall in daily intake in the ecstasy group in the week following weekend use of MDMA (p = 0.003 for the within group contrast). Meal sizes and enjoyment of food ratings were also lower in the ecstasy user group following weekend MDMA use (p=0.05). Day-by-day data showed that, within the ecstasy group, calorie intake in the week following ecstasy use was depressed compared to the week without use, on all days except days 4 and 7. The single largest effect was for the day immediately after use (p=0.001), with intake reduced by over 50%. These data add to research in regular ecstasy users showing an appetite altering effect of MDMA. In particular this work shows that in addition to the expected acute and powerful anorectic effect of the drug, ecstasy use may be associated with a longer lasting disturbance of eating patterns. Whilst this does not equate to a problematic alteration within a single week, the findings perhaps point towards an area of concern for longer term regular use.

TG01

EFFICACY OF DULOXETINE FOR GENERALIZED ANXIETY DISORDER: A META-ANALYSIS AND SYSTEMATIC REVIEW

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Introduction: Recommendations are to treat generalized anxiety disorders (GAD) with either serotonin receptor inhibitors or norepinephrin receptor inhibitors. Duloxetine is a dual reuptake inhibitor of serotonin and norepinephrin. Published data on success of Duloxetine in treating GAD has been varied. Aim: To evaluate the success of Duloxetine in treating GAD when compared to placebo. Method: Study Selection Criteria: Only randomized, double-blinded, placebo-control trials were selected. Studies comparing success of Duloxetine to placebo in treating GAD. Success was defined as improvement of Hamilton Anxiety Scale total score by 50 % at 10 week interval. Data collection & extraction: Articles were searched in Medline, Pubmed, Ovid journals, CINAH, International pharmaceutical abstracts, old Medline, Medline nonindexed citations, and Cochrane controlled trials registry. Statistical Method: The summary estimates are expressed as pooled proportions. First the individual study proportions of success are transformed into a quantity using Freeman-Tukey variant of the arcsine square root transformed proportion. The pooled proportion is calculated as the back-transform of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed effects model and DerSimonian-Laird weights for the random effects model. Publication bias was calculated using Egger bias indicator Results: Initial search identified 503 reference articles, in which 89 relevant articles were selected and reviewed. Data was extracted from 4 studies (N = 1319), which met the inclusion criteria. All the studies used 60 to 120 mg of Duloxetine. The assessment was made 10 weeks after starting treatment. Pooled proportion of success in treating GAD with Duloxetine was 52.39 % (95% CI = 48.58 to 56.1). The same with placebo was 35.53 % (95% CI = 31.95 to 39.19). The pooled odds ration of patient with GAD to improve with Duloxetine when compared to placebo was 2.03 (95% CI = 1.63 to 2.54) ie odds of patients on Duloxetine to improve are twice when compared to placebo. The pooled proportions given here are ones obtained with fixed effects model. Test of heterogeneity gave a p value of > 0.10. The publication bias calculated by Egger bias indicator was -25.74 (95% CI = -554.01 to 502.53, p = 0.85), indicating no publication bias. Conclusion: Patients with GAD on Duloxetine are two times more likely to improve when compared to placebo. With its dual action, Duloxetine is effective in treating patients with GAD.
TG02

SYSTEMATIC REVIEW AND META-ANALYSIS OF THE EFFICACY OF PHARMACOLOGICAL TREATMENT OF GENERALIZED ANXIETY DISORDER

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Introduction: There are a number of evidence-based pharmacological treatments available for generalised anxiety disorder (GAD), but relatively little is known about their comparative efficacy and tolerability. Method: Systematic review of double-blind randomised placebo-controlled trials (phase II, III or IV) (RCTs) conducted in adult patients. Primary, Bayesian, probabilistic mixed-treatment meta-analyses (MTMAs) allowed pharmacological GAD treatments to be ranked in terms of relative effectiveness with respect to each outcome measure. Secondary, frequentist MTMAs were conducted using a random-effects model; effect size was reported as an odds ratio (OR) and 95% confidence interval (CI). Data sources were Medline, Embase, Biosis, PsycInfo, Health Economics Evaluations Database, NHS Economic Evaluation Database and Database of Abstracts of Reviews Effects via DataStar and the Cochrane Database of Systematic Reviews (January 1980 to February 2009). Articles were screened using a positive exclusion method. Titles and/or abstracts were reviewed initially, followed by review of full-text publications for citations remaining after the first pass. A three-person team conducted the screening and an independent reviewer checked a random selection (10%) of articles. All data extracted for meta-analysis were independently reviewed. Main outcome measures were response (proportion of patients experiencing ≥50% reduction from baseline Hamilton Anxiety Scale [HAM-21] score); remission (proportion with a final HAM-A score ≤7); and tolerability (withdrawal from the trial due to adverse events [AEs]). Results: 3,249 potentially relevant publications were identified: 43 RCTs met the inclusion criteria. Nine drugs (duloxetine, escitalopram, fluoxetine, lorazepam, paroxetine, pregabalin, sertraline, tiagabine and venlafaxine) were compared with each other. In the primary, probabilistic MTMAs, fluoxetine was ranked first in response and remission (probability of 62.9% and 60.6%, respectively), and sertraline first (49.3%) in terms of tolerability. In a sub-analysis of current UK-licensed GAD treatments, duloxetine was ranked first in response (third across all treatments; 2.7%); escitalopram was ranked first in remission (second across all treatments; 26.7%); pregabalin was ranked first in terms of tolerability (second across all treatments; 7.7%). Conclusions: Although the frequentist analysis was inconclusive due to the high level of uncertainty in the effect sizes (based on the relatively small number of comparative trials), the primary probabilistic analysis, which did not rely on statistically significant outcomes, showed that fluoxetine (response and remission) and sertraline (tolerability) appear to have some advantages over other treatments while, among the 5 treatments licensed specifically for GAD in the UK, duloxetine, escitalopram and pregabalin may offer some advantages over venlafaxine and paroxetine. Funding: The costs of the literature search and preliminary data analysis were supported by Lundbeck Ltd.

TG03

TREATMENT OF GENERALIZED ANXIETY DISORDER IN ROUTINE CLINICAL PRACTICE: AN INTERNATIONAL SURVEY

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Introduction: Generalized Anxiety Disorder (GAD) affects approximately 5% of the general population at some time in their life and between 1-2% in any given time. It usually occurs concurrently with other disorders, most often major depression or other anxiety disorders. It is associated with considerable functional impairment and imposes a substantial demand on health services. Despite its prevalence and associated individual and societal burden, little is known about psychiatrists’ experiences in managing the condition. Method: An international steering committee developed a multiple choice questionnaire as part of an educational programme. The questionnaire was completed by psychiatrists from 18 countries who attended one of two meetings in 2009. Questionnaires were available in English and other European languages. Results: A total of 501 questionnaires were completed sufficiently fully to be included in the analysis (‘respondents’, 42%). 70% of respondents had worked in clinical practice for at least 10 years (45% were hospital based): 70% saw at least 50 patients per month. Routine use of screening tools or structured diagnostic interviews for GAD was infrequent; 34% used local practice guidelines for management. In over one-third of respondents, patients did not attend their first appointment until 1 month or longer, following referral by their primary care physician; 45% of patients were considered to have had symptoms for at least two years, before being diagnosed and treated. Psychiatrists rated (1=always, to 5=never) the frequency with which referred GAD patients had undergone previous treatment. Benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) were the most commonly used treatments prior to referral. Among psychiatrists, 80% prescribed SSRIs, 43% serotonin-norepinephrine reuptake inhibitors (SNRIs), and 35% pregabalin: 26% of respondents used benzodiazepines as first-line treatments. SNRIs (41%) and pregabalin (36%) were the most commonly recommended second-line treatments. Most respondents rated SSRIs, SNRIs, pregabalin and benzodiazepines as being effective in relieving psychological and somatic anxiety symptoms. Nearly all respondents prescribed benzodiazepines for only short periods. Concentration difficulties, fatigue, excessive worrying and pain were reported to be the symptoms that were most difficult to manage. Almost half of respondents ‘often’ recommended psychotherapy to patients with GAD. Conclusion: Patients with GAD have frequently been treated with benzodiazepines prior to referral. Psychiatrists prescribed benzodiazepines for only short periods, and preferred using SSRIs as first-line treatment. SNRIs and pregabalin were preferred in second-line treatment. Reported practice in this sample is largely consistent with evidence-based treatment guidelines, but not necessarily representative of broader clinical practice. Development of the questionnaire and the educational programme was supported by Pfizer Ltd.
TG04

COGNITIVE AND PERCEPTUAL PROCESSING IN BODY DYSMORPHIC DISORDER
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Body Dysmorphic Disorder (BDD) is characterised by obsessive preoccupation with imagined physical defects, usually focussed on the face, and associated compulsive checking and camouflaging behaviours. BDD has been proposed to share a close relationship with obsessive-compulsive disorder (OCD) and social anxiety disorder. Previous research supports the existence of cognitive differences between individuals with BDD and healthy controls suggesting a disparity in the processing of emotional stimuli (Buhlmann et al. 2006 Journal of Psychiatric Research, 40, 105–111) and face processing as well as neurocognitive differences using neuropsychological measures testing executive functioning (Hanes, K. R. (1998) Journal of the International Neuropsychological Society, 4, 167–171.). In the current study we investigated executive and emotional processing in BDD. We compared individuals with a primary DSM-IV diagnosis of BDD (n=12; 7 female) with IQ and age matched healthy controls (n=16; 10 female) on neurocognitive tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB).

TG05

MATERNAL DEPRESSION AND SEPARATION ANXIETY DISORDER IN MIDDLE CHILDHOOD: ACADEMIC ACHIEVEMENT IN ADOLESCENCE
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Introduction: Separation anxiety disorder (SAD) is a common childhood disorder. Many children with SAD are not identified or do not seek help. Studying SAD in a prospective, longitudinal, community sample may identify risk factors and improve detection. Our hypotheses are that: 1. Maternal mental health and in particular postnatal depression is associated with childhood SAD. 2. Childhood SAD is a risk factor for low cognitive abilities and poor academic achievement in adolescence. Methods: The sample was recruited from antenatal clinics at two general practices in SE London. Of 149 families where the mother’s mental health was assessed in pregnancy and at 3 months post partum, 134 (90%) were interviewed at the child’s 11th birthday, 123 (92%) of whom were interviewed at 16 years. Maternal mental health was assessed (SADS-L) and, in independent interviews, mothers and children were asked about the child’s psychological problems (Child and Adolescent Psychiatric Assessment). The children’s cognitive abilities were assessed. Class teachers completed the Strengths and Difficulties Questionnaire at 11 years and gave details of academic achievements at 16 years. Results: Thirteen children (10.6%) were diagnosed with SAD at 11 years. Children of mothers depressed at 3 months postpartum were significantly more likely to have a diagnosis of SAD than children whose mothers were not depressed (χ2 (1) = 9.48 p < .002, OR = 5.7). This association was not explained by maternal depression at other times in the child’s life. Compared with children without SAD, those with SAD reported more emotional and peer difficulties, which interfered with their friendships at age 11 years (χ2 (1) = 9.49 p < .01, OR = 7.4). Children with SAD also had significantly lower IQ, reading and mathematics scores. At 16 years the adolescents who had a diagnosis of SAD at 11 years gained significantly fewer passes in the end-of-school national examinations and this was not accounted for by maternal depression in the post partum. Conclusions: The findings suggest that maternal depression at 3 months postpartum is a risk factor for childhood SAD. Children with SAD describe real difficulties in other domains of their lives that may be identified in school settings and may continue to have an effect throughout their school years. SLCDS has been funded by the Medical Research Council UK project grants G08292999N and G0539878N awarded to the late Channi Kumar, Deborah Sharp, Dale Hay, the Psychiatry Research Trust, and the South West G.P. Trust.
TG06
A PROSPECTIVE INVESTIGATION OF POSTCONCUSSIONAL SYMPTOMS AFTER MILD TRAUMATIC BRAIN INJURY
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Objective: Traumatic brain injury (TBI) is the leading cause of disability under the age of 45. However, the majority of cases 85% are actually mild. Because of the delay in seeking medical attention and difficulty in detecting early invisible symptoms, mild traumatic brain injury (MTBI) remains a major, unrecognized public health issue and has been called a “silent epidemic”. A significant proportion (15-30%) of MTBI patients are at risk of developing Post Concussional Syndrome (PCS). The aim of this study was to investigate the contributions of cognitive, emotional and behavioural factors to the development of PCS after MTBI, particularly the role of attentional bias (AB). Methods: A prospective cohort design was employed. 80 MTBI patients completed baseline questionnaire assessments and 39 completed computer tasks. 42 patients completed the follow-up assessments. A series of self-report measures including the Brief Illness Perceptions Questionnaire, the Impact of Events Scale, the Anxiety Sensitivity Index, the Behavioural Responses to Illness Questionnaire, and the Hospital Anxiety and Depression Score questionnaire were used to assess cognitive, behavioural and emotional responses, and the visual probe task was adopted to measure reaction time (RT) and assess attentional bias (AB) for health-threat information. The main outcomes were measured by the Rivermead Postconcussional Symptoms Questionnaire (RPQ) to assess the severity of PCS, and the Diagnosis of PCS was based on the ICD-10 Code F07.2. Results: A number of PCS symptoms were evident at baseline and 3 months and 9 out of 42 (21.43%) MTBI patients developed PCS at 3 months. PCS symptoms at 3 months were positively correlated with measures of stress response (r=0.397, p=0.011), particularly stress AVOIDANCE (r=0.497, p=0.001), anxiety (r=0.33, p=0.035), illness perception (r=0.528, p=0.000), and all or nothing behaviour (r=0.42, p=0.006). There were also significant correlations between PCS symptoms and Mean RT (r=0.507, p=0.012) and total AB (r=0.425, p=0.039). The positive correlations between PCS and RT symptoms indicates that PCS symptoms may be associated with slow information processing, whereas the negative correlation between AB and PCS cognitive symptoms may reflect that PCS symptoms are associated with threat avoidance. Conclusions: There were significant correlations between PCS symptoms and a number of cognitive, emotional and behavioral factors, which is consistent with the proposed cognitive behavioral model. The significant findings from RT/AB reflect that PCS symptoms may be associated with slow information processing and trauma-related threat avoidance. This study provides a cognitive behavioural approach to a better understanding of PCS.

TG07
INTERPRETATION BIAS IN SOCIAL ANXIETY: THREAT DETECTION AND COST ATTRIBUTIONS
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Anxiety is associated with attentional and interpretational biases which favour the detection and perception of threat. The specificity hypothesis states that these biases are specific to the fear which defines the anxiety disorder. A fear of negative evaluation is central to social anxiety. It should follow, therefore, that social anxiety is associated with biases which favour the perception of threat in the form of social disapproval. This study assessed potential forms of cognitive bias: 1) emotion recognition in faces; and, 2) social cost attributions to facial expressions. We hypothesised that social anxiety would be associated with enhanced recognition of emotions signalling social disapproval relative to other emotions, and would be associated with increased attributions of cost to expressions of social disapproval relative to other emotions. Healthy females (n = 162) selected for high or low scores on the Brief Fear of Negative Evaluation (BFNE) scale made emotional classification judgments for a series of facial expressions signalling social disapproval (anger, disgust) and other, less socially disapproving, emotions (happiness, fear, sadness). In the cost attribution task, participants rated the same facial expressions for how good or bad it would be for them to interact with the person depicted. Task performance was assessed modelling outcome as a function of emotion (social disapproval vs other) and social anxiety (BFNE continuous variable) using random effects regression modelling (RMM). RMM indicated general expression recognition did not vary with social anxiety (0.07; 95% CI -0.06, 0.21; p = 0.29), and social anxiety was not associated with enhanced recognition of social disapproval emotions relative to less socially disapproving expressions (interaction coefficient 0.03; 95% CI -0.08, 0.15; p = 0.55). However, RRM did indicate a general association between social anxiety and increased ratings of social cost (-0.02; 95% CI -0.04, -0.0006; p = 0.04), but this was not specific to expressions signalling social disapproval (interaction coefficient -0.0002; 95% CI -0.007, 0.007; p = 0.95). Social anxiety does not appear to be associated with biased recognition of briefly presented emotions, but is associated with a general increase in attributions of social cost. Contrary to our hypothesis, the effect of social anxiety on cost attribution is not specific to emotions signalling social disapproval.

TG08
ATTENTION CONTROL IN ANXIETY: THE EFFECTS OF 7.5% CO2 INHALATION ON VISUO-SPATIAL ATTENTION IN THE ANTISACCADe TASK
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Introduction: Inhalation of 7.5% CO2 increases self-report anxiety and autonomic arousal and provides a putative experimental model of generalized anxiety disorder (Bailey et al. 2005). We report findings from the first study to examine the effect of 7.5% CO2 challenge on cognitive mechanisms considered to underlie anxiety. Integrated neuro-cognitive models posit that increased activation of threat-appraisal mechanisms, coupled with a failure to use controlled processing to regulate attention and emotional response increase anxiety (e.g. Bishop, 2007). Previous research has used the antisaccade task to reveal deficits in top-down attention control (required to inhibit reflexive eye-saccades toward abrupt peripheral visual stimuli) in high trait anxious individuals compared to low anxious controls (Garner et al. 2009; Ansari et al. 2008). Methods: Twenty seven healthy volunteers (13 females, 14 males, mean age = 22.3yrs, SD =+5.9yrs) attended a single test session in which they completed an emotional variant of the antisaccade task during inhalation of 7.5% CO2 and air, with order of gas presentation counterbalanced across participants. Task instructions required participants to look either towards or away from negative and neutral picture stimuli that were presented peripherally either to the left or right of central fixation (Garner et al. 2009). The accuracy of horizontal eye-movements was recorded throughout. Results: Eye-movement accuracy was analyzed using repeated measures analysis of variance with inhalation (7.5% CO2 vs. air), trial type (pro vs. antisaccade), and image valence (negative vs. neutral) as independent variables. A significant three-way gas x trial type x image valence interaction was characterized by a gas x valence interaction for antisaccade, but not prosaccade trials. CO2 inhalation increased antisaccade errors (i.e. erroneous eye-movements) towards negative stimuli compared to i) neutral stimuli presented during CO2 inhalation; p < .05; and ii) negative stimuli presented during air inhalation; p < .05. CO2 increased state anxiety, heart rate and blood pressure consistent with previous findings. Conclusions: This study demonstrates that 7.5% CO2 inhalation can induce dysfunction in cognitive mechanisms implicated in the aetiology of anxiety. The observed pharmacological modulation of visuo-spatial attention to threat is discussed with reference to the possible effects of 7.5% CO2 challenge on bottom-up threat appraisal mechanisms (which increase the salience of threat cues), and top-down goal directed control mechanisms that inhibit maladaptive/erroneous responses to anxiogenic distracter stimuli. Our findings further validate the 7.5% CO2 model as a tool with which to examine the links between pharmacological and neuro-cognitive mechanisms in anxiety.
TG09

TOBACCO-SMOKING MAY INDICATE AN IMPULSIVE SUBTYPE OF OCD: A CASE-CONTROL STUDY

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INTRODUCTION Obsessive-compulsive disorder (OCD) is a biologically heterogeneous disorder. It is variably underpinned by impulsive as well as compulsive mechanisms. Where cigarette smoking is common among psychiatric patients, OCD patients are thought to smoke less. OCD smokers may possibly represent a relatively rare OCD subtype, characterised by increased impulsivity. The aim of this study was to establish the prevalence of smoking in a large, well-defined OCD cohort. OCD-smokers were compared with OCD non-smokers on measures of behavioural impulsivity and personality domains including reward dependence and novelty seeking, which we expected to be increased, and harm avoidance, which we expected to be reduced. The val 158 COMT allele is associated with greater vulnerability to nicotine dependence in normal individuals. Other research has reported that males with OCD show an increased prevalence of met 158 COMT alleles. We explored whether there was a higher proportion of val/val relative to met/met COMT polymorphisms in smokers compared to non-smokers with OCD. METHODO The study was passed by the Hertfordshire Research Ethics Committee. All subjects gave informed written consent. 183 of 200 outpatients with DSM-IV OCD were interviewed to determine smoking status. Of these, 131 (72%) had COMT polymorphisms available on file from a previous study. A sub-sample of 10 smokers was compared with 10 non-smokers, pairwise matched for age and gender. Patients were assessed for DSM comorbidity (Mini International Neuropsychiatric Interview), symptom profile (Dimensional Yale-Brown Obsessive Compulsive Scale), OCD severity (Yale-Brown Obsessive Compulsive Scale), depression (Montgomery and Asberg Depression Rating Scale), behavioural impulsivity (Barratt Impulsivity Scale) and personality dimensions (Cloninger’s Temperament and Character Inventory-TCI). Primary outcome data was analysed using Chi-Square Test. All secondary measures of association were analysed using ANOVA. RESULTS: Only 10 individuals (5.46%; five males) were smokers. Compared to OCD non-smokers, OCD-smokers were significantly more impulsive on the Barratt Impulsivity Scale (82.20, SD 10.1) vs. (62.50, SD 9.1) t= 4.55, p= 0.001. They also scored significantly higher on TCI measures of novelty seeking, (p < 0.005) and reward dependence (p < 0.001) and significantly lower on measures of harm avoidance (p= 0.001). Amongst the OCD smokers, six presented with val/val COMT alleles, none showed the met/met COMT genotype while four were heterozygote. Amongst the OCD non-smokers, two showed val/val and two met/met COMT alleles, while six were heterozygote. When smokers were compared with non-smokers, the allelic differences did not reach statistical significance, presumably because of the small sample size. CONCLUSIONS: Tobacco smoking is uncommon in OCD. OCD smokers are distinguished from their non-smoking counterparts by significantly higher levels of behavioural impulsivity and temperament factors associated with reward – driven impulsivity. The non –significant trend toward higher levels of val 158 COMT and lower levels of met 158 COMT alleles merit further exploration in a larger group of OCD smokers. DECLARATION: No funding received for this study.

TG10

IMPAIRED EXECUTIVE FUNCTION IN HIGHLY IMPULSIVE AGGRESSIVE MALES LACKING CALLOUS UNEMOTIONAL TRAITS

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Impulsive aggression (IA) is an automatic, instinctive response to a stimulus that leads to increased arousal to result in an aggressive act. Violent IA behaviour is problematic for society. The literature that has so far examined executive deficits (EF) in IA individuals has focused more broadly on aggression, either in the context of pathology i.e. antisocial personality disorder (ASPD) (Dolan & Park, 2002, Psychologicial Medicine, 417-427) or in college students (Stanford et al.1998, Personality and Individual Differences, 23 961-965). We argue that the aggression dichotomy distinguishing between IA and callous unemotional (CU) aggression has been largely overlooked, limiting our neuropsychological understanding of IA. The present study aims to investigate neuropsychological abilities in high IA, non-CU individuals from the general population. We extended earlier neuropsychological studies of aggression by using a population-derived sample, which controlled for potentially confounding CU traits. We hypothesised that EF differences (between high-IA and low-IA volunteers) will be associated with the impulsivity that leads to provoked, unplanned IA violent behaviour. A second exploratory hypothesis predicted that the degree of reported childhood adversity would be associated with impaired cognitive performance. A population dimensional approach sampled the highest and lowest impulsivity and aggression scores in our recruited population, controlling for CU. Using this approach we identified 25 non-CU high-IA and 31 non-CU low-IA males. These participants performed a series of neuropsychological tests probing EF: Stockings of Cambridge and IDET set shifting (from the CANTAB test battery), stop signal and Iowa Gambling tasks. Statistical analysis was conducted in SPSS using two sample t-tests and ANOVAs, thresholded at p<0.01. High-IA, non-CU volunteers were significantly impaired on EF tasks compared to low-IA. Specifically, high-IA had impaired planning, associated with impulsive responding, and deficits inhibiting prepotent response on a stop signal task. High-IA individuals also showed perseverative responding on a set-shifting task and impaired rewarded decision making on the Iowa Gambling task. The magnitude of impairment was associated with impulsivity scores on self-report scales and was predicted by negative early life experiences. High-IA groups were characterised by neuropsychological impairments characteristic of motor and cognitive impulsivity. This pattern is similar to that observed in mixed groups of patients with ASPD, such that impulsivity may be a critical determinant of neuropsychological deficit in these groups. An obvious extension of this study would be to compare explicitly the neuropsychology of IA and CU traits. Aggression defined by CU traits may differ significantly from neuropsychology of IA as described here. Funding source: Strategic Studenship Award - University of Manchester
TG11

EFFECTS OF NICOTINATED AND DENICOTINIZED CIGARETTE SMOKING ON RESPONSE TO 7.5% CARBON DIOXIDE ANXIETY CHALLENGE

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Cigarette smokers frequently report that smoking is anxiolytic, and that exposure to stress increases the likelihood of relapse. Furthermore, cigarette smoking and affective disorders are highly co-morbid. We have explored this relationship using a carbon dioxide (CO2) challenge, which acts as a robust anxiogenic stimulus, and we have previously reported reduced increases in anxiety following this challenge in abstinent compared to non-abstinent smokers. Here we extend this work to investigate the effects of smoking a nicotinized or denicotinized cigarette on response to CO2 challenge among acutely abstinent regular smokers. Cigarette smokers (N=24) who reported smoking within 60 minutes of waking abstained from smoking for 12 hours, and were randomized to smoke either a nicotinized or denicotinized cigarette on the test day. They then underwent a 20-minute inhalation of 7.5% CO2-enriched air. Measures of anxiety, affect, heart rate and blood pressure were taken before and after inhalation. For each measure, a 2 (gas: CO2, air) x 2 (cigarette: nicotinized, denicotinized) mixed model ANOVA was employed. There was a significant gas × cigarette interaction for positive affect (F [1, 20] = 10.87, p = 0.004) and a trend towards a significant gas × cigarette interaction for ratings of anxiety (F [1, 20] = 3.70, p = 0.069), reflecting a lesser reduction in positive affect, and a lesser increase in anxiety, among those who smoked a nicotinized cigarette compared to those who smoked a denicotinized cigarette. These data extend our previous findings, and suggest that the acute administration of nicotine via smoking may reduce response to physiological anxiety challenges. These findings are apparently at odds with our previous data suggesting greater anxiety reactivity in non-abstinent compared with abstinent smokers. One possibility is that nicotine administration via smoking after a period of acute abstinence may reduce responding to such challenges in the short-term, but that over longer periods the presence of nicotine potentiates anxiety reactivity. Another possibility is that relative reductions in self-reported anxiety may reflect associative learning processes governed by the amelioration of withdrawal symptoms following cigarette smoking. The relationship between abstinence, smoking and anxiety is complex and requires further research. Funded by the National Alliance for Research on Schizophrenia and Depression.

TG12

JITTERINESS SYMPTOMS AT 3 AND 7 DAYS PREDICT POOR OUTCOME AT 6 WEEKS IN SSRI TREATMENT OF ANXIETY

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Introduction: Early worsening of anxiety, agitation and irritability are thought to occur when some individuals start antidepressant treatment, especially in anxiety disorders. In a systematic review (Sinclair et al 2009, British Journal of Psychiatry 194(6), p483-490) we found little evidence on whether early “jitteriness” symptoms predict subsequent therapeutic response. We explored whether early “jitteriness” symptoms were predictive of outcome in SSRI treatment. Methods: This was a naturalistic cohort study of adult outpatients starting SSRIs prescribed by their GP or psychiatrist for anxiety disorders (n=14), or symptoms, having received no antidepressants/benzodiazepines within 2 months. Diagnosis was verified via the Mini v.5 semi-structured interview and the CIS-R computerised assessment. Two days before commencing treatment participants completed baseline Generalised Anxiety Disorder Inventories (GADI) and “Jitteriness” Rating Questionnaires (JRQ, derived from the above systematic literature review and including symptoms described in the “jitteriness” syndrome in domains of restlessness, sleep, mood, anger, anxiety, panic, energy and suicidal thoughts). Participants completed the same questionnaires 3, 7 and 42 days after SSRI commencement. We performed linear regressions with change from baseline JRQ after three and seven days’ SSRI treatment as independent variables and improvement in GADI from baseline to 42 days as outcome. Results: 16 subjects completed the protocol. By DSM-IV criteria: 6 had panic disorder, 5 social phobia, 5 generalised anxiety disorder and 4 major depression. Four (25%) had higher JRQ scores at day 3 than baseline. Overall JRQ scores declined slightly but not significantly between baseline and day 3 (34.6 (± 4.7) vs. 31.3 (± 4.7)). There was a significant reduction in JRQ between baseline and day 7 (34.6 (±4.7) vs. 22.5 (±3.4), p=0.001). GADI scores improved significantly from baseline to day 42 (25.5 (±4.5) vs. 15.9 (±3.1), p=0.012). Linear regression revealed a significant negative association between change in JRQ from day 3 - baseline to improvement in GADI from baseline - day 42 (r2=0.282, p=0.034). Change in JRQ from baseline to day 7 showed a stronger negative association with improvement in GADI from baseline to day 42 (r2=0.586, p=0.001). Conclusions: An increase in early activation symptoms (“jitteriness”) on SSRIs predicts poor prognosis for control of anxiety symptoms at 6 weeks, the relation being stronger with “jitteriness” symptoms present 7 days prior to treatment. Despite limitations of small sample size and heterogeneity this study suggests early appearance of “jitteriness” symptoms, linked to poor subsequent response, may constitute a rationale for considering alternative treatments. Larger studies are required to address this issue. Funding: AWP NHS R&D Grant

TG13

OXOTOCIN ATTENUATES AMYGDALA RESPONSE TO FEAR IN SOCIAL ANXIETY DISORDER

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Background: The neuropeptide oxytocin plays an important role in the modulation of pro-social and anxiety-related behaviours including attenuation of responses to stress, anxiety and fear in both animals and humans. In healthy volunteers, oxytocin attenuates amygdala reactivity to social signals of threat (i.e. fearful faces), putatively by localized enhancement of GABAergic inhibition within the amygdala. If oxytocin can selectively modulate fear behaviour, then it may serve as a novel therapeutic strategy to treat anxiety disorders, such as generalized social anxiety disorder (GSAD), in which amygdala threat-related hyper-sensitivity is a cardinal pathophysiological feature. Here, we examined the acute effects of intra-nasal oxytocin on amygdala reactivity to social visual cues in both patients with GSAD and healthy controls (HC). Methods: 18 male patients with GSAD and 18 HC (mean age ± SD: 29.5 ± 10.2) participated in the study using functional magnetic resonance imaging coupled with an emotional face assessment (matching) task that has been shown to reliably activate the amygdala. All participants were non-smokers and medication free. Patients met DSM-IV criteria for social anxiety disorder, generalized type, with no other primary Axis I or neurological disorders, and HC had no history of Axis I psychiatric disorders and neurological disorders. The study utilized a double-blind placebo controlled within group design separated by a minimum 1 week washout period. The treatment conditions were (a) Intranasal oxytocin (24 IU or 40.32 micrograms) and (b) Intranasal placebo/saline. MRI of the emotional faces task was performed 60 minutes post-administration to coincide with the peak behavioural effects of oxytocin. Results: Compared to controls, GSAD patients exhibited greater left amygdala reactivity only to fearful faces during the placebo session ([1,0, 2, -18], Z-score=3.48; corrected>0.007; volume=440mm3). Follow-up analyses of the extracted BOLD signal from the left amygdala showed that oxytocin attenuated amygdala reactivity to fearful faces in the GSAD group (mean β weights±SEM [arbitrary units]: GSADPO: 0.33±0.08 vs. GSADOX: 0.13±0.06, paired t=2.27, p=0.04), such that the pattern of hyperactivity (GSAD>HC) observed in the PBO session (GSADPO: 0.33±0.08 vs. HCPBO: 0.17±0.04, two-sample t=1.77, p=0.041), was not observed during the OXT session (0.13±0.06 vs. HC0XT: 0.14±0.05, two-sample t=0.17, p=0.86). Discussion: These findings suggest a potential anxiolytic effect of oxytocin on amygdala response to fear and that oxytocin may be a novel treatment strategy for disorders marked by exaggerated fear behaviour and amygdala reactivity to social cues of threat.
TG14

EFFECTS OF SYSTEMIC AND CENTRALLY-ADMINISTERED D-AMPHETAMINE ON RESPONDING FOR A SAFETY SIGNAL AS A CONDITIONED REINFORCER

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Consistent evidence has demonstrated potentiating effects of d-amphetamine on positive conditioned reinforcement via DA dependent mechanisms in the nucleus accumbens. Much less is known however, of the effect of similar mechanisms on responding for the presentation of a safety signal associated with successful avoidance behaviour in aversive situations, with relevance to psychiatric conditions such as obsessive compulsive disorder. We trained Lister-Hooded, male rats with an inhibitory stimulus signifying the omission of a footshock which was otherwise presented in the context. Subsequent experiments then tested the ability of this safety signal to support the acquisition of a novel instrumental choice response, i.e. pressing on one of two novel levers resulting in the presentation of the conditioned inhibitor and in doing so acting as a conditioned reinforcer. During inhibitory training, presentation of the safety signal reduced fearful responding to the context between the first and last days of inhibition and retardation training (Stimulus x Day interaction F = 11.4). This signal also passed a retardation test for inhibition (effect of Group F = 5.11). A second order stimulus supported the acquisition of a new conditioned response when paired with a safety signal but not with a neutral stimulus (Stimulus x Lever interaction F = 6.6). We compared effects of i.p. (0.5 and 1.5mg/kg) and intra-accumbens (1, 3, 10 ug/ul) d-amphetamine on responding with the safety signal as a conditioned reinforcer. Systemic d-amphetamine dose-dependently decreased responding for the presentation of the safety signal (effect of Dose F = 4.0), an effect that may have arisen due to the heightened aversiveness of the context with increasing doses of drug (i.e., a general effect). The results shed light on the differential effects of anphetamine on responding for appetitive conditioned reinforcers and safety signals and have implications for theories of the role of dopamine-dependent functions of the nucleus accumbens. Supported by an MRC CASE studentship and the Wellcome Trust Programme grant to TWR

TG15

D-CYCLOSERINE, A HIGH EFFICACY GLYCINE/NMDA RECEPTOR PARTIAL AGONIST, FACILITATES FEAR MEMORY CONSOLIDATION IN THE PLUS-MAZE RETEST PARADIGM

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The role of NMDA receptors in the consolidation of aversive memories has been extensively studied, with the bulk of evidence supporting the view that NMDA receptor activation promotes fear memory consolidation (Izquierdo et al., 2006, TINS 29: 496-505). It is now well-established that glycine is an obligatory ‘coagonist’ for activation of NMDA receptors (e.g. Danyus & Parsons 1998; Pharmacol Rev 50: 597-664). Although currently best known for its effects in facilitating extinction learning, the glycineB receptor partial agonist, D-cycloserine (DCS), also enhances fear memory consolidation in mammals (e.g. Kalisch et al., 2009, Cerebral Cortex 19:187-196). As prior experience of the elevated plus-maze (EPM) typically increases anxiety-like behaviour yet eliminates sensitivity to conventional anxioselective (EPM retest effect), we have assessed the effects of post-training administration of DCS on plus-maze trial 2 behaviour in mice. Subjects were adult male BKW albino mice (Bantin & Kingman, Hull, UK) housed 10/cage under a 12h reversed LD cycle. All testing was performed under dim red light (18 lx) during the dark phase and using well-established EPM methods (e.g. Mathiasen et al., 2008, PBB 90: 19-36). Animals were randomly assigned to 5 conditions (n=10): vehicle, positive control (chloridiazepoxide HCl, CDP, 15 mg/kg; Sigma-Aldrich UK), 7.5, 15.0 or 30.0 mg/kg DCS (Sigma). Drugs were dissolved in saline and administered IP (10 ml/kg) immediately after initial exposure (5 min) to the EPM. Animals were returned to their homes cages and, 24h later, re-exposed (drug-free) to the maze. DVD-recorded tests were scored blind to drug condition, and data analysed by parametric or non-parametric one-way analyses of variance. Statistical analysis revealed significant treatment effects for % open arm entries, % open arm time and % closed arm time (all p < 0.05). Although no other measures were significantly altered, analysis of absolute open arm entries closely approached significance (7%). Post-hoc analyses confirmed that, whereas CDP had no significant behavioural effects, DCS (15 mg/kg but not lower or higher doses) significantly reduced open entries, % open entries and % open time while reducing % closed arm time, i.e. induced an anxiogenic-like profile relative to saline control. As DCS was administered post-training, present analyses of variance. statistical analysis revealed significant treatment effects for % open arm entries, % open arm time and % closed arm time (all p < 0.05). later, re-exposed (drug-free) to the maze. dVd-recorded tests were scored blind to drug condition, and data analysed by parametric or non-parametric one-way analyses of variance. Statistical analysis revealed significant treatment effects for % open arm entries, % open arm time and % closed arm time (all p < 0.05). although currently best known for its effects in facilitating extinction learning, the glycineB receptor partial agonist, D-cycloserine (DCS), also enhances fear memory consolidation in mammals (e.g. Kalisch et al., 2009, Cerebral Cortex 19:187-196). As prior experience of the elevated plus-maze (EPM) typically increases anxiety-like behaviour yet eliminates sensitivity to conventional anxioselective (EPM retest effect), we have assessed the effects of post-training administration of DCS on plus-maze trial 2 behaviour in mice. Subjects were adult male BKW albino mice (Bantin & Kingman, Hull, UK) housed 10/cage under a 12h reversed LD cycle. All testing was performed under dim red light (18 lx) during the dark phase and using well-established EPM methods (e.g. Mathiasen et al., 2008, PBB 90: 19-36). Animals were randomly assigned to 5 conditions (n=10): vehicle, positive control (chloridiazepoxide HCl, CDP, 15 mg/kg; Sigma-Aldrich UK), 7.5, 15.0 or 30.0 mg/kg DCS (Sigma). Drugs were dissolved in saline and administered IP (10 ml/kg) immediately after initial exposure (5 min) to the EPM. Animals were returned to their homes cages and, 24h later, re-exposed (drug-free) to the maze. DVD-recorded tests were scored blind to drug condition, and data analysed by parametric or non-parametric one-way analyses of variance. Statistical analysis revealed significant treatment effects for % open arm entries, % open arm time and % closed arm time (all p < 0.05). Although no other measures were significantly altered, analysis of absolute open arm entries closely approached significance (7%). Post-hoc analyses confirmed that, whereas CDP had no significant behavioural effects, DCS (15 mg/kg but not lower or higher doses) significantly reduced open entries, % open entries and % open time while reducing % closed arm time, i.e. induced an anxiogenic-like profile relative to saline control. As DCS was administered post-training, present results cannot be due to an acquisition effect nor, given the short half-life of DCS, to a drug carry-over effect. Rather, our findings are entirely consistent with a facilitation of fear memory consolidation. The DCS-typical bell-shaped dose-response function most likely reflects dose-related potency differences at multiple NMDA receptor subtypes. Research supported by the University of Leeds.

TG16

INTRINSIC ANXIOLYTIC ACTIVITY OF D-CYCLOSERINE, A PARTIAL AGONIST AT THE STRYCHNINE-INSENSITIVE GLYCINEB RECOGNITION SITE ON THE NMDA RECEPTOR COMPLEX

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As the anxiolytic potential of NMDA receptor antagonists is hampered by clinically relevant side-effects, attention has recently been drawn to a possibly key role for the strychnine-insensitive glycineB recognition site on the NMDA receptor complex. Preclinical evidence, accumulated since 1989, supports the anxiolytic potential of glycineB receptor partial agonists (e.g. ACPC) and full antagonists (e.g. 5,7-DCKA) (reviewed by Cryan & Dev, 2008, Handbook of Anxiety & Fear, Vol 17, eds Blanchard et al, pp269-301). These findings are relevant to the intriguing observation that another glycineB receptor partial agonist, D-cycloserine (DCS), facilitates extinction therapy for clinical anxiety disorders (reviewed by Norberg et al 2008; Biol Psychiat 63: 1118-1126). Although typically attributed to cognitive-enhancing effects, the findings reviewed above suggest that intrinsic anxiolytic activity may not be unimportant. As few studies to date have directly addressed this possibility, we have employed ethological methods to profile the behavioural effects of DCS in a well-validated animal test for anxiety. Subjects were adult male BKW albino mice (Bantin & Kingman, Hull, UK) housed 10/cage under a 12h reversed LD cycle. All testing was performed under dim red light (18 lx) during the dark phase. Mice were randomly assigned to 5 conditions (n=10): vehicle; positive control (chloridiazepoxide HCl, CDP, 15 mg/kg; Sigma-Aldrich UK), 7.5, 15.0 or 30.0 mg/kg DCS (Sigma). Drugs were dissolved in saline and administered IP (10 ml/kg) 30 min prior to testing. Using well-established plus-maze methods (e.g. Mathiasen et al 2008, PBB 90: 19-36), mice were tested in an order counterbalanced for treatment condition. DVD-recorded tests were scored blind to drug condition, and data analysed by parametric or non-parametric one-way analyses of variance. Analyses revealed significant treatment effects on all measures of open arm avoidance, exploratory head-dipping and risk assessment (F(4,45) > 5.27, p < 0.002; H (4, n=50) > 10.47, p < 0.05). Post-hoc tests not only confirmed the robust anxiorelative profile of CDP, but also indicated significant anxiorelative activity for DCS at 15 mg/kg (but not lower or higher doses). DCS-induced anxiolysis, while significant, was weaker than that observed in response to CDP. The acute anxiolytic profile of DCS in mice is consistent with the behavioural pharmacology of other partial agonists, while the clear bell-shaped dose-response function is similar to that seen in other behavioural paradigms. These results suggest that intrinsic anxiolytic activity should not be ignored in the interpretation of the effects of this compound on exposure-based extinction therapy. Research supported by the University of Edinburgh.
A NEW MODEL OF ANXIETY-LIKE RESPONSES IN RODENTS: THE ELEVATED MINUS MAZE (EMM)

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Introduction: Progress in psychopharmacology is underpinned by the need for reliable animal models of the disorders being studied, particularly in the fields of depression and anxiety. The latter field has typically been dominated by tests which show inherent flaws (e.g. Trier et al., 1993 Pharmacol Biochem. Behav. 33: 463-469; Ferranti et al., 1998 Pharmacol. Biochem. Behav. 63: 821-827). The aim of this study was to validate a novel model of anxiety-like behaviour in rodents that is intended to have fewer of these limitations. Method: The test apparatus consisted of an open, elevated (30 cm high to avoid animal escape), clear plexiglass platform (40 x 40 cm) zonally divided on the underside into 9 zones with zone 5 containing a clear Plexiglass wall (15 x 15 cm). To determine the utility of the model, the behavioural effects of the test and of acute treatment with either vehicle (1% methylcellulose) or two clinically prescribed anxiolytics; diazepam (2 & 4 mg/kg, i.p) and chloridazepoxide (CDP) (5 & 10 mg/kg, i.p.) were assessed in group housed male Swiss-Webster mice (40-56 g, n=10). Zonal activity and general behaviour of all animals were recorded on video and later scored by a trained observer blind to the experimental conditions. Data were analysed using ANOVA with planned comparisons (Statistica 5.5, Statsoft, USA). Results: Results showed that vehicle treated mice on the EMM spent the most time in close proximity to the central wall (zone 5) and this was reduced in drug treated animals (diazepam 2 mg/kg, p<0.03 & 4 mg/kg, p<0.007; CDP 10 mg/kg, p<0.004). No corresponding differences in general activity and/or locomotion (according to ethogram AND zonal crossing) were found between the vehicle and drug treated animals. Conclusion: Proximity to the central wall (zone 5) may be equated to normal thigmotaxic responses generally seen in mice and increased activity away from that location may be due to a reduction in fear if this is the motivation for the former. Vehicle treated animals thus displayed an anxious-like behavioural profile on the EMM compared to those animals treated with both clinically effective anxiolytic drugs. The EMM is therefore a novel model of anxiety that eliminates possible confounds of behavioural interpretation due to ambiguous areas (such as the central square in the elevated plus maze, EPM), and offers the quick, easy method for screening for new anxiolytic drugs that the EPM promised to be. Further validation work is clearly necessary, but the current studies strongly suggest that this will be a worthwhile investment.

LACK OF EFFECT OF CAPSAZEPINE, A TRPV1 RECEPTOR ANTAGONIST, ON BENZODIAZEPINE-SENSITIVE EMOTIONAL BEHAVIOUR IN THE MOUSE ELEVATED PLUS-MAZE

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Endocannabinoids may exert their behavioural effects not only via cannabinoid CB1 receptors but also as endovanilloids via vanilloid TRPV1 receptors (e.g. Starowicz et al., 2008 Curr Pharm Des 14: 42-54). Recent research suggests opposing roles for CB1 and TRPV1 receptors in the modulation of anxiety (e.g. Naidu et al., 2007 Psychopharmacology 192: 61-70; Starowicz et al., op cit). Thus, while genetic or pharmacological reduction in CB1 receptor function generally produces anxiogenics, systemic administration of the TRPV1 receptor antagonist Capsazepine (CSP) (Kaskow et al., 2004 Prog Neuropsychopharmacol Biol Psychiatry 28: 291-295) or germline deletion of TRPV1 receptors (Marsch et al., 2007 J Neurosci 27: 832-839) seem to exert the opposite effect. As work to date has been limited, our aim was to contrast the effects of a systemically-administered capsaicin (a TRPV1 receptor agonist) and chloridiazepoxide in a well-validated test of anxiety-like behaviour. Adult male BKW albino mice (Bantin & Kingman, Hull, UK) were housed 10/cage under a 12h reversed LD cycle. All testing was performed under normal lab illumination during the day. Mice were randomly assigned to 5 conditions (n=10): vehicle, positive control (chloridiazepoxide HCI, CDP, 15 mg/kg; Sigma-Alrich UK), 2.5, 5.0 or 10.0mg/kg capsaicin (CAP; Tocris Bioscience, UK). Drugs were dissolved in a few drops of DMSO, made up to final volume in 0.5% methylcellulose (Sigma), and administered IP (10 ml/kg) 40 min prior to testing. Using well-established plus-maze methods (e.g. Mathiasen et al 2008, PBB 90: 19-36), mice were tested in an order counterbalanced for treatment condition. DVD-recorded tests were scored blind to drug condition, and data analysed by parametric or non-parametric one-way ANOVA. Significant treatment effects were found for total arm entries, open arm entries, % open entries, % open time, % mid time and % protected head-dipping (all p < 0.001). Posthoc tests showed all these effects to be due soley to CDP which significantly and selectively reduced all measures of open arm avoidance (p < 0.002). The current failure to detect anxiolytic-like activity with CAP cannot be due to problems with test sensitivity (anxioselective profile of CDP), and is unlikely to be due to the dose range employed. In view of consistent anxiolytic-like effects observed following intracerebral administration of CAP (e.g. PAG; Terzian et al., 2009 Eur Neuropsychopharmacol 19: 188-195), our results may reflect poor brain penetration of CAP following systemic administration and/or opposing roles in anxiety modulation of TRPV1 receptors in different brain regions. Research supported by the University of Leeds.

MANIPULATION OF ENVIRONMENTAL CONDITIONS ALTERS THE MAGNITUDE OF THE INSTRUMENTAL SUCCESSIVE NEGATIVE CONTRAST EFFECT IN RATS

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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, Harding et al., 2005, NeurosciBiobehavRev 29(3):469-91). Previous studies from our group have shown a significant effect on correct latency, collection latency and premature responding to reward loss using a modified forced choice serial reaction time task (FCSRTT). Using a runway successive negative contrast (SNC) task, Burman et al, 2008 showed that rats housed in unenriched cages, which typically exhibit indicators of poorer welfare and a more negative affective state than those in enriched housing, display a prolonged contrast effect following a decrease in anticipated value of reward (Burman, O. H., R. M. Parker, et al., (2008), Biol Lett 4(4): 330-3). This suggests that the unenriched animals have an enhanced sensitivity to reward loss. In the present study, we have tested the effects of reward loss on performance variables using our modified FCSRTT in enriched and unenriched groups of animals. Male Lister-hooded rats were housed in enriched or unenriched conditions from the start of the experiment and remained under these housing conditions during training and testing in an instrumental SNC task. All procedures were carried out using standard Med Associates 5-hole boxes and KLimbic software (Conclusive solutions Ltd) and animals received a four pellet reward for each correct trial throughout the training. At the end of training, individual devalue sessions were introduced where animals received only a single pellet outcome for each correct response. The animals were then exposed to series of 10 consecutive devalue sessions to observe recovery from any devalue effect. Repeated measures ANOVA revealed a significant effect of devalue for correct latency (F(1, 14) = 25.079; P<0.0001) and premature responding (F(1, 14) = 20.261; P<0.0001) but not for collection latency (F(1, 14) = 0.278; P = 0.606) on devalue sessions with the unenriched animals having faster correct latencies and higher levels of premature responding. The unenriched animals also show a tendency for a reduction in the devalue effect on correct latency over the 4 initial sessions although this interaction is not significant (F(12, 175) = 1.626; P=0.085). These data suggest that animals housed in unenriched conditions are in a more positive affective state during testing in the operant chamber. Although this is opposite to the predicted effect, it may reflect an enrichment effect associated with daily training and testing in the operant chamber and the contrast between the test chamber and their barren home cage. ESJR is an RCUK Academic Fellow support by the British Pharmacological Society Integrative Pharmacology Fund EM is funded by the BBBSRC and MSD HM is Section Head at MSD, Newhouse.
TH01

EFFECTS OF NORADRENALEN RE-UPTAKE INHIBITORS ATOMOXETINE AND REBOXETINE ON PERFORMANCE IN THE RAT STOP SIGNAL REACTION TIME TASK

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Atomoxetine is a noradrenaline re-uptake inhibitor (NaRI), treatment for attention deficit hyperactivity disorder, and has previously been shown to improve impulse control in animal models (Robinson et al., 2008, Neurropsychopharmacology, 33:2398-406). One of the models tested, the stop-signal reaction time task (SSRT), assesses the subject’s ability to inhibit an already initiated motor response. To determine if blockade of noradrenaline re-uptake sites is a key site of action for atomoxetine, the present study has investigated two different NaRI in a version of the rat SSRT task. Male Lister-hooded rats (n=24) were trained and tested using standard 5-hole operant boxes and KLimbic software (Med Associates, USA). Animals were trained to make a fast ‘GO’ response between the two outer nospoke holes, cut-outs and maintained using a short limited hold duration. For 25% of trials, a tone cue was used to signal a ‘STOP’ trial when animals were required to inhibit the GO response in order to obtain a food reward. Stop cues were presented at stop signal delays of zero, meanRT/1.4 and mean reaction time/1.2. Atomoxetine (0.3-3.0mg/kg, i.p.) followed by reboxetine (0.3-3.0mg/kg, i.p) were tested using a within-subject, fully randomised study design and results were analysed using a repeated measures ANOVA with TREATMENT as factor. Atomoxetine and reboxetine induced dose-dependent improvements in stop trial accuracy (ATO: F(2,24)=5.14, p=0.009, REB: F(3,69)=7.0, p=0.0001). A significant improvement in stop accuracy was observed following 0.3, 1.0 or 3.0mg/kg (p=0.05). Stop accuracy revealed improvements when the stop signal was delayed but no effect at zero delay was observed however, all rats performed at near maximal stop accuracy of 100%. Both NaRIs induced effects on other variables including a dose dependent decrease in go trial accuracy, increase in omissions and reduction in the mRT (p<0.05). These data suggest that inhibition of the noradrenaline re-uptake transporter improves stop trial accuracy in this model of SSRT task but also slowed the rats’ reaction times and reduced overall task performance. At the lowest dose tested, atomoxetine improved stop accuracy and reduced go accuracy but did not significantly increase mean reaction time or omissions. These results suggest that NA re-uptake inhibition is a common site of action for improvements in stop accuracy in this task but also affects motor performance. The increased motor effort in this task may reduce sensitivity to specific actions on SSRT. Funded by Nuffield Foundation, BAP in-vivo training initiative award and Medical Research Council.

TH02

CHRONIC PRAVASTATIN BUT NOT ATORVASTATIN IMPAIRS COGNITIVE FUNCTION IN TWO RODENT MODELS OF LEARNING AND MEMORY

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Statins are a class of drug which inhibit HMG coenzyme A reductase, reducing the production of cholesterol. They are generally well tolerated drugs, but a number of reports have suggested that they can induce cognitive side effects such as memory impairments in some patients. In the present study, we have investigated the effects of chronic treatment with two statins, pravastatin and atorvastatin, on recognition memory and working memory in rats. Male Lister-Hooded rats (Harlen, UK) weighing ~450g were trained to perform a simple discrimination learning and reversal learning assay. Animals were trained to associate a particular substrate with the presence of reward adapted from the attentional set shifting procedure. On each day, rats had to learn which substrate was associated with reward (criterion = 6 consecutive correct trials). Once a criterion was achieved, the test was immediately followed by a reversal of the rewarded substrate and trials to criteria again recorded. Once rats had learnt the basic procedure and were consistently learning the novel discrimination and reversal on each day, rats were orally dosed daily with pravastatin (10 mg kg-1 day-1), atorvastatin (10 mg kg-1 day-1) or control (strawberry milkshake). Animals were treated for 18 days and tested in the simple discrimination and reversal learning task three days/wk. On the last day of treatment, rats were also tested in a novel object discrimination (NOD) paradigm (inter-trial interval (ITI) ~ 4 h). Treatment was stopped and the rats were re-tested in both paradigms following a five day washout. All animals showed a significant improvement in the performance in the simple discrimination and reversal task across the duration of the study (p<0.05). Chronic treatment with pravastatin significantly impaired performance in both the NOD test (p<0.05) and the SD and reversal tasks (p<0.001 and p<0.05 respectively) during the last 3 days of drug treatment when compared to the control animals and pre-treatment baseline. Chronic treatment with atorvastatin did not affect performance in either task. The effects observed with pravastatin were fully reversed 5 days after the end of treatment. These data suggest that chronic treatment with a high dose of pravastatin impairs working and recognition memory in rodents but further studies are needed to determine if these effects are related to its actions on cholesterol or through another site of actions. The mechanism underlying the differing effects observed following treatment with pravastatin and atorvastatin also remain unclear. Funded by RCUK, BBSRC and PFR

TH03

TIME-DEPENDENT CHANGES IN PARVALBUMIN IMMUNOREACTIVE CELL DENSITY IN THE CA2/3 REGION OF THE RAT HIPPOCAMPUS FOLLOWING SUB-CHRONIC PHENCYCLIDINE TREATMENT

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Introduction Although animal models of schizophrenia are inevitably limited in validity there are certain approaches that are capable of mimicking certain aspects of the disorder. One such approach is based on the sub-chronic administration of the NMDA receptor antagonist phencyclidine (PCP). We have demonstrated that this treatment regime results in profound deficits in a number of cognitive domains, similar to those observed in schizophrenia. One of the most robust findings in post-mortem tissue from schizophrenics are deficits of a subset of GABAergic neurons (parvalbumin positive). It is not clear whether these neurons are lost or hypo-functioning in the brains of schizophrenics. These neurons are critical for normal synchronisation of neuronal activity and have been postulated to play a role in the cognitive deficits observed in the illness. The aim of this study was to investigate time dependent changes in parvalbumin immunoreactive (IR) neurons in the PCP animal model. Methods Adult female hooded-Lister rats (n=32) were treated with PCP at 2 mg/kg intraperitoneally or vehicle (0.9% saline in a volume of 1 ml/kg) bi-daily for seven days. Following a seven-day drug free washout period, 16 vehicle and 16 PCP rats were then given an acute challenge of PCP (2 mg/kg) or vehicle and assessed for locomotor activity (LMA); 2 and 8 weeks following PCP treatment, 8-vehicle and 8-PCP treated rats were sacrificed and brains were removed for immunohistochemical analysis of parvalbumin IR cell density in the hippocampus. Results Following acute PCP, there was a significant increase in LMA in the sub-chronic PCP-treated rats only (P<0.001), showing that sub-chronic PCP induces sensitisation to a subsequent acute challenge. Immunohistochemical analysis at 2 weeks post-chronic treatment revealed a significant reduction in parvalbumin IR cell density in the CA2/3 region in PCP-treated animals (P=0.058 vs. vehicle). In contrast, at 8 weeks post-treatment, parvalbumin IR cell density was unchanged in the CA2/3 region in PCP-treated animals (P=0.981 vs. vehicle). Conclusions The PCP sensitisation data show that the sub-chronic PCP dosing regime was effective. In a separate cohort of animals we have previously reported reductions in gamma oscillations (these oscillations arise from networks of parvalbumin interneurons) following PCP treatment (2-5 weeks post-PCP-treatment). Interestingly, a time-dependent increase in gamma oscillations was observed 6-8 weeks post PCP-treatment. These preliminary studies demonstrate a link between altered gamma-frequency oscillations and abnormalities in parvalbumin interneurons, which may underlie some of the cognitive deficits previously reported in this animal model of schizophrenia.
TH04

SUB-CHRONIC KETAMINE EXPOSURE IMPAIRS REVERSAL LEARNING BUT NOT ATTENTIONAL SET FORMATION IN A RODENT ATTENTIONAL SET SHIFTING TASK

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Cognitive deficits in schizophrenia represent a clear unmet clinical need with existing treatment being seen as insufficient by sufferers and clinicians alike. Acute administration of NMDA antagonists such as phencyclidine and ketamine have long since been successfully used to model the cognitive symptoms of schizophrenia in monkeys and rodents. Recent literature suggests a sub-chronic regimen may however, be more representative of cognitive deficits seen within this disorder (Pedersen et al, 2009, Neuroscience Methods, 185, 66-69). Attention is significantly impaired in patients with schizophrenia and therefore the attentional set-shifting task (ASST), a measure of attention in animals (Birrell and Brown, 2000, J Neurosci, 20, 4320-4324) was used to investigate the effect of sub-chronic ketamine exposure on attentional flexibility in rats. Thirty-six male hooded Lister rats were treated with 30mg/kg ketamine or vehicle daily for 5 days and allowed a two day washout before habituation and testing. The animals were trained to dig in bowls for a food reward, half a Honey Nut Cheerio™ and habituated to the task one day prior to testing, which involved digging in a choice of two bowls, differentiated by odour or media. The animals had to complete six consecutive correct digs in order to progress to the next discrimination. In experiment 1, the animals used an extended version of the standard ASST, using more ID discriminations and fewer reversals. In experiment 2 the animals undertook the standard ASST. Statistical tests were conducted using multifactorial ANOVAs for repeated measures followed by Bonferroni pairwise comparisons (SSPS version 17). Animals exposed to sub-chronic ketamine demonstrated a significant impairment in reversal learning when compared to vehicle treated animals, p<0.01. There was however, no significant difference in the ability of ketamine treated animals to complete an ID/ED shift using the ASST, suggesting a lack in formation of an attentional set. These findings partially replicated the findings of a previous study (Wood et al, 2009, Examination of cognitive deficits produced by sub-chronic ketamine in rats, University of Newcastle-upon-Tyne). Furthermore, experiment 1, an extended version of the standard ASST, did not highlight any different effects of sub-chronic ketamine, compared to those found using the standard ASST. In a human analogue of the ASST, known as the Wisconsin card sorting task (WCST) schizophrenia patients are able to form attentional sets, but do present an ID/ED shift. This indicates that using this revised design, sub-chronic ketamine offers less translational value as a cognitive symptom model of schizophrenia, with regard to clinical studies in man.

TH05

CHOLINE RESTORES KETAMINE-INDUCED WORKING MEMORY DEFICITS IN THE RODENT ODOUR SPAN TASK

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Choline is a selective agonist of n7/nAChRs (nAChRs) and this nicotinic receptor subtype has been implicated in various forms of cognition in laboratory animals. The psychomimetic agent ketamine has previously been used in sub-chronic regimens to model cognitive deficits associated with schizophrenia. Using the odour span task (OST), this study aims to assess the ability of choline in restoring ketamine-induced deficits on working memory. 12 hooded Lister male rats were trained in the OST, which involved identifying a novel odour from an increasing number of presented odours. Rats were performance matched and randomly allocated to two treatment groups (n=6/group). Animals were sub-chronically exposed to ketamine daily (10mg/kg i.p. or vehicle) for 5 consecutive days after reaching baseline performance on the OST. All animals (n=12) were then maintained on a 2% choline diet for 2 weeks and then returned to standard rat chow for the remainder of the study. Ketamine-treated animals exhibited significant deficits that were present over 10 weeks of tests. Choline treatment over the 2 week period significantly improved ketamine-induced deficits (p<0.05) restoring performance to pre-ketamine levels. Significant differences in performance were observed upon cessation of choline treatment (p<0.01). No significant changes were observed in performance of control animals throughout the study. Ketamine-induced deficits on OST performance was persistent over the 10-weeks of tests and was restored when presenting the subjects with a 2% choline diet. The restoration of the deficits on OST confirm that improvements were not as a result of ketamine wearing off and highlight the long term nature of the deficits produced by sub-chronic ketamine exposure. More significantly, this study suggests that supplementing the diet with choline may be a beneficial adjunct to anti-psychotic therapy for treatment of cognitive deficits seen in psychiatric disorders such as schizophrenia. Key Words: Schizophrenia• Choline• Ketamine• Working Memory

TH06

INTERACTIONS BETWEEN SELF-REPORT ATTENTION CONTROL AND ANXIETY ON ANTISACCADE PERFORMANCE

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Introduction: In the antisaccade task top-down attention control is required to suppress (inhibit) reflexive saccades (eye-movements) toward abrupt peripheral visual stimuli and instead generate a volitional saccade in the opposite direction (antisaccade). Enhanced activity in prefrontal cortex (dorsolateral & ventro-lateral) during (correct) antisaccade trials supports the involvement of these regions in regulating attention allocation by inhibiting reflexive attentional capture by distractors (Ettinger et al. 2008). Cognitive models propose that a failure to use controlled processing to regulate attention to (emotional) distractors increases vulnerability to anxiety (Eyseckn et al. 2007), and suggest a role for attention training in reducing negative biases in emotion processing and anxiety. The present study examined whether self-report attention control moderates the effect of anxiety on performance measures of attention control in an antisaccade task. Methods: Sixty-two healthy volunteers (mean age = 20.8yrs, SD =1.54yrs; 37 female, 25 male) completed a modified antisaccade task in which they were instructed to look towards or away from a peripheral picture stimulus (negative or neutral) presented either to the left or right of central fixation. The accuracy of horizontal eye-movements was recorded throughout. Participants were allocated to one of four groups according to their scores on standardized self-report measures of anxiety (State-Trait Anxiety Inventory, STA1) and attention (Attention Control Scale, ACS): high anxiety-high control; high anxiety-low control, low anxiety-high control, low anxiety-low control. Results: Eye-movement accuracy was analyzed using mixed design analysis of variance with trial type (pro vs. antisaccade), image valence (negative vs. neutral), anxiety group (high vs. low) and attention control (high vs. low) as independent variables. Participants made significantly more eye-movement errors on antisaccade than pro-saccade trials (p < .01), with antisaccade errors significantly greater in individuals reporting a combination of high state anxiety and low attention control, (p’s < .05). Furthermore, erroneous orienting towards negative images on antisaccade trials was significantly associated with increased state anxiety immediately following the task in individuals reporting low (but not high) levels of attention control p < .05. Discussion: Results provide some support that high levels of attention control may protect against i) anxiety-related deficits in cognitive control, and ii) increases in state anxiety following attention to threat cues. Implications for neuro-cognitive models and attention training interventions for emotional disorders are considered.
TH07

MUSCARINIC ACETYLCHOLINE RECEPTOR REGULATION OF THE GABA-A RECEPTOR ALPHA4 SUBUNIT GENE

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The GABA-A receptor is a target for a number of clinically important drugs, including many anxiolytic and sedative drugs, and its inappropriate function or expression has been implicated in various diseases. The alpha4 subunit is of particular interest as it confers distinct pharmacological properties on the receptor, particularly when combined with a delta subunit (e.g. insensitivity to classical benzodiazepines and sensitivity to neurosteroids). The function of alpha4 subunit-containing receptors is modulated by alcohol or neurosteroids, and application or withdrawal of the same agents causes changes in expression of the corresponding gene. These properties have been implicated in various anxiety behavioural states and provide a molecular basis for disorders such as premenstrual dysphoric disorder (Smith et al., 2006, Psychopharmacology, 186, 323-333). Little is known, however, about the molecular mechanisms that regulate the alpha4 subunit gene expression.

Using bioinformatic analysis we identified three potential Egr-1 (early growth response 1) transcription factor binding sites in the rat alpha4 gene promoter. Egr-1 has been shown to be increased upon administration of amphetamine (Ningning et al., 2010, Neuropharmacology, 58, 806-817) and this finding questions whether radioligands selective to GABA-A receptors may be more sensitive to changes in ionic environment in vivo. Since the alpha4 subunit is sensitive to changes in ionic environment, it will be less sensitive to changes in vivo. This finding suggests that radioligands selective to alpha4 subunit-containing receptors may be more sensitive to changes in vivo. The present study aimed to investigate the transcriptional regulation of the rat GABA-A receptor alpha4 subunit gene using this model system. SH-SY5Y neuroblastoma cells were transfected with an alpha4 promoter-luciferase construct followed by drug treatment. 1 mM carbamol was applied for 1 hour at 6, 24 and 30 hours post-transfection, either with or without atropine (10 microM) pre-treatment. Carbamol dose-dependence was determined (1 microM, 10 microM and 1 mM) using 1 hour exposure at 6 hours post-transfection. Signalling mechanisms downstream of carbamol stimulation were investigated using PKC inhibition (10 microM bisindolylmaleimide 1 (BIM-1) or chelerythrine chloride, 15 min pre-treatment) or stimulation (0.5 microM phorbol 12-myristate 13-acetate (PMA), 1 hr treatment). Luciferase activity was determined 48 hrs post-transfection and data analysed using Student’s t-test. Carbamol significantly increased alpha4 promoter activity at 6 and 24 hours post-transfection (p=0.001), an effect blocked by atropine pre-treatment (p=0.001). BIM-1 decreased (40%, p=0.05) whereas direct PKC activation with PMA increased (86%, p=0.0001) alpha4 promoter activity. Chelerythrine chloride treatment had no effect. Cholinergic stimulation regulates alpha4 promoter activity via a PKC-mediated process in SH-SY5Y cells. Previous studies have demonstrated that this signalling pathway leads to activation of Egr-1. Taken together with our findings of potential Egr-1 binding sites in the alpha4 promoter, our data suggest that Egr-1 may regulate alpha4 gene transcription.

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TH08

EFFECTS OF CELLULAR COMPARTMENTS ON THE BINDING OF [3H]SC23390 TO THE PORCINE D1-DAR

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PET radioligands selective for the D2-dopamine receptor (D2-Dar) such as raclopride, have been shown to be more sensitive to internalisation of their target receptor rather than direct competition (Ningning et al., 2010, Neuropharmacology, 58, 806-817). The binding of [3H]SC23390 to the striatal D1-Dar has been shown to be increased upon administration of amphetamine (Ningning et al., 2006, NeuroImage:31) and this finding questions whether radioligands selective to the D1-Dar would show altered binding properties when subjected to different ionic conditions. This abstract reports saturation characteristics of [3H]SC23390 in porcine striata when exposed to physiological media reflective of the Extracellular, Intracellular and Endosomal cellular compartments. Homogeneous binding assays were performed using a tritiated form of the PET ligand, [3H]SC23390. Three buffers were prepared to represent the physiological conditions of cellular compartments: 1) Extracellular 50 mM Tris HCl, 140 mM NaCl, 5 mM KCl, 1.5 mM MgCl2, 1.5 mM CaCl2, pH 7.4, 37°C 2) Intracellular 50 mM Tris HCl, 100 mM NaCl, 140 mM KCl, 0.5 mM MgCl2, pH 7.0, 37°C 3) Endosomal 20 mM MES, 100 mM NaCl, 140 mM KCl, 0.5 mM MgCl2, 0.003 mM CaCl2, pH 6.0, 37°C. Tissue was prepared in three physiological buffers and incubated at 37°C for 60 mins with increasing concentrations of radioligand (300 pM-100 nM). Butaclamol (10μM) was used to define specific binding. Data analysis was performed using GraphPad Prism 5.0. Saturation analysis revealed [3H]SC23390 was able to recognise two independent binding sites (H=1/D1-Dar and Lo=5HT1C) in the Extracellular (BmaxH:64±26; BmaxLo:845±313 fmol/mg protein and KDH:0.98±0.27; KDLo:55.6±22.4 nM) and Intracellular condition (BmaxH:731±58; BmaxLo:497±85 fmol/mg protein and KDH:0.78±0.02; KDLo:57.4±4.9 nM), consistent with Nicklaus et al. (1988, JPET, 247, 343-348), and the Endosomal condition was only able to detect the D1-Dar binding site (Bmax:664±107 fmol/mg protein and KD:3.05±0.46 nM). The Bmax across all three conditions did not alter for D1-Dar however the affinity of the D1-Dar for [3H]SC23390 decreased in the Endosomal condition (not significant). These data strongly suggest [3H]SC23390 behaves in a similar manner in all three physiological conditions with a trend to decrease in the Endosomal condition. The Bmax and KD values for the D2-Dar radioligands, raclopride and PhNO, have previously been shown to decrease from Extracellular> Intracellular> Endosomal conditions, reflecting their sensitivity to ionic environments (Withey et al, 2010, NeuroImage). SC23390 binding to the D1-Dar was not altered between Extracellular and Endosomal conditions strongly suggesting this ligand will be less sensitive to changes in ionic environment in vivo and would be more sensitive to changes via direct competition. This is extremely useful for analysis of [11C]SC23390 PET data where interpretation could reflect changes in binding signals as direct competition rather than receptor internalisation.
TH09

INVOLVEMENT OF NMDA RECEPTORS OF THE MEDIAN RAPHE NUCLEUS IN THE BEHAVIOURAL CONSEQUENCES OF RESTRAINT STRESS.

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Introduction: Exposure to uncontrollable stressors leads to behavioural and neurochemical changes, which has been associated to mal functioning of the Median Raphe Nucleus (MnRN)-Dorsal Hippocampus (DH) cholinergic pathway. These deficits can be attenuated by intra-hippocampal injections of NMDA antagonists (such as AP7) or 5-HT1a agonists. Activation of MnRN glutamatergic NMDA receptors (NMDAr) increases serotonin release in both MnRN and DH. Therefore, the aim of this work was to investigate whether activation of MnRN NMDAr could prevent or attenuate restraint-induced exploratory deficits depending on the moment of pharmacological intervention. Methods: Rats with cannulas aimed to the MnRN were restrained for two hours and tested in the elevated plus maze (EPM) twenty four hours later. Intracerebral injections (0.2µl each) of Saline (SAL), AP7 (3nmols) and/or NMDA (1nmol) (5 min interval) were administered as follows: SAL+SAL, SAL+NMDA, AP7+SAL and AP7+NMDA. Treatments were given immediately before or after restraint or twenty four hours after it. Non-stressed rats were treated twenty four hours or five minutes before test. Percentage of entries (%EOA) and time spent (%TOA) in the open arms were registered and analyzed by One way ANOVA for each experimental protocol. Results: When give after restraint stress NMDA increased %EOA (25.8±3.4) and %TOA (16.9±3.5) when compared to saline (%EOA=16.8±3.0; F3,46=4.7; p<0.05; %TOA=8.4±3.1; F3,46=4.5; p<0.05). AP7 did not change %EOA (16.6±3.0) but decreased %TOA (4.9±3.4) when compared to control. When administered before NMDA, AP7 did not block its effects on %EOA (29.1±3.3) and %TOA (16.1±3.4). Intra-MnRN injections of NMDA and/or AP7 immediately before restraint increased %TOA (F3,38=3.9; p<0.05; Sal+NMDA=23.4±3.9; AP7+Sal=22.9±3.9; AP7+NMDA=19.9±3.0), but not %EOA (F3,38=2.1; p>0.05; Sal+NMDA=31.9±3.8; AP7+Sal=32.2±3.8; AP7+NMDA=30.3±2.9), when compared to control (%EOA=23.2±3.6; %TOA=11.7±3.7). In previously stressed rats, NMDA and/or AP7 increased %EOA (F3,40=9.7; p<0.05; Sal+NMDA=37.5±3.0; AP7+Sal=47.6±3.8; AP7+NMDA=45.2±3.8) and %TOA (F3,40=11.96; p<0.05; Sal+NMDA=31.3±3.1; AP7+Sal=38.0±3.9; AP7+NMDA=39.8±3.9), when compared to Saline treated animals (%EOA=23.3±1.1; %TOA=14.8±3.2). No changes on behaviour were observed when treatment was performed twenty four hours after restraint (%EOA=23.8±0.2; p>0.05; Sal=30.4±3.6; Sal+NMDA=31.2±3.3; AP7+Sal=27.9±3.3; AP7+NMDA=30.2±3.8; %TOA=33.8±2.1; p>0.05; Sal=21.4±3.7; Sal+NMDA=24.7±3.4; AP7+Sal=18.1±3.4; AP7+NMDA=18.8±3.9) or immediately before test (%EOA=23.6±2.0; p>0.05; Sal=31.9±3.9; Sal+NMDA=38.8±6.5; AP7+Sal=48.5±6.8; AP7+NMDA=46.5±3.0; %TOA: F3,26=1.8; p>0.05; Sal=32.4±6.1; Sal+NMDA=28.6±8.5; AP7+NMDA=37.2±6.5; AP7+NMDA=38.0±5.7) in non-stressed rats. Discussion: Our results show that both blockade and facilitation of NMDAr neurotransmission within the MnRN interfere in processes involving acquisition, consolidation and retrieval of unpleasant memories. These results suggest the existence of intrinsic MnRN NMDAr-mediated neurotransmission mechanisms in the behavioural effects of stress. Financial Support: CAPES, CNPq and FAPESP.

TH10

EVALUATION OF CHOLINERGIC MECHANISMS IN A RODENT MODEL OF THE IOWA GAMBLING TASK

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Impulsive behaviour is a pathological trait commonly found in a number of psychiatric disorders. Its neurochemical basis is poorly understood, and despite widespread recognition of a functional role in cognition, little research has explored the cholinergic system as a mediator of impulsivity. The present study investigated the effects of cholinergic compounds on performance in a novel rodent version of the Iowa gambling task (rGT) - an effective model of impulsivity and decision-making. Rats are presented with four different options that govern the amount of food earned within 30 minutes. Each option is associated with the delivery of a different number of food pellets, but also with a different probability and duration of punishing time-out periods during which reward cannot be earned. Rats distinguish the optimal strategy of choosing smaller rewards with smaller penalties, as this ultimately results in a greater number of food pellets earned over time. Persistent choice of larger rewards associated with larger penalties, however, is indicative of impulsivity. Sixteen male hooded Lister rats were habituated, trained, and assessed daily on their performance in the rodent gambling task (rGT) which consisted of standard operant chambers run on Med PC IV software. Rats were pre-treated with nicotine (0.05, 0.1, 0.2, 0.4 mg/kg), mecamylamine (0.3, 1, 3, 5 mg/kg), scopolamine (0.01, 0.03, 0.1 mg/kg), and vehicle on designated days. Behavioural parameters were recorded and compared to vehicle. A two-way ANOVA for repeated measures confirmed a significant interaction (F(3, = 4.38, p<0.001) between Dose and Hole Choice (F(3,42 = 41.47, p<0.0001)) following scopolamine administration, with the muscarinic receptor antagonist significantly reducing choice preference for the optimal pellet option at the highest dose (0.1 mg/kg: p<0.02). Behavioural indices such as total pellets earned, premature responses and trials omitted also confirmed scopolamine to be behaviourally active. Nicotine did not produce significant effects on rGT performance despite being behaviourally active (F(3,4 = 1.19, NS), and mecamylamine was also unable to produce significant differences in choice preference when compared to vehicle (F(3,42 = 2.07, NS). This is the first study to assess the cholinergic system in a novel rodent model of the rGT. The muscarinic antagonist, scopolamine, was shown to form a robust change in rodent performance in the rGT, while nicotine and mecamylamine were observed to have no effect. Our findings suggest a modulatory role of the muscarinic cholinergic system in impulsive behaviour, while the nicotinic system may not be relevant despite previous hypotheses.
TH11

SUBJECTIVE AND OBSERVED MOOD CHANGES WITH ACUTE DEEP BRAIN STIMULATION OF THE VENTRAL CINGULATE (SGC), OF THE VENTRAL CAPSULE OR OF THE NUCLEUS ACCUMBENS (VACNAc): PRELIMINARY RESULTS FROM A DOUBLE BLIND CROSSOVER STUDY

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Deep brain stimulation (DBS) is emerging as a possible treatment for chronic and treatment resistant depression. Some authors have reported acute changes in mood following acute stimulation. Here we report on a prospective study of subjective and observed mood changes during brief acute stimulation of the subgenual cingulate (SGC) and of the ventral anterior capsule/nucleus accumbens (VACNAc). Eight patients were implanted with DBS electrodes in both SGC and VACNAc under general anaesthesia. Each electrode has four contacts 1.5 mm apart which therefore stimulate different brain locations. After a two week rest period acute stimulation was started (randomised and double-blind) in one of the two locations testing single and paired contacts acutely in turn. After each stimulation period of about 2 minutes patients reported their experiences using the profile of mood states (POMS) and visual analogue scales (VAS). In addition a psychiatrically qualified observer scored observed changes over the same period of time using a simple scale. If at the end of at least four months of chronic stimulation remission had not been achieved, the alternate location was stimulated following the same protocol. Friedman’s tests were used for repeated measures. Here we report results for the six patients who have been stimulated in both locations. Two patients had little response to acute stimulation. For the whole group, observed mood changes were not significantly different between single pairs of contacts in VACNAc (p=0.15) while SGC contacts were significantly different (p=0.01) from each other with the largest (but not significant) difference in sum rank being between the most distal contact and the second most proximal. POMS scores were significantly different for anger (both targets p=0.009 in SGC (distal contacts) and p=0.04 in VACNAc (proximal contacts)) and depression (VACNAc p=0.03; proximal contact). Although not all patients responded to stimulation acutely, both observed and reported mood parameters were significantly altered in this small group by acute deep brain stimulation. The differences were driven by stimulation of brain areas germane to mood regulation. These findings will be discussed in detail. We are grateful to Friends of Frenchay hospital for donations to support this work.

TH12

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

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INFLAME-BEAT: Understanding the role of inflammation in predicting depression in patients with heart disease Project goal: The primary goal of this project is to identify the biological risk factors associated with depression in patients with symptomatic coronary heart disease (sChD). Background: Depression in patients with sChD increases the risk for cardiac morbidity and mortality. Indeed, depression is more prevalent in patients with sChD than in the general population. Around 20% of outpatients and 35-70% of inpatients with sChD meet criteria for major depression compared to 2-4% in the general population. The mechanisms underlying the increased incidence of depression in patients with CHD are, however, yet to be understood, despite the severe consequences for these patients’ health. Methods: The INFLAME-BEAT study is a 2-year project to test the hypothesis that activated inflammatory responses in patients with coronary heart disease (CHD) is associated with future development of depressive symptoms. Until now it comprised of 37 patients with sChD. Depressive symptoms were assessed by means of Beck Depression Inventory (BECK) and Patients Health Questionnaire (PHQ). Blood was collected for plasma measurement of C-reactive protein (CRP), cortisol, triglycerides, high density lipoproteins (HDL), low density lipoproteins (LDL), total cholesterol, full blood count, fasting glucose. A t-test was used to compare two variables. Anova was used to compare more than two variables. Values were considered significant when p<0.05. Results: From a total of 37 patients with sChD 8 had depressive symptoms. Depressive patients had lower levels of Hemoglobin (sChD 13.7±3.04, sChDdep 12.85±0.15), increased levels of Red blood cells Distribution Width (RDW) (sChD 13.71±0.162, sChDdep 15.00±1.2), lower levels of lymphocytes (sChD 1.9±0.154, sChDdep 1.36±0.1), higher levels of neutrophils (sChD 4.10±0.02, sChDdep 5.37±0.09) and lower levels of HDL (sChD 1.43±0.098, sChDdep 1.2±0.041). Furthermore, only in sChD depressed patients we also found a trend positive correlation between PHQ scores and the number of neutrophils (P=0.74, p=0.08), the HDL/LDL ratio (P=0.76, p=0.02) and negative correlation between PHQ scores and HDL (P=0.75, p=0.03). There was no difference in the levels of cortisol or CRP in sChD and sChDdep. Conclusions: The presence of depressive symptoms seems associated with increased risk for cardiovascular disease possibly due to the lower levels of the protective HDL, lower levels of lymphocytes, but higher levels of neutrophils. These disturbances may contribute to worsening of cardiovascular outcome in sChD patients with depression. This work was funded by Narsad Young Investigator Award to Livia Carvalho, the Biomedical Research Centre and the European Union Framework 7
TH13

BASELINE ROUTINE INFLAMMATORY MARKERS DO NOT PREDICT SWITCH TO MAJOR DEPRESSION IN A COHORT OF INTERFERON-TREATED HEPATITIS C PATIENTS

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Hepatitis C (Hep C) is increasingly common, affecting approximately 3% of the world’s population and almost 70,000 people in the UK. Since Interferon-α (IFN-α) was approved for Hep C treatment 14 years ago, it has proven effective in clearing the virus. However, IFN-α has potentially severe side-effects, including development of Major Depressive Disorder (MDD) in at least 30% of those treated (Wichers et al. 2006, Biol Psychiatry 60:77-79) which may influence quality of life and treatment concordance. Recent studies have established that inflammatory biomarkers are raised in depression (Maes et al., 2009, Metab Brain Dis 24:27-53). We hypothesised that raised, routinely tested, baseline inflammatory markers conferred a greater vulnerability to MDD development during subsequent IFN treatment. Forty-five consecutively referred patients with Hep C were recruited from the Royal Sussex County Hospital who were to receive at least 24 weeks of IFN-α and ribavirin combination therapy and consented to the study. Baseline CRP, ESR, white cell, lymphocyte, neutrophil and monocyte counts, Hep C viral load and genotype were determined. Participants received the structured clinical interview for DSM-IV (SCID) for MDD and Hamilton depression scale (HAMD) questionnaires at baseline and every 4 weeks. Two subjects with baseline SCID-defined MDD were excluded from the study. Twenty-four of 43 participants (56%) developed MDD by 24 weeks. All HAMD scores increased from baseline. Mean HAMD scores at each period were significantly higher than baseline, with the greatest difference of 14.3 units at 20 weeks (p<0.001). No significant correlation was found between HAMD area-under-curve over 24 weeks and baseline ESR, white cell, neutrophil, lymphocyte and monocyte counts or viral load (p>0.2 for all factors). Similarly, these measures had no effect on switch to MDD by 24 weeks (p>0.2 for all factors). Dichotomised CRP (<5 or >5) and viral genotype had no significant association with HAMD area-under-curve or switch to MDD by 24 weeks (p>0.35 for all factors). MDD is clearly a common consequence of IFN-α treatment. We were however unable to demonstrate an association between baseline routinely tested inflammatory markers and subsequent development of MDD. Adding the cytokine IFN-α may therefore negate pre-existing inflammation as an influence on depression emergence. Limitations of our study include low sensitivity of CRP assay and cohort number. More robust predictors of MDD in this patient group appear to include baseline raised HAMD, hypothalamic pituitary adrenal axis hyperactivity (measured via waking salivary cortisol), as we have previously demonstrated, and serotonin transporter genotype (Pierucci-Lagha et al. 2010 Psychosomatics 51:137-148).

TH14

THREE YEARS OF NEW PATIENTS SEEN WITHIN AN NHS TERTIARY SERVICE FOR REFRACTORY AFFECTIVE DISORDERS: REASONS FOR REFERRAL, PREVIOUSLY UNRECOGNISED ILLNESS, AND TREATMENT RECOMMENDATIONS

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Introduction. Many evidence-based interventions for patients with mood and anxiety disorders are available, but a substantial proportion remain troubled by persistent, distressing and impairing symptoms, even after a succession of treatments delivered in primary and secondary medical care. Tertiary referral services provide additional support in the management of patients with complex and treatment-resistant illnesses, but comparatively little data are available on reasons for referral, possible maintaining factors and treatment recommendations for this patient group. Methods. We extended an initial pilot scheme, to include full data on new referrals, seen over three years (April 2007-March 2010) within a single tertiary referral service, through a retrospective case-note survey. We examined reasons for referral, previously unrecognised or undocumented maintaining factors, and pharmacological treatment recommendations following the first consultation. Results. 114 patients (42 men, 72 women: mean age 49.6, range 18-84 years) were referred as new cases during the three-year period: 3 patients were assessed twice as new cases, 1 patient did not attend, and two files could not be traced. Six patients were assessed whilst receiving inpatient psychiatric care. Principal reasons for referral were for non-response to previous and current treatment (103 patients, 90.4%), frequent relapse of illness (88 patients, 77.2%), uncertainty about diagnosis (21 patients, 18.4%), troublesome specific symptoms (25 patients, 21.9%) and patient request for a second opinion (20 patients, 17.5%). Principal primary diagnoses were recurrent unipolar depressive disorder (55 patients, 48.2%) bipolar disorder (37 patients, 32.5%) and anxiety disorders (6 patients, 5.3%); secondary diagnoses were recorded in 46 patients (40.4%), mainly being comorbid anxiety disorders in patients with primary mood disorders. Important maintaining factors were not recognised or addressed in 24 patients (21.1%) and co-morbid diagnoses were unrecognised in 21 patients (18.4%); 8 patients (7.0%) had unrecognised bipolar disorder. Alcohol abuse was a maintaining factor in 25 patients (21.9%). Most frequent recommendations for antidepressant treatment were for escitalopram, clomipramine and phenelzine; for mood-stabilisers, lamotrigine and lithium; and antipsychotics (usually as augmenting agents), quetiapine and aripiprazole. A significant proportion of treatment recommendations were for unlicensed applications, principally for lamotrigine in bipolar disorder and quetiapine as an augmenting agent in unipolar depression. Conclusion. Unrecognised bipolar disorder and/or alcohol use disorders were present in a substantial minority of patients referred to this tertiary referral affective disorder service. A unified database from a network of similar services would help establish whether these observations are more widespread.
TH15

IS THERE A CORRELATION BETWEEN SUBJECTIVE AND OBJECTIVE MEASURES OF COGNITIVE FUNCTION IN PATIENTS WITH BIPOLAR DISORDER AND HOW IS THIS INFLUENCED BY AFFECTIVE PSYCHOPATHOLOGY?

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Bipolar disorder (BD) is associated with cognitive dysfunction, which often persists into periods of remission and impair patients’ social and occupational function. However, the relationship between subjectively experienced cognitive difficulties and objective cognitive dysfunction is still controversial and has not been investigated in patients with affective disorder. It is also unclear to which degree objective and subjective measures of cognitive function are predicted by affective psychopathology. We hypothesised 1) that there is poor correlation between subjective and objective measures of cognitive function and 2) that subjective measures of cognitive function are predicted to a higher degree than objective measures by affective psychopathology. Fifteen patients with BD (aged 20-54) were recruited consecutively from the waiting room at the Clinic for Affective Disorders, Department of Psychiatry, Copenhagen University Hospital. Patients’ subjective experience of cognitive difficulties was assessed with the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) (1) and objective cognitive function with the Screen for Cognitive Impairment in Psychiatry (SCIP) (2). Intelligence was estimated with the Danish Adult Reading Test (DART) and affective symptoms evaluated with the Beck Depression Inventory (BDI), Young Mania Rating Scale (YMRS), State- Trait Anxiety Inventory (STAI), and Cohen’s perceived stress scale. Non-parametric correlation analysis demonstrated no correlation between objective and subjective measures of cognitive function (P<0.22). Multiple regression analysis for the CPFQ using the enter method revealed a significant model (F=7.4, 11.14, p=0.017). Adjusted R squared = 0.87. Significant variables were BD (Beta=1.68, P=0.014), YMRS (Beta=0.55, P=0.044) and STAI-trait (0.49, P=0.040). SCIP, DART, gender and perceived stress were not significant predictors in this model (P>0.08). Regression analysis for the SCIP revealed no significant model (P=0.31) or predictor variables (P=0.21). This preliminary evidence points to an absence of correlation between subjective and objective measures of cognitive function in BD, as hypothesised. Subjective complaints, but not objective cognitive function, were predicted by depression, mania and anxiety symptoms. If confirmed in a larger sample, this would cast doubt on the clinical relevance of patients’ cognitive complaints and highlight the importance of neuropsychological assessment to elucidate the role of cognitive dysfunction in psychosocial difficulties seen in BD. References (1) Fava M, Iosifescu DV, Pedrelli P, Baer L: Reliability and Validity of the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire. Psychotherapy and Psychosomatics 2009, 78:91-97. (2) Purdon S: The Screen for Cognitive Impairment in Psychiatry: Administration and Psychometric Properties. Edmonton, Alberta, Canada: PNL Inc.; 2005.

TH16

ROLE OF 5-HT1A RECEPTORS OF THE MEDIAN RAPHE NUCLEUS ON THE BEHAVIOURAL CONSEQUENCES INDUCED BY FORCED SWIM STRESS

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Introduction: The forced swim test (FST) is a widely used animal model of depression in which animals previously submitted to fifteen minutes of forced swim display increased immobility when re-tested twenty four hours later. This phenomenon is known as behavioural despair and can be attenuated by chronic treatment with antidepressants and intra-hippocampal injections of serotoninergic agonists. Since hippocampal serotoninergic afferents arrives from the Median raphe nucleus (MnRN) and this pathway has been involved in the development of tolerance to stress, the aim of this work was to investigate the role of 5-HT1a receptors (5-HT1aR) within the MnRN in the FST. Methods: Male wistar rats with cannulas aimed to the MnRN were submitted to fifteen minutes of exposure (pre-exposure, PE) of forced swim and tested twenty four hours later. All animals received two intra-MnRN injections (0.2µL each; five minutes interval) of Saline (Sal), 8-OH-DPAT (DPAT) and/or WAY100635 (WAY), administrated as follows: Sal+Sal, Sal+DPAT (3nmols/0.2µL), WAY+Sal (0.3nmols/0.2µL) and WAY+DPAT. Animals received the injections immediately before or after PE. Another group of animals was treated twenty four hours after PE. Control rats received treatment twenty four hours or five minutes before test. Latency to display immobility (LAT) and total time spent immobile (TSI) were registered and analyzed by One-way ANOVA followed by Duncan for each experimental protocol. Results: When given after PE, DPAT increased LAT (185±45) and decreased TSI (26.8±10.8) when compared to saline (LAT=58.9±14.1; TSI=91.2±7.2) or WAY (WAY+Sal: LAT=58.7±23.2; TSI=123.5±12.3) treated rats (LAT: F3,49=4; p<0.05; TSI: F3,49=6.2; p<0.05). This effect of DPAT was prevented by previous treatment with WAY (WAY+DPAT: LAT=131.3±36.4; TSI=80.4±22.6). Similar results were observed when treatment was performed before PE (LAT: Sal+DPAT=103±19.8; Sal+Sal=74.8±12.4; WAY+DPAT=184±20.7; WAY+Sal=76.7±11.7; F3,39=10.3; p<0.05) (TSI: Sal+DPAT=76.9±8.8; Sal+Sal=133.1±9.6; WAY+DPAT=51.1±11.6; WAY+Sal=102.8±33.8; F3,39=12.4; p<0.05). Although DPAT also increased LAT (172.3±21.9) and decreased TSI (27.1±9.7) when given before test in stressed rats, previous treatment with WAY did not block DPAT effects (LAT: Sal+Sal=108.4±15.5; WAY+DPAT=203.5±19.9; WAY+Sal=91.1±19.5; F3,40=7.5; p<0.05) (TSI: Sal+Sal=83.4±4.1; WAY+DPAT=17.6±4.1; WAY+Sal=58.9±17.5; F3,40=8.8; p<0.05). No effects of drugs were observed when treatment was performed in non-stressed rats (PE4: LAT: F3,29=1.7; p<0.05; WAY: LAT: F3,29=0.7; p>0.05; PE5: LAT: F3,22=1.7; p>0.05 TSI: F3,22=0.5; p>0.05). Conclusion: Our results suggest that 5-HT1aR localized in the MnRN are important in processes involving acquisition and consolidation of stressful memories, but not for retrieval. Affiliation: none. Financial Support: CAPES, CNPq and FAPESP.
Introduction: Postpartum depression (PPD) is the most serious postpartum disorder estimated to affect 10-15% of women after giving birth, although it is both under-diagnosed and under-treated. PPD interferes with the woman’s ability to care for her baby which can lead to adverse developmental effects. The mechanisms underlying PPD are unclear however; stress and/or fluctuations of stress hormones during pregnancy are thought to play a major role. The chronic mild stress (CMS) procedure is widely used as a model of depression in rodents. Here, we evaluated the impact of CMS applied to gestating female mice on a series of behavior tests relevant to maternal depression. Methods: 23 virgin B6D2F1 female mice were divided into a control (n=10) and stressed (n=13) group following a 3-day mating period. The CMS procedure involves the sequential application of mild stressors such as confinement, paired housing, cage tilt (30°) and was then applied until parturition. On postpartum day (PD) 1, the litters were equalized to 7 pups/female and maternal behavior was assessed through the pup retrieval test. Maternal anxiety was assessed on PD6 using the elevated plus maze. On PD23 to PD28, after weaning of the litters, locomotor and cognitive function were assessed in the open-field, novel object recognition and contextual fear conditioning tests. Results. Maternal behavior was unaffected by CMS since stressed and control dams did not differ for the latency to retrieve the first pup (p=0.28) and the whole litter (p=0.33) to the nest. On PD6, stressed dams showed increased locomotor activity (p=0.02) in the elevated-plus maze but no changes in anxiety-related behavior (p=0.32). Following weaning of the litters stressed dams showed reduced anxiety-related behavior (p=0.009) and increased locomotion (p=0.005) in the open-field on PD23. Cognitive function was not impaired in stressed dams which did not differ from control mice for object recognition memory (p=0.12) as well as acquisition (p=0.58), retention (p=0.46) and extinction (p=0.28) of contextual fear memory. Conclusion. Consistent with our previous work (Pardon et al. Biol Psychiatry, 2000, 47(10) 858-863), prepartum CMS did not alter maternal behavior in B6D2F1 dams. The procedure, however, induced a behavioral dishinhibition in anxiety-related tasks that persists for at least 23 days following termination of the stress. Cognitive performance was unaltered 24-28 days after prepartum CMS. This behavioral profile may reflect an altered response to stressful stimuli, as seen in depression.

TH18

EFFECT OF CHRONIC DELTA-9-TETRAHYDROCANNABINOL (DELTA-9-THC) ON THE REWARDING PROPERTIES OF SUCROSE

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Cannabis use has been suggested to lead to mental ill-health, including depression, one core symptom of which is anhedonia. On the other hand, it is suggested that cannabis use increases sensitivity to reward and thus acts as a gateway drug leading to use of other drugs of abuse. Research into the effects of delta-9-tetrahydrocannabinol (delta-9-THC) in reward processes has provided contradictory results in experimental animals. The aim of this project was to investigate the effects of THC on reward processes. First we aimed to validate the model of Conditioned Place Preference (CPP) to sucrose in mice and, if successful, to investigate the CPP to sucrose in chronically THC treated mice. A second aim of the study was to compare this with sucrose preference in THC treated mice. In order to validate the model of sucrose CPP, C57Bl6/J mice were conditioned to one side of the CPP box initially using sucrose pellets and, in a second series of trials, to condensed milk. A new group of mice was chronically treated over 21 days with delta-9-THC (1 or 5 mg/kg or vehicle; n=8/g) and their preference towards 1% sucrose solution over water was measured over a period of 5 days. Mice were individually housed and tested in their home cages. The sucrose solution bottles and water bottles were placed according to a randomised design and their position changed every day. Sucrose preference was determined by weighing the two bottles every 24 hrs and calculating the intake of sucrose solution as % total fluid intake. We found that a CPP to neither sucrose pellets nor sweetened condensed milk could be established. In the sucrose preference test, chronic treatment with delta-9-THC tended to increase the preference to sucrose over the 5 day experimental period (vehicle: 66.1 +/- 3.2%; 1 mg/kg delta-9-THC: 76.3 +/- 4.9%; 5 mg/kg delta-9-THC: 89.2 +/- 2.6%; values are mean of the 5 days +/- SE). This increase, however, missed significance at the 5% level (mixed 2-way ANOVA, effect of treatment: F(2,15) = 4.5, p=0.119). Further research into validating CPP to natural rewards would either require mice to be conditioned to a different rewarding substance or the making of methodological improvements to the paradigm. Results from the sucrose preference test suggest support for the cannabis gateway hypothesis rather than a depression-like effect, as mice chronically treated with delta-9-THC tended to increase their preference towards the sucrose solution rather than exhibiting anhedonia. This study was funded by a British Pharmacological Society Vacation Studentship and the British Association of Psychopharmacology in vivo training initiative vacation studentship.

TH20

ATTENTIONAL BIASES IN A CLINICAL POPULATION OF PATIENTS WITH ALCOHOL USE DISORDERS (AUDS): THE INFLUENCE OF DISORDER SEVERITY AND ABSTINENCE

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The incentive sensitisation theory predicts cues regularly associated with alcohol consumption acquire incentive motivational properties through the process of classical conditioning. This theory is supported by previous research using the modified Stroop and visual probe tasks (VPT) which suggest alcohol-related stimuli ‘grab’ addicted individual’s attention, resulting in an alcohol attentional bias (AAB). Participants at various stages of treatment were recruited from two community alcohol services for this study. Attentional bias to alcohol was assessed using modified Stroop and VPT computerised tasks. Details of participant’s clinical histories were obtained using a structured pro forma. Patients also completed the Alcohol Use Disorders Identification Test (AUDIT). Analyses examined the effect of AUD severity and abstinence on AAB. The two attentional bias tasks were compared to determine their concurrent validity. 123 participants (64.2% male) were recruited into the study. The mean age of all participants was 44.5 yrs and the mean duration of AUD was 15.5 yrs. 60.2% of participants reported abstinence at the time of participation, the median duration of abstinence was 56 days. Non-abstinent participants reported a median weekly consumption of 89.3 units of alcohol (IQR 32.5-187.3). Modified Stroop AAB score was calculated for the sample (M=7.30 milliseconds, SD=40.62ms). A one sample t-test showed the AAB score was significantly different from 0; t(116)=1.96, p=0.05. The same analysis performed for VPT AAB score (M=8.76 ms, SD=40.29ms) also indicated mean AAB score was significantly different from 0; (t(116)=2.35, p=0.02). Thus both attentional bias tasks indicated an overall attentional bias to alcohol words was present in this sample. The level of correlation between each participant’s AAB score on VPT and modified Stroop was found to be non-significant. No significant correlations were found between AAB and the drinking-related variables investigated (AUDIT score, duration of AUD or units of alcohol consumed per week). A split of the sample into participants who were drinking at the time of participation and those who were abstinent revealed drinkers demonstrated a significant AAB on the VPT (M=16.66ms, SD=43.03ms; t(44)=2.57, p=0.01) whereas abstinent participants did not (M=3.98, SD=38.00, t(71)=0.88 p=0.38). Participants who had been abstinent for 3 weeks or less had significant negative correlation between VPT AAB and length of abstinence (r=-0.78, p<0.01). This study provides evidence for the existence of an AAB in clinical populations with AUDs. Our findings suggest that with abstinence, AAB returns to non-significant levels and in the early stages of abstinence, reduces as a function of time.
TH21
ARE THERE PROGRESSIVE BRAIN CHANGES IN SCHIZOPHRENIA? A SYSTEMATIC REVIEW AND META-ANALYSIS OF STRUCTURAL MAGNETIC RESONANCE IMAGING STUDIES

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Background: It is well-established that schizophrenia is associated with structural brain abnormalities, but whether these are static or progress over time remains controversial. Method: A systematic search was conducted for published, longitudinal volumetric studies using region-of-interest structural MRI techniques in patients with schizophrenia and healthy controls. The percentage change in volume during the between-scan interval for each brain region under study was obtained, and Cohen’s estimator of standardised effect size, and its variance, was calculated. Data were then combined using random effects meta-analysis. Results: Twenty-seven studies were identified for inclusion in the meta-analyses, including a total of 1795 subjects (928 patients with schizophrenia and 867 healthy controls) and 32 different brain regions of interest. The length of time between baseline and follow-up MRI scans ranged from 1 to 10 years. Subjects with schizophrenia showed significantly greater decreases over time in whole brain volume (n = 14; difference: -0.40; 95% CI: -0.62, -0.19), whole brain grey matter (n = 12; difference: -0.52; 95% CI: -0.76, -0.28), pre-frontal lobe tissue grey matter (n = 9; difference: -0.34; 95% CI: -0.66, -0.02), parietal lobe white matter (n = 4; difference: -0.53; 95% CI: -0.84, -0.23) and temporal lobe white matter volume (n = 6; difference: -0.49; 95% CI: -0.76, -0.21) than healthy control subjects. They also showed larger increases in lateral ventricular volume over time than controls (n = 10; difference: 0.53; 95% CI: 0.28, 0.78). Conclusions: These findings suggest that schizophrenia is associated with progressive abnormalities of brain structure, affecting both grey and white matter. We found no evidence to suggest progressive medial temporal lobe involvement, which may be partly explained by heterogeneity between studies in the clinical parameters of included patients. The causes and clinical correlates of these changes should now be the focus of investigation.

PW1
STUDYING THE BIOLOGICAL PATHWAYS FROM STRESS TO PSYCHOSIS AND HOW THEY ARE INFLUENCED BY ANTISYPHOTIC TREATMENT IN FIRST-EPSODE PSYCHOSIS

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Introduction: High levels of stress have been widely reported in psychosis. The study of biological pathways influenced by stress is essential to understand how psychosis develops and to identify effective treatment strategies. Cortisol, pro-inflammatory cytokines and neurotrophic factors are among the main biological targets influenced by stress; changes in these markers can influence neurotransmission and neuroplasticity and ultimately play a role in the development of psychosis. The first aim of the study was to investigate the activity of biological pathways influenced by stress and their interplay in patients with first-episode psychosis and controls; the second aim of the study was to investigate how antipsychotic treatment affects these biological pathways in first-episode psychosis.

Methods: Seventy-first-episode psychosis patients (mean±SEM age: 27.6±0.7 years) and 63 healthy controls (26.5±0.6 years) were recruited. Salivary cortisol levels were measured at 0 minutes after awakening and at 12 and 8pm. Serum levels of IL-6, TNF-alpha and mRNA expression of IL-6, TNF-alpha and BDNF were assessed in both patients and controls. To test the effect of antipsychotic treatment, we assessed differences among patients with less and patients with more than two weeks of antipsychotic treatment and controls. Results: Patients had a trend for higher diurnal cortisol levels (d=0.35; p=0.09), higher levels of IL-6 (Cohen’s d=0.49; p=0.03) and TNF-alpha (d=0.50; p=0.02) and increased expression of IL-6 (d=1.1; p<0.001), TNF-alpha (d=1.7; p<0.001) and lower expression of BDNF (d=1.3; p<0.001) when compared with controls. In the patients’ group IL-6 expression was inversely correlated with BDNF expression (r=-0.331, p=0.02). Patients with less than 2 weeks of antipsychotic treatment had higher diurnal cortisol levels and higher IL-6 levels than controls (respectively d=0.5, p=0.02 and d=0.6, p=0.01). No significant difference in cortisol or IL-6 levels was found between patients with more than two weeks of antipsychotic treatment and controls. TNF-alpha levels and BDNF expression were not different between patients with less than two weeks and those with more than two weeks of antipsychotic treatment.

Conclusions: Biological pathways influenced by stress are significantly affected in patients with first episode psychosis. Enhanced inflammation could possibly contribute to a reduced BDNF expression. Our findings also suggest that the first two weeks of antipsychotic treatment can only partially restore these abnormalities in patients with first-episode of psychosis.

PW2
EXPLORATION BROADENS ONES HORIZON: INSIGHTS FROM THE CROSS-SPECIES TEST THE BEHAVIORAL PATTERN MONITOR

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Introduction: Exploration allows one to learn about one’s environment. Examining the manner of exploration can also provide information about the one exploring. This premise has been widely used in preclinical studies for many decades to delineate the various effects of modulating neurotransmitter systems. Since the 70’s the Behavioral Pattern Monitor (BPM) has utilized a multivariate approach toward quantifying the exploratory behavior of rats, including measures of: a) diverse exploration e.g. distance traveled; b) specific exploration e.g. holepoking and rearing; plus c) locomotor patterns including the fractal geometric path analysis spatial d. The BPM has provided insight into the diverse neurochemical effects of various stimulants. The BPM has now also been developed for use in mice and humans. There are a myriad of psychiatric disorders that exhibit altered activity, yet their quantification with translational potential has been limited. To date the human BPM has provided information on the altered exploration of patients with bipolar disorder (BD) mania and schizophrenia. These data have assisted in the development and refinement of animal models of BD with putative translational validity. Methods: Dopamine transporter (DAT) knockout (KD) mice have 10% DAT expression when compared to their wildtype (WT) littermates. These KD mice exhibit a phenotype in the mouse BPM that is consistent with the behavioral profile of patients with BD mania in the human BPM. Results: Specifically, increased specific and diverse exploration as well as lower spatial d is observed in both groups compared to controls. Interestingly DAT KD mice exhibit stimulant sensitivity when compared to WT mice, consistent with BD. Increased diverse exploration in DAT KD is attenuated with chronic valproate treatment when plasma levels reach the clinical therapeutic range. Chronic valproate did not remediate increased specific exploration or reduced spatial d however. This lack of efficacy in specific exploration is most poignant when coupled with the link between this measure in a) humans with frontal lobe dysfunction, and b) Wisconsin card sorting errors, c) COMT allele variation, as well as d) mice with increased risk taking as observed in the mouse Iowa Gambling Task. Conclusion: Reverse translation of the BPM has provided a means to quantify exploration across species leading to the identification of novel animal models of BD mania. In validating this model we have observed not only face and predictive validity, but also perhaps an insight into the importance of specific exploration in patients with BD mania. These studies were funded by R21-MH085221 (JWY) a NARSAD Young Investigators Award (JWY), the Veterans Affairs VISN 22 Mental Illness Research, Education, and Clinical Center (MG) and R01MH071916 (WP and MG).
PD1

PHARMACOLOGICAL REGULATION OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS ACTIVITY IN RAT

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Depression and other stress-related disorders are a major cause of disability and there is evidence implicating the hypothalamic-pituitary-adrenal (HPA) axis in the etiology of depression. Over-activity of the HPA axis is characterized by dysfunction of glucocorticoid receptor (GR)-mediated negative feedback. Furthermore, changes in the levels of vasopressin and the vasopressin V1b receptor regulating ACTH release have been found in depressed patients. We report the effects of recently developed modulators of the HPA axis activity in the rat. Specifically, we present the effects of a GR antagonist and a V1bR antagonist on the basal diurnal and ultradian rhythm of corticosterone release and on stress-induced activation of the HPA axis. Furthermore, the effects of a V1bR antagonist on chronic stress induced adaptation and the sensitization of the HPA axis to a subsequent exposure to stress are discussed. These data provide important information with respect to possible targets for future pharmacological intervention in man.

PD2

STRESS AND ITS CONSEQUENCES ON HPA AXIS ACTIVITY, INFLAMMATION AND BRAIN STRUCTURE IN FIRST EPISODE PSYCHOSIS

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Introduction: An excess of stressful life events has been suggested to contribute to the onset and clinical outcome of psychosis. The study of the main biological system involved in the stress response, the hypothalamic-pituitary-adrenal (HPA) axis, is relevant for a better understanding of how stress participate to the development of psychosis. Moreover, stress has been previously associated with increased inflammation and decreased hippocampal volume, but this association has never been investigated in first-episode psychosis. The first aim of the study was to investigate the association between stress and HPA axis activity in first-episode psychosis and healthy controls. The second aim of the study was to investigate if stress and HPA axis activity contribute to increased inflammation and decreased hippocampal volume in first-episode psychosis. Methods: We collected information about recent stressful life events and childhood trauma in 50 first-episode psychosis patients (mean±SEM age: 29.2±1.1 years; gender: 64% males) and 36 healthy controls (27.3±0.8 years; 72.2% males), using validated instruments. Salivary cortisol levels were measured at 0, 15, 30 and 60 minutes after awakening and at 12 and 2pm. Serum levels of IL-6, TNF-alpha and hsCRP were measured in both patients and controls. Hippocampal volume was measured by magnetic resonance imaging (MRI) in 24 of the same patients. An independent t-test was used to analyze differences between patients and controls. Parametric and non-parametric correlation analyses, as appropriate, were conducted to investigate the association between the different variables. Results: Patients had a significant blunted cortisol awakening response compared with controls (p=0.049). Diurnal cortisol levels were negatively correlated with number of recent stressful events (r=−0.36, p=0.01), and cortisol awakening response was positively correlated with history of sexual childhood abuse (r=0.33, p=0.03) in the group of patients. Patients showed higher levels of hsCRP (p=0.04), IL-6 (p=0.02) and TNF-alpha levels (p=0.005) than controls. Correlation analyses in the patient’s group showed a positive correlation between number of childhood trauma and hsCRP (r=0.43, p=0.03), and TNF-alpha (r=0.38, p=0.02); and a negative correlation between both cortisol and IL-6 levels with left hippocampal volume (respectively r=−0.45, p=0.03; r=−0.66, p=0.02). Conclusions: These findings suggest an abnormal HPA axis response to stress and a role of childhood trauma in the development of increased inflammation in first-episode psychosis. Moreover, high levels of cortisol and inflammation appear also to be associated with smaller hippocampal volume in first-episode psychosis and possibly explain cognitive dysfunction in these individuals.

PD3

CHANGES IN HPA AXIS, MEMORY AND EMOTIONAL PROCESSING IN YOUNG PEOPLE AT RISK OF DEPRESSION

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A number of relevant neurobiological abnormalities are reliably seen in patients with acute depression. These include exaggerated hypothalamic-pituitary-adrenal (HPA) axis activity, impaired declarative memory, diminished hippocampal volume and dysregulation of the frontal-limbic circuitry involved in emotional processing. Intriguingly all these abnormalities have now been reported in recovered depressed patients. There are two main explanations for the latter phenomena. On the one hand, they might represent a “scar” of illness. On the other, they may be true “vulnerability” markers, that is, trait abnormalities which predate the onset of depression. Another interesting line of enquiry is how far these changes might be a reflection of persistent cortisol hypersecretion, because excessive cortisol is known to be associated with impaired memory and reduction in hippocampal volume, though its effects on the neural basis of emotional processing have not been much explored. Our work has focused on carrying out similar neurobiological investigations in young people who have never been depressed but who are at increased familial risk of depression by virtue of a history of parental depression (FH). The presence of similar abnormalities in this group of subjects would suggest that they are indeed trait markers of vulnerability to illness. Our findings have shown that, compared to age-matched, non-vulnerable controls, FH participants demonstrate (i) elevated waking salivary cortisol; (ii) impaired declarative memory; (iii) decreased volume of the right hippocampus; and (iv) decreased cortical-limbic regulation following an aversive emotional stimulus. We also found hyperactivation of the neural circuitry supporting working memory, an abnormality similar to that reported in acutely depressed patients. Our findings suggest that young people at risk of depression manifest several abnormalities that resemble those seen in patients with established depression. These changes therefore are not necessarily correlated with the presence of depressive symptomatology but might instead predispose to depressive illness by impairing subtle aspects of cognition (for example, decision making) and diminishing the ability to regulate negative affect. A further intriguing question is whether some of these abnormalities are a direct consequence of persistent cortisol hypersecretion. A larger study is now underway to test this hypothesis specifically.
PD4

IMPROVING NEUROPSYCHOLOGICAL FUNCTION IN BIPOLAR DISORDER WITH ANTIGLUCOCORTICOIDS

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Patients with bipolar disorder (BD) show significant impairments in a broad range of neuropsychological processes. Recent evidence has also shown that individuals exhibit hypothalamic-pituitary-adrenal (HPA) axis dysfunction and hypercortisolaeinia. Cortisol is known to modulate memory processes, as described in a number of animal and human models and therefore administration of treatments that regulate HPA axis function may be beneficial. Data will be presented from a program of research into the effects of mifepristone (RU-486), a glucocorticoid receptor antagonist, in bipolar depression. Pilot data from a crossover study in 20 patients indicated that adjunctive administration (600mg/day for 1 week) selectively improved spatial memory processes compared to placebo (19.8% improvement over placebo); an effect recently confirmed in a larger parallel group design. These findings have been extended using a novel object-location memory paradigm (Kessels RPC, et al. Behavior Research Methods, Instruments, & Computers 31:423-428;1999) to explore the selectivity of these effects within different spatial memory processes. These results will be discussed in terms of the efficacy of this treatment approach in bipolar disorder and also increasing our understanding of the role of glucocorticoids in cognitive processing.

GL1

FROM IMPULSIVITY TO COMPULSIVITY; TOWARDS A MULTIDIMENSIONAL PSYCHOPHARMACOLOGY

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Seismic shifts in the neuroscience programmes of ‘big Pharma’ demand re-appraisals of the role of psychopharmacology in drug discovery. A major issue has been the poor predictability of animal models. Another has been the profligacy of Phase 3 trials which have often been handicapped by heterogeneous patient samples occluding possible benefits in patient sub-groups. Big Pharma have also been reluctant to take on novel or ‘difficult’ targets such as addiction. This lecture will illustrate how a careful study of new forms of drug addiction could possibly inspire a new approach to drug discovery. Addiction has arguably the most effective animal model available, intra-venous drug self-administration, although there is, of course, more to addiction than drug self-administration. Impulsivity, the tendency to respond prematurely without foresight for possible adverse consequences is a plausible endophenotype for addiction, but it is difficult to be sure whether impulsivity is produced by drug-taking or is predisposing to it. Impulsivity can be measured in animal models in which premature responding occurs in a 5-choice serial reaction time task. There is evident individual variability in premature responding, with a bimodal distribution of high and low impulsive individuals. The impulsivity is not simply a product of poor learning, impaired timing or novelty reactivity (which has been related to ‘sensation-seeking’), and is also exhibited in a temporal discounting paradigm by steeper discounting functions, as also occurs in drug abusers. The high impulsive rats have a propensity for enhanced cocaine self-administration in an escalation paradigm measuring drug-taking binges. They also exhibit changes in dopamine D2/D3 receptor binding, even prior to drug exposure. This result is comparable to other findings with rhesus monkeys and also in drug addicts. It is significant that we have also found reductions in D2/D3 binding in humans linked to impulsivity on the Barrett Scale. Not only do the high impulsive rats take more cocaine, they also develop compulsive patterns of self-administration, which has supported a hypothesis that addiction, at least to stimulants, occurs as a consequence of a transition from impulsive to compulsive modes of responding. This definition of dimensions of behaviour, such as impulsivity and compulsivity, may help refocus drug discovery on symptoms rather than diagnostic categories. I will explore implications of this viewpoint with studies in experimental medicine relevant to the treatment of addiction, attention-deficit hyperactivity disorder and obsessive compulsive disorder, in which the dimensions of impulsivity or compulsivity are predominant.

SO01

POSITIVE EFFECTS OF THE NICOTINIC CHANNEL BLOCKER TC-5214 AS AUGMENTATION TREATMENT IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER WHO ARE INADEQUATE RESPONDERS TO A FIRST-LINE SSRI

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Introduction Step 1 of the STAR*D trial demonstrated a poor (36.8%) remission rate following citalopram monotherapy and in Step 2 the possible relative superiority (35% vs. 27%) of augmentation over switching (Rush et al, 2006, Am. J. Psychiat. 163, 1905-1917). It has been postulated modulation of the neuronal nicotinic receptor could have antidepressant properties (Shytle et al, 2002, Molecular psychiat. 7, 525-535). TC-5214 is a non-competitive nicotinic channel blocker that modulates different forms of the α4β2 neuronal nicotinic receptor subtype in distinct ways (Fedorov et al, 2009, J. Pharmacol. Exp. Therapeut. 328, 1-8). TC-5214 is active in preclinical models of depression (Lippiello et al, 2008, Cns neuroscience. therapeut. 14, 266-277). Methods in the present study, an initial 579 patients received 8 weeks open label treatment with the SSRI citalopram hydrobromide. Patients with an inadequate response (n = 270) were randomized to 8 weeks double blind treatment with add-on TC-5214 or add-on placebo. Dosage of TC-5214 could be increased from 1 mg bid to 4 mg bid at the investigator’s discretion. The trial was undertaken at 20 sites in India and 3 sites in the USA. The primary outcome measure was mean change from week 8 to week 16 on the hamilton depression rating scale-17. Possible treatment differences were assessed using analysis of covariance (ANCOVA) with treatment as a main factor and baseline depression as a covariate. Results There was a highly statistically significant advantage (p<0.0001) in favor of TC-5214 + citalopram over placebo + citalopram on an intent to treat basis. Secondary measures assessed depression, irritability, disability, cognition, severity of illness and global improvement. A highly statistically significant advantage for TC-5214 + citalopram was also seen over placebo + citalopram on all of these secondary measures. The TC-5214 + citalopram treatment combination was generally well tolerated. The most common adverse events for TC-5214 + citalopram in excess of placebo + citalopram were headache, constipation and dizziness, all of which were seen in less than 10% of patients and were of mild to moderate intensity. Conclusions The results of the study, together with earlier results from a very similarly designed citalopram augmentation trial with racemic mекamylamine, demonstrate the potential for modulation of neuronal nicotinic receptors in the brain as augmentation to first-line therapy as a new treatment paradigm for depression. Declaration: The trial was funded by and G C Dunbar MD works for Targacept Inc. Winston Salem, NC, 27104, USA.
Introduction step 1 of the STAR*D trial demonstrated a poor (36.8%) remission rate following citalopram monotherapy and in step 2 the possible relative combination was generally well tolerated. The most common adverse events for TC-5214 + citalopram in excess of placebo + citalopram were headache, significant advantage for TC-5214 + citalopram was also seen over placebo + citalopram on all of these secondary measures. The TC-5214 + citalopram treatment depressed disorder who are inadequate responders to a first-line SSRI.

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The high impulsive rats have a propensity for enhanced tendency to respond prematurely without foresight for possible adverse consequences is a plausible endophenotype for addiction, but it is difficult to be sure of "big Pharma" demand re...
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