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S01

INDIVIDUALISED PREDICTION OF FUNCTIONAL OUTCOMES IN EARLY PSYCHOsis: FIRST RESULTS FROM PRONIA: MULTIMODAL, MULTI-SITE MACHINE LEARNING ANALYSIS

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Introduction: The clinical high-risk state for psychosis does not only confer an elevated risk for developing psychotic disorders but is associated with pluripotent risks for adverse clinical and functional outcomes. Establishing generalizable tools that provide quantitative risk estimates for these outcomes is a key step toward the implementing personalized preventive intervention that scale to clinical real-world settings.

Methods: The talk will present recent findings from the PRONIA study (Personalised Prognostic Tools for Early Psychosis Management) demonstrating the feasibility of predicting functional and clinical outcomes in adolescents and young adults in a clinical high-risk state for psychosis or with recent-onset depression. The talk will highlight the use of machine learning and multivariate data mining concepts and link those applications to potential clinical utility of these models for an improvement of early recognition and prevention.

Results: I will present and discuss the performance and decision rules generated by the machine learning analysis of clinical, imaging-based, genetic and combined data for the individualized prediction of (1) social and role functioning outcomes, (2) transition to psychosis, and (3) remission vs. non-remission from symptomatic states in CHR and ROD patients.

Conclusions: The recent findings generated by the PRONIA consortium suggest that generalizable and clinical useful prediction pathways can be established to support the early recognition of adverse outcomes in CHR and ROD patients. External and prospective validation of these prognostic pathways is needed across healthcare systems to benchmark the clinical and health economic utility of these precision psychiatry methods.

Funding: European 7th Framework Programme, Grant Agreement 602152

S02

PREDICTING OUTCOMES IN PEOPLE AT CLINICAL HIGH RISK FOR PSYCHOsis

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Introduction: A key challenge in the management of people at clinical high risk for psychosis is that it is difficult to predict whether they will recover, have persistent symptoms, or develop a first episode of psychosis. This issue can be addressed by identifying biomarkers that can help to predict clinical outcomes in this group.

Methods: People at clinical high risk for psychosis were recruited using standardised criteria across multiple sites and assessed using environmental, cognitive, neuroimaging and peripheral blood measures. Subjects were then followed up to determine clinical outcomes. The relationship between these measures and symptomatic remission, level of functioning and transition to psychosis was then examined.

Results: The onset of psychosis was associated with baseline alterations in hippocampal volume and glutamate levels, and with elevated subcortical dopamine function, and with longitudinal changes in these measures. The later onset of psychosis was also linked with baseline differences in the levels of proteomic, metabolomic and inflammatory markers.

Conclusions: These data suggest that biological measures may be useful in predicting clinically meaningful outcomes in psychosis. Current work aims to develop tools that can facilitate the integration of these measures to permit individual outcome prediction in a clinical setting.

Funding: MRC, Wellcome Trust, EU Framework 7
COMORBID DEPRESSION PHENOTYPES: RESULTS FROM PRONIA

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Introduction: Major depressive disorder is one of the most common mental health disorders with considerable impact and significant life limitation. Depression is also the most common co-morbidity seen in schizophrenia: reported occur in 40% to 80% of individuals. When psychosis and depression co-occur outcomes are worse: with increased relapse, higher risk of suicide, greater substance-related problems and poorer recovery. There remains significant debate around the heterogeneity and specificity of depressive symptoms, and their significance within diagnostic structures. Neuroimaging and data science hold some potential to address the challenge of co-morbidity; to further understand the influence and position of depressive features in emerging mental disorders.

Methods: Cross sectional descriptive data from the EUFP7 funded PRONIA study (n716) from participants with recent onset depression (ROD), clinical high risk (CHR) and recent onset psychosis (ROP) are used to demonstrate the prevalence and clinical impact of depression across diagnostic groups together with exploratory factor analysis of individual depression items. Further, to test the hypothesis that the ‘weight’ of clinical importance remains with the primary diagnostic group, supervised machine learning classification algorithms were developed using common clinical symptoms seen across depression and psychosis phenotypes (anhedonia, social functioning, cognition), sMRI and a combined model. This was developed in groups without co-morbidity (‘pure’) and tested in co-morbid groups with primary diagnosis as the classification outcome.

Results: Factor analysis of depression symptoms suggests a classical phenotype with CHR groups more similar in phenotypic signature to ROD than ROP. In ‘pure’ ROP and ROD groups, nested pooled cross validation with classifiers of clinical variables predicted primary diagnostic group with a balanced accuracy of 80%. When applied to co-morbid groups, the model’s balanced accuracy fell to 61%. The majority of patients in the ROP with depression group were misclassified to the ROD diagnostic group. In sMRI data, ROP patients showed pronounced difference in the thalamus and the cerebellum, whereas ROD patients showed orbitofrontal, limbic and paralimbic volume reductions; this was seen only in groups without co-morbidity. In co-morbid groups, classification neuroanatomical was only the same as chance. In the combined models, neuroimaging did not add any significant classification accuracy to clinical data.

Conclusions: Results presented have important implications for the accurate identification depression as a potentially malleable target for treatment in early psychosis. The concept of depression as a ‘co-morbidity’ is also challenged- affective dysfunction may be at the centre of the development of psychotic disorders yet is currently hidden by hierarchical diagnostic models. Results lend support towards where a more individual approach, able to capture complexity, seen as the norm.

Funding: PRONIA is a Collaborative Project funded by the European Union under the 7th Framework Programme (grant 602152).
**S04**

**EXPANDING THE SCOPE – MACHINE LEARNING PREDICTION OF OUTCOMES IN TRANSDIAGNOSTIC YOUTH**

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Introduction: Mental health problems typically arise during adolescence and young adulthood, and put those who experience them at greatly increased risk for poor functional outcomes. In the early phase of illness most presenting problems are non-specific, and predicting likely outcomes at the individual level has not been possible.

Methods: We developed prognostic models to predict symptomatic (K10) and functional (SOFAS) outcomes at 12-month follow-up, using data from 507 individuals recruited to the Transitions study from four headspace sites in Melbourne and Sydney. Specifically, we aimed to predict those individuals with K10>25 and/or SOFAS<70 at follow-up (referred to as ‘poor outcome’) with a support vector classifier generated from extensive clinical data (both interview and self-report), and further explored this prediction using support vector regression models. Following identification of a single optimal model jointly predicting K10 and SOFAS outcomes, we tested its generalizability against an independent validation sample (TransitionsUK) of 75 young people recruited from the Youthspace clinic in south-west Birmingham, UK and followed up at 3, 6, and 12 months.

Results: From those predictive models explored, optimum performance was achieved using direct-stacked, multi-dimensional, support vector machines, while linear decision surfaces were retained for interpretability. Classifiers were assessed using cross-validation of Transitions data alone (with nested cross validation for any hyper-parameter selection) indicating possible accuracy scores of around 65-70% for both targets, with consistently lower accuracy for K10 targets than SOFAS. Classifiers were retrained using the full Transitions data set for both component assessment and prediction of the TransitionsUK data. Baseline features with the greatest predictive value included subclinical psychotic symptoms as well as depression scores and measures of social support. The classifier demonstrated reasonable external validity, with an accuracy of 70% for K10 and 72% for SOFAS.

Conclusions: Individual prediction of symptomatic and functional outcome using support vector machines could lead to improved engagement and better targeting of therapeutic interventions in youth mental health. The contribution of subclinical psychotic symptoms to prediction indicates the value of assessing these in general youth mental health settings, even when psychosis prediction is not the specific outcome of interest. The ability of our classifier to generalize to individuals assessed in a different healthcare system and without consensus inter-rater training suggests that this approach could be feasibly implemented internationally.

Funding: NHMRC Program Grant 566529 NHMRC Clinical Career Development Award 628711

**S05**

**TAINI - AN ULTRA-LIGHTWEIGHT WIRELESS NEURAL RECORDING SYSTEM FOR IMPROVED RESEARCH AND 3RS OUTCOMES IN ELECTROPHYSIOLOGY**

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(1) As presenting author

Introduction: Recent advances in the development of transgenic mice have provided unprecedented insight into the mechanisms of brain function and human disease processes and led to a dramatic shift from rats to mice as the preferred preclinical model used in drug discovery. But, understanding brain function at the cell and circuit level requires the representation of neuronal activity through multiple recording sites and at high sampling rates. The ability to make direct electrophysiological recordings from populations of neurons requires multiple parallel recording channels and high sampling-rates in order to properly characterize action potentials. The circuitry required is consequently energy-intensive,
traditionally requiring a multi-wire tether to provide power and to carry the analogue signal to the recording equipment. While, being very disruptive, this is still practical in larger rodents, but it presents a serious burden for a mouse due to its smaller size.

Methods: The research team addressed these issues by creating a size-record-breaking wireless neural monitoring system. The system, TaiNi, is wireless, weighs ~1.5g, and is able to provide 16-channels of continuous brain monitoring in several animals simultaneously for over three days.

Results: The lightweight resulted in significant improvements in the ability to complete trials on the T-maze task compared to the most similar commercially available alternative. While the relatively unimpaired animals showed no concomitant reduction in the percentage of correct choices on the T-maze task, the ability to complete additional trials increases statistical power and reduces the number of animals required for a given experiment.

Conclusions: The 3Rs impact of this new system includes less handling of animals, and the associated stress, due to its 72-hour battery life, and more freedom of movement for the animals due to the system’s low weight. In addition, apart from the placement of a single mobile receiver, it is not necessary to modify the animal cage at all. This allows straightforward, fast transfer between experimental protocols without reinvestment in new cages. TaiNi represents a significant advance in both animal welfare in electrophysiological experiments and the scope for continuously recording large amounts of data from small animals. TaiNi is now a commercial system and widely available to neuroscientists around the world.

Funding: Development of the TaiNi system at Imperial College London was funded by the NC3Rs Crack-it program.

S06
HOME CAGE MONITORING TO GET A BETTER UNDERSTANDING OF BEHAVIOUR AND ITS RELEVANCE TO HUMAN CONDITIONS
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Conventionally the assessment of phenotype and welfare of mice used in pre-clinical studies is monitored through daily cage side assessment, where the animal carer examines the animals in the cage and only opens it if there is cause for concern or at cage changing. Whilst this is a very effective way of identifying obvious deviations from the normal such as wounds and weight loss, more subtle indicators of developing or improving phenotypes can be missed altogether. It is also important to note that mice are nocturnal animals; therefore most behavioural phenotypes may actually be expressed in the dark phase when there are no animal carers to observe them. Remote home cage monitoring can over-come these issues and identify new, potentially clinically relevant phenotypes and welfare concerns earlier and provide a much more detailed characterisation of the pre-clinical model. Here we discuss examples and demonstrate the utility of using home cage monitoring mouse welfare, collecting scientifically relevant data at earlier time points allowing earlier capture of data and husbandry interventions.

Funding: Medical research council and NC3Rs

S07
PSYCHOPHARMACOLOGY - ENHANCING RESEARCH OUTCOMES BY APPLYING THE 3RS: THE USE OF INDUCED PLURIPOTENT STEM CELLS FOR NEUROPSYCHIATRIC RESEARCH
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“Man is the experimental animal of the 21st Century”, said Nobel Laureate Sydney Brenner in 2000. Indeed, it has been proposed that to better understand the basis of human disease we need to understand human cells and this is especially true when we consider the study of the human cerebral cortex and neuropsychiatric disorders. Animal models have traditionally been used in psychopharmacology studies yet cortex development and organisation is very different in animal models compared to humans. For
example, the outer subventricular zone (OSVZ) of the cerebral cortex, which is only present to a limited degree in rodents, is populated by a unique stem cell subset termed outer radial glia (oRG) that allow for the expansion in neuronal output and brain size seen in humans. Therefore, neurodevelopmental disorders cannot be consistently recapitulated in animal models. Furthermore, efforts have been made by the research community to replace, reduce and refine (the 3Rs) this use of animals. In this talk, I will explore how implementing new technologies can impact the 3Rs. Specifically, I will present examples of how stem cell-based technologies for neuropsychiatric research hold much promise for the future and discuss examples from my own research where these technologies have already been used to elucidate pathways and mechanisms underlying complex human genetic and neurodevelopmental disorders such as schizophrenia, intellectual disability and autism. By generating platforms of human induced pluripotent cells (hiPSCs) from patients with these disorders, who are known to have genetic variants associated with increased risk of disease, we have undertaken comparative studies between mutant and control cell lines and directly compared our findings with human brain imaging from the same patients from whom the cellular materials were derived. Furthermore, we have also been able to utilise these in vitro disease models to rescue the phenotypes both genetically and pharmacologically. These studies show as a proof-of-principle that patient-derived stem cell models hold much promise to probe the mechanistic underpinnings of these disorders. Studying neurodevelopmental disorders in both two-dimensional and three-dimensional in vitro cultures can teach us fundamental aspects of the development of the human cortex, that are beyond reach in current animal model systems.

Funding: This research was funded by a Clinical Research Career Development Fellowship from The Wellcome Trust to MJ (103406/Z/13/Z) and The RS Macdonald Charitable Trust, and The Sackler Foundation.

S08
TOUCHSCREEN TECHNOLOGY AS A REFINEMENT FOR RODENT BEHAVIOURAL ASSESSMENT
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Rodent behavioural models represent a valuable platform from which insights into the neurobiology underlying neurodegenerative and neuropsychiatric diseases can be derived. Such models also offer important opportunities for the preclinical evaluation of promising pharmacological interventions. Successful translation of findings from these models into the clinical environment remains challenging and the disparity between the cognitive assessments used in the preclinical laboratory and in the clinical context is often considered a critical barrier in translational pipelines. The continuing improvements in touchscreen computing have enabled the development of a range of cognitive assessments for use in both humans and rodent models. This computerised approach has facilitated improved harmonisation of cognitive assessment across species and may in turn enhance translational efficacy. In tandem with these translational research-related outcomes, implementation of touchscreen assessment in rodents has also yielded a range of important 3Rs-related benefits for preclinical behavioural research. In this talk I will present a summary of the key features of the rodent touchscreen cognitive assessment approach and the associated 3Rs-related impacts, focusing on recent work concerning the optimisation of a range of motivation and affective state-targeted assessments. The potential for these assessments to be co-opted for use in rodent welfare evaluation and as an approach for best practice characterisation will also be outlined.

Funding: Elements of the presented research were funded by an NC3Rs Project Grant (NC/N001451/1).

S09
NEURAL AND EMOTIONAL RESPONSES TO ANTIDEPRESSANTS
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Introduction: Antidepressants affect how we process emotional information prior to clinically reported changes in symptoms. These early changes may be important as a mechanism of antidepressant drug action and are associated with later clinical response. Such effects may provide an experimental medicine model to test out candidate treatments for depression prior to full scale clinical trials, allowing key
questions regarding dose, likely efficacy and patient group to be addressed.

Methods: This talk will consider the body of evidence characterising the early effects of antidepressant
drugs on emotional processing using fMRI and cognitive measures. Initial attempts to use these as
intermediate outcomes in drug development will also be considered. The obstacles to this kind of
application will be reviewed as well as the potential steps we need to make to overcome them.

Results: larger scale studies are needed to refine the criteria for accepting a potential drug as a candidate
for future studies in depression. Further work on understanding the different components of depression
such as negative affect and anhedonia are needed. Models need to be validated across centres and with
with an understanding of different dose-relationships.

Conclusions: There is potential for the use of human experimental medicine models to characterise drug
treatments early in development; to improve the design of subsequent randomised controlled trials and to
prioritise the most promising agents. However, the evidence base needs to be more comprehensive with
preset criteria and a knowledge of how this relates to different symptom clusters in depression.

Funding: MRC, NIHR Oxford Health BRC

S10
IMAGING BIOMARKER CANDIDATES FOR RESPONSE TO ANTIDEPRESSANT TREATMENT
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Major depression is a heterogeneous disorder which is not linked to aetiology, and treatment selection
for an individual patient often seems like a case of trial and error. A well replicated finding has been that
increased anterior cingulate activity is predictive of clinical response to treatment, in particular in the
pregenual anterior cingulate which has been observed under numerous task conditions. This talk will
present how baseline predictors of clinical outcome reflect factors which indicate the general likelihood
of response to a variety of treatments and those which are selective for a particular form of treatment.
Irrespective of the mechanism of treatment, the capacity for response will moderate the outcome. If there
is an inherent capacity, then there would be general predictor of clinical responsivity to current first line
treatments. Inherent models of interpersonal relationships could be associated with genetic risk load
and represented by patterns of functional and structural neural correlates as a predictive biomarker.
The absence of such marker/s would indicate a reduced likelihood of response. There could also be
independent markers of treatment resistance, in which the treatment-resistant forms of depression
could be identified in the first episode or early in the course of illness. Methods that directly address
heterogeneity are essential in which a synergistic combination could bring together data-driven inductive
and symptom-based deductive approaches.

Funding: Rosetrees Trust, Wellcome Trust

S11
CHALLENGES AND OPPORTUNITIES FOR IDENTIFYING NEUROIMAGING MARKERS OF MAJOR
DEPRESSIVE DISORDER
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Introduction: Despite intensive genetic and neuroimaging research in the past decades, we still have a
limited understanding of the neurobiological mechanisms underlying Major Depressive Disorder (MDD),
hampering the development of more effective strategies to treat this debilitating psychiatric disorder. This
limited progress is partly due to a lack of reproducible findings and underpowered studies, resulting in
false negatives and a potential exaggeration of true effect sizes. One approach to tackle these issues is the
worldwide pooling of existing genetic and/or neuroimaging datasets. This is done within the Enhancing
NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium, which makes use of harmonized
protocols to process neuroimaging data prior to meta- or mega-analysis, thereby reducing heterogeneity between studies. The Major Depressive Disorder working group within the ENIGMA consortium aims to identify robust patterns of brain alterations associated with MDD and to test their replicability and reliability across many different samples (and scanners) worldwide. At this time the working group includes neuroimaging data from ~4,000 MDD patients and ~9,000 healthy participants from 39 different samples worldwide. During this talk, recent findings from the ENIGMA MDD working group will be presented and opportunities and challenges of large-scale data sharing initiatives such as ENIGMA MDD for identifying neuroimaging biomarkers of MDD will be discussed.

Funding: The ENIGMA-Major Depressive Disorder working group gratefully acknowledges support from the NIH Big Data to Knowledge (BD2K) award (U54 EB020403 to Paul Thompson) and NIH grant R01 MH116147 (Paul Thompson)

S12
THE ROLE OF NEUROIMAGING IN PROGNOSTIC STRATIFICATION OF MAJOR DEPRESSIVE DISORDER
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Introduction: Depression is a leading cause of disability, mainly because of recurrent major depressive (MDD) episodes. Why some patients experience recurring MDD whilst others remain well is poorly understood. Identifying the neurocognitive mechanisms of how MDD evolves from its asymptomatic precursors and predicting recurrence risk will enable the development of better treatments and improve long-term outcomes. Yet, translating group level predictors into clinically relevant risk prediction models at the individual level remains challenging. We have previously described that patients with MDD show biases towards blaming themselves for failure (Zahn et al., European Psychiatry, 2015). We have identified the associated neural network including anterior temporal and limbic forebrain regions (Green et al. Arch Gen Psych, 2012) and shown its predictive value for recurrence risk in remitted MDD (Lythe et al., 2015). Yet, estimating the generalisability of predictive values from a given dataset cannot be achieved using standard statistical approaches.

Methods: Using our previously published data in medication-free patients with remitted MDD with clinical follow-up over 14 months to determine recurrence (Lythe et al., JAMA Psychiatry, 2015), we employed a statistical/machine learning approach, called elastic-net regularised logistic regression with 10-fold nested cross-validation. The elastic net is a machine learning extension of logistic regression which alleviates overfitting by shrinking the regression coefficients towards zero and thus provides automatic variable selection by omitting some predictors. The nested cross-validation is vital to provide realistic estimates of out-of-sample prediction accuracy and thereby estimate “internal validity”.

Results: We compared 4 prediction models 1) Clinical Only, 2) Adding a novel cognitive task to clinical information which probes self-blame-related action tendencies such as feeling like creating a distance from oneself, 3) Adding self-blame-related fMRI betas from a priori ROIs to clinical information, and 4) Information from all modalities (n=50). As expected, the “all modalities” model produced the best predictive effects with 83% accuracy (cross-validated positive PV=83%, negative PV=79%, sensitivity=67%, specificity=90%). Relying solely on standard clinical and psychological measures, previously associated with vulnerability to MDD, achieved a poor predictive accuracy of 62% in keeping with most previous literature showing that clinical predictors are inaccurate. We found that adding information either from fMRI or our novel cognitive task, the accuracy improved to a similar degree (added fMRI: 68%, added cognitive task: 71%).

Conclusions: Clinical information alone is probably insufficient to predict recurrence risk, although a recent study by Ruhe et al., (Frontiers in Psychiatry, 2019) showed remarkably high predictive accuracy when including childhood trauma into the prediction model. fMRI made an important contribution to achieving individual level prediction of recurrence risk in our study. Future studies are needed to replicate this result in a larger independent sample.

Funding: MRC, NIHR BRC for Mental Health at the Maudsley
S13
USING STEM CELLS TO EXPLORE THE GENETICS UNDERLYING NEUROPSYCHIATRIC DISEASE
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Introduction: Schizophrenia (SZ) is a debilitating psychiatric disorder for which the complex genetic mechanisms underlying the disease state remain unclear. Whereas highly penetrant variants have proven well-suited to human induced pluripotent stem cell (hiPSC)-based models, the power of hiPSC-based studies to resolve the much smaller effects of common variants within the size of cohorts that can be realistically assembled remains uncertain. We consider the successes and limitations in applying human induced pluripotent stem cell (hiPSC)-based models to study the impact of rare and common variants in SZ risk.

Methods: We reprogrammed fibroblasts from patients and controls into hiPSCs and subsequently differentiated these disorder-specific hiPSCs into neural progenitor cells (NPCs) and neurons, with the objective of better understanding how both rare and common variants contribute to SZ risk. To facilitate isogenic analyses of the impact and penetrance of rare and common variants across genetic backgrounds, we integrated CRISPR-mediated gene editing, activation and repression technologies with our hiPSC-based neural platform, developing a scalable system to test the effect of manipulating the growing number of SZ-associated variants and genes in NPCs, neurons and astrocytes.

Results: First, to explore the neuronal impact of rare variants, we investigated the relationship between heterozygous 2p16.3 deletions, alternative splicing of NRXN1, and perturbations in neuronal activity, finding some commonalities with idiopathic SZ. We identified ~100 NRXN1α isoforms in control hiPSC neurons; patient-derived 2p16.3 neurons show perturbed NRXN1 isoform repertoires, reduced neuronal branching and decreased neuronal activity, which unexpectedly can be partially ameliorated by overexpression of a single NRXN1 isoform. Second, we present a genetics-driven hiPSC-based CRISPR-mediated approach for the functional validation of common variants and genes associated with SZ, evaluating the impact of one putative causal SZ SNP (FURIN rs4702) and two SZ-associated genes (SNAP91 and TSNARE1) on global gene expression patterns and synaptic function.

Conclusions: We predict a growing convergence between hiPSC and post-mortem studies as both approaches expand to larger cohort sizes. We demonstrate a systematic and scalable strategy to interpret and evaluate the growing number of SZ-associated variants and genes across neural cell types and genetic backgrounds. Altogether, our objective is to dissect the genetic origins of SZ while developing a precision medicine approach to screen for novel therapeutics with which to prevent or reverse disease course.

Funding: NIMH, NYSCF, BBRF, BRF

S14
USING PATIENT-DERIVED INDUCED PLURIPOTENT STEM CELLS TO UNDERSTAND THE BENEFICIAL EFFECTS OF OESTROGENS IN SCHIZOPHRENIA
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(1) As presenting author

Introduction: Recent clinical studies have demonstrated that adjunct treatment with oestradiol, the main biological oestrogen, or the selective oestrogen receptor modulator (SERM) raloxifene, ameliorate positive and negative symptoms, and improves working memory and attention deficits in male and female schizophrenic patients. However, how these oestrogenic-compounds exert their beneficial effects are not fully understood. This is in part, owing to a lack of animal and cellular models which capture the complexities of this disorder to study the effects of oestrogenic-compounds in a disease context. Critically, oestrogenic-based compounds are not an effective long-term treatment options owing to a number of side effects. Thus, determining how oestradiol exerts its positive effects in a disease may aid in the development of safer and effective oestrogenic-based compounds.
Methods: To gain an insight into how oestrogenic-compounds may be beneficial in schizophrenia, we have used human induced pluripotent stem cell (iPSC)-derived from healthy individuals or patients diagnosed schizophrenic. Interestingly, oestradiol has repeatedly been shown to exert powerful influences over cognitive domains including learning, attention as well as anxious and depressive behaviours. These cognitive enhancing effects have been shown to be dependent on modulating the structure and function of glutamatergic synapses. Thus, we have focused on determining whether oestradiol and raloxifene can modulate glutamatergic synapses in neurons from healthy or patient iPSCs (iPSC-neurons).

Results: iPSC derived from healthy and schizophrenic patients were successfully differentiated into immature cortical neurons. This was confirmed by the demonstrating that both healthy and patient iPSC differentiated into neuroepithelium, neural progenitors cells and finally into TBR1- and EMX1-positive neurons efficiently. Characterisation of patient iPSC-neurons displayed a divergent gene expression profile, as expected from a polygenic disorder. Patient iPSCs exhibited altered expression of synaptic protein indicating potential deficits in synaptic function. Treatment of iPSC-neurons from healthy donors demonstrated that oestrogens were able to modulate neuronal structure, as well as to modulate the expression of specific synaptic genes. We further have explored the ability of oestrogens to rescue cellular and molecular deficits in iPSC-neurons derived from schizophrenic patients. Critically, treatment of patient iPSC-neurons with oestradiol or raloxifene increased in synaptic protein expression to a level similar to that observed in untreated healthy iPSC-neurons was observed.

Conclusions: These data demonstrate that oestrogens are capable of modulating synaptic proteins in human neurons taken from schizophrenic patients. Moreover, this study exemplifies how iPSC-based cellular models could be used to further understand how potential therapeutic agents exert their beneficial effects in a cellular model that recapitulates the complex genetic architecture associated with polygenic disorders.

Funding: Brain and Behavior Research Foundation; MRC

S15

MODELLING NEUROINFLAMMATION USING HUMAN INDUCED PLURIPOTENT STEM CELL-DERIVED MICROGLIA

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Human induced Pluripotent Stem Cells offer unparalleled opportunities to study cellular physiology and pathology in vitro using authentic human, karyotypically normal, fully differentiated cells. We are interested in using this technology to model the cellular processes that underpin neurodevelopmental and neurodegenerative diseases. Microglia are increasingly implicated in neurodevelopment, where they play a role in synaptic pruning. They are also implicated in degenerative conditions, including Alzheimer’s disease (AD) and Parkinson’s disease (PD), with numerous disease-associated genes being expressed in microglia/macrophage lineages. We have previously pioneered protocols for the efficient differentiation of macrophages from induced Pluripotent Stem Cells. We have adapted these protocols for modelling microglia, skewing patient iPSC-derived macrophages to microglial phenotypes by coculture with iPSC-derived neuronal cultures. The system allows analysis of macrophage/microglia activation and its role in neuronal cell survival/death, both via cytokine release and direct cell-cell interaction, using patient-derived and gene-edited iPSC.

Funding: Parkinson’s UK
S16
ANALYZING THE ROLE OF INTERNEURON MIGRATION IN HUMAN NEUROPSYCHIATRIC DISORDERS USING FUSED BRAIN ORGANOIDS

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(1) As presenting author

The etiology of many neuropsychiatric disorders is thought to arise from an imbalance of excitatory and inhibitory activity within neural circuits. Recent research specifically implicates defects in the development of GABAergic interneurons which are responsible for inhibitory neural circuit function. A crucial feature of interneuron development is their long distance migration from subcortical into cortical brain regions. Although defects in interneuron migration are implicated in neuropsychiatric diseases such as Epilepsy, Autism, and Schizophrenia, model systems to study this process in humans are currently lacking. To fill this gap we recently developed a novel 3D in vitro brain organoid co-culture model of human interneuron migration. By combining separate dorsal and ventral forebrain organoids through organoid fusion, we recreated interneuron migration from ventral into dorsal forebrain regions. These migrating interneurons can produce various interneuron subtypes, and live-imaging analysis shows features consistent with tangential interneuron migration. Moreover, our previous results showed reduced migration through drug-induced inhibition of chemotaxis receptors, which highlights the utility of this system for drug-screening. Following our previous efforts, we refined the genetically encoded reporter strategy to label particular subpopulations of cells within brain organoids. By combining fluorescent cell sorting with both bulk and single-cell RNAseq, we find that the migrating interneurons express many psychiatric disease-associated genes, as well as exhibit subtype diversity. Using genome engineering CRISPR/Cas9 technology, we generated cells containing loss of function mutations in disease-relevant genes to test the role of these genes in human interneuron migration. Our brain organoid model provides the exciting opportunity to study neural cell biology in developmental human brain tissue with patient-specific genetic backgrounds. This approach further brings the power of genome editing and genetically encoded fluorescent reporters to a human experimental model of brain development.

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S17
TRANSGENERATIONAL AND EPIGENETIC EFFECTS OF PRENATAL IMMUNE ACTIVATION

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Introduction: Non-genetic transgenerational transmission of behavioral traits has gained increasing recognition in view of its potential importance in the etiology of multi-factorial psychiatric disorders. Here, we explored whether maternal immune activation (MIA), which is a known risk factor for various neuropsychiatric and psychiatric disorders, can induce pathological effects across multiple generations.

Methods: We used an established MIA model that is based on maternal exposure to the viral mimetic poly(I:C) in mice (C57BL6/N). First-generation (F1) MIA offspring and control offspring were either assigned to behavioral testing when they reached adult age, or they were used as breeders to obtain second- (F2) and third- (F3) generation offspring. Adult F2 and F3 offspring were then also assigned to behavioral testing. In addition, we performed next-generation mRNA sequencing and epigenetic analyses in all generations so as to explore the molecular mechanisms of non-genetic transgenerational inheritance.

Results: Compared to F1 control offspring, F1 MIA offspring showed a number of behavioral
abnormalities, including reduced sociability in the social interaction test, impaired sensorimotor gating in the prepulse inhibition test, and increased sensitivity to the dopamine-stimulating drug, amphetamine. While F2 and F3 offspring of MIA-exposed ancestors similarly showed deficits in sociability, they developed novel phenotypes that were not seen in F1 MIA offspring, including blunted amphetamine sensitivity (p<0.05), behavioral despair in the forced swimming test (p<0.05), and cognitive deficits that depend on the integrity of the medial prefrontal cortex. Contrary to the F1 generation, F2 and F3 offspring of MIA-exposed ancestors also displayed transcriptional abnormalities in the prefrontal complement system, leading to increased expression of C1q protein on presynaptic terminals and loss of presynaptic markers such as synaptophysin and bassoon. Finally, a number of epigenetic changes were detected in both sperm and brain tissue, the latter of which partly reflected the corresponding transcriptional changes in F1 and F2 generations.

Conclusions: MIA can cause non-genetic transgenerational inheritance under controlled experimental conditions. Moreover, this form of early-life adversity can lead to modification of pathological phenotypes across generations. The further identification of epigenetic and transgenerational effects of prenatal adversities such as in-utero immune exposure appears relevant to brain disorders independently of existing diagnostic classifications and may help identifying complex patterns of transgenerational disease transmission beyond genetic inheritance.

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S18

CHILDHOOD ADVERSITY AND PSYCHOsis: THE POTENTIAL ROLE OF EPIGENETICS

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Psychotic symptoms are common during adolescence and include paranoid thoughts, hearing or seeing things that others do not, and believing that others can read one's mind. Adolescent psychotic symptoms are often distressing and highly predictive of schizophrenia, other psychiatric disorders, and suicide attempts in adulthood. Thus elucidating early risk indicators is crucial to target prevention efforts. Indeed, exposure to adversity early in life, such as physical or sexual abuse, neglect, bullying by peers, and witnessing domestic violence, appears to play an aetiological role in the development and persistence of psychotic symptoms and disorders. However, psychotic symptoms often appear several years after adversity exposure suggesting that indirect risk pathways must be operating. Greater understanding of the underlying mechanisms would provide invaluable opportunities for intervention. One potential risk pathway is via dysfunctional changes in epigenetic processes. Epigenetics involves reversible modifications to DNA, histone proteins and chromatin structure that influence the regulation of gene expression and which may ultimately impact on brain development and how we perceive the world. Epigenetic variation has been found in adults with a history of abuse compared to unexposed controls and young twins discordant for bullying, as well as in genetically-identical twin children discordant for psychotic symptoms and adult twins discordant for clinically-relevant psychosis. Thus epigenetic pathways between early adversity and psychotic symptoms seem plausible and will be discussed as a potential mechanism through which the social world can get under the skin to influence the development of psychosis.

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S19
FOXO1 AND IMMUNE RELATED PATHWAYS AS NOVEL VULNERABILITY SIGNATURE FOR GxE INTERACTION IN DEPRESSION

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Introduction: Several studies have underscored a strong heritable component in psychiatric disorders, that, however, cannot be only attributed to genetics only. The “missing heritability” may be covered by environmental factors and by the interaction between environment and the genome. Epigenetic changes have been suggested to be major actors in such phenomena and they may also underlie the different responses to stress. To date, GxE interaction studies have been limited to hypothesis-based candidate genes, since genome-wide (GWAS)-based GxE interaction studies would require enormous datasets with genetics, environmental and clinical variables.

Methods: During the talk, I will show data obtained from a novel approach, a cross-species and cross-tissues “omics” approach, that we used to identify novel genes predicting depression in response to stress in GxE interactions. In particular, we integrated the transcriptome and miRNome profiles from the hippocampus of adult rats exposed to prenatal stress (PNS) to identify top-hit genes that were both modulated by PNS exposure and also targeted by the miRNAs that were modulated by PNS. To translate findings from animals to humans, we integrated the top-hit genes in PNS animals with transcriptome data obtained from blood samples of control subjects exposed to childhood trauma.

Results: We identified overlapping genes across the different species and tissues, which were involved in several biological pathways including those related to inflammation and Glucocorticoid Receptor Signaling. A network analyses on the overlapping genes identified one cluster of highly interacting genes which were: Forkhead box protein O1 (FOXO1), Alpha-2-Macroglobulin (A2M) and Transforming Growth Factor Beta 1 (TGFB1) that were suggested to act as vulnerability genes for depression development upon stress exposures. Importantly, when we tested FOXO1, A2M and TGFB1 for GxE interactions in the two clinical cohorts we indeed observed that several SNPs within all the three genes showed significant GxE interactions with emotional abuse in both the clinical cohorts.

Conclusions: We therefore provide a successful ‘hypothesis-free’ approach for the identification and prioritization of candidate genes for GxE interaction studies that can be investigated in GWAS datasets.

Funding: The work was funded by Italian Ministry of Health and by ERANET Neuron to AC.

S20
ROLE OF FKBP5 IN THE LINK BETWEEN PSYCHOSOCIAL STRESS, INFLAMMATION, AND DISEASE RISK

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Introduction: Psychosocial stress and aging are associated with increased inflammation and disease risk, but the underlying molecular mechanisms are unclear. Because both stress and aging are also associated with lasting epigenetic changes, a plausible hypothesis is that stress along the lifespan could confer disease risk through epigenetic effects on molecules involved in inflammatory processes.

Methods: The effects of aging and stress-related phenotypes on FKBP5 DNA methylation were examined with the Infinium HumanMethylation450 BeadChip, and identified CpGs were further validated with targeted bisulfite sequencing. Genome-wide gene expression data were measured using Illumina HumanHT-12 v3 and v4 Expression BeadChips. Cell culture experiments were performed in peripheral blood mononuclear cells from healthy donors, as well as Jurkat, THP-1, or IMR-90 cell lines.

Results: Across independent human cohorts (total n > 3,000), aging synergized with stress-related phenotypes, measured with childhood trauma and major depression questionnaires, to epigenetically
upregulate FKBP5 expression. These age/stress-related epigenetic effects were recapitulated in a cellular model of replicative senescence, whereby we exposed replicating human fibroblasts to stress (glucocorticoid) hormones. Unbiased genome-wide analyses in human blood linked higher FKBP5 mRNA with a proinflammatory profile and altered NF-κB-related gene networks. Accordingly, experiments in immune cells showed that higher FKBP5 promotes inflammation by strengthening the interactions of NF-κB regulatory kinases, whereas opposing FKBP5 either by genetic deletion (CRISPR/Cas9-mediated) or selective pharmacological inhibition prevented the effects on NF-κB. Further, the age/stress-related epigenetic signature enhanced FKBP5 response to NF-κB through a positive feedback loop and was present in individuals with a history of acute myocardial infarction, a disease state linked to peripheral inflammation.

Conclusions: These findings suggest that aging/stress-driven FKBP5-NF-κB signaling mediates inflammation, potentially contributing to disease risk, and may thus point to novel biomarker and treatment possibilities.

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S21
PRACTICALITIES OF PRESCRIBING: ADHD GUIDELINES AND BEYOND
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Introduction: Several ADHD guidelines have been published and updated over the last years: BAP 2014, RCPsych Scotland 2017, CADDRA 2018, NICE 2018 and ENAA 2019.

Methods: Algorithms for the pharmacological treatment of ADHD in young people will be summarised and compared.

Results: All guidelines recommend the treatment with stimulants like methylphenidate and lisdexamfetamine as first-line approach. Non-stimulants like atomoxetine and bupropion are third-line options. Patients with ADHD transitioning from CAMH to adult services are often on combinations of medications, including guanfacine and melatonin, which have no positive evidence for adults with ADHD. Titration regimens for prescribed stimulants vary in RCTs, guidelines and in clinical practice. NICE 2018 recommend slower titration for patients with co-morbidities.

Conclusions: The evidence-base for treatment of patients with ADHD and comorbid anxiety, Emotional unstable personality disorder (EuPD), autism spectrum disorder (ASD) and substance use disorder (SUD) is limited, so that guidelines have to rely on expert consensus. The practicalities of prescribing ADHD medications for athletes, members of faith groups, perinatal women and men who have sex with men (MSM) will be discussed as examples of clinically relevant scenarios that are not covered by most guidelines.

Funding: No sponsorship

S22
ADHD AND STIMULANTS IN UNIVERSITY STUDENTS
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How is it possible for a young person with ADHD to get into and graduate from a Russell Group university? I will talk about university students with ADHD as a group of young people transitioning into adulthood and their patterns of substance misuse. This is a relevant topic for prescribing practitioners who raise
concerns about university students malingering with ADHD to get a diagnosis and prescription for stimulants. University students coin stimulant medications used for the purpose of enhancing academic performance as “study drugs”, “smart drugs”, “brain dope” or “academic steroids” (Sedgwick, 2018). I will present evidence for the efficacy of stimulant medications in improving academic performance in students with ADHD and discuss the controversial issues of diversion, non-medical and pro re nata (PRN) uses of these drugs.

Funding: N/A

S23
SUPPORTING FAMILIES WITH ADHD FROM ADOLESCENCE TO ADULTHOOD
Bilbow A, London
No abstract provided for this session

S24
SOMATIC CONDITIONS ASSOCIATED WITH ADHD: EVIDENCE, MECHANISMS, AND IMPLICATIONS FOR THE CLINICAL PRACTICE
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Recently, it has become clear that many conditions classically thought to be nervous system disorders also include alterations in other physiological systems. This has prompted a line of research on the possible association between neuropsychiatric and somatic conditions. Within this framework, there has been an increasing body of research on somatic disorders related to ADHD. In my talk, I will review the evidence on the association between ADHD and major somatic conditions, such as obesity, asthma, and cardiovascular diseases. I will highlight the relevance of this association for the daily clinical management of ADHD and for the understanding of the pathophysiology of the disorder, with a particular focus on possible pro-inflammatory mechanisms.

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S25
adolescent Brain development: Risk taking
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Introduction: Adolescence is associated with major changes in hormone levels, brain function and social environment. One of the major changes in behavior is an increase in risk taking behavior. Risk taking is an important public health issue, in that risk taking during adolescence can result in both short-term and lifelong negative consequences. However, it is unknown exactly which mechanisms give rise to increased risky decision making in adolescence.

Methods: In this talk I will show data from recent studies investigating how changes in testosterone levels, striatum responses to rewards and peer influence are related to risky decision making. These studies employ a combination of neuroimaging methods and a decision science approach.

Results: The results of these studies show that neural responses to rewards peak in adolescence and that this neural activation is positively related to testosterone levels and real life risk taking behavior. Peers are an important influence on risky decision making and different types of peer influence have different effects on risky decision making.

Conclusions: The ultimate goal of this work is understanding which developmental processes underlie increases in risky decision making and how these processes lead to health risk behavior in adolescence.

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S26
ARE ADOLESCENTS MORE VULNERABLE TO ACUTE AND CHRONIC EFFECTS OF CANNABIS USE?
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In recent decades it has become clear that the brain continues to develop throughout adolescence. Alongside clear behavioural and cognitive changes, dramatic functional and structural changes occur in the teenage brain, with development extending into early adulthood. With these revelations has come increased concern about the potentially harmful effects of adolescent substance use, and in particular cannabis use, on typical developmental trajectories. Acutely, cannabis leads to pleasurable subjective feelings (“being stoned”), but can also lead to transient cognitive impairment and psychotic-like experiences. Furthermore, cannabis users are often found to have impaired cognitive abilities relative to non-using controls, alongside an increased risk of psychotic disorders, and it has been suggested that earlier age of cannabis use may result in a greater risk of these putative harms. In this context, I will present data from our lab investigating whether cannabinoids do indeed have differential effects on adolescent and adult humans. I will first present results from a double-blind placebo-controlled study comparing acute effects of cannabis in adolescents and adults. Next I will present preliminary data from our ongoing multi-study project ‘cannTEEN’, in which we are utilising both behavioural and neuroimaging methodologies in a longitudinal design to investigate whether cannabis use in adolescence is related to altered developmental trajectories.

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S27
ALCOHOL AND THE ADOLESCENT BRAIN
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Adolescent alcohol use is a major public health problem. Risky drinking during adolescence is associated with other adolescent risk-taking behaviours and a wide range of adverse outcomes in the physical health, psychological, social and behavioural domains. The adolescent brain is vulnerable to the effects of alcohol, with girls being at particular risk. Early adolescent alcohol use increases the risk of developing alcohol dependence in adulthood and is also associated with the emergence of adult mental health problems, co-morbid substance use disorders and suicidality. It is important to monitor trends in this field to understand the influence of digital technology and how best to implement interventions.

Funding: N/A

S28
CAUSAL RELATIONS BETWEEN BRAIN STRUCTURE AND PERSONALITY DEVELOPMENT DURING ADOLESCENCE, AND THE INCREASE OF BINGE DRINKING
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Introduction: There is a correlation between increase in binge drinking (BD) and grey matter (GM) development in healthy adolescents, but its directionality remains unknown. We determined the directionality of the association between GM development and increase of BD in the 726 participants of the IMAGEN prospective cohort of healthy adolescents recruited from 8 European centers.

Methods: BD and personality were assessed at 14 years (Baseline), 16 years (Follow-up 1) and 19 years (Follow-up 2). Structural brain imaging measures were acquired at BL and FU2. We controlled for gender, site, socio-economic status, family-history, puberty, negative life-events, personality, cognition and polygenic-risk-scores were controlled. Directionality of the relationship relies on four complementary approaches: 1) causal Bayesian networks; 2) time precedence of the cause over the effect; 3) longitudinal prediction of the increase of binge drinking from grey matter volumes at 14 years; 4) Analysis of quantitative dose response relationship. Main outcomes included increase of BD frequency (latent growth-modelling), voxel-wise grey matter development (tensor-based morphometry). The hypotheses were formulated before data analysis.
Results: Increase in BD was associated with accelerated GM atrophy in the left posterior temporal cortex, right posterior-temporal cortex and left pre-frontal cortex. The CBN revealed that a directionality from GM development to BD increase. Accelerated GM atrophy in the late bingers compared to the sober controls), the association of BD increase with GM volume at 14 years and the absence of dose-response relationship also suggest the directionality of the association suggested by CBN. This GM development pathway was predominant in girls while an independent, impulsivity-related, pathway was predominant in boys.

Conclusions: In our sample, alcohol drinking in normal adolescents does not affect GM development. Instead, we describe structural brain and cognitive developmental trajectories in boys and girls that result in increased BD.

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S29

CHALLENGES AND OPPORTUNITIES OF FMRI IN TRANSLATIONAL PHARMACOLOGICAL RESEARCH

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Functional MRI (fMRI) has been applied to pharmacological research in humans for approximately 20 years and has yielded a wealth of valuable information concerning the systems-level effects of drug administration on task-related brain activity and, more recently, resting-state connectivity. However, traditional blood oxygenation level dependent (BOLD) fMRI has some uncertainties over the interpretation of signal changes observed. These uncertainties derive from the mixed nature of the physiological changes that contribute to the BOLD signal, including cerebral blood flow (CBF), cerebral blood volume (CBV) and the rate of cerebral metabolic oxygen consumption (CMRO2), along with the need to assume a stable coupling between neural activity and the haemodynamic response (neurovascular coupling). There are opportunities to aid interpretation of pharmacological fMRI using multi-modal approaches by incorporating receptor-based studies with PET, and electrophysiological approaches such as electroencephalography (EEG) and magnetoencephalography (MEG) to reveal changes in neuronal activity. As an alternative, or in addition, more quantitative versions of fMRI are becoming available based on CBF, using arterial spin labelling techniques, as well as relative changes in, and absolute levels of, CMRO2. These techniques are showing promise in the assessment of pharmacological effects (Germuska & Wise 2019 Neuroimage 187:145-153) in neuroscientific studies and as biomarkers for drug and disease effects. In this presentation we will discuss, in particular, the methodology for advancing pharmacological fMRI and its applications such as those in which there are combined effects on the neuronal activity levels and haemodynamic behaviour (Merola et al 2017 Neuroimage 155:331-343).

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S30

INVESTIGATION OF SSRI EFFECTS USING HYBRID PET/MR IMAGING

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Introduction: Given the prevalent use of selective serotonin reuptake inhibitors (SSRIs) in psychiatry, characterization of their effects using brain imaging is eminent as it might help to elucidate the mechanisms contributing to the alleviation of symptoms and lead to the identification of early markers for long-term treatment response. Hybrid PET/MR imaging allows for the association of simultaneously acquired data on brain function and target engagement during drug challenge, potentially increasing the specificity and sensitivity of pharmacological responses.

Methods: Using hybrid PET/MR imaging the acute response of brain activation and networks was
measured simultaneously with the occupancy of the serotonin transporter (SERT) after a single infusion of 8mg citalopram. Each subject underwent two scans and received citalopram or placebo during either their first or second session, in a randomized placebo-controlled cross-over study design (Gryglewski G et al, 2019, European Neuropsychopharmacology, in press). The SERT specific tracer [11C]DASB was applied as bolus plus constant infusion. Functional MRI was acquired for 40 minutes during which subjects were instructed to keep their eyes open and let their mind wander. Drug infusion was performed over 8 minutes starting 10 minutes into resting state scans.

Results: 38 healthy subjects (21 female) completed both measurements successfully. Average SERT occupancy in the thalamus was 69% (SD 7%). Dynamic occupancy was calculated from [11C]DASB time-activity curves and used as a regressor for modeling of the fMRI signal. In separate analyses, regressors corresponding to the cumulative dose applied and citalopram plasma levels were used. Paired t-tests did not identify any regions with significant differences in regression coefficients between placebo and citalopram scans after correction for family-wise error. Furthermore, no significant differences in deviation of average fMRI signal from baseline in any 2 minute time-bin acquired during or after drug challenge were found between scans.

Conclusions: The fact that no effects on brain activation measured using fMRI could be detected despite of occupancy of the majority of SERT sites is in line with the lack of subjective effects of SSRIs in the time-frame of 40 minutes. Preliminary analyses indicated alterations in functional connectivity potentially reflecting the influence of SSRIs on neuromodulation which might not manifest in absolute changes in fMRI signal.

Funding: This project was supported by a grant from the Else Kröner-Fresenius-Stiftung (2014_A192) and was funded partly through a research agreement between the Medical University of Vienna and the Siemens Healthcare GmbH. It was carried out with the support of the Medical Imaging Cluster (MIC).

S31

DRUG FINGERPRINTING OF RS-FMRI NETWORKS USING NORMATIVE POPULATION-BASED PET MAPS

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Introduction: One of the main limitations of pharmacological-fMRI is its inability to provide a molecular insight into the main effect of compounds. To address the open question on the relationship between drug effects and haemodynamic response, we propose a novel multimodal method (Receptor-Enriched Analysis of functional Connectivity by Targets - REACT) to enrich the resting-state fMRI (rs-fMRI) analysis with the information about the distribution of specific targets in the brain. We used REACT to explore the acute effects of 3,4-methylenedioxymethamphetamine (MDMA) on functional connectivity (FC), given its known multiple serotonergic actions.

Methods: Rs-fMRI images were acquired from twenty healthy volunteers under placebo and MDMA. An in vivo atlas of four serotonin receptors (5-HT1A, 5-HT1B, 5-HT2A, and 5-HT4) and its transporter (5-HTT) was used as a template in a two-step multivariate regression analysis to estimate the spatial maps reflecting the whole-brain FC related to each target under the two conditions. An additional analysis was done by including in the model the maps of the targets to which MDMA has a higher affinity (i.e., 5-HT1A, 5-HT2A and 5-HTT) and their products, in order to look for interactions related to their co-localisation. The spatial maps of the two conditions estimated in the main and in the interaction analyses were then compared.Linear relationships were also tested between the FC maps and pharmacokinetic levels of MDMA and changes in oxytocin plasma levels 45 (PK45 and ΔOXT45) and 165 (PK165 and ΔOXT165) minutes after the dose administration.

Results: The networks exhibiting significant changes after MDMA administration are the ones informed by the main targets of this compound (i.e. 5-HTT and 5-HT1A). Changes in the 5-HT1A-enriched FC maps were also associated with PK45. The interaction analysis confirmed the main results and highlighted other FC changes in the maps derived by the 5-HT1A–5-HT2A interaction. Significant correlations were found between increased ΔOXT165 and MDMA-induced FC decreases in the 5-HT1A, 5-HT1A–5-HTT and 5-HT1A–5-HT2A–5-HTT maps.
Conclusions: By enriching the rs-fMRI analysis with molecular data of the distribution of serotonin receptors across the brain, we showed that MDMA effects on FC can be understood through the distribution of its main targets. This result supports the ability of this method to characterise the specificity of the brain functional response to MDMA binding to serotonergic receptors, paving the way to the definition of a new fingerprint in the characterization of new compounds and potentially to a further understanding to the response to treatment.

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S32
COUPLING OF NEUROVASCULAR RESPONSE AND RECEPTOR OCCUPANCY WITH SIMULTANEOUS PET/fMRI
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Introduction: Neurovascular coupling to receptor occupancy has been shown to occur for antagonist and agonist drugs specific to the D2/D3 dopamine receptor system using simultaneous receptor-specific PET and fMRI measurements. In this study, we extend this concept to current third generation antipsychotic drugs that are classified as partial agonists at the D2/D3 dopamine receptor. Our goal was to characterize the in vivo functional response at D2/D3 receptors of partial agonists in the context of full D2/D3 antagonists and agonists using simultaneous PET/fMRI.

Methods: Dynamic [11C]raclopride PET (specific to D2/D3 dopamine receptors) and fMRI were acquired in two anesthetized non-human primates (rhesus macaque) on an integrated PET/MR scanner. The antipsychotic aripiprazole was injected intravenously as a within-scan challenge at ~35 minutes and/or 70 minutes after radiotracer injection. Comparisons were made to two full antagonists (prochlorperazine, raclopride) and two agonists (ropinirole, quinpirole). Gradient-echo EPI was acquired throughout the dynamic PET acquisition of 100 minutes. Before each scan, iron oxide was injected to improve fMRI contrast and detection power. fMRI data were analyzed with the GLM and cerebral blood volume (CBV) changes were derived. PET data were analyzed with a simplified reference tissue model (SRTM) that included a term for dynamic binding changes and used the cerebellum as the reference tissue in order to determine receptor occupancy.

Results: The full agonists consistently showed a negative response and full antagonists a positive CBV response in the striatum. Interestingly, the atypical antipsychotic aripiprazole showed an overall positive CBV response that was markedly lower in magnitude, despite higher D2/D3 receptor occupancy, compared to the full ant-/agonist. D2/D3 occupancy values for the three doses of aripiprazole were 49%, 74% and 92% in the putamen. Simultaneously acquired %CBV values were not significant for the lowest dose of aripiprazole, but showed positive %CBV of 1.2% and 4.5% for the two higher doses in the putamen. A neurovascular coupling model that demonstrates how the efficacy of drugs affects the CBV response in relation to a simulated occupancy timecourse can help interpret a classification of drug classes using PET/fMRI.

Conclusions: The atypical antipsychotic aripiprazole showed partial agonist characteristics, with antagonism being the dominant functional readout. Together with the results from full agonist and antagonists, this brings together a comprehensive dataset that shows that the combination of PET/fMRI can be used to classify D2/D3 drugs according to their in vivo pharmacodynamic profile. Our in vivo results agree with classifications from in vitro studies, but will be especially useful for drugs that are classified as partial agonists or atypical and may not have a defined functional response in vivo.

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S33
OVER EXPRESSION OF SCHIZOPHRENIA SUSCEPTIBILITY FACTOR C4A PROMOTES SYNAPTIC LOSS AND BEHAVIOR CHANGE
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The complement component C4 gene has been implicated in both schizophrenia and synaptic refinement. While it is tempting to hypothesize that C4-mediated synaptic refinement leads to schizophrenia, it has not been proven. To address this, we generated BAC DNA transgenic mice expressing human C4A and C4B. We found that C4A, but not C4B, is required for normal synapse refinement and binds more efficiently than C4B to synapses. Importantly, the over expression of C4A in the mouse brain induces excessive synapse loss and increased microglia-mediated synapse elimination. Cognitive and social mouse behavior were also altered with increased C4A expression. These results strongly suggest that enhanced complement C4A-mediated synaptic pruning causes abnormal brain development.
Funding: National Institutes of Health, USA

S34
THE COMPLEMENT SYSTEM IN DEMENTIA
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Introduction: The complement system plays critical roles in development, homeostasis and regeneration in the central nervous system (CNS) throughout life; however, complement dysregulation in the CNS can lead to inflammation, damage and disease. A role for complement as a driver of inflammation in dementia has emerged in recent years from a combination of genetic studies, cerebrospinal fluid (CSF) and plasma biomarker measurements, pathological analyses and evidence from animal models.
Methods: Here I will focus on roles of complement in Alzheimer’s disease (AD), the commonest type of dementia and a huge and growing health burden.
Results: I will describe the evidence implicating complement and discuss how this evidence might be used to design better diagnostics, predictors and therapies for this devastating disease.
Funding: Dementia Research Institute UK

S35
COMPLEMENT C3 AND C3AR DIFFERENTIALLY IMPACT LEARNED FEAR AND INNATE ANXIETY
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Introduction: Alterations in the immune system, in particular the complement system, may contribute to psychiatric and neurodegenerative disorders. Altered emotional function is a pervasive and clinically important symptom that is comorbid across several psychiatric disorders. While links between inflammation and emotional function have been established there has been little investigation of the specific influence of complement. We used knockout mouse models to investigate the role of the central complement component, C3, and the C3a receptor (C3aR) in emotional behaviours. Upon activation, C3 is cleaved to produce the fragment C3a, which binds to the C3a receptor (C3aR). Since C3 cleavage is the sole
source of C3a, and C3aR is the canonical receptor for C3a, we hypothesised that any phenotypes dependent on the C3a-C3aR pathway would be present in both models.

Methods: Wildtype, C3/-, C3aR/- and C6/- mice (male, 3-8 months of age) were tested in a battery of behavioural tests. The elevated plus maze (EPM) and elevated zero maze (EZM) were used to assay innate anxiety, whereas fear potentiated startle (FPS) was used to probe conditioned/learned fear. Blood was collected 30 minutes post-EPM for measurement of plasma corticosterone. The anxiolytic drug diazepam (2mg/kg) was used to probe sensitivity of anxiety phenotypes to benzodiazepines. Wildtype mice received doses of SB290157 (10mg/kg) to determine whether acute antagonism of the C3aR was sufficient to produce anxiety phenotypes.

Results: C3aR/- mice but not C3/- mice demonstrated profound anxiety phenotypes in both the EPM and EZM, paralleled by enhanced corticosterone levels in C3aR/- mice post-EPM. Anxiety-like behaviour in C3aR/- mice was not reduced by diazepam, at a dose that was anxiolytic in wildtype mice. Furthermore, administration of the C3aR antagonist SB290157 in wildtype mice did not phenocopy C3aR/- mice. In contrast to the findings on innate anxiety, C3/- mice, but not C3aR/- mice, showed enhanced reactivity to a conditioned aversive stimulus measured by FPS. Using C6/- mice, we probed downstream complement pathways responsible for the C3-specific effects on conditioned fear and excluded contributions from the terminal pathway, C6 to C9.

Conclusions: Our findings indicate an unexpected double dissociation in that deletion of C3aR resulted in a selective enhanced innate anxiety phenotypes and stress responses to anxiety-provoking stimuli whereas deletion of C3 selectively influenced learned fear responses. These findings provide evidence for dissociable effects of closely related complement pathways in aspects of emotional reactivity relevant to psychiatric disorders. Our findings also indicate novel roles of the C3aR that are independent of C3a.

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S36

COMPLEMENT AS A THERAPEUTIC TARGET IN INFLAMMATORY DISEASE

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Despite a wealth of knowledge in the complexities of the complement cascade, and many decades of endeavour, very few drugs have progressed to the clinic. Recently, strong genetic associations of complement with common diseases have emerged and fuelled the fire of complement drug discovery leading to an explosion in complement therapies in development; while many of these agents and others before them have failed to progress, their legacy is key to future success. Obstacles to successful drug development include target concentration and turnover rates, and ability to target to the appropriate site. The drug development landscape is littered with agents that have failed at the preclinical or early clinical stage; their modes of action and modalities are wide-ranging. It is becoming increasingly clear that an understanding of disease mechanism and matching of drug modality and mode of action to the right disease and patient population (or stratified sub-population) is critical to success. A number of drugs are now in phase 3 clinical development for a number of different diseases. In this talk, innovative approaches that are emerging to overcome obstacles blocking success will be explored, highlighting drugs in development which employ new state-of-the-art strategies. These include ‘homing’ drugs and a new generation of orally bioavailable molecules. Complement biomarkers that can decipher disease mechanism and be applied for patient stratification will be discussed. It is clear that a range of different drugs, or combination of drugs, will be needed for effective management of the many and diverse complement-mediated diseases.

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**S37**

**COMPLEX DECISIONS IN SIMPLE MINDS: STUDYING MODEL-BASED COGNITION IN RODENTS**  
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Humans and other mammals are thought to employ multiple action selection systems that use distinct computational strategies. Habitual actions comprise direct mappings from particular stimuli or states of the world to behavioural responses. By contrast, goal-directed actions are mediated by internal models of the world that predict the consequences of action, allowing flexible behaviour to satisfy current goals. A growing body of evidence indicates that model-based action selection is impaired in a range of psychiatric disorders. However, though we have a reasonable computational and mechanistic understanding of simple stimulus-response behaviours, a comparable understanding of model-based action selection is lacking. In this talk, I will describe the development of behavioural paradigms in rodents in which the contribution of model-based decision making to behaviour can be isolated, while generating large behavioural datasets well suited for quantifying and manipulating brain activity. One approach we and other groups have used are decision tasks inspired by the ‘two-step’ task developed by Nathaniel Daw and colleagues, which has been widely applied in human clinical populations. The behaviour of rodents on these tasks looks broadly similar to that of humans, and exhibits characteristics consistent with model-based decision making. However, animals learn these tasks very differently - by trial and error over many sessions rather than explicit instruction. I will discuss some ambiguities about whether apparently model-based rodent behaviour on two-step tasks is generated by the same mechanisms as overtly similar human data. I will also briefly outline a second, novel maze-based approach, which we believe holds much promise for investigating planning mechanisms in the brain. Together, these provide a foundation that, with care, can enable us to probe model-based decision mechanisms in rodents in a manner that can also be translated back to humans.

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**S38**

**PREDICTIVE CODING AS A FRAMEWORK FOR UNDERSTANDING PSYCHOSIS**  
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The term psychosis refers to an altered model of reality which may arise across a range of circumstances and with a large set of possible underlying causes. It is important to remember that the term is descriptive, referring to the presence of an array of altered perceptions (hallucinaitons) and beliefs (delusions) and is not in itself a diagnosis. Indeed, it emerges across a wide range of psychiatric, neurological and other physical disorders as well as, in various forms, as a consequence of stress, trauma, drug use and other perturbations to the nervous system. Moreover, attention has more recently focused on the existence of attenuated psychosis-like thinking distributed within the healthy population: a phenomenon that has long been recognised. The increasingly sophisticated approaches to non-invasive human neuroscience will demand credible theoretical frameworks if they are to fulfil their potential since, alone, they provide only partial and ambiguous insights. Attempts to embed high level descriptions of the experience, characteristics and circumstances of psychosis in deeper principles emerging from neuroscience will be immensely challenging and, without suitable models, likely impossible. I argue therefore that it will be important to find a mechanistic understanding of how the features of psychosis arise and persist. Such an understanding will involve the development of models at different levels of explanation, and with different explanatory aims and scope. They will provide a set of frameworks for scrutinising psychosis and for identifying causal pathways by which it may arise. One increasingly influential framework draws on the idea of the brain facing the challenge of trying to make sense of its world by deriving a model of the causes of its sensory inputs. It does this through a process of prediction and inference. Application of this “Predictive Processing” idea offers remarkably powerful and comprehensive opportunities to think about perception and belief in ways that link both to the underlying neurobiology and to higher order cognitive and social functions. It can be applied fruitfully to understanding delusions and hallucination and to generating testable hypotheses about the array of disturbances that may culminate in psychosis.

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S39
THE RETURN OF SADNESS: TOWARDS THE PREDICTION OF DEPRESSION RELAPSE AFTER ANTIDEPRESSANT DISCONTINUATION
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Depression is common and an episode of depression can be devastating. However, depression is amongst the most burdensome disorders worldwide because it often takes a chronic relapsing-remitting course, with periods of health punctuated repeatedly by illness. Antidepressant medications are important in the treatment of depression, but those fortunate enough to respond often relapse after discontinuing. The mechanisms leading to relapse are as yet poorly understood, and hence the decision cannot be properly informed. Here, I will present first results from a longitudinal study examining neural and behavioural predictors of relapse after antidepressant discontinuation. Behaviourally, we find that patients with a remitted depression are averse to making decisions to invest effort, and take long to make these decisions. Computational modelling identified a prominent tendency to change their mind after deciding to invest effort, which contributes to the longer decision-times amongst those who go on to relapse. Strikingly, the discontinuation of antidepressants does not affect this, but rather the exertion of effort itself, suggesting that relapse after antidepressant discontinuation entails a complex process involving both vigour and evaluation. We also find that an EEG measure of emotional reactivity to sad mood indexes relapse risk. I will discuss these findings in the context of the cognitive and computational neurobiology of depression, and describe key next steps for the translation of these findings into the clinic.
Funding: Swiss National Science Foundation, MINZ, EMDO Stiftung and Deutsche Forschungsgemeinschaft

S40
DEFINING AND DISSOCIATING TRANSDIAGNOSTIC PSYCHIATRIC TRAITS BASED ON COMPUTATIONAL MODELS OF COGNITIVE FUNCTION
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Introduction: Dimensional definitions of transdiagnostic mental health problems have been suggested as an alternative to categorical diagnoses, having the advantage of capturing heterogeneity within diagnostic categories and similarity across them, thus bridging more naturally to pathophysiology in psychological and neural substrates. Here, we test if self-reported compulsivity is a better fit to goal-directed and related higher order cognitive deficits compared to a diagnosis of OCD.
Methods: Participants were 285 individuals, 111 with a diagnosis of OCD, 82 with GAD, and 92 with concurrent diagnosis of both OCD and GAD. 110 participants completed the follow-up assessment. Patients completed a telephone-based diagnostic interview by a trained rater and internet-based cognitive testing and self-reported clinical assessments. Follow-up data were collected to test for reproducibility after an average of 413 days. We measured performance on a test of goal-directed (“model-based”) planning, in addition to cognitive flexibility (Wisconsin card sorting) and a test of abstract reasoning (similar to Raven’s matrices). Clinical variables included DSM diagnosis of OCD and GAD and three trans-diagnostic factors (psychiatric dimensions) — general distress, compulsivity and obsessionality — that were derived from a factor analysis of self-report measures.
Results: A diagnosis of OCD was not associated goal-directed performance, β=-.05(.03), p=.18. In contrast, a transdiagnostic compulsivity factor showed a strong and reproducible association with deficits in goal-directed control, β=-.05(.02), p=.003. The compulsivity factor also mapped on to cognitive flexibility (e.g. WCST categories completed, p<.001) and abstract reasoning scores (p<.001), while OCD diagnosis (all p>.38) did not. In contrast to compulsivity, other transdiagnostic factors, obsessionality and general distress, showed no reliable association to goal-directed planning, cognitive flexibility or abstract reasoning.
Conclusions: This study demonstrates that well-documented and neurobiologically-defined deficits in goal-directed planning in OCD are better captured by a trans-diagnostic compulsivity dimension than by a diagnosis of OCD. This has substantial implications for basic research aiming to link brain mechanisms to clinical manifestations, and for our understanding of the structure of mental illness itself.
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**S41**

**NEUROANATOMY AND PHYSIOLOGY OF THE OREXINERGIC SYSTEM**

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Introduction: As indicated in the general presentation for this session, the orexinergic system is best known for its role in the stabilization of the different vigilance states. This is most dramatically seen in narcolepsy – thought to be caused by the death of orexinergic neurons – in which especially the separation of wakefulness and REM sleep is distorted. Another side of this is that sleep can be induced and maintained by orexin receptor antagonists. However, the orexinergic system is also involved in many other CNS processes. Different animal studies have suggested orexinergic involvement in, for instance, addiction, pain gating, appetite and metabolism, stress response, depression, and anxiety – with different levels of proof. Number of tools have been generated and utilized in these investigations, including different genetic animal models, viral vectors and small molecular ligands; the physiological investigations have significantly benefitted from the commercial interest in the orexinergic system-targeting therapy. Orexin peptides and especially receptors are also expressed outside the CNS, for instance in the adrenal cortex, male reproductive tract and some cancer cells, but their (patho)physiological role is essentially unknown. The orexin neurons have attracted significant attention. Orexin neurons receive inputs widely and regulate physiologically different outputs. There probably are subpopulations of these neurons but these have been difficult to identify. Orexin receptor response in the orexin target neurons has been mainly attributed to depolarization and possible Ca2+ elevation, but the molecular mechanisms of this are unclear. One suggestion is activation of non-selective cation channels, possibly of the TRP family. In detailed investigations, the receptors appear to be promiscuous in their signalling, and different pathways are involved in different cell types. One suggested mechanism for the direction of signalling is heteromeric complexing of the receptors with other G-protein-coupled receptors. In my talk, I aim at presenting the brief fundamentals of the orexin system from the gross anatomy and physiology to some molecular properties of the orexin receptors, though the drug discovery, addiction and sleep are mostly left for the dedicated talks. I will also focus on the significant white areas on the map as well as our collective blind spots, i.e. the problems and pitfalls in the studies. Especially central issues concern lack of functional/validated antibodies for orexin receptor and peptide measurements. As concerns the anatomical and physiological studies we need to remember that no tools are perfect, and the findings, coming mostly from the rodents, cannot always be extrapolated to human.

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**S42**

**DEVELOPMENT OF OREXIN RECEPTOR ANTAGONISTS AND AGONISTS**

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The role of orexin receptors in sleep regulation, arousal and beyond is supported by extensive preclinical and clinical studies. Orexin A and B (also known as hypocretins 1 and 2) and their two receptors (OX1R and OX2R) have major effects on arousal, sleep/wake regulation, addiction and stress. In humans, the absence of orexin producing cells in the lateral hypothalamus and/or of orexins in the CSF results in narcolepsy with cataplexy (narcolepsy type I). The nature of various sleep phenotypes in orexin peptide or OXR KO rodents (double OX1R / OX2R KO or peptide KO with full blown narcolepsy/cataplexy, OX2R KO with moderate sleep phenotype, OX1R KO with little effects on sleep), have triggered drug discovery programmes on OXR antagonists for the treatment of insomnia and other disorders. Several OXR antagonists, most of which are dual OX1R / OX2R antagonists (DORAs), are close to registration or on the market. Suvorexant (Belsomra®), registered in Japan, US and Australia for insomnia, is the first hypnotic of this new orexinergic class. DORAs promote sleep primarily by increasing REM (rapid eye movement) sleep, with little effect on NREM (non rapid eye movement), especially slow wave sleep (SWS) stages. In rodents,
the OX2R is the primary target mediating sleep promotion by DORAs and other OXR antagonists. We shall briefly review preclinical and clinical data of OXR antagonists and agonists in insomnia and various neurological diseases. REM sleep enhancement by DORAs may provide opportunities to treat specific neurological disorders, whereas OX2R antagonists such as seltorexant (JNJ-54717793 / MIN-202), may have broader applications since they promote balanced sleep in preclinical models and thus have a lower narcoleptic/cataplectic potential. These concepts require further validation as more OXR antagonists move beyond early stages of clinical development and for instance lemborexant, although a DORA, appears to promote balanced sleep. The development of orexin receptor agonists is in very early stages, due to the inherent and notorious difficulties with the medicinal chemistry of low molecular weight peptide receptor agonists. In preclinical models such agonists produce arousal and have anti narcolepsy/cataplexy effects as expected. In the clinic, only peptide agonists have been tested so far with very limited success. In summary, OXR antagonists represent an exciting new class of hypnotics. As has been experienced with many other drug classes, all orexin receptor antagonists are not equal, and the concept of “me too” eventually shows its limitations as clinical experience with OXR antagonists accumulates.

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S43

RELEVANCE OF OREXINS FOR ADDICTION
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Addiction continues to be one of the major contributors to global health and social burden. New approaches for treatment are being developed from greater understanding of neurobiology of substance use and addiction. One such system is the orexin/hypocretin system which consists of two neuropeptides, orexin A and B and their receptors, orexin-1 (OX1) and 2 (OX2) which are distributed throughout the brain. Initially investigated for their role in feeding behaviour, orexins are now regarded to have a role in wider appetitive behaviours, including that related to addiction. This talk will provide an overview of the evidence regarding orexins in addiction. The largest body of evidence comes from preclinical models of addiction such as conditioned place preference, self-administration or drug seeking. There is evidence for a role of orexins in addictions involving ethanol, stimulants (cocaine, amphetamine) or morphine. It has been proposed that the orexin system is preferentially engaged by situations of high motivational relevance rather than modulating the primary reinforcing effects of drugs of abuse. Therefore orexin-dependent behaviours are conceptualised to be regulation of motivated responding for drugs eg in response to cues or stress. In addition a role for the orexin system has been suggested in other behaviours or function that can be dysregulated and comorbid with addiction such as sleep. This talk will cover preclinical evidence and how that may translate to improving our understanding and treatment of human addiction.

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S44

RELEVANCE OF OREXINS FOR SLEEP DISORDERS
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Within a year of the initial discovery of the neuropeptide orexin in 1998, it was demonstrated that a mutation in one of its receptors led to a form of familial canine narcolepsy with cataplexy. This totally unexpected finding in Dobermans was soon followed by studies in human sporadic narcolepsy that confirmed a virtual total loss of the neuropeptide in cerebrospinal fluid (CSF) samples in the vast majority of patients displaying the full syndrome. Almost two decades later, it is established that the highly specific loss of orexin-containing neurons in the region of the lateral hypothalamus, usually around adolescence, is by far the commonest pathophysiological process underlying narcolepsy. Indeed, assays of CSF orexin are now considered a key diagnostic test in so-called narcolepsy type 1. Increasing evidence suggests an
auto-immune basis for narcolepsy with particular involvement of an abnormal T cell response. Alongside the remarkable observation that a specific neurochemical deficit involving a relatively small number of neurons causes narcolepsy, our notions of its key clinical features have evolved. This primary and often disabling condition is best viewed as a disorder of sleep-wake regulation over the full 24-hour period, especially with regard to rapid eye movement (REM) sleep. In typical narcolepsy, apart from irresistible episodes of sleepiness, elements of REM sleep stage will characteristically intrude inappropriately into the wakeful state. However, it is also clear that overnight sleep in narcolepsy is frequently chaotic and discontinuous with dysregulated architecture and the presence of variety of parasomnias. The lack of hypothalamic orexin correlates most closely with the specific phenomenon of cataplexy, brief episodes of partial or total voluntary muscle weakness triggered by positive emotional stimuli. The potential involvement of orexin in emotional processing has led to further defining its role in areas outside sleep regulation. Partial loss of orexin in a variety of situations such as neurodegeneration or head injury is likely to contribute to abnormalities in the sleep-wake cycle of affected subjects. Although mostly in development, pharmaceutical agents that influence the orexin system are likely to play an increasing role in the treatment of narcolepsy and a variety of other sleep disorders.

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S45

PHARMACOLOGICAL ACTIONS AND POTENTIAL NOVEL THERAPEUTIC USES OF SOME PLANT AND SYNTHETIC CANNABINOIDS

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Results obtained from preclinical pharmacological experiments have been triggering ever growing interest in the potential therapeutic benefits of developing medicines from (1) phytocannabinoids that are produced by cannabis; (2) synthetic analogues of some of these phytocannabinoids; (3) positive allosteric modulators (PAMs) of cannabinoid CB1 or CB2 receptors, that can strengthen orthosteric (direct) CB1 or CB2 receptor activation induced by exogenously administered agonists or by endogenously released endocannabinoids. Turning first to phytocannabinoids. I will focus on cannabidiol (CBD), cannabidiolic acid (CBDA), cannabigerol (CBG) and Δ9-tetrahydrocannabivarin (THCV), none of which is psychoactive, and present reasons for predicting that (1) CBD would be effective against many kinds of disorder, including certain mental, neurodegenerative and inflammatory disorders; (2) CBD, CBDA and THCV would ameliorate anxiety and chemotherapy-induced nausea and vomiting because they can enhance the activation of 5-HT1A receptors; (3) CBG would relieve inflammatory pain by activating α2-adrenoceptors; (4) THCV would also ameliorate diabetes-related kidney damage and nicotine dependence because it is a CB2 receptor agonist but a CB1 receptor antagonist (e.g. Pertwee, R.G., 2014, Handbook of Cannabis, Oxford University Press; Pertwee et al., 2018, Br. J. Pharmacol., 175, 100-112). Moving on to synthetic phytocannabinoid analogues, I will focus on just CBDA methyl ester (HU-580). CBDA is more potent than CBD at targeting 5-HT1A receptors, and at reducing signs of anxiety and chemotherapy-induced nausea in animal models, but is not “druggable” as it is very unstable. However, HU-580 displays even greater potency than CBDA in these assays, and is very stable, and hence might well be highly effective against anxiety and/or chemotherapy-induced nausea in the clinic (Pertwee et al., 2018, Br. J. Pharmacol., 175, 100-112). Turning finally to cannabinoid receptor allosteric modulators, there is convincing preclinical evidence that GAT211 and GAT229 are CB1 PAMs, and that by strengthening the endogenous activation of CB1 receptors, (1) GAT211 reduces signs of inflammatory and neuropathic pain in mice without producing any signs of tolerance to this analgesia, or of dependence, (Slivicki et al., 2018, Biol. Psychiatry 84: 722-733), and (2) GAT229 reduces intraocular pressure in ocular hypertensive mice, and so may be effective against glaucoma (Cairns et al., 2017, J. Ocular Pharmacol. Ther. 33: 582-590). There is a growing need for research with human subjects directed at evaluating the clinical relevance of at least some of the many potential novel therapeutic uses of plant and synthetic cannabinoids that have been revealed by preclinical research.

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CANNABIS THERAPEUTICS IN TOURETTE PATIENTS

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Tourette syndrome (TS) is a chronic neuro-psychiatric disorder with childhood onset characterized by motor and vocal tics. The majority of patients also suffers from psychiatric comorbidities including obsessive-compulsive disorder (OCB), attention deficit/hyperactivity disorder (ADHD), depression, sleeping disorder, and anxiety disorder. During the last years, an increasing number of case studies has been published suggesting that use of smoked cannabis might be effective in the treatment of tics and behavioral symptoms in patients with TS. These anecdotal reports have been corroborated by case series including a total of more than 200 patients. Interestingly, beneficial effects of different kinds of cannabinoids have been reported including cannabis, cannabis extracts such as nabiximols, and dronabinol (tetrahydrocannabinol, THC). However, until today, only two small randomized controlled trials (RCT) have been performed using dronabinol in the treatment of 12 and 24 adult patients with TS, respectively. In both studies dronabinol was superior to placebo demonstrating a significant reduction of tics. Currently, a large RCT (N=96) is recruiting investigating efficacy and safety of the cannabis extract nabiximols in adult patients with TS (ClinicalTrials.gov Identifier: NCT03087201). In addition to beneficial effects of exocannabinoids, data from a phase 1b study suggest that the monoacylglycerol lipase (MGLL) inhibitor ABX-1431 is also effective in the treatment of tics and premonitory urges in adult patients with TS (ClinicalTrials.gov Identifier: NCT03058562). ABX-1431 inhibits the hydrolysis of the physiological endocannabinoid 2-arachidonoylglycerol (2-AG) resulting in an elevation in brain 2-AG that acts on central cannabinoid CB1 receptors. Currently, a phase 2 trial of ABX-1431 in adult patients with TS is in underway (ClinicalTrials.gov Identifier: NCT03625453). Based on beneficial effects of exocannabinoids and endocannabinoid modulators in the treatment of patients with TS, it has been speculated that TS might be caused by a dysfunction in the endocannabinoid (eCB) neurotransmitter system. In line with this hypothesis, it has been demonstrated that levels of the two most important endocannabinoids "N"-arachidonoylethanolamine (AEA, anandamide) and 2-AG as well as of the endocannabinoid-like molecule palmitol ethanolamide (PEA) and the metabolite arachidonic acid (AA) in cerebrospinal fluid (CSF) are significantly elevated in adult patients with TS (N=20) compared to a control group. In summary, from available data it is suggested that stimulation of the eCB system results in an improvement of tics and further symptoms in patients with TS. This might be due to an underlying dysfunction in the eCB system which results in a compensatory increase in endocannabinoid levels.

Funding: RCTs using ABX-1431 have been funded by Abide Therapeutics. For the study NCT03087201, nabiximols and placebo have been offered by GW. A substudy of this RCT is sponsored by Almirall investigating driving ability in patients with TS during treatment with nabiximols.

THE EVOLUTION OF CANNABIDIOL IN EPILEPSY

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Introduction: Historically, many anecdotal claims have been made for the use of cannabis in the treatment of a variety of diseases, including convulsive disorders such as epilepsy (Rosenberg et al, 2016). The behavioural pharmacology of the principal psychoactive component derived from cannabis, Δ9-tetrahydrocannabinol, in preclinical animal models and human epilepsies remains conflicted (Whalley, 2013). However, by virtue of its lack of affinity for cannabinoid receptors, the similarly abundant plant-derived cannabinoid, cannabidiol (CBD) is more amenable to study. This presentation will summarise the findings from a programme of preclinical research of CBD in well-established, in vitro and in vivo, animal models of seizure initiated by GW in partnership with preclinical epilepsy specialists to demonstrate a broad, well tolerated and reproducible anticonvulsant profile. These findings led to the initiation of further partnerships between GW and leading paediatric and adult epilepsy clinicians to provide CBD (formulated as Epidiolex®) through an
FDA authorised, Expanded Access Programme (EAP). On the basis of initial open-label data from the EAP, GW initiated the GWPCARE Phase III clinical trial programme to assess CBD's safety and efficacy for the treatment of seizures associated with childhood onset epilepsy disorders that are not adequately controlled with current antiepileptic drugs (AEDs). The GWPCARE Phase III clinical trial programme includes six double-blind, placebo controlled studies evaluating the safety and efficacy of Epidiolex® as adjunctive therapy across four epilepsy indications. Here, data describing the preclinical evidence base for CBD's non-clinical efficacy and underlying molecular mechanism, plus summary safety and efficacy results of Epidiolex® in the four Phase III trials to have thus far completed (GWPCARE1 & GWPCARE2: Dravet syndrome (DS); GWPCARE3 & GWPCARE4: Lennox-Gastaut syndrome (LGS)) will be presented.


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S48
CANNABINOIDS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RANDOMISED-CONTROLLED TRIAL

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Introduction: Adults with ADHD describe self-medicating with cannabis, with some reporting a preference for cannabis over ADHD medications. A small number of psychiatrists in the US prescribe cannabis medication for ADHD, despite there being no evidence from randomised controlled studies.

Methods: The EMA-C trial (Experimental Medicine in ADHD-Cannabinoids) was a pilot randomised placebo-controlled experimental study of a cannabinoid medication, Sativex Oromucosal Spray, in 30 adults with ADHD. The primary outcome was cognitive performance and activity level using the QbTest. Secondary outcomes included ADHD and emotional lability symptoms. From 17.07.14 to 18.06.15, 30 participants were randomly assigned to the active (n=15) or placebo (n=15) group.

Results: For the primary outcome, no significant difference was found in the intent to treat analysis although the overall pattern of scores was such that the active group usually had scores that were better than the placebo group (Est= -0.17, 95%CI-0.40 to 0.07, p=0.16, n=15/11 active/placebo). For secondary outcomes Sativex was associated with a nominally significant improvement in hyperactivity/impulsivity (p=0.03) and a cognitive measure of inhibition (p=0.05), and a trend towards improvement for inattention (p=0.10) and emotional lability (p=0.11). Per-protocol effects were higher. Results did not meet significance following adjustment for multiple testing. One serious (muscular seizures/spasms) and three mild adverse events occurred in the active group and one serious (cardiovascular problems) adverse event in the placebo group.

Conclusions: Adults with ADHD may represent a subgroup of individuals who experience a reduction of symptoms and no cognitive impairments following cannabinoid use. While not definitive, this study provides preliminary evidence supporting the self-medication theory of cannabis use in ADHD and the need for further studies of the endocannabinoid system in ADHD.

Funding: This study was funded through a departmental research account for PA. The work by PA was supported by the NIHR Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology and Neuroscience, Kings College London and by the European Community's Seventh Framework Programme (FP7/2007–2013) under Grant agreement no.602805. The placebo and active medication were provided free of charge by GW Pharma Ltd. GW Pharma played no other role in study design, in the collection, analysis and interpretation of data or in the writing of the report.
A01

REFINING STRESS-ENHANCED FEAR LEARNING AS A RODENT MODEL OF POSTTRAUMATIC STRESS DISORDER

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Introduction: Post-traumatic stress disorder (PTSD) is an anxiety disorder that develops in a subset of individuals after exposure to a traumatic event, and results in exaggerated and maladaptive fear responses. Understanding of the neural and behavioural mechanisms underlying PTSD has been greatly aided by translational animal models, of which stress-enhanced fear learning (SEFL) is one of the most robust. In the standard SEFL procedure, socially isolated rats are exposed to 15 inescapable 1.0mA, 1-second electric footshocks, which subsequently produce enhanced fear learning compared to context-exposed controls. However, it is yet to be determined whether the SEFL procedure can be refined, minimising harm to the animals while still providing a robust model of enhanced fear learning in PTSD. We investigated whether robust behavioural effects could be observed in an SEFL procedure in which: (i) the magnitude of shock was reduced; (ii) rats were group-housed rather than socially isolated, and; (iii) the number of shocks was reduced.

Methods: Male Lister-Hooded rats (n=14 per experimental group, total n=84), housed in groups of four, were exposed to varying numbers (0, 4, 9, 12, 13 and 15) of 0.5mA, 0.5-second electric footshocks in a single 91-minute inescapable shock (IS) session in Context A (Day 1), before undergoing contextual fear conditioning with a single 0.5mA, 0.5-second footshock in a distinct context (B) 24 hours later (Day 2). On Day 3, rats were exposed to Context B for 30 minutes to extinguish conditioned fear to the context, and tested in an 8-minute retention test on Day 4. All sessions were video-recorded and conditioned freezing quantified offline by an experimenter blind to experimental condition. Data were analysed using repeated measures and univariate ANOVAs and Sidak-corrected pairwise comparisons as appropriate.

Results: During contextual fear conditioning, all rats froze more following shock delivery [Bin: F(1,78)=145, p<.001], with rats that had received greater inescapable shock exposure showing greater fear [Group: F(5,78)=5.19, p<.001]. Rats that had received 12 or more shock exposures during the IS session showed greater levels of fear in Context B at the start of extinction training [Group: F(5,78)=4.86, p=.001; pairwise comparisons showed the 12-,13- and 15-shock groups differed from the 0- shock group at p's<.031]. These animals also showed higher levels of fear throughout the contextual extinction session [Group: F(5,78)=4.44, p=.001] and showed deficits in the acquisition of extinction [Group x Bin: F(38.3,1126)=2.16,p<.001].

Conclusions: These data show that robust behavioural changes can be observed following a stress-enhanced fear learning procedure that does not require social isolation, uses a lower shock magnitude, and fewer numbers of shocks that the standard procedure. This represents an important refinement to the model, reducing animal harm while also providing robust behavioural data.

Funding: This research was supported by the Department of Psychology, University of Cambridge. ALM was further supported as the Ferreras-Willetts Fellow in Neuroscience at Downing College, Cambridge.
CENTRAL AMYGDALA ANGIOTENSIN TYPE 2 RECEPTOR (AGTR2) EXPRESSING NEURONS INFLUENCE FEAR-RELATED BEHAVIOR

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Introduction: The renin-angiotensin system (RAS) has been implicated in post-traumatic stress disorder (PTSD), however the mechanisms responsible for this connection and the therapeutic potential of targeting the RAS in PTSD remains unknown. Using an angiotensin receptor bacterial artificial chromosome (BAC) reporter mouse combined with neuroanatomical, pharmacological and behavioral approaches we examined the role of angiotensin II type 2 receptor (AT2R) in fear-related behavior.

Methods: Dual immunohistochemistry with retrograde labeling was used to characterize AT2R-eGFP+ cells in the amygdala of the (AT2R)-eGFP-BAC reporter mouse. Pavlovian fear conditioning and behavioral pharmacology analyses were used to demonstrate the effects of AT2R activation on fear memory in male C57BL/6 mice. All mice used in this study were on a C57BL/6J background and AT2R-eGFP reporter mice that express eGFP (enhanced green fluorescent protein) in cells that express the AT2R were utilized for immunohistochemical (IHC) and tracing studies. All mice used were adult males 8-10 weeks old and animal experimental group sizes were n=10-15. Data are expressed as mean ± SEM, and p<0.05 were considered statistically significant. Unpaired two-tailed Student t tests were used when comparing two groups. When comparing more than two groups a one-way ANOVA followed by Newman-Keuls post hoc test was used.

Results: AT2R-eGFP reporter mice showed dense eGFP expression in the amygdala, particularly within the central (CeA: 154.5 ± 7.9 cells/mm2) and medial (MeA: 221.2 ± 15.3 cells/mm2) sub-nuclei, and less so in the basolateral amygdala (BLA: 11.7 ± 1.8 cells/mm2). Animals received CeA microinjections of saline or C21 and 10 minutes later were exposed to 20 CS trials in a novel context. A reduction in initial fear expression was observed in the C21 group during the first 5 CS block (Vehicle CS 0-5: 75±5 % freezing; C21 CS 0-5: 55±7 % freezing; F (3,42)=6.52, p<0.05) while during CS 6-20 no differences in percent freezing were found between groups (Vehicle CS 6-20: 55±7; C21 CS 6-20: 38±6; F (3,42)=6.52, p>0.05). Over the course of extinction training (CS0-20) freezing behavior in the vehicle group significantly decreased (Vehicle CS 0-5: 75±5 % freezing, Vehicle CS 6-20: 52±5 % freezing; F (3,42)=6.52, p<0.05), indicating within-session extinction, however this did not occur in the C21 group.

Conclusions: These findings suggest that CeM AT2R-expressing neurons can modulate CeA outputs that play a role in fear expression and provide evidence for a novel CeM cell type and angiotensinergic circuit in the regulation of fear.

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A03

THE ACUTE EFFECTS OF CANNABIDIOL ON EMOTIONAL PROCESSING AND ANXIETY: A NEUROCOGNITIVE IMAGING STUDY

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Introduction: There is growing interest in the therapeutic potential of cannabidiol (CBD) across a range of psychiatric disorders. In the context of anxiety, CBD has been found to reduce anxiety during induced-stress in anxious individuals and healthy controls (Bergamaschi et al., 2011, Neuropsychopharmacology, 36(6), 1219-1226; Zuardi et al., 1993, J. Psychopharmacol., 7(1), 82-88). However, the mechanisms underlying these potential effects are unknown. We therefore sought to investigate the behavioural and neural effects of a single dose of CBD vs. placebo on a range of emotion-related measures, to evaluate CBD's anxiolytic potential and to test cognitive-mechanistic models of its effects on anxiety. We hypothesised that CBD would be anxiolytic and modulate cognition in relation to this anxiolytic effect.

Methods: We conducted a randomised, double-blind, placebo-controlled, crossover, acute oral challenge with 600 mg of CBD in 24 healthy participants, with neuroimaging (fMRI emotion viewing) and cognitive (emotional appraisal) measures of emotional processing, and a measure of emotional response to experimentally-induced anxiety (a stressful arithmetic task with subjective anxiety measures). The behavioural data were analysed via repeated-measures analyses-of-variance comparing the effects of drug and task factors on task indices. FMRI was performed at 3T and thresholded by voxel at α = .001 (uncorrected).

Results: CBD increased responses to fear in dorsal striatal, dorsomedial-prefrontal and inferior parietal regions (z = 3.32, 3.17, 3.54, respectively; puncorrected ≤ .001) relative to placebo, and this CBD-mediated striatal activation during fear processing was associated with lower arousal ratings (r24 = -.60, p = .002) and faster valence judgments (r21 = -.61, p = .002) for angry faces in the emotional appraisal task. Contrary to predictions, CBD also increased experimentally-induced anxiety (F2,49 = 3.17, p = .048, η2 = .12), relative to placebo.

Conclusions: To our knowledge, this is the first study to find an anxiogenic effect of CBD under induced stress. Further, we also found a seemingly contradictory effect of dampened emotional arousal in response to negative emotions mediated by the caudate nucleus, which may represent a mechanism of CBD's potential anxiolytic effect. These inconsistent findings may reflect differences across tasks in time of measurement and therefore bioavailability, and thus suggest complex and bidirectional effects of CBD on emotional processing and anxiety. Given growing use of CBD for its putative medical benefits, urgent further research is warranted to investigate CBD's anxiogenic effects, and its suitability as a therapeutic agent for anxiety disorders.

Funding: The British Medical Association and the UCLH Biomedical Research Centre supported this study.
A04
SOCIAL REWARD AND SOCIAL ANXIETY IN ADOLESCENCE
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Introduction: Reward processing and sensitivity undergoes marked changes in adolescence (van Duijvenvoorde et al 2016, Neurosci Biobehav Rev, 70, 135-147), with social interactions representing a powerful source of reward. Reward processing has also been emphasised as an important factor in the development of social anxiety, a disorder which has a particularly high rate of onset during early adolescence (Caouette & Guyer, 2014, Dev Cog Neurosci, 8, 65-76).
Methods: This study used hierarchical linear regression to investigate: 1) developmental changes in processing social rewards, in the context of another salient reward, money; and 2) whether reward processing during adolescence was associated with individual differences in social anxiety in two symptom domains: fear/avoidance of social interactions and fear/avoidance of performance situations. Eighty females aged 13-34 years performed two versions of a probabilistic reward anticipation task, in which a speeded response could result in either social or monetary rewarding feedback. Participants also completed self-report assessments of social reward value, trait anxiety and social anxiety symptomatology.
Results: At high reward probabilities, performance on both reward tasks was best characterised by a quadratic effect of age, with the fastest responses at around 22 years (R2 > .058, p's < .037). A similar quadratic effect was found for subjective liking ratings of both reward stimuli (R2 > .231, p's < .042), however liking did not account for variance in task performance (R2 < .004, p's > .556), highlighting the fact that although often correlated, liking of a stimuli, and its salience as a reinforcer represent two distinct components of motivational processing. Although there were age-related changes in self-reported anxiety symptoms, these did not account for developmental changes in subjective liking or reward task performance. Social anxiety was not associated with liking of the reward stimuli but did predict performance on both reward tasks at all reward probability levels (R2 > .109, p's < .012), over and above variation in trait anxiety, which did not predict performance. Different domains of social anxiety symptoms were associated with opposing directions of effects on task performance, which is discussed within the framework of a performance monitoring hypothesis.
Conclusions: The results suggest that both social anxiety and age were associated with variation in reward sensitivity, but their effects were largely independent from one and other. Future research should take into account the fact that the presence of an experimenter may have a greater effect on cognitive task performance in socially anxious individuals than non-anxious participants.
Funding: This study was supported by a MRC PhD studentship to (EJK).

A05
ENDOCYTOSIS OF ALPHA 2 NA,K-ATPASE IN ASTROCYTES AS A POSSIBLE MECHANISM OF ANXIETY IN THE 7.5% CO2 MODEL OF GENERALISED ANXIETY DISORDER
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Introduction: Many patients with generalised anxiety disorder (GAD) do not respond to current psychological or pharmacological treatments, and better understanding of the neurobiology of GAD could lead to development of more effective and acceptable interventions. The 7.5% CO2 inhalation experimental medicine model of GAD mimics subjective, autonomic and neurocognitive features. (Baldwin, D.S. et al (2017) CNS Drugs, 31(4), pp. 307-317). To enhance understanding of potential underlying mechanisms, we examine astrocytes (the most abundant glial cell type in the brain) which uniquely possess alpha

Methods: A pilot study was performed on brain tissue collected from adult male mice that underwent euthanasia, either by exposure to CO2 (to a final concentration of 100%) prior to cervical dislocation, or by cervical dislocation alone. This enabled pilot data and feasibility of the approach to be evaluated prior to a potential study using controlled exposures to 7.5% CO2. Brains were rapidly dissected, processed and embedded in paraffin. Tissue was sectioned at 10um and regions of interest collected. Immunohistochemistry was performed, followed by the capture of low and high-power images by light microscopy. Images were analysed using ImageJ (using the colour deconvolution plug-in, followed by consistent thresholding) to determine the density of ATP1α2 expression in the hippocampus, amygdala, nucleus accumbens, and bed nucleus stria terminalis. SPSS software was used to analyse data using the Kruskal-Wallis test (data was non-parametric) with Bonferroni correction for multiple comparisons.

Results: A significant difference in the density of ATP1α2 was found between brain regions (p=0.008); when multiple comparisons were performed, the amygdala was found to have a significantly higher density of ATP1α2 than the hippocampus (p=0.033).

Conclusions: Differing densities of ATP1α2 across brain regions indicate possible regional specificity of these transporters: the highest density of ATP1α2 was found in the amygdala. We are currently investigating endocytosis of ATP1α1 in lung tissue (positive control). We will then use this method to identify possible endocytosis of ATP1α2 in the 7.5% CO2 mouse brain model of GAD. These findings could encourage the development of novel anxiolytics, targeted at ATP1α2 function.

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**FUNCTIONAL NEUROIMAGING CORRELATES OF PEAK RESPONSE IN THE 7.5% CO2 INHALATIONAL MODEL OF GENERALISED ANXIETY: A PILOT STUDY**

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**Introduction:** Experimental medicine models in healthy volunteers can be a cost-effective and timely approach to explore potential novel treatments for psychiatric disorders. An example is the 7.5% CO2 inhalational model, which mimics the subjective and autonomic features of generalised anxiety (Bailey et al., 2011, J Psychopharmacol, 25(9): 1192-98). However, it remains unknown whether inter-individual variability in the functional architecture of negative affective valence systems might affect the subjective response to CO2 challenge. Here we explore how task-evoked functional connectivity during an emotional processing task in healthy volunteers is associated with peak response to CO2 challenge.

**Methods:** We carried out functional magnetic resonance imaging (fMRI) in 13 healthy volunteers while they completed a validated passive emotional face perception task (Schneider et al., 2011, NeuroImage, 56: 1847-53). Psychophysiologic interaction (PPI) was used to explore task-evoked functional connectivity between a priori regions of interest when volunteers viewed angry compared with happy facial expressions (angry > happy contrast). The regions of interest used in this study were 6mm radial spheres identified from an identical task on a separate dataset of 100 young adult volunteers. Within 7 days of the scan, participants underwent the CO2 challenge. We correlated PPI results with CO2 outcome measures.

**Results:** CO2 challenge significantly increased subjective anxiety ($F(1,15) = 12.89, p = 0.002$), systolic blood pressure ($F(2,22) = 6.57, p = 0.007$), and heart rate ($F(2,19) = 12.26, p = 0.001$). PPI analysis of the contrast angry>happy showed that functional connectivity between ventromedial prefrontal cortex and right
amygdala significantly correlated with peak heart rate ($R = 0.831, p < 0.001$) and subjective anxiety ($R = 0.700, p = 0.008$) on CO2 challenge. Functional connectivity between dorsal anterior cingulate cortex and left amygdala was negatively correlated with peak subjective anxiety ($R = -0.726, p = 0.005$).

Conclusions: This is the first study to explore the neural correlates of the CO2 challenge. We found that subjective response to CO2 challenge was related to task-evoked functional connectivity between regions known to be important in processing anxiety. Such approaches have potential for use in stratifying healthy volunteers and examining correlates of response in trials using experimental medicine models.

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A07

SOCIAL EVALUATION LEARNING IN SOCIAL ANXIETY DISORDER AND DEPRESSION: A MEGA ANALYSIS

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Introduction: Depression and social anxiety are highly co-morbid disorders, characterised by negative self-beliefs and widespread social difficulties. Social evaluation learning, the ability to learn what others think about oneself, may therefore contribute to these disorders. However, specific patterns of learning may differ. Whereas social interactions are characterised by fear of negative evaluation in individuals with social anxiety, in depression social interactions are characterised by a lack of engagement and pleasure. In this study, we aim to examine the role of social evaluation learning in anxiety and depression, exploring commonalities and differences.

Methods: A mega analysis was conducted on seven datasets with a combined sample of 337 participants. In each dataset, a social reinforcement task was used to measure how participants learnt social evaluations about themselves and a fictional ‘other’, based on feedback to a series of negative or positive words. Feedback contingencies corresponded to two rules, ‘like’ (80% positive words correct) and ‘dislike’ (20% positive words correct). Participants also completed self-report measures of depression (PHQ-9) and social anxiety (BFNE). Multivariate mixed-effects linear regression models were used to evaluate the relationship between learning of social evaluations and depression and social anxiety symptoms.

Results: Both social anxiety and depression were associated with learning the self-dislike rule; for every fewer error, depression and anxiety scores increased by 0.27% (95% CI: 0.07, 0.48, $p = 0.010$). Depression, but not anxiety, was also associated with learning the self-like rule; for every additional error, depression scores increased by 0.73% (95% CI: 0.29, 1.17, $p = 0.001$). Other-referential learning was not associated with anxiety or depression.

Conclusions: In keeping with findings of increased fear of social threat, we found that social anxiety was associated with greater learning of negative evaluation. Likewise, supportive of theories of impaired social enjoyment, we found that depression was associated with worse learning of positive evaluation. However, depression was also associated with increased learning of negative evaluation. Depressive self-beliefs may therefore be maintained by both decreased sensitivity to social reward and increased sensitivity to social threat. While social evaluation learning therefore seems to play a role in internalising disorders, different treatment approaches may be beneficial for specific disorders. Future research should implement computational models to provide a deeper understanding of the mechanisms underlying these differences in social evaluation learning.

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A08
NEURAL SUBSTRATES OF AFFECTIVE BIAS IN THE INTERPRETATION OF AMBIGUOUS INFORMATION

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Introduction: Cognitive biases are a core feature of clinical anxiety; one of the expressions of these biases is that clinically anxious individuals tend to lean towards negative and pessimistic interpretations of ambiguous phenomena (Aylward et al., 2017, Psychological Medicine, 1, 1-10) that affect their overall quality of life (Craske et al., 2017, Nature Reviews Disease Primers, 3, 17024). Following recent findings on cognitive biases in anxious individuals (Aylward et al., 2017, Psychological Medicine, 1, 1-10) the present study aims to investigate the neural substrates of ambiguity interpretation.

Methods: During the acquisition task 48 healthy participants learned the associations between two circles (big and small) and high or low reward values (100% contingency, associations counterbalanced across participants). Participants had to press one of two buttons to correctly predict the high/low outcomes. Participants then underwent fMRI during a subsequent test phase, in which a medium-sized circle (ambiguous stimulus) was also included to the task and participants were required to select one of the two buttons. In other words, they had to say whether they thought this stimulus would be followed by high or low reward providing a measure of affective bias in interpretation of ambiguity. Images were analysed with SPM 12; one-sample T-tests were run to investigate the main population effect of interpreting the ambiguous circle as high or low-reward.

Results: Whole-brain analyses yielded a statistically significant (all T-scores are FEW error-corrected) p < 0.05) main population effect of interpreting the ambiguous stimuli as high or low reward>baseline. Peaks of increased activity were found in the left (-32 18 -2) (T=9.26) and right insula (38 14 -4) (T=7.01), left (-14 -2 14) (T=7.29) and right caudate (10 8 6) (T=6.87) and left putamen (-22 8 -4) (T=7.38). A high>low-reward-interpretation contrast showed a single area within the left temporal cortex (Broadman area 21) with statistically significant greater activity (-52 -36 -4) (T=3.73 at p (uncorrected) < 0.001).

Conclusions: Increases in brain activity were observed in the same areas irrespective of the valence given to the ambiguous stimulus, suggesting that the left insula, right caudate and left putamen are involved in the process of interpretation of ambiguous information. Broadman area 21 might, however, be specifically involved in predicting high rewards – i.e. in affective bias in interpretation of ambiguous information. Future work will explore whether this activity is different in clinical samples and whether it is influenced by antidepressant medication.

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A09
THE NEURAL BASIS OF TIME PERCEPTION UNDER INDUCED ANXIETY

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Introduction: Anxiety alters how we perceive the world and also aspects of cognitive performance. Prominent theories of anxiety suggest that one explanation for the effect of anxiety on cognition is that anxious thoughts “overload” limited cognitive resources, competing with other processes, in a dual-task fashion. In other words, anxiety (e.g. anxious thoughts) might be acting as an extra “task” on top of what else individuals might be doing. Having found evidence of this in previous behavioural studies, we expect that performing a task under anxiety would activate neural networks associated with dual-task processing (divided attention), including the prefrontal and the anterior cingulate cortex.
Methods: To test this, we combined a widely-used translational anxiety manipulation (threat of shock) with a simple time perception task, which we have previously found to be affected by anxiety. During this task, participants had to watch a picture which flashed briefly on the screen and then decide whether its duration was more similar to short or long exemplars presented earlier. Thirteen healthy participants performed this task during functional magnetic resonance imaging under threat (during which they could receive a shock anytime without warning; 144 trials in total) and safe (during which they were guaranteed not to receive any shocks; 144 trials in total) conditions. Each safe and threat block lasted around 2.5 min and the order was counterbalanced across participants. The task lasted 30 min and the functional data was analysed with SPM.

Results: Threat increased activation in the anterior cingulate cortex ($x=-18, y=11, z=26; Z=3.26$, puncorrected=.001) relative to safe blocks, consistent with previous studies. In addition, the interaction between threat and stimulus duration produced clusters in frontopolar areas (left: $x=-24, y=47, z=5; Z=3.15$, puncorrected=.001, right: $x=27, y=56, z=8; Z=2.75$, puncorrected=.003). Post-hoc analysis of the interaction showed that there was stronger pre-frontal activation for the shorter durations in the safe condition which was abolished under threat. However, the effect of threat on time perception was not significant ($t(12)=-1.36, p=0.196, Cohen's d=0.37$), but on the same direction as in our previous studies.

Conclusions: These results are consistent with the hypothesis that anxiety affects cognition by overloading cognitive resources, since it leads to activations of key neural networks that are strongly associated with dual-task processing. However, our results should be interpreted with caution until independently replicated given the relatively small sample size and lack of effect of the anxiety manipulation on behaviour.

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### A10
**LEARNING TO BE LIKED: COMPUTATIONAL AND NEURAL MECHANISMS OF SOCIAL EVALUATION LEARNING IN SOCIAL ANXIETY**

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Introduction: Social anxiety is characterised by fear of negative social evaluation. However, the process by which social evaluation is inferred remains poorly understood. We previously demonstrated the existence of a positive self-referential bias, wherein healthy individuals display increased sensitivity to learning positive vs negative self-referential social evaluation. This bias is absent in highly socially anxious individuals (Button et al. 2015. PLOS ONE 10(4):e0119456). Here, we used computational modelling and fMRI to characterise mechanisms underlying social evaluation learning, and effects of social anxiety.

Methods: Participants with low (n=25) or high (n=24) social anxiety completed a social evaluation learning task in which they ‘met’ four personas while undergoing fMRI. For each persona, participants chose between sequentially presented pairs of positive and negative descriptors (e.g. ‘boring-interesting’) reflecting the persona’s attitude (like vs dislike) towards themselves/another individual. Participants were instructed to learn the attitude of each persona. Attitude-incongruent/misleading feedback was given on 20% of trials. Hierarchical associative learning models were fitted using the Stan probabilistic programming language. Parametric modulators derived from the winning model for trial-by-trial subjective probability of being liked (P(L)) were incorporated into a general linear model of the BOLD time series using FSL.

Results: The winning model included separate group hyperparameters for positive self-referential feedback learning rate (LR-PS). Subject-level LR-PS differed between groups (low-anxiety 0.16±0.02, high-anxiety 0.10±0.03; p<10-9). This difference remained when LR-PS was modelled with a single
hyperparameter (low-anxiety: 0.15±0.04, high-anxiety 0.12±0.04; p<0.01). The high-anxiety group showed greater positive decision bias (capturing tendency to believe that one/another is liked, over-and-above learning effects) in other-referential conditions (0.01±0.16, 0.10±0.10, p=0.02). The high-anxiety group displayed reduced BOLD response to self-referential P(L) in dorsolateral and medial prefrontal cortex (Z=4.38, p<0.01; Z=4.56, p<0.01), as well as to differential self- vs other-referential P(L) in right temporoparietal junction (Z=4.38, p<0.01).

Conclusions: High-anxiety participants showed a selective deficit in learning from positive self-referential feedback, meaning they were more likely to infer they were disliked, as well as a learning-independent bias towards believing that others were more liked. These effects were linked to reduced BOLD response in the self-attention network. Impaired learning of positive self-referential feedback and corresponding reduced activity in the self-attention network may maintain social anxiety by preventing updating of negative self-beliefs. Future work should explore the specificity of this effect to social anxiety symptoms, and test whether evaluative training can lead to functional changes in the self-attention network which improve symptoms.

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A11
A META-ANALYSIS OF FUNCTIONAL ACTIVATION ACROSS PATHOLOGICAL AND ADAPTIVE ANXIETY
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Introduction: Anxiety can be an adaptive response to unpredictable threats, like walking down a dark alley. At the same time, pathological anxiety disorders describe when symptoms exceed clinical threshold, and can adversely impact daily life. Whether or not adaptive and pathological anxiety are on two different ends on the same spectrum and/or share mechanisms remains unknown. A large body of studies examining neuroimaging correlates of pathological anxiety, have now been joined by growing body of work exploring adaptive anxiety (usually via induced threat of shock). Here, we therefore meta-analytically explore commonalities and differences across adaptive and pathological anxiety.

Methods: We conducted a meta-analysis to determine similarities and differences in fMRI BOLD activation across anxiety disorders. The PUBMED database was systematically searched for whole-brain fMRI studies contrasting anxious patients (post-traumatic stress disorder[PTSD], generalized anxiety disorder[GAD], social anxiety disorder [SAD], specific phobia[SpP], and panic disorder/agoraphobia[PDAG]) to healthy controls, as well as for induced anxiety studies contrasting an unpredictable-threat condition and a safe condition. Studies had to be published in English and clinical studies had to report activation at untreated baseline. Meta-analyses for each disorder and multimodal meta-analyses comparing disorders were conducted with Seed-based d Mapping software (SDM).

Results: The most consistent groups were SpP (22 studies), PDAG (14 studies) and induced anxiety (15 studies), which all demonstrated increased activation (all p≤0.0005) in the cingulate (MNI average: [-3.33, 10.67,36], z ranging from 2.15 to 4.91) and insular cortices (right insular cortex: MNI average [36, 8.67, -4], z ranging from 1.6 to 4.13; left insular cortex: [-35.33, 10.67, 4], z ranging from 1.52 to 4.49). The other anxiety disorders differed from this pattern: while SAD (29 studies), GAD (13 studies) and PTSD (24 studies) all showed activation in left insula/IFG cluster, they demonstrated deactivation in the cingulate cortex.

Conclusions: We show a consistent pattern of activation across induced anxiety and two anxiety disorders, which might indicate they are different ends of the same spectrum. Alternatively, this might be explained by the high state-anxiety common to both the induction of anxiety and symptom-provocation tasks commonly adopted in studies of SpP and PDAG patients. The inconsistent effects across SAD, GAD and PTSD may thus reflect more trait-related or disorder-specific activation. Either way, some mechanisms do appear to be common across adaptive anxiety and pathological anxiety supporting the proposition that some mechanisms overlap and that the former may be used as a model for the latter.

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SAME AUTHORS AS ABOVE

Introduction: There is a need for novel, evidence-based treatments for treatment-resistant post-traumatic stress disorder (PTSD); a disabling condition with a large individual and societal burden. 3,4-Methylenedioxymethamphetamine (MDMA) has been found to beneficially augment psychotherapy in several small clinical trials. However, uncertainty remains regarding the efficacy of MDMA-augmented psychotherapy for producing sustained improvement in PTSD symptomatology. The aim of this review was to determine the efficacy of MDMA-augmented psychotherapy for the treatment of treatment-resistant PTSD.

Methods: Systematic searches of six databases (clinicaltrials.gov, CENTRAL, EMBASE, MEDLINE, PubMed and PsycINFO) were conducted from inception to February 2019. Included trials were double-blinded, randomised, and compared MDMA-augmented psychotherapy with a control group receiving psychotherapy with either active- or inactive-placebo. Selection of studies, assessment of trial quality, and extraction of relevant data were performed independently by two reviewers. A meta-analysis was performed on data from the included trials. The pre-defined primary outcome-measure was the difference in Clinician Administered PTSD Scale (CAPS-IV) score from baseline at 1-month post-intervention. Secondary outcome measures included the difference in incidence of neurocognitive and physical adverse effects between intervention and control groups.

Results: Six randomised controlled trials (RCTs) reporting data from a total of 92 participants met inclusion criteria. The included trials were relatively small, ranging from 6 to 28 participants. The largest reduction in CAPS-IV was seen for ‘intervention vs active placebo’, with a statistically significant overall effect (MD = -27.58, 95% CI -41.87, -13.29). There was also a significant reduction in CAPS-IV for ‘intervention vs inactive placebo’ (std. MD -1.24; 95% CI -2.00, -0.48). Secondary outcomes were analysed using risk ratios for both physical (jaw-clenching, headache, insomnia, nausea) and psychological (anxiety, low mood) adverse effects at the time of intervention and within the subsequent 7 days. Jaw-clenching during intervention was the only adverse effect across all studies that was reported as occurring significantly more frequently in the intervention than control groups (RR 3.44; 95% CI 1.71, 6.91).

Conclusions: These results further support the use of MDMA-augmented psychotherapy in the management of treatment-resistant PTSD. To-date the literature demonstrates significant potential therapeutic benefit and minimal physical and neurocognitive risk for this intervention. It is evident that data from larger scale RCTs with longer follow-up periods are required.

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**B01**

**ISOLATION REARING FROM WEANING IN RATS AFFECTS BDNF DNA METHYLATION**

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**Introduction:** Life stressors during critical periods are prominent risk factors for numerous psychiatric illnesses, including mood and anxiety disorders and psychosis. These stressors in early life can also disrupt epigenetic programming in the brain with lasting consequences for brain gene expression and behaviour (Levine et al. 2012, Neurobiology of Disease, 1:488-498). Isolation rearing in rats from weaning models the behavioural and neurochemical consequences of adverse early life experiences in humans and is reported to cause long-lasting brain changes that mimic schizophrenia (Fone and Porkess 2008, Neurosci Biobehav Rev, 6:1087-1102). It has been suggested that BDNF plays a role in the pathophysiology of schizophrenia; a deficit in BDNF mRNA in animal models of psychosis has been demonstrated (Katanuma et al. 2014, Synapse, 6:257-65). One mechanism that controls gene expression and is highly influenced by environmental changes is DNA methylation. Our aim was to investigate if isolation rearing from weaning over 10 weeks in rats would affect BDNF DNA methylation in the brain compared to group housed rats (n=10 each).

**Methods:** Male Wistar rats were housed in isolation (21 days old; n= 10) or in groups (n = 10) post weaning; after 10 weeks the animals were behaviourally tested (open field arena), killed and the hippocampus and prefrontal cortex (PFC) subsequently dissected for genomic DNA extraction. The DNA was bisulphite-converted and a pyrosequencing method was developed to determine the extent of methylation in a sequence containing 3 CpG sites in exon IV of the BDNF gene. Statistical evaluation was made using Student T test.

**Results:** Isolation rearing resulted in hyperlocomotion in the open field test (Corsi-Zuelli et al., 2019, Front Neurosci,12:1011.) and produced greater methylation at CpG1 of BDNF in PFC (t = -2.20 , p = 0.046) and at CpG1 and 2 in hippocampus (CpG1: t = -3.14, p = 0.007; CpG2: t = - 2.35, p = 0.038) compared to the group-housed animals. A bioinformatic search indicated that CpG 1 and 2 are binding sites for promoter transcription factors CREB and HSF2.

**Conclusions:** Our data indicate that the alterations in methylation seen in this animal model may underlie changes in gene expression previously reported (Cirulli et al., 2017, Frontiers in Behavioral Neuroscience, 11:101) caused by isolation rearing. Our results also reinforce the idea that early-life stress causes important epigenetic changes during neurodevelopment, which may underlie the mechanisms involved in psychosis.

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**B02**

**CHRONIC HALOPERIDOL EXPOSURE DOES NOT AFFECT TOTAL SV2A LEVELS IN THE RAT FRONTAL CORTEX BUT MAY INDUCE LOCAL SYNAPTIC PERTURBATION**

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**Introduction:** Studies in human post-mortem tissue investigating synaptophysin protein levels suggested that synapse loss is a hallmark of the pathophysiology in schizophrenia (SCZ) [Osimo et al., 2019, Mol. Psych.24:549-561]. The recent development of the radioligand [11C]-UCB-J, which specifically binds synaptic vesicle glycoprotein 2A (SV2A), enables the evaluation of putative synapse density in the live human brain by Positron Emission Tomography (PET) [Finnema et al., 2016, Sci.Transl.Med.8:348-356]. A preliminary study with this tracer in SCZ patients suggests reduced global SV2A binding relative to controls [Radhakrishnan et al., 2017, Biol.Psych.81:S389]. This study, however, does not allow distinguishing between the effect(s) of illness versus antipsychotic drug (APD) exposure. To address this, we investigated SV2A protein levels and SV2A specific binding in a rat model of clinically comparable APD exposure [Vernon et al., 2011, Biol.Psych.69:936-944].

**Methods:** Osmotic mini-pumps were implanted subcutaneously in adult male (8-10 weeks old) rats to continuously deliver either common vehicle (VEH), 0.5 or 2mg/kg/day Haloperidol (HAL) for 28 days (n=10-12 animals/group). Post-treatment, brains were hemisected and snap frozen or drop-fixed. Total SV2A protein levels in synaptosomes isolated from the frontal cortex were quantified by western blot. The opposite hemisphere was cryo-sectioned and brain sections containing the prefrontal cortex (PFC) or anterior cingulate cortex (ACC) were analysed by either quantitative autoradiography using [3H]-UCB-J, or SV2A immunostaining and confocal microscopy to calculate both total SV2A intensity and the number of synaptic SV2A clusters. Data were analysed in GraphPad by Kruskall-Wallis test (western blot), or 2x2 ANOVA, with main effects of treatment, region, and treatment x region interactions; post-hoc Bonferroni-corrected multiple comparisons were performed when p(ANOVA)<0.05. Effect sizes are reported using partial eta2 (ηp2).

**Results:** Chronic HAL exposure did not affect SV2A protein levels in frontal cortex synaptosomes, or [3H]-UCB-J specific binding in either the PFC or ACC. For SV2A total intensity measured by immunostaining there were significant main effects of region (F(1,20)=5.11, p<0.05, ηp2=0.20) but no effect of treatment, or region x treatment interaction. For SV2A cluster number, there were significant main effects of region (F(1,20)=12.49, p<0.01, ηp2=0.38) and a significant region x treatment interaction (F(1,20)=5.51, p<0.05, ηp2=0.22). Post-hoc testing on this interaction confirmed a significant decrease in SV2A cluster count in the ACC of HAL-exposed rats (p<0.05).

**Conclusions:** Chronic HAL exposure does not affect SV2A protein level or ligand binding, but reduced SV2A cluster number in the rat cingulate cortex. Hence, whilst chronic APD exposure is unlikely to affect SV2A PET, subtle synaptic perturbations may occur.

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SUBCHRONIC PHENCYCLIDINE ATTENUATES RECOGNITION MEMORY AND SOCIAL INTERACTION WITHOUT ALTERING PROSOCIAL VOCALISATIONS OR BRAIN OXYTOCIN LEVELS IN RATS

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Introduction: Understanding the neurobiological aetiology of cognitive deficits and negative symptoms of schizophrenia (Millan et al. 2014 Eur Neuropsychopharmacol 24; 645-92) could enhance development of new therapeutics. Subchronic phencyclidine (PCP) administration to rodents produces behavioural and neurochemical deficits resembling cognitive and negative symptoms of schizophrenia. This study examined the effect of subchronic PCP on novel object recognition and social interaction, and characterised changes in prosocial ultrasonic vocalisations (USVs) during social interaction, as well as post-mortem prefrontal cortical and hippocampal oxytocin levels to determine their potential as markers for observed deficits.

Methods: 48 male Lister Hooded rats (Charles River UK 158-234g) housed 4/IVC cage received PCP (3mg/kg i.p., n=24) or 0.154M saline (1ml/kg) bi-daily for 7 days. Following 7 days washout rats underwent locomotor activity (1h), novel object recognition (2h inter-trial interval) and social interaction (recording 8 behaviours by Ethovision in drug- and weight-matched pairs for 10 minutes in a 75cm diameter unfamiliar arena at 40Lux following 24h individual housing) during which USVs were recorded (Avisoft software). Data (mean+s.e.m.) were analysed by Student’s t-test unless otherwise stated.

Results: The time course and total locomotor activity and rears were similar in PCP and vehicle controls in an activity box. PCP-treated rats showed a mild impairment in novel object recognition; the choice trial discrimination ratio being significantly (p<0.05) lower in PCP than controls (0.33±0.05 and 0.17±0.04, respectively) although both groups spent significantly longer (p<0.001 and p<0.01) exploring the novel object. During social interaction, PCP-treated rats showed a different behavioural profile than controls including significantly more (3.4 +1.3 compared to 0.6+0.1, p<0.05) turns away from the approaching conspecific. 2-Way ANOVA showed a main effect of PCP (F(7,154)=2.099, p=0.0467) on the time spent in each prosocial behavioural component during social interaction, although no individual behaviour changed significantly. PCP tended to increase anogenital sniffing (from 8.9+1.8 to 15.9+3.0s, p=0.07) and reduce the number of frequency modulated 50kHz prosocial calls (from 209+70 to 95+23) during social interaction but neither reached significance. PCP did not alter cortical and hippocampal oxytocin levels.

Conclusions: Previous studies show subchronic PCP impairs novel object recognition and attenuates prosocial behaviour, consistent with this study, but underlying mechanisms are unclear. Interestingly PCP tended to reduce frequency modulated prosocial 50kHz calls (associated with positive affective states including social reward, Burgdorf et al. 2008 J Comp Psychol 122; 357-67) during social interaction warranting further study. However neither the number of calls, any prosocial behaviour or cortical or hippocampal oxytocin were correlated.

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THE PRENATAL MATERNAL RESPONSE TO IMMUNE ACTIVATION PREDICTS OFFSPRING COGNITIVE DYSFUNCTION IN A RAT MODEL OF SCHIZOPHRENIA

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Introduction: Converging evidence from epidemiological studies and animal models has implicated maternal immune activation (mIA) as a risk factor for neurodevelopmental disorders such as schizophrenia. The transient increase in maternal pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), elicited following mIA is thought to perturb fetal neurodevelopment and results in cognitive deficits. Here, we employed a split-litter cross-fostering design to investigate how the prenatal (maternal cytokine response) and postnatal (maternal care) environments interact to predict offspring cognitive deficits in a rodent model of mIA.

Methods: 22 female Wistar rats were timed-mated and treated with a single intraperitoneal injection of 10mg/kg bodyweight polyinosinic-polycytidylic acid (poly I:C; low-molecular weight, InvivoGen) or vehicle (endotoxin-free 0.9% saline) on GD15. A tail vein blood sample was taken 3h post-treatment to measure maternal cytokine concentration. Offspring were culled to 10 pups/litter on postnatal day 1 (PD1) and either crossed to a dam in the opposite treatment group or remained in their home litter. Offspring ultrasonic vocalisations (USVs) were recorded on PD6, 10, and 14 and analysed using the open-source MATLAB script MUPET. Offspring were tested on the attentional set-shifting task (ASST) in adulthood.

Results: mIA resulted in a significant increase in maternal plasma TNF-α concentration at three hours post-treatment (GLM treatment, F(1,13)=17.92, p=0.001). Prenatal exposure to poly I:C, independent of postnatal maternal effects, significantly increased the number of syllables emitted by female (GLM treatment group, F(1,295)=16.65, p<0.001) and male (GLM treatment, F(1,298)=13.05, p<0.001) pups across all time-points. Cross-fostering had no effect on the number of syllables emitted by female (GLM cross-fostered, F(1,295)=0.23, p=0.631) or male (GLM cross-fostered, F(1,293)=0.91, p=0.341) pups. In adult female offspring, poly I:C caused an increase in the number of trials taken in the ASST (GLMM trials, F(1,11)=10.14, p=0.009). Furthermore, the concentration of the maternal TNF-α response predicted a more severe set-shifting deficit (GLMM trials, F(1,11)=5.70, p=0.036).

Conclusions: Poly I:C induced a rise in maternal TNF-α concentration. Neonatal and adult offspring from poly I:C treated dams exhibited a range of behavioural and cognitive deficits. Prenatal exposure to maternal pro-inflammatory cytokines, but not the postnatal maternal environment, affected USVs in male and female offspring. Our data suggests that the prenatal environment, specifically the maternal inflammatory cytokine response, is an important predictor of later life cognitive deficits and contributes to the pathogenesis of cognitive dysfunction.

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B05
EFFECTS OF HANDLING IN RATS AS A FORM OF ENVIRONMENTAL ENRICHMENT ON COGNITION IN THE SUB-CHRONIC PHENCYCLIDINE MODEL FOR SCHIZOPHRENIA

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Introduction: Cognitive impairment is a serious problem for patients who suffer from a number of psychiatric disorders, with little to no effective treatments available. Environmental enrichment is recommended by NC3R's as a method of improving laboratory animal welfare; e.g. handling from early life. Neonatal handling has been shown to prevent the effects of sub-chronic phencyclidine to impair working memory performance (Tejedor-Real et al, 2007.Biological Psychiatry; Vol 61(7)(pp 865-872)). In order to test the hypothesis that enrichment via handling in adulthood can protect against scPCP induced deficits, we handled rats for 10 days prior to dosing with PCP and then, following washout, tested them in the novel object recognition task (NOR).

Methods: 4 groups of adult female Lister Hooded rats (n=10/group) were used; vehicle handled/non-handled, scPCP handled/non-handled. Rats in the handling groups were handled by 2 experimenters for 5 minutes per rat per day for 2 weeks; this was in addition to the standard handling procedures that the non-handled rats received (e.g. weighing & tail marking). Rats then received either 2 mg/kg PCP or 0.9% saline bi-daily for 7 days followed by 7 days wash-out and then tested in NOR (1 minute inter-trial interval - ITI) 2, 4 and 7 weeks post handling. Rats were also tested in NOR with a 6 hour ITI at 5 weeks post handling. Data were analysed by ANOVA and post-hoc Students t-test.

Results: At 2 weeks post handling (1 minute ITI) scPCP handled rats successfully discriminated between the novel and familiar object (p<0.001) This effect persisted at 4 weeks (p<0.01) and 7 weeks (p<0.05). As expected, scPCP non-handled animals were unable to discriminate between the novel and familiar objects during these 3 NOR tasks. Following a 6-hour ITI, non-handled rats, both naive and scPCP treated, were unable to discriminate between the novel and familiar object. However, handled rats in both groups showed a robust discrimination of the novel and familiar object; (p<0.05) and (p<0.01).

Conclusions: The results demonstrate that deficits in cognition normally induced by sub-chronic PCP administration can be prevented through handling of female Lister Hooded rats. Work to investigate the mechanism for this beneficial effect could identify novel therapeutic strategies to improve the lives of patients which suffer cognitive impairments. Subsequent work will investigate the contribution of dendritic spine density to the improvement in cognition displayed by the handled rats. (Glantz et al, 2000. Arch Gen Psychiatry; Vol 57 (pp 65-73.).)

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B06
This abstract has been withdrawn.
CHARACTERIZING THE TRANSCRIPTIONAL PROFILE OF THE CALCIUM CHANNEL GENE CACNA1F IN HUMAN BRAIN

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Introduction: Voltage-gated calcium channels (VGCCs) play a significant role in many aspects of brain function including neuronal excitability and synaptic plasticity. Large-scale genomic studies have shown association of VGCC genes to various psychiatric and cognitive phenotypes. Each VGCC gene encodes multiple functionally-distinct isoforms via transcriptional mechanisms. However, the complement of VGCC isoforms present in human tissues, including brain, remains largely unknown. The aim of this research is to elucidate the full-length coding sequences of the CACNA-genes that encode the key VGCC alpha subunits in human post-mortem brain tissues. Here, we present our findings for the CACNA1F gene, which encodes CaV1.4. CACNA1F is not reported to be expressed in brain tissue, but there is little direct investigation of this possibility of humans. This lack of expression is perhaps surprising, given genetic associations of the CACNA1F locus with educational attainment.

Methods: We examined publicly-available short-read RNASeq data obtained from human brain (LIBD Developmental Dataset) for evidence of reads localized to the CACNA1F locus. Guided by this information, CACNA1F in human post-mortem tissue from 8 brain regions which are Striatum, Thalamus, Parietal lobe, Cingulate, Dorsolateral prefrontal cortex, Superior temporal lobe, Cerebellum, and Occipital lobe in 6 healthy subjects were examined to characterize the isoform profile of CACNA1F in those regions. For the experiment, we used a long-range PCR coupled with nanopore long-read sequencing and 5’ RACE (rapid amplification of cDNA ends).

Results: The RNASeq data indicated the presence of a putative truncated mRNA transcript at the CACNA1F locus. Consistent with this, we were unable to amplify the full-length isoform of CACNA1F, but could amplify the predicted truncated isoform which is 1298bp in length and maps to the 3’ end of the gene. Nanopore sequencing revealed the diversity of CACNA1F isoforms arising from this locus, and 5’-RACE defined the transcriptional start site. The diversity of CACNA1F isoforms across individuals and brain regions will be presented using Principal Components Analysis (PCA) plots.

Conclusions: We have demonstrated for the first time the presence of a truncated isoform of CACNA1F mRNA present in human brain. The functional significance of this isoform is currently unknown, and will be investigated in our future studies. It is unlikely to encode a functional VGCC subunit, since it lacks the necessary transmembrane domains. However, several other VGCC genes are reported to encode transcription factors from their 3’ ends; thus, it is possible that the isoform that I have identified plays a role in regulating gene expression. Finally, our findings highlight how much remains to be found out about the complement of full-length mRNA isoforms present in human tissues, and highlights the potential of nanopore amplicon sequencing to clarify this question.

Funding: The presenter is a self-funded PhD student and lab resources are funded by MRC grant.
B08

HAPLOINSCUFIENCY OF PSYCHIATRIC RISK GENE CYFIP1 IMPAIRS MIGRATION OF ADULT BORN HIPPOCAMPAL NEURONS IN AN ARP2/3-ACTIN DEPENDENT MECHANISM

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Introduction: Neuronal migration is crucial for the correct patterning and functioning of all brain areas. Although this is largely a developmental process, continued generation and migration of new neurons occurs in the dentate gyrus of the hippocampus in adulthood, where newly born cells migrate into the granular layer. Adult born neurons contribute to a range of behaviours. Adult hippocampal neurogenesis is disturbed in several psychiatric conditions and may contribute to symptoms. Genetic risk factors contribute significantly to risk of development of psychiatric conditions. Loss of one copy of the 15q11.2 BP1-BP2 chromosomal interval, containing four genes, significantly increases risk for schizophrenia and autism. The most prominent gene in this locus Cytoplasmic FMR1 Interacting Protein 1 (Cyfip1). CYFIP1 can affect mRNA translations though interaction with FMRP, and affect actin branching and polymerisation through the WAVE regulatory complex and Arp2/3. Here we show haploinsufficiency of Cyfip1 disrupts migration of newly born neurons in the mouse hippocampus through an actin dependent mechanism.

Methods: Cyfip1 heterozygous knockout mice and wildtype littermate controls of mixed sex were used. In vivo, we studied immature neurons by immunohistochemistry for doublecortin (n=16), and mature adult born neurons by BrdU/NeuN staining following a 30 day BrdU pulse-chase paradigm (n=26), in animals 8-12 week old. Primary hippocampal progenitors for time-lapse imaging were prepared from P7 animals (n=12) through enzymatic digestion and density gradient purification, and cultured with EGF and FGF2. For rescue experiments, cultures were incubated with Arp2/3 inhibitors CK-548 or CK-666 for two hours prior to time-lapse imaging. Analysis was by Student T test or two factor ANOVA.

Results: In vivo, we show that in Cyfip1+/- animals, compared to controls, more proliferative cells are located in the subgranular zone (80.4±1.1% vs 88.2±0.6%, p=3.2x10-5) and adult born mature neurons are found less far into the granular zone (13.6±2.3 vs 6.0±0.7 µm, p=0.004) suggesting a deficit in migration. We confirm this deficit by in vitro time-lapse imaging of primary hippocampal progenitors, showing a reduced distance moved in Cyfip1+/- cultures (133.0±4.7 vs 90.7±12.0 µm, p=0.003). Cyfip1+/- cells have increased F-to-G actin ratios (0.67±0.3 vs 1.48±0.28, p=0.034), and inhibition of the CYFIP1 regulated actin branching and polymerisation initiator Arp2/3 normalises the migration phenotype in vitro.

Conclusions: This work shows for the first time how a psychiatric risk gene can impact on the migration ability of newly born neurons. Misllocalisation of new neurons could have profound consequences for their ability to integrate correctly into existing local circuitry and their eventual functioning.

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B09
THE TOPOGRAPHY OF STRIATAL DOPAMINE AND SYMPTOMS IN PSYCHOSIS: AN INTEGRATIVE PET AND MRI STUDY
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Introduction: Striatal dopamine dysfunction is thought to underlie symptoms in psychosis, yet it remains unclear how changes in a single neurotransmitter could underlie the diverse and heterogeneous presentations that are observed in clinical practice. The striatum is a central processing hub, receiving input from almost the entire cortex, and plays a role in sensory, motor, affective, and cognitive processes. Thus, the precise localization of dopamine dysfunction within the striatum may determine which particular corticostriatal circuits are affected and determine symptomatology. We tested this hypothesis using a multimodal imaging approach in 29 unmedicated and minimally-treated patients with first episode psychosis and 21 healthy controls.
Methods: Patients were clinically assessed at baseline, and following a minimum of four weeks’ treatment with a dopamine antagonist. Each participant was also scanned at baseline using 18F-DOPA positron emission tomography to index striatal dopamine synthesis capacity, and resting state functional MRI to map corticostriatal functional connectivity. For each participant, we used functional connectivity between cortical resting state networks and the striatum to generate individualised connectivity-defined striatal maps. We use these maps to calculate dopamine synthesis capacity for striatal subregions preferentially connected to each cortical network, and investigated whether dopamine function within these different striatal regions showed a relationship with both baseline symptomatology and change in symptoms.
Results: 50 participants took part in the study (21 controls and 29 patients). We demonstrated significantly greater orthogonality in our individualised connectivity-based approach compared to standard parcellation methods, which allowed, for the first time to our knowledge, specific subregion-symptom relationship to be investigated. Dopamine synthesis capacity in striatal areas showing strong functional connections to sensorimotor cortex was related to the severity of motor symptoms at baseline (p=0.01), and to the change in motor symptoms following treatment (p=0.001). We also found significant associations between the severity of negative symptoms and striatal dopamine synthesis capacity in striatal regions connected to the default mode network, and between affective symptoms and regions connected to a cinguloopercular cortical network.
Conclusions: We show that motor retardation associated with schizophrenia is specifically linked to dopamine dysfunction within regions of the striatum linked to the sensorimotor cortex. We also find that dopamine dysfunction within striatal regions linked to the default mode network, and cinguloopercular network may relate to negative and affective symptoms respectively.
Funding: Wellcome trust ( 200102/Z/15/Z, 094849/Z/10/Z)

B10
THE USE OF COMBINATION AND HIGH-DOSE ANTIPSYCHOTIC TREATMENT IN AN EARLY INTERVENTION SERVICE IN SOLIHULL
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Introduction: Combination (i.e. two or more different antipsychotics) and high-dose antipsychotic treatment is associated with an increased risk of adverse side effects, including extrapyramidal side effects (EPSEs), QTc prolongation and sudden cardiac death. For this reason, the Royal College of Psychiatrists Standards for Early Intervention In Psychosis Services states that patients should not be prescribed more
than one antipsychotic medication and that dosages should not exceed British National Formulary (BNF) recommendations. However, in exceptional cases where these recommendations are not adhered to, a rationale should be recorded for this and physical health assessments should be repeated at least annually. The aims of this clinical audit are to identify the prevalence of combination and high-dose antipsychotic treatment in an Early Intervention Service (EIS) and determine whether there is sufficient physical health monitoring of these patients.

Methods: A cross-sectional audit was carried out by examining the RiO electronic records of all patients on the caseload of Solihull EIS (as of 24th October 2018).

Results: Amongst the 103 records examined, the prevalence of combination and high-dose antipsychotic treatment was 13% (n=13) and 4.9% (n=5) respectively. There was documentation of the rationale in all cases, which included improvement of symptom control and for cross titration when switching from one antipsychotic to another. Of these patients, 100% had received a physical health assessment but only 71% (n=73) had undergone an electrocardiogram (ECG) within the last 12 months.

Conclusions: A small proportion of patients were prescribed combination or high-dose antipsychotics but there is optimal documentation of the clinical reasoning behind this. Although all of these patients were receiving regular physical health assessments, there was no evidence of a recent ECG recording within the last 12 months for 29% (n=30). The results of this audit highlight the need for improved ECG monitoring amongst high-risk patients within this Early Intervention Centre. In order to achieve this, the following recommendations have been made: (1) to flag patients on combination and high-dose antipsychotic treatment with addition of this onto 6-monthly care programme approach (CPA) review documentation; (2) to offer annual ECG testing to all of these patients; (3) to inform patients of the importance of annual ECG testing and encourage attendance to appointments; (4) to regularly update and document ECG results on the RiO electronic record system.

Funding: No sponsorship was received for the study.

B11

EVIDENCE SUPPORTING THE SYNAPTIC DYSFUNCTION HYPOTHESIS OF SCHIZOPHRENIA USING \[11C\]UCB-J PET AND \[3H\]UCB-J AUTORADIOGRAPHY

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Introduction: Converging lines of evidence from genetic and post-mortem studies and indirect neuroimaging findings implicate synaptic dysfunction in schizophrenia pathoaeiology. Using positron emission tomography (PET) with novel radioligand \[11C\]UCB-J, we can test this hypothesis directly by quantifying synaptic vesicle glycoprotein 2A (SV2A) in vivo. Furthermore, confounding effects of dopamine antagonist administration on SV2A can be explored with \[3H\]UCB-J autoradiography in a rodent model of antipsychotic exposure.

Methods: Sixteen volunteers with schizophrenia and 16 healthy volunteers underwent \[11C\]UCB-J PET and T1-weighted structural MRI. Volumes of distribution (VT) and corrected grey matter volumes (GMV) were estimated for three regions of interest (ROIs): frontal and anterior cingulate cortices (FC and ACC) and the hippocampus. Two-way analysis of variance (ANOVA) was used to test for effects of group and ROI and group-by-ROI interactions. Post hoc t-tests were used to test the effect of group at each ROI, with false discovery-rate adjustment for multiple comparisons. We explored relationships between clinical variables (chlorpromazine equivalent dose, PANSS score, duration of illness [DOI]) and VT. Sprague-Dawley rats (9-10
weeks old) underwent vehicle (n=7) or haloperidol (0.5 [n=3] or 2 mg/kg/day [n=5]) administration for 28 days and post-mortem [3H]-UCB-J autoradiography, with SV2A specific binding measured in the prefrontal cortex (PFC) and ACC. Autoradiography data were analysed by two-way ANOVA with Bonferroni’s post hoc test.

Results: The groups were not significantly different in age (mean years [standard error of the mean] schizophrenia volunteer age=41.4 [3.0], healthy volunteer age=38.4 [3.4], p = 0.42). There were significant effects of group (P<0.05) and ROI (P<0.0001), with a significant group-by-ROI interaction (P=0.0005) in VT. There were significant reductions in VT in the FC and ACC (Cohen’s d=0.9 and 1.0, p=0.03 and 0.03 respectively), but not in the hippocampus (p=0.13). There were no significant group differences in corrected GMV, nor significant associations between VT and corrected GMV in any of the ROIs. There were no relationships (P>0.05) in any of the ROIs between VT and chlorpromazine-equivalent dose, PANSS scores or DOI. In the rats, there was no significant effect of treatment (p=0.27) nor region (p=0.18), nor treatment-by-region interaction (p=0.25) for [3H]UCB-J specific binding.

Conclusions: SV2A levels are lower in the FC and ACC in schizophrenia, and dopamine antagonist treatment at clinically relevant levels does not alter SV2A levels in the PFC and ACC in rats. This supports the hypothesis that synaptic dysfunction occurs in vivo in schizophrenia, irrespective of antipsychotic exposure.

Funding: ODH and ACV acknowledge financial support for this study from the Medical Research Council.

B12
IMPAIRED 1-8 HZ PHASE-COUPLING BETWEEN HIPPOCAMPUS AND MEDIAL PREFRONTAL CORTEX IN SCHIZOPHRENIA
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Introduction: Impaired communication between hippocampus and prefrontal cortex has long been thought to be a key pathology in schizophrenia, but its electrophysiological nature has never been demonstrated in humans. A genetic mouse model of schizophrenia has impaired hippocampal-prefrontal synchrony during working memory performance (Sigurdsson et al., 2000, Nature). Specifically, these Df(16) A(+/−) mice (models of the 22q11.2 microdeletion in humans) showed impaired prefrontal phase-locking to hippocampal theta oscillations that predicted performance on a T-maze task. We sought to reproduce and extend these findings in human subjects with a schizophrenia diagnosis.

Methods: 18 early course Scz (15 male, 3 female; 8 unmedicated) and 26 age and IQ-matched controls (19 male, 7 female) performed: 1) A spatial memory task in a 3D environment (Fig 1A, Kaplan et al, 2014) whilst undergoing magnetoencephalography (MEG). Oscillatory activity was compared between the intertrial interval and a cue period, when subjects had to recall the location of one of four objects in the environment prior to navigating there. 2) An associative memory (Paired Associates) task (Fig 1C) known to depend on mPFC-HC theta coupling (Backus et al, 2016). A larger, partially-overlapping group of 29 controls and 33 Scz also had [11C]Ro15-4513 PET to assess cortical GABAα5-R density.

Results: Compared with controls, Scz showed: 1) mildly impaired spatial memory (Fig 1B), relating to the furthest object (p=0.027, one-tailed), and markedly impaired indirect association (p<0.005) –performing no different to chance (Fig 1D). 2) a marked loss of cue-induced 1-8 Hz power, especially around left frontotemporal sensors (Figs 2A & 2B), which localised to mPFC and left hippocampus (Fig 2C right, peak pFWE(SVC)=0.019). 3) reduced 1-8 Hz phase-locking value (PLV) between mPFC and left anterior hippocampus (aHC; corrected for medication, movement and power differences: peak pFWE(SVC)=0.019, Fig 3A), most marked in those off medication (Fig 3B), and diminished GABAα5-R density there (assessed using [11C]Ro15-4513 PET, Fig 3D). mPFC 1-8 Hz PLV with right aHC correlated with performance in controls (peak pFWE(SVC)=0.06, Fig 3C) and weakly in Scz (peak p(unc)=0.03). 4) Both Scz and controls
showed θ phase-γ amplitude coupling from left aHC to PFC, and the extent of this coupling correlated with GABAα5-R density there (assessed using [11C]Ro15-4513 PET).

Conclusions: Overall, we demonstrate that HC-mPFC phase coupling at 1-8 Hz is reduced in schizophrenia, as predicted by animal models, and this loss is specific to theta frequency, not caused by medication or cannabis use, and not related to movement or changes in theta power in these areas. This phase coupling is related to performance at both spatial and associative memory tasks, and thus may underlie numerous cognitive deficits in schizophrenia.

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B13

OXYTOCIN MODULATES HIPPOCAMPAL BLOOD FLOW IN PEOPLE AT ULTRA-HIGH RISK OF PSYCHOSIS

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Introduction: Preclinical and human studies suggest that hippocampal dysfunction is a key factor in the onset of psychosis. Dysfunction appears to begin in the Cornu Ammonis 1 (CA1) subregion before spreading to the subiculum and extra-hippocampal regions as psychosis develops. People at Ultra-High Risk (UHR) of psychosis present with attenuated psychotic symptoms and have a 20% risk of developing psychosis within 2 years. Recent research shows that resting hippocampal blood flow is altered in UHR individuals and predicts non-remission/transition to psychosis. Oxytocin, a neuropeptide with anxiolytic and potential antipsychotic properties, is currently under investigation as a novel therapeutic. Previous work in healthy males indicates that a single dose of intranasal oxytocin has marked effects on cerebral blood flow, including in medial temporal regions such as the hippocampus. However, the effects of oxytocin in UHR individuals remain unknown.

Methods: We examined the effects of intranasal oxytocin on hippocampal blood flow in UHR individuals. In a double-blind, placebo-controlled, crossover design, 30 UHR males underwent two MRI scans at 3 Tesla, once after 40IU intranasal oxytocin and once after matched placebo. Pseudo-continuous Arterial Spin Labelling was used to measure left hippocampal blood flow in a region-of-interest analysis of data acquired at 22-28 and at 30-36 minutes post-dosing. Exploratory analyses tested for effects on hippocampal subregions CA1, CA2, CA3, subiculum and dentate gyrus.

Results: Compared to placebo, administration of oxytocin was associated with increased hippocampal blood flow at both the first (F(1,27)=9.06, p[FWE]<.05) and second (F(1,27)=4.96, p[FWE]<.05) time point, although the effect at the second did not survive adjustment for effects on global blood flow. Exploratory analyses demonstrated that oxytocin increased perfusion in all hippocampal subregions (p<.05, uncorrected) with the largest effects in the dentate gyrus and CA1.

Conclusions: Our data suggest that oxytocin can modulate hippocampal blood flow in UHR individuals and therefore merits further investigation as a potential novel treatment for this patient group. Future studies employing a parallel group of healthy controls are needed to interpret the direction and specificity of the effects, and larger-scale trials should examine whether these neurophysiological effects translate into clinical efficacy.
VARIANTS IN THE ZINC TRANSPORTER 3 ENCODING GENE (SLC30A3) MODULATE GLUTAMATERGIC ACTIVITY DURING A WORKING MEMORY TASK IN SCHIZOPHRENIA

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Introduction: The SLC30A3 gene, which encodes the Zinc Transporter 3 (ZnT3), is localised to synaptic vesicles in glutamate synapses, is known to be involved in cognitive function, and single nucleotide polymorphisms (SNPs) of this gene have been shown to be associated with schizophrenia (Perez-Becerril C et al. European Psychiatry. 2014;20(3):172-178). Previous work from our team, using functional magnetic resonance spectroscopy (1H-fMRS), has demonstrated significant increases in glutamatergic measures between N-back task conditions in a healthy control group but not in schizophrenia (Jelen LA et al. European Neuropsychopharmacology. 2019;29(2): 222-234). Here, we perform post-hoc analyses on this data-set to consider how variants in the SLC30A3 gene impact on dynamic glutamate measures in schizophrenia.

Methods: 14 patients with schizophrenia underwent a 15-min N-back task in a 48-s block design during 1H-fMRS acquisition (TE=105ms, TR=2000ms, NEX=8, GE Discovery MR750 3T scanner). Data from the averaged 0-back and 2-back conditions were processed using TARQUIN (Wilson M et al. Magn Reson Med 65:1-12). Genotyping was performed on two SNPs in SLC30A3 (rs11126929 and rs11126936) and patients were divided into two groups according to allele status for each SNP: (1-Common): Homozygous for common allele; (2-Rare): Heterozygous or homozygous for rare allele. Levels of glutamate and Glx (glutamate + glutamine), scaled to total creatine (TCr), across the 0-back and 2-back conditions were analysed using 2x2 repeated-measures analyses of variance (rmANOVA) with allele status as a between-subjects factor.

Results: 6 patients were homozygous for the common allele, while the remaining 8 had either one or two copies of the rare allele, for both the rs11126929 and rs11126936 SNPs. 2x2 rmANOVAs determined a significant time by allele status interaction for Glu/TCr (P=0.026) and Glx/TCr (P=0.016) for both the rs11126929 and rs11126936 SNPs, with no significant main effects of time or allele status. In patients with the common allele, levels of Glu/TCr and Glx/TCr increased between task conditions, while in the rare allele group levels of both metabolites decreased.

Conclusions: Patients with common versions of the two tested SNPs of the SLC30A3 gene showed a general increase in glutamatergic metabolites between task conditions, reflecting a pattern previously seen in a healthy group. However, those patients with rare allele versions showed a general reduction, suggesting abnormalities of glutamatergic neurotransmission. Further work investigating SNP variants in the ZnT3 encoding gene may prove valuable in identifying patients that could benefit from compounds that act to modulate glutamate neurotransmission.

Funding: This work was supported by the NIHR BRC for Mental Health at the SLaM NHS Foundation Trust and IoPPN, KCL.
**B15**

**GENE TO COGNITION AND CONNECTIVITY IN CONSANGUINEOUS SCHIZOPHRENIA MULTIPLEX FAMILIES**

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**Introduction:** BACKGROUND The number of polymorphisms unearthed by GWAS in huge multinational samples keeps on multiplying, however, it is difficult if not impossible to establish causative correlations with complex heterogeneous conditions like schizophrenia. Consanguineous families with multiple cases, from higher risk populations such as Yorkshire Pakistanis (Saleem et al 2019), afford the opportunity of studying gene – endophenotype - clinical disorder relationship in relatively homogeneous samples.

**AIMS** To ascertain the relationship between familial relatedness, cognition and white matter structural connectivity in members of a consanguineous family with multiple cases of schizophrenia

**Methods:** Affected (n=4), unaffected family members (n=11) and healthy volunteers (n=30) were tested with CANTAB, an automated neuropsychological testing battery. Tests used were the pattern recognition memory (PRM) task for visual memory, spatial recognition memory (SRM) task for spatial memory, intra/extra dimensional set shifting (IED) task for executive function, stockings of Cambridge (SOC) task for working memory and spatial planning and choice reaction time (CRT) for attention. Patients (n=4), unaffected homozygotes (n=4), unaffected heterozygotes (n=3) and healthy volunteers (n=3) underwent functional magnetic resonance imaging whilst performing an n-back working memory task inside an MRI scanner with an MR compatible in-room LCD and fibre optic response button. Images were run through FSL for DTI, and MATLAB and SPM 12 for pre-processing fMRI. DTI data was run through Nordic Ice4 to determine Fractional Anisotropy (FA) and Mean Diffusivity (MD).

**Results:** Patients and their homozygous relatives performed significantly worse on PRM and SRM tasks, whilst on CRT only patients performed significantly worse than the healthy controls. The cognitive deficits in affected and unaffected family members correspond with lower fractional anisotropy in anterior cingulate cortex (ACC) and left dorsolateral prefrontal cortex (DLPFC).

**Conclusions:** Based on this small single family sample, results indicate that degree of familial relatedness appears to influence the cognition and structural white matter integrity in this family. REFERENCE Saleem M, Brewin A, Ding C, Nazari J, Garnham M, Robinson J, Hossali P, Cardno AG, Inglehearn CF, Mahmood T (2019) Risk of psychosis in Yorkshire South Asians. Journal of Psychiatric Intensive Care (under publication)

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**B16**

**THE EFFECTS OF ANTIpsychotic TREATMENT ON BRAIN FUNCTION DURING A COGNITIVE TASK: A PROspective FMRI STUDY IN FIRST EPISODE PSYCHOSIS**

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**Introduction:** Aim: To explore whether antipsychotic treatments affect neural response during the N-Back working memory task. Secondly whether a change in neural response linked to clinical change.

**Methods:** 16 patients with first-episode psychosis (FEP) and 30 healthy control (HC) volunteers were included in the study. 7 patients were treatment-naive, 5 were treatment-free and 4 were minimally treated (with up to two weeks of antipsychotics) at baseline. The average duration of treatment from the commencement of treatment until the follow-up MRI scan was 52 days (± 17.60). This was a naturalistic study and the clinical team, in discussion with the patient, made the choice of antipsychotic medication.
Participants were studied using functional magnetic resonance imaging whilst performing the n-back working memory task. Blood oxygen level-dependent (BOLD) response, task performance, and the Positive and Negative Syndrome Scale (PANSS) were measured.

Results: Results: There was hypoactivation in the DLPFC (BA 9 and 46, xyz = -58, 6, 30, p(FWE-corrected) = 0.043), superior frontal gyrus (xyz = 24, 0, 58, p(FWE-corrected) = 0.018), and thalamus (xyz = 20, -30, 12, p(FWE-corrected) = 0.036) in patients compared to healthy controls at baseline during a higher working memory load compared to a lower working memory load. There was a trend-level result in the hippocampus (xyz = 22, -34, 10, p(FWE-corrected) = 0.059) in patients compared to healthy controls at baseline. With treatment, there was no significant change in activation from baseline to follow-up nor were there any significant correlations between a change in negative symptoms and a change in BOLD response during a higher working memory load.

Conclusions: Our findings indicate that treatment does not affect neural response during the n-back working memory task and symptomatic improvement is not associated with altered cortical brain function in psychosis. These findings indicate that antipsychotic treatments do not have a significant effect on the neural mechanisms underlying working memory impairment in psychosis.

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B17
INVESTIGATING THE ASSOCIATION BETWEEN POLYGENIC SCORES FOR SCHIZOPHRENIA AND CHILDHOOD TRAUMATIC EVENTS

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Introduction: There is a wealth of literature on the observed association between childhood trauma and subsequent psychotic experiences. It has been argued that childhood trauma is a causal environmental risk factor for psychotic symptoms. However, the relationship between childhood trauma and psychotic experiences is complex and gene-environment correlation could explain part of this effect.

Methods: We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Norwegian Mother and Child Cohort Study (MoBa) to disentangle this association. Polygenic scores (PGS) for schizophrenia liability were derived for individuals in ALSPAC and MoBa with data on both childhood trauma and genome-wide genotyping data. This included mothers, children and fathers where possible. In ALSPAC, measures of trauma were derived based on questionnaire data collected throughout childhood and adolescence (0-17 years), while in MoBa trauma data was collected as part of the questionnaire measured at age 8 years. We investigated the association between the PGS for schizophrenia liability and experiencing childhood trauma.

Results: Within ALSPAC, we found evidence of an association between the PGS for schizophrenia liability and increased trauma at each of our ages of interest (0-5, 6-11 and 11-17 years), and across of childhood and adolescence (0-17 years). These effect sizes were consistent when using both child and maternal PRS. In ALSPAC, we also investigated the association between PGS for schizophrenia liability and different subtypes of trauma, and found strong evidence of an association between the majority of trauma domains when using both maternal and child PGS. We identified evidence of an association with increased domestic violence (OR=1.16, p=1.7x10-6), sexual abuse (OR=1.15, p=0.009), emotional cruelty (1.16, p=3.3x10-5) and physical cruelty (1.15x10-4). However, we found no strong evidence of an association with either maternal or child PRS and bullying.
Conclusions: Analyses across two international birth cohorts indicate that genetic liability for schizophrenia is associated with experiencing childhood trauma. We also found evidence to suggest that this association has some specificity to the home environment and is therefore likely that gene-environment correlation and indirect genetic effects play a role in this relationship. The observed association between childhood trauma and subsequent psychotic experiences may in part reflect this correlation, so that the causal effect of childhood trauma may be smaller than that reported in most observational studies to date.

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B18
INVESTIGATING THE ASSOCIATION BETWEEN CHILDHOOD TRAUMA AND CANNABIS USE EARLY IN LIFE IN A SAMPLE OF FIRST EPISODE PSYCHOSIS PATIENTS AND CONTROLS

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Introduction: A recent study identified that greater frequency of cannabis use increased odds of psychosis, and the association was also related to cannabis potency (Di Forti et al., 2019. Lancet Psychiatry; doi:10.1016/S2215-0366(19)30048-3). Other studies demonstrate increased substance abuse with physical and/or sexual abuse in childhood (Tomassi et al., 2017. British Journal of Psychiatry;211:151-156). Furthermore, combined presence of substance abuse and childhood trauma increases risk of psychosis, beyond that of each factor alone (Harley et al., 2010. Psychological Medicine;40(10):1627-1634). The present study aimed to investigate the association between childhood trauma and cannabis use early in life.

Methods: 423 participants were recruited as either controls (n=224) or first-episode psychosis patients (n=199) within the South London and Maudsley NHS Foundation Trust. Data were collected using the Childhood Experience of Care and Abuse Questionnaire and Cannabis Experiences Questionnaire. Exposure to childhood trauma entailed experience of either separation, loss, physical and/or sexual abuse before age 17. Chi-square tests with odds ratios calculated explored associations between childhood trauma and use of cannabis in the lifetime, and frequency of use early in life (before age 16).

Results: Associations were found between exposure to childhood trauma and lifetime cannabis use (OR=1.964, 95% CI: 1.295-2.980, p=.002). Furthermore, a trend emerged between childhood trauma and lower frequency of use early in life (OR=.883, 95% CI: .368-2.120, p=.780). The sample was divided to explore associations in patients and controls separately. In patients, the association between exposure to trauma and lifetime cannabis use was apparent but not statistically significant (OR=1.556, 95% CI: .831-2.914, p=.168), and a non-significant trend with lower frequency was found (OR=.769, 95% CI: .195-3.038, p=.708). In controls, the association between exposure to trauma and lifetime cannabis use was significant (OR=2.06, 95% CI: 1.147-3.701, p=.016), and a non-significant trend with higher frequency of use identified (OR=1.52, 95% CI: .422-5.476, p=.522).

Conclusions: Findings suggest exposure to childhood trauma increases likelihood of lifetime cannabis use but at a low frequency of use early in life. Lifetime cannabis use was more likely in both patients and controls who reported childhood trauma but there were potential differences in frequency between the groups. Given the modest sample sizes, findings should be considered with caution and further investigation in larger samples is needed.

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B19

GAMIFIED MOBILE EEG FOR EARLY DETECTION OF PSYCHOTIC DISORDERS: IDENTIFYING NEEDS FROM CLINICIANS AND END-USERS

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Introduction: Psychotic illnesses can be debilitating and severe, but their impact on affected individuals can be minimised if patients are identified in the early stages of the disease and receive appropriate treatment. In recent years, research efforts have focused on better characterising those individuals classified as being at ‘high risk’ of transition to psychosis. Reliable predictive biomarkers of transition could help with the selection of the most appropriate interventions and improve long-term health outcomes. Electroencephalography (EEG) represents a potentially scalable tool to accurately predict risk of transition among a large population of patients categorised as clinically high-risk of psychosis (Pantlin & Davalos, 2016, Schizophr. Res. Treatment, 1-5). Several predictive markers have already been identified, including ‘mismatch negativity’ (MMN), a translational auditory-evoked event-related potential (ERP) (Light & Naatanen, 2013, Proc. Natl. Acad. Sci, 110, 15275-15176). With the availability of very large EEG datasets, it may be possible to use machine-learning to accurately classify individuals at risk. However, existing EEG hardware of sufficient quality to generate this data is expensive and requires expert supervision to administer. In this study we assess the suitability and usability of a 16-channel prototype dry-EEG headset and accompanying gamified neurocognitive tests – designed to be used to record EEG longitudinally, at home.

Methods: Focus groups were conducted with 1) 17 healthy young adults (18-35), 2) 3 young adults identified as ‘high-risk’ of psychosis, and 3) 9 clinicians experienced working with at-risk young adults. Participants tested the headset and games and reviewed trial management dashboards (clinicians only). All commented on how the platform might fit into their current schedule/practice. 5 healthy young adults recorded sessions at-home in a 2-week field trial.

Results: For clinicians, themes identified included interpretability of output, proven accuracy of risk detection, and the need for the platform to be sensitive the psychosis continuum. Most agreed that there was space in the current clinical pathway for integration of the proposed platform. For young adults, depth and variety of gameplay was important. Finally, caution was urged by the clinicians and ARMS group that individuals managing low-level symptoms of psychosis might prefer a reduced-frequency at-home recording schedule. Data submitted from the at-home trial yielded data of sufficient quality to extract event-related potentials (MMN, P300, ERN).

Conclusions: With a greater focus on motivating long-term trial adherence, gamified mobile EEG could feasibly be used to generate large datasets amenable to machine-learning analysis and early identification of at-risk individuals.

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B20

CHILDHOOD MALTREATMENT AND BDNF METHYLATION CHANGES IN FIRST-EPODE SCHIZOPHRENA, UNAFFECTED SIBLINGS AND CONTROLS

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Introduction: Exposure to early-life stress, such as childhood maltreatment can disrupt epigenetic programming in the brain (Kundakovic et al. 2015, PNAS, 22:6807-13) with lasting consequences for brain gene expression and behaviour. It also increases susceptibility to cognitive deficits in adult life and psychiatric illnesses, such as schizophrenia (De Bellis 2005, Child maltreatment, 2:150-72). We investigated if differences in one of the epigenetic factors, DNA methylation, in the BDNF gene are present in the blood of first-episode psychosis patients, their unaffected siblings and population-based controls.

Methods: DNA was extracted from blood of 35 individuals with first-episode schizophrenia, 35 age-, sex- and years of schooling-matched population-based controls, and 21 unaffected siblings of patients. The genomic DNA was bisulphite converted and pyrosequencing was used to determine methylation levels in four CpG sites within exon IV of the BDNF gene and compared to the global measure of methylation, LINE-1. The subjects provided a history of childhood maltreatment using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003, Child Abuse and Neglect, 2:169-190). We used general linear model with Bonferroni corrections, including methylation levels as dependent variables, groups (patients, siblings and controls) and childhood maltreatment (yes or no) as fixed factor, controlling for the effects of age and gender. In the patient group, correlations between methylation levels and CTQ scores (global and subtypes of abuse and neglect) were tested by Spearman's correlation.

Results: No differences were found in BDNF methylation between the subject groups; however, those individuals who had experienced childhood maltreatment presented higher levels of BDNF methylation than those without trauma (CpG1: F = 4.0, p = 0.049; CpG2: F = 7.15, p = 0.009). Additionally, considering the FEP patients, we found positive correlations between the methylation levels at CpG2 and different categories of childhood maltreatment (Emotional Abuse: rho=0.483, p=0.005; Physical abuse: rho= 0.380, p=0.032; Sexual abuse: rho=0.383, p=0.03; Physical Neglect: rho=0.532, p=0.002; Emotional Neglect: rho=0.537, p=0.002; CTQ total score: rho=0.595, p<0.001) and no significant correlations were found when considering only controls and siblings and CTQ. These results were independent of LINE-1 methylation, which showed increased levels for siblings and patients compared to controls but no significant differences between trauma and no trauma (p=0.180).

Conclusions: Our results highlight that childhood maltreatment may bring about epigenetic changes, such as DNA methylation, which could be a possible biological mechanism underlying association between early-life stress and psychosis.

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B21
ASSOCIATIONS BETWEEN GENETIC VARIANTS OF NMDAR GENES AND FIRST EPISODE PSYCHOSIS IN A BRAZILIAN SAMPLE
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Introduction: Genetic predisposition (Harrison et al., 2015, J Psychopharmacol, 2:85–96) and dysfunction of N-methyl-d-aspartate receptor (NMDAR) genes have been hypothesized to play a major role in schizophrenia pathogenesis (Weickert et al., 2013, Mol Psychiatry, 11:1185–92). As we previously found low NR2 plasma concentrations in first-episode psychosis (FEP) patients when compared to siblings and controls (Loureiro et al., 2018, Schizophr Res, 202:55-63), we have undertaken a study of single nucleotide polymorphisms (SNPs) in the NMDAR genes to determine their association with FEP. We evaluated the frequency of SNPs of GRIN1, GRIN2A and GRIN2B genes in FEP patients compared to their unaffected siblings and community-based controls in the blood and verified the association between SNPs variants, clinical features and NR2 plasma concentrations.
Methods: Eight SNPs [rs4880213, rs11146020 and rs10747050 (GRIN1), rs1420040 (GRIN2A), rs890, rs2098469, rs7298664 and rs1806194 (GRIN2B)] were genotyped in 406 participants composed by 164 FEP patients, 76 siblings and 166 controls. Statistical evaluation was made using the binary logistic regression and ANOVA one-way. To examine the joint effects of SNPs, we assumed that the minor allele of the genotype contributed to the risk of psychosis.

Results: The genotype frequencies of the eight SNPs were in Hardy-Weinberg equilibrium for the groups. We found a significant difference in genotype frequency of the GRIN1 rs4880213 between FEP patients compared to siblings and controls, demonstrating that the genotype C/T was significantly a risk factor (OR=1.637, p=0.043) of developing psychosis. In addition, FEP patients with the A/A genotype for GRIN2A rs1420040 showed low NR2 plasma concentrations compared to those with A/G or G/G genotypes (p=0.016).

Conclusions: Our study reveals that variants of GRIN1 may be associated with psychosis, as recent findings have showed that T and C alleles may be involved in NMDAR-mediated glutamatergic excitation (Lee et al., 2016, Neural Plast, 6851592). However, the functional effect of the GRIN1 rs4880213 on the NMDAR has yet to be determined. Furthermore, the A/A genotype for GRIN2A may be responsible for the low NR2 plasma concentrations of FEP patients in relation to siblings and controls, suggesting more vulnerability to develop psychosis, as mentioned before (Loureiro et al., 2018, Schizophr Res, 202:55-63). Altogether, NMDAR subunits have SNP variants that affect the genetic susceptibility to schizophrenia and other psychosis.

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B22

REDUCED GRIN2A DNA METHYLATION IN FIRST-EPOISODE SCHIZOPHRENIA AND UNAFFECTED SIBLINGS

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Introduction: Increasing evidence points to a role for hypofunctional N-methyl-D-aspartate receptor (NMDAR) neurotransmission in schizophrenia (Uno and Coyle, 2019, Psychiatry and Clinical Neurosciences [ahead of print]). In addition, epigenetic dysregulation of NMDAR subunits has been implicated in the neurobiology of psychosis (Gulchina et al., 2017, Journal of Neurochemistry; 143:320-333). We have investigated an epigenetic factor, DNA methylation, in the promoter sequence of one NMDAR subunit gene, GRIN2A, in DNA from blood of people with first episode schizophrenia (FES), their unaffected siblings and population-based controls and verified the association between DNA methylation and clinical features.

Methods: We selected 35 FES patients, 21 unaffected siblings and population-based controls matched for age and gender. Diagnosis and clinical characteristics were assessed using the Structured Clinical Interview for DSM-IV Axis I disorders. Methylation of a DNA sequence containing three CpG sites within GRIN2A was performed by pyrosequencing and data were analyzed using non-parametric tests with a Bonferroni correction. LINE-1 sequence methylation as a measure of global genomic DNA methylation was also determined (Fachim et al., 2019, Epigenomics, 4:401-410).

Results: Both FES patients and siblings showed reduced methylation at CpG2 compared to controls (p=0.05; p=0.025, respectively) and these results are independent of LINE-1 methylation, which showed an overall increase in DNA methylation for unaffected siblings and FES patients in comparison to controls (p=0.001, for both).

Conclusions: Our results demonstrate altered GRIN2A DNA methylation in FES patients and siblings as
a potential indicator of environmental risk. This low methylation occurred at sites that bind the FOXP3 repressor transcription factor exerting inhibitory function of regulatory T-cells that express NMDAR (Sofia et al., 2012, Neurosignals; 20:61-71). Thus, these findings are consistent with increased GRIN2A transcriptional repression and hence reduced expression of this NMDA receptor subunit (Loureiro et al., 2018, Schizophr Res, 202:55-63), resulting in abnormal glutamatergic activity as a potential risk for developing schizophrenia. They also indicate epigenetic mechanisms involved in the pathophysiology of schizophrenia may also be valuable targets for future pharmacotherapeutic strategies.

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**B23**

**CARDIAC STRUCTURE AND FUNCTION IN SCHIZOPHRENIA: A CARDIAC MR IMAGING STUDY**

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Introduction: Patients with schizophrenia have a 2- to 3-fold mortality compared to the general population (Laursen et al, 2007, The Journal of clinical psychiatry). Cardiovascular disease accounts for approximately 60% of this loss of life in schizophrenia (Parks et al, 2006, NASMHPD, 25;4). There is limited evidence from previous studies using ultrasound showing LV hypertrophy and reduced LV ejection fraction in patients with schizophrenia. However, interpretation of these findings is complicated by the fact that one study did not include healthy controls, and other studies did not match for BMI or gender, or did not exclude metabolic conditions, which may confound findings. In fact, their findings are compatible and could be due to co-morbid metabolic syndrome. We aimed at investigating cardiac changes responsible for higher cardiovascular mortality in schizophrenia using gold standard cardiac magnetic resonance, and whether changes were due to medical comorbidity.

Methods: A total of 40 patients with schizophrenia were recruited. 39 healthy controls were recruited after matching participating patients for age, sex, ethnicity, and BMI. Inclusion criteria for patients were: ICD-10 diagnosis of schizophrenia, no history or family history of other major psychiatric disorders. Exclusion criterium for healthy controls was: previous history or first-degree family history of SMI. Exclusion criteria for all participants were: age <18 or >65 years, pregnancy or breastfeeding, a history positive for, or current or past treatment with medication for any main medical condition; history of continuing substance abuse.

Results: Patients with schizophrenia showed reductions in bi-ventricular end-diastolic, end-systolic and stroke volumes, and increases in concentricity and septal thickness. These findings were unchanged when adjusted in sensitivity analyses for smoking or exercise levels, other than bilateral end-systolic volumes, which were no longer significantly different. These changes were independent of medication dose and duration.

Conclusions: Our results suggest that treated patients with schizophrenia show evidence of premature heart aging, including increases in septal thickness and left ventricular concentricity, which are changes independent of medical comorbidity. These have been associated with increased risk of cardiovascular death. As patients were all taking antipsychotics, future studies should assess the contribution of antipsychotic medication on these changes.

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B24

MYOCARDIAL FIBROSIS AND INFLAMMATION IN SCHIZOPHRENIA: A CARDIAC MRI STUDY

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Introduction: Cardiovascular disease (CVD) is a major cause of excess mortality in schizophrenia. Preclinical evidence shows antipsychotics can cause myocardial fibrosis and myocardial inflammation in murine models. However, it is not known if a similar fibro-inflammatory process occurs in patients receiving antipsychotics. We therefore set out to determine if there is evidence of cardiac fibrosis and/or inflammation using cardiac MRI in medicated patients with schizophrenia compared with matched healthy controls.

Methods: 31 participants (14 patients and 17 controls) underwent cardiac MRI assessing myocardial markers of fibrosis/inflammation, indexed by native myocardial T1 time, and cardiac structure (left ventricular (LV) mass) and function (left/right ventricular end-diastolic and end-systolic volumes, stroke volumes, and ejection fractions). Depending on the data being normally distributed, SCZ and HV groups were compared using either unpaired t-tests or Mann Whitney U tests, as appropriate. Participants were physically fit, and matched for age, gender, smoking, blood pressure, BMI, HbA1c, ethnicity, and physical activity.

Results: Compared with controls, native myocardial T1 was significantly longer in patients with schizophrenia, with a large effect size (1212.38 ±21.23 ms vs 1190.96 ±26.01 ms, p = 0.02; Cohen's d effect size = 0.89). Moreover, patients had significantly lower LV mass, and lower left/right ventricular end-diastolic and stroke volumes (effect sizes, d=0.86-1.08; all p-values <0.05). There were no significant differences in left/right end-systolic volumes and ejection fractions between groups (p>0.05).

Conclusions: These results suggest an early diffuse fibro-inflammatory myocardial process in patients that is independent of established CVD-risk factors. Taken in the context of previous preclinical studies that have observed myocardial fibrotic and inflammatory changes accompanying antipsychotic administration, the cardiac alterations observed in the current study may be the consequence of antipsychotic treatment. However, there is an emerging body of evidence suggesting that psychotic illness is independently associated with increased markers of oxidative stress and inflammation, systemic alterations that are associated with myocardial fibrosis and functional myocardial impairment. Regardless, in various cardiac disease states, including non-ischaemic dilated cardiomyopathy and valvular pathology, myocardial fibrosis independently predicts both cardiovascular and all-cause mortality. Thus, future studies are required to determine if the observed fibro-inflammatory changes are due to antipsychotic treatment or are intrinsic to schizophrenia. Such studies may provide insight into novel future therapeutic strategies that will serve to narrow the mortality gap in schizophrenia.

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ACQUISITION OF VISUAL PRIORS AND INDUCED HALLUCINATIONS IN CHRONIC SCHIZOPHRENIA

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Introduction: An increasingly popular idea is that perception and decision-making can be well described in terms of probabilistic inference processes. For example, statistical/perceptual learning studies show that the perceptual systems continuously extract and learn statistical regularities of the environment (Seriès & Seitz, 2013, Frontiers in Human Neuroscience. 7:668). This learning results in the construction of internal models of the environment, or expectations, which are used automatically and unconsciously to predict and disambiguate perceptual inputs in situations of uncertainty and to guide decisions. Prominent theories suggest learning deficiencies or inference deficits would lead to distorted internal models of the world, which could then explain the existence of abnormal beliefs (delusions), while incorrect perceptual inference could lead to hallucinations that are part of the positive symptoms of schizophrenia.

Methods: To test these theories, we used a visual statistical learning task known to induce rapid implicit learning of the stimulus statistics (Chalk et al., 2010, Journal of Vision. 10:8). In this task, participants are presented with a field of coherently moving dots and need to report the presented direction of these dots (estimation task) and whether they saw any dots or not (detection task). Two of the directions were more frequently presented than others. In controls, the implicit acquisition of the stimuli statistics influences their perception in two ways: 1-motion directions are perceived as being more similar to the most frequently presented directions than they really are (estimation biases); 2-in the absence of stimuli, participants sometimes report perceiving the most frequently presented directions (a form of hallucinations). Such behaviour is consistent with probabilistic inference (combining learnt perceptual priors with sensory evidence). We investigated whether patients with chronic schizophrenia (n=20) differ from controls (n=23) in the acquisition of the perceptual priors and/or their influence on perception.

Results: Although patients were slower than controls (F1, 41=4.11, p<0.05), they showed comparable acquisition of perceptual priors, correctly approximating the stimulus statistics (e.g. estimation bias - F2.45,100.52=15.37, p<0.001). Intriguingly however, patients made significantly fewer hallucinations of the most frequently presented directions than controls (p=0.016, two-sided rank-sum test) and fewer prior-based lapse estimations (p=0.024, two-tailed rank-sum test).

Conclusions: This suggests that patients appear to have no statistical learning deficits for low-level perceptual priors. However, while the impact of the patients’ acquired priors is the same to that of controls in the estimation task, it is weaker in the detection task suggesting that prior expectations had less influence on patients’ perception when stimuli were absent or below perceptual threshold.

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B26
ACUTE EFFECTS OF COMBINATIONS OF DELTA-9-TETRAHYDROCANNABINOL AND CANNABIDIOL ON FACIAL EMOTION RECOGNITION: A RANDOMISED, DOUBLE-BLIND, CROSSOVER STUDY

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Introduction: Emotional processing is a key domain of social cognition that is impaired in psychosis, with emotional recognition ability showing an association with illness severity, positive and negative symptoms of psychosis (Penn et al., 2000). Previous studies have similarly shown acute administration of THC induces positive psychotic symptoms (Morrison et al., 2009) and impairment of emotional recognition (Hindocha et al., 2015; Bossong et al., 2013), with the addition of CBD reversing this (Hindocha et al., 2015; Englund et al., 2013). However, the optimal ratio of CBD:THC to minimize psychotomimetic effects and cognitive impairment is unknown. This study aimed to determine the effects of different ratios of CBD:THC on emotional facial affect recognition and acute psychotomimetic symptoms.

Methods: 45 healthy volunteers attended a baseline visit and received THC (10mg) with varying amounts of CBD (0mg, 10mg, 20mg, 30mg) on separate visits at least one week apart in a randomized, double blind, crossover design. They completed an emotional facial affect recognition task including fearful, angry, happy, sad, surprise and disgust faces varying in intensity from 20% to 100%. At the end of each session, psychotic-like symptoms were measured using the Positive and Negative Syndromes Scale (PANSS).

Conclusions: This project hopes to increase our understanding of the interaction between cannabinoids. In particular, this study is designed to assess the ratio of CBD:THC that optimally reverse impairments of emotional facial affect recognition and psychotomimetic symptoms. Currently, it is known that a ratio of 2:1 is effective in normalizing emotional facial affect recognition (Hindocha et al., 2015) but it is not known whether 1:1 or 3:1 will outperform this and whether there will be subsequent effects on psychotomimetic symptoms

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B27
ASSOCIATIVE LEARNING ABNORMALITIES IN PSYCHOSIS

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Introduction: Associative learning is fundamental to how we construct reality, providing a mechanism to create predictive constructs about the world. People with psychosis have been shown to have ‘abnormalities’ in associative learning which may help to explain how reality distortions arise. Recent studies have also indicated that associative learning may distinguish genetic subpopulations in schizophrenia. We investigated two associative learning phenomena latent inhibition and Kamin blocking. These both involve predictions of outcomes based on prior exposure to stimuli. We predicted that if patients have a generalised abnormality in forming new associations based on prior experience then they would show correlated abnormalities in both tasks.

Methods: Latent inhibition was reduced in patients compared to controls, the control group showing faster reaction times to the non-pre-exposed stimuli, while patients showed no difference in reaction times between pre-exposed and non-pre-exposed stimuli, which was particularly evident in the early test trials. (ANOVA Pre-exposure X trial X patient status interaction F 19,741 =1.76,p<0.05, between group effect of
patient status $F(1,39)=5.2, P<0.05$). Kamin blocking was also significantly reduced. There was a difference in rating of blocked versus control stimulus in controls (Wilcoxon, signed rank: $Z=-2.7, P<0.005$) versus no effect in patients ($Z=-.975, NS$). Chlorpromazine equivalent doses were not correlated with latent inhibition or Kamin blocking. Kamin blocking was associated with PANSS negative symptoms while reduced latent inhibition was associated with positive symptoms.

Results: Latent inhibition was significantly reduced in patients compared to controls, the control group showing faster reaction times to the non-pre-exposed stimuli, while patients showed no difference in reaction times between pre-exposed and non-preexposed stimuli, which was particularly evident in the early test trials. (split plot ANOVA Pre-exposure X trial X patient status interaction $F(19,741)=1.76, p<0.05$, between group effect of patient status $F(1,39)=5.2, P<0.05$). Kamin blocking was also significantly reduced. There was a difference in rating of blocked versus control stimulus in controls (Wilcoxon, signed rank: $Z=-2.7, P<0.005$) versus no effect in patients ($Z=-.975, NS$). Chlorpromazine equivalent doses were not correlated with global measures of latent inhibition and Kamin blocking. Kamin blocking was associated with PANSS negative symptoms while reduced latent inhibition was associated with positive symptoms.

Conclusions: These data show that patients with psychosis have reductions both in latent inhibition and Kamin blocking. However unexpectedly, these reductions are not correlated within patients and are associated with different symptom profiles. Reduced Kamin blocking was associated with higher negative symptoms and reduced latent inhibition with higher positive symptoms. This suggests that the different mechanisms of aberrant salience allocation represented by reduced latent inhibition and Kamin blocking are dissociable with respect to positive and negative symptoms.

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B28

**ALPHA (8-13HZ) OSCILLATORY ACTIVITY DURING WORKING MEMORY IN SCHIZOPHRENIA**

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Introduction: Schizophrenia is a psychiatric illness with a lifetime prevalence of 1%. (Picchioni M, Murray R, 2007, BMJ, 335, 91–5.) Working memory (WM) deficits are a key symptom and reliable prognostic indicator of patients with schizophrenia. (2) These often provide a ‘functional glass ceiling’ for patients as, unlike positive and negative symptoms, they are not mediated by currently available medication and remain stable throughout the disease course. A meta-analysis revealed that the WM impairment seen in these patients occurs during the encoding phase, but the underlying mechanism remains unknown. (Lee J, Park S, 2005, J Abnorm Psychol, 114, 599–611.) In healthy adults, a well-establish pattern of alpha-desynchronization followed by synchronization is seen upon the presentation of novel stimuli. (Zumer JM, Scheeringa R, et al, 2014, PLoS Biol, 12. Chen Y, Huang X, Front Psychol, 2016, 6.) The present study aimed to assess if this neural pattern is conserved in patients with schizophrenia.

Methods: Thirty-six patients with schizophrenia and 35 matched healthy controls performed an N-back WM task, whilst electroencephalography (EEG) data was recorded. Ethical approval was provided by The National Research Ethics Committee, Derbyshire. Pre-processing of the data was performed using the Matlab Toolbox, EEGLAB. (Delorme A, Makeig S, 2004, J Neurosci Methods, 134, 9–21.) Behavioural data (accuracy and reaction time [RT] during the WM task) was compared between groups using a repeated-measure ANOVA. Event-related spectral perturbation (ERSP) values of alpha-oscillations recorded at the occipital electrode were compared between groups using a repeated-measure ANOVA. Behavioural data and a measure of clinical severity of schizophrenia (Signs and Symptoms of Psychotic Illness score) were correlated with the ERSP values.
Results: Patients exhibited significantly longer RT's throughout the WM task (F(1,69)=15.619, p<0.001) compared to controls. Patients demonstrated significantly worse accuracy throughout the task compared to controls (F(1,69)=11.386, p=0.001.) Furthermore, in both groups, increasing WM load resulted in prolonged RT (F(1,153,79.559)=13.172; p<0.001) and a reduction in accuracy (F (1,453,100.252) = 79.060, p<0.001.) Patients with schizophrenia demonstrated reduced alpha-desynchronization (ERSP values) throughout the WM task compared to healthy controls (F(1,69) =3.768, p=0.056.) Both groups demonstrated significantly greater ERSP-values for target, as opposed to non-target stimuli (alpha ERSP- F(1, 69)= 28.81, p <.001.)

Conclusions: The observations of this study corroborate and extend previous findings that patients with schizophrenia perform worse compared to healthy controls in WM tasks, and show reduced alpha-desynchronization after stimulus onset. This provides converging evidence that aberrant cortical activity, and possibly impaired filtering of task irrelevant information, may underlie the WM encoding deficits seen in these patients.

Funding: This work was supported by the University of Birmingham Public Health and Population Sciences BMedSc intercalation student fund.

B29

USING SEQUENTIAL WINDOW ACQUISITION OF ALL THEORETICAL FRAGMENT ION SPECTRA (SWATH) MASS SPECTROMETRY (MS) TO IDENTIFY POSSIBLE CIRCULATING PROTEINS THAT PREDICT FUTURE EARLY WEIGHT GAIN IN EARLY PSYCHOSIS

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Introduction: Weight gain remains a major issue in people with schizophrenia with immediate/long-term consequences for health. We have shown that proteomic profiling with sequential window acquisition of all theoretical fragment ion spectra (SWATH) mass spectrometry (MS) can identify individuals more likely to experience weight change in relation to changes in treatment or lifestyle (Malipatil et al, 2018, Journal of Clinical Medicine, 8:141). We investigated how weight trajectory in people with recent onset schizophrenia in the BeneMin prospective study (Deakin et al, 2018, Lancet Psychiat, 5: 885-894) related to baseline proteomic profile.

Methods: Within the BeneMin dataset, there were 207 recent onset participants (estimated duration ≤6years of illness) who were randomised to receive adjunctive Minocycline(n=103) or Placebo(n=104) in addition to standard therapy and routine care. Weight and body mass index (BMI) were available for 109 participants and proteomic measurements were available for 84 participants at 12 months. Weight changes were divided into categories. Follow-up (FU) period was 12 months and the visit for the 109 participants was conducted on average approximately 387 days after the Baseline visit (SD=27, median=386, IQR=28, min=326 and max=505). SWATH-MS was carried out using SCIEX (Framingham, Boston) 6600 instrumentation.

Results: From the 109 participants, 6 individuals who lost 10kg or more had a higher BMI at baseline (35.2 vs <30 for other weight change categories) and had numerically higher Positive and Negative Syndrome Scale (PANSS) scores, reaching statistical significance for the PANSS General Score at 42.5 vs 35 or less for other weight change categories (p=0.04). Of the 84 participants with available baseline proteomics data, 23/84 of those with proteomic data showed weight change of +/-<3kg and 38/84 increased their weight by ≥3kg, 23/84 lost 3kg or more over the 12 months FU. Principal Component Analysis and Hierarchical Clustering analysis of the baseline proteomics data did not reveal distinct separation between participants in different weight change categories.

Conclusions: Those individuals with the highest weight loss had higher PANSS scores indicating a possible influence of level of symptomatology on weight change over time. Using the technique of SWATH-MS we were not able to discriminate individuals with early years psychosis who would subsequently gain weight, from those who remained weight stable or lost weight. The novel nature of the BeneMin
study intervention may be a factor in the failure to determine any association between the SWATH-MS profile and phenotypic outcome. Our findings imply that the mode of treatment i.e. the pharmacological intervention for psychosis may be the determining factor in weight change after diagnosis, rather than any underlying proteomic factors.

Funding: There was no external funding for the analysis that was carried out.

**B30**

**ASSOCIATION OF MONTHLY SUNSHINE MEAN VARIATIONS WITH HANDEDNESS AND CREATIVITY - EXPLORATORY ANALYSES OF A PRIMARY CARE SELF-REPORT SAMPLE**

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Introduction: Schizophrenia birth rates increase by around 10 percent in winter/early spring as the season of birth effect, concluded in a recent UK Biobank cohort gene-environment test study to reflect a true pathogenic effect of an environmental exposure. In the search for a proxy variable peri-natal light exposure has been investigated in case registers in schizophrenia and more recently in bipolar disorder. In order to link these findings with indices of cerebral specialisation, hand preference and creativity can be regarded as phenotypic indicators and seasonal anisotropy in hand preference has been shown in several studies. Here we aimed to investigate further a hypothesis that pre- or perinatal environmental light (EL) exposure could be associated with variations in these measures.

Methods: An existing data-set of 300 primary-care patients was utilised for the study. Measures of perinatal EL exposure were divided into trimesters before and after birth. Individual histories of EL exposure were calculated from MET Office data and deseasonalization was possible with two sets of 50 year means for England and Wales, or Scotland, of monthly sunshine data subtracted from the individual's own monthly data to generate a personal light record. A self report questionnaire included a question on creativity and a handedness scale.

Results: Handedness scores were significantly lower in males compared to females (Z=-2.24, p=.025). Prenatal second trimester EL exposure was negatively correlated with the total handedness score in the overall sample (p=.019, r=-.14). In the exploratory subgroup analyses, this correlation was only evident in males (p=.023, r=-.244) and in subjects with no family history of mental illness (p=.035, r=-.14). The creativity score correlated with the third trimester EL measure.

Conclusions: These findings suggest that the amount of EL during the pre-natal 2nd trimester is negatively associated with an increase in non-right handedness in males. Given that male foetuses are exposed to higher levels of testosterone than females including the mid-foetal phase of cerebral mass increase, these results may suggest an EL-linked maternal influence on some aspects of cerebral organisation. Further study will need to include replication and an elucidation of interactional mechanisms underlying a putative effect of EL in schizophrenia and bipolar disorder, where early exposures leading to later dysfunction have been proposed.

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**B31**

**THE LOST DRUGS OF SCHIZOPHRENIA**

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Introduction: Many prospective drug treatments for people with schizophrenia fail to progress beyond early phase studies. Others undergo further testing in clinical trials, but only a proportion progress to
market. Some medications are found to be ineffective or too toxic but other potentially useful drugs fail to progress for less clear reasons, and are then lost.

Methods: The Cochrane Schizophrenia Group’s Register holds all reports of all relevant randomised studies (with medications coded according to WHO Anatomical Therapeutic Chemical (ATC) Classification System). As part of routine ‘housekeeping’ drug interventions not listed on ATC were sought on Adis Insight, then [if the drug was new] ClinicalTrials.Gov, and then [if the drug was old] Google (including Google Books) and information obtained on each drug’s [potential] clinical class, developmental and market status. We included drugs only if they met two criteria: •not listed in ATC; and •not traced as being marketed anywhere. We considered the developmental status as ‘stopped’ if there was no available trial of the drug in past three decades.

Results: The register contains 859 drug names; 236 of which were investigational drugs (27.5% of all schizophrenia drugs). 172 fell into 23 different existing clinical classes, the most common being antipsychotics (112) and antiparkinsonian medications (17); 65 remained unclassified. In Adis Insight 33 drugs were ‘still developing’, 72, ‘stopped’ and 29 of ‘unclear’ status. Checking the remainder on ClinicalTrials.Gov we found 5 more ‘developing’ and one ‘stopped’; On Google we found 7 more ‘developing’ and 64 ‘stopped’. We failed to identify the development status of 25 drugs. Thirteen drugs had been marketed but had been withdrawn for reasons that remain unclear.

Conclusions: We knew that many drugs do not reach market. This study, however, attempts to quantify the proportion of compounds that are developed to the stage of testing in clinical trials which fail to progress. That this is around quarter of antipsychotic drugs highlights the enormous attrition in this research. Perhaps, much of this is difficult to avoid. What is entirely avoidable is the doubt caused by poor reporting. It remains important to know if compounds were too toxic or ineffectual. Of those drugs ‘stopped’ or of ‘unclear’ status, we should have full clarification. It remains likely that a small proportion of these compounds are effective drugs not marketed because of reasons other than clinical effects. One lost drug represents millions of lost opportunities for people with schizophrenia.

Funding: N/A

B32
PRESCRIBING CLOZAPINE IN THE UK: OPPORTUNITIES FOR QUALITY IMPROVEMENT

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Introduction: An audit-based quality improvement programme focussing on clozapine use in UK mental health services was initiated in 2018.

Methods: 63 NHS Trusts/healthcare organisations participated in the baseline audit. The data collected principally related to performance against practice standards for clozapine treatment, derived from NICE guideline 178. Data were submitted for 6948 patients prescribed clozapine under the care of 872 clinical teams.

Results: Information on regular antipsychotic medication prescribed immediately before starting clozapine was collected in a subsample of patients (n=481): 21% were prescribed combined antipsychotic medications and 6% a single antipsychotic in high dose. In 499 patients established on clozapine for less than a year, men were twice as likely as women to be prescribed a daily dose greater than 400mg (16% and 9% respectively). Three months after starting clozapine, the mean daily dose was 294mg in women and 324mg in men. Seventy-seven patients had been discharged from a smoke-free ward. In 52 (68%), the impact of the potential change in smoking status on clozapine dose/plasma levels and the implications for monitoring and/or dosage change had not been considered in their care plans. For 3902 patients under the care of a community mental health team, information about prescribed medicines contained in the
primary care Summary Care Record (SCR) was submitted. The SCR prescribing summary did not include clozapine in 42% of these cases.

Conclusions: Antipsychotic regimens with a limited evidence base for efficacy in treatment-resistant psychosis were prescribed for over a quarter of cases immediately before starting clozapine. Use of such strategies may delay clozapine treatment, potentially compromising the likelihood of a positive therapeutic response. The difference in mean daily clozapine dose between men and women early in treatment was smaller than might be warranted given known sex differences in the dose/plasma level relationship. This finding suggests that there may be scope to reduce the clozapine dosage in some women without compromising efficacy. Failure to anticipate the consequences of a change in smoking status on discharge from hospital, as found in two-thirds of relevant cases in this audit, may increase the risk of sub-therapeutic plasma clozapine levels and thus likelihood of relapse. It is important for patient safety that the SCR lists all currently prescribed treatments. If an SCR that fails to include a patient's clozapine prescription is used by a hospital doctor to inform acute treatment plans, clinical symptoms suggestive of serious clozapine-related adverse effects such as agranulocytosis, myocarditis or severe constipation may be missed or an interacting medicine may be inadvertently prescribed.

Funding: POMH-UK is funded by subscriptions from member mental health services.

B33

A TWO-YEAR MIRROR-IMAGE STUDY OF THE EFFECT OF TREATMENT WITH ARIPIPRAZOLE LONG-ACTING INJECTION ON NEED FOR INPATIENT CARE AND HOME TREATMENT INTERVENTION

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Introduction: Long acting injections of second-generation antipsychotics such as aripiprazole have become more commonly prescribed over the past decade. They have much higher acquisition costs when compared to first generation depot antipsychotics. It is therefore essential to demonstrate their tolerability and cost-effectiveness.

Methods: We undertook an observational, retrospective two-year mirror study for all patients who started treatment with aripiprazole long acting injection between April 2014 and July 2017 (n=154). 61 individuals were excluded from further analysis (21 had incomplete information, 19 were forensic patients, 18 had fewer than 3 doses of aripiprazole long acting injection, 3 started aripiprazole long acting injection during a period of inpatient treatment and discontinued it before discharge). Clinical notes were examined to determine the number of admissions, inpatient days, home treatment episodes and number of home treatment days, in the 12 months preceding and following the commencement of the long acting injection.

Results: 58 of the 93 patients (62%) remained on aripiprazole at the end of the one-year period. The most common reason for discontinuation was poor response (48%), with 17% discontinuing due to adverse effects, the remainder being attributed to patient choice. There was a significant reduction in inpatient episodes from 1.05 (SD1.18) in the year before aripiprazole long acting injection was started to 0.62 (SD 1.22) in the year after (p=0.002). The mean number of bed days decreased from 66.51 days (SD 85.44) to 32.7 days (SD 64.35) (p=0.0006). There was a significantly greater reduction in occupied bed days in those who remained on aripiprazole at one year than those who discontinued (p=0.037) There was no significant reduction in days spent under the care of home treatment teams (p=0.4)

Conclusions: Treatment with aripiprazole long-acting injection was associated with a reduction in admissions and occupied bed days of a magnitude that delivered an overall cost-saving despite the high drug acquisition costs. It remains to be determined how this reduction compares with other second-generation long-acting injections and first-generation depot antipsychotics.

Funding: nil
**B34**

**CLINICAL OUTCOMES FOLLOWING SWITCHING ANTIPSYCHOTIC TREATMENT DUE TO MARKET WITHDRAWAL: A RETROSPECTIVE NATURALISTIC COHORT STUDY OF PIPOTIAZINE PALMITATE**

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Introduction: Pipotiazine palmitate depot (Piportil ®) was a first generation antipsychotic withdrawn from the UK marketplace by March 2015. Uniquely, patients, in discussion with clinicians had to switch to alternative antipsychotics, not due to poor efficacy or side effects. There are no large studies examining such a cohort. We aimed to examine clinical outcomes of these patients within 12 months from switching from pipotiazine, including factors influencing both discontinuation of the next medication prescribed and utilisation of acute mental health services. Our primary outcomes were 1) time to discontinuation of the switched medication, and 2) whether or not acute mental health services were used.

Methods: A naturalistic retrospective cohort study was conducted in one publicly-funded mental health trust in the South East of England, UK. Patients were identified by manual searching and electronic patient database meta-searching. Age, gender, illness duration, pipotiazine treatment duration, diagnosis, four-weekly pipotiazine dose, concurrent antipsychotic use, switch setting, and class of antipsychotic switched to were analysed. Multivariate logistic regression analyses and survival analyses were performed to explore associations.

Results: 100 eligible patients were identified, mean age 51 and 67 male. 83 had a primary psychotic disorder. Mean pipotiazine treatment duration was 5.4 years, and mean illness duration was 19.8 years. 42 were taking a concurrent antipsychotic at switching. 90 switched as outpatients. 67 remained on their new medication over 12 months. 57 switched to typical depots, 26 atypical depots, and 16 atypical orals. 28 used acute services following switch. No identified variables were statistically associated with 12 month discontinuation, however those discontinuing atypical oral medications did so earlier. No variables except inpatient switch setting were associated with use of acute services within 12 months (P=0.003).

Conclusions: Contrary to expectations, it made no difference which antipsychotic patients were switched to after pipotiazine, when considering discontinuation and acute service use by 12 months. Only switch setting- being an inpatient- was associated with likelihood of acute service use by 12 months.

Funding: There is no funding associated with this abstract.

**B35**

**IS SCHIZOTYPIC MATERNAL PERSONALITY LINKED TO SENSORY GATING ABILITIES DURING INFANCY?**

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Introduction: The influence of maternal personality on childhood risk factors for mental health is widely acknowledged with links identified between specific parental psychopathology and event-related potential (ERP) components. Core neuropsychological dysfunctions of potential future psychopathologies may be present during childhood, which shape the development of adult personality. Consequently, it is of fundamental interest to determine whether maternal personality influences development during infancy. Schizotypy is a personality dimension within the general population elevated among schizophrenia-spectrum patients and their first-degree relatives. Sensory gating is the pre-attentional habituation of responses distinguishing between important and irrelevant information, measured by ERPs, which have been found to display abnormalities in schizophrenic disorders.
Methods: The present research investigated whether 6-month-old infants of mothers with schizotypic traits display sensory gating abnormalities. A paired-tone paradigm: two identical auditory tones, Stimulus 1 and Stimulus 2, probed the selective activation of the brain during 15-minutes of continuous sleep. Mothers completed the Oxford and Liverpool Inventory of Feelings and Experiences-Short Form as an index of schizotypy dimensionality. Thirty-five infants (M age = 5.88 months; SD = 8.57 days; 18 male) and fifty-three mothers (M age = 32.9 years; SD = 4.25 years) were included in final analyses.

Results: The infants’ P50 ERPs displayed differences between Stimulus 1 and Stimulus 2 (t(34) = 2.062, p = .047, d = .05), but there was no clear group distinction. Nonetheless, a series of significant correlations were observed between suppression ratio/differences measures and maternal schizotypy dimensionality. This could be perceived as the beginning of differences between groups, although deficits are not robust enough to drive distinctions. Schizotypic traits can be undetected by the unaided eye; thus, at 6-months maternal schizotypy may not be extensively experienced to influence a measure as sensitive as sensory gating. In contrast, the maternal cohort displayed differences between Stimulus 1 and Stimulus 2 (F(1,51) = 8.56, p = .005, η2 = .14), but also dissociations between the two groups (F(1,51) = 6.14, p = .017, η2 = .11); control mothers illustrated differences between Stimulus 1 and Stimulus 2, whereas the lack of significance in the schizotypic mothers illustrates a sensory gating deficit compliant with that across the schizophrenia-spectrum.

Conclusions: We have demonstrated two important findings: sensory gating can be detected in 6-month-old infants. Data revealed that the 6-month-old infants’ P50 ERPs did not display clear group differences. Therefore, the infants of schizotypic mothers appear not to be at higher risk than normal, at least at 6-months-of age. Although, the sensory gating deficit observed among the schizotypic mothers supported the continuous nature of the schizophrenia-spectrum and supported sensory gating as a stable endophenotype of the spectrum.

Funding: This research was funded by the Leverhulme Trust Doctoral Scholarship Program in Interdisciplinary Research on Infant Development.

B36

A SYSTEMATIC REVIEW ON THE CLINICAL EFFECTIVENESS OF PALIPERIDONE PALMITATE FOR THE TREATMENT OF SCHIZOPHRENIA IN THE UK

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Introduction: A number of studies have evaluated the real-world effectiveness of the 1-monthly maintenance formulation of paliperidone palmitate (PP1M) in the UK, regarding: clinical effectiveness, associated resource use, impact on patient/caregiver health-related quality of life (HRQoL), and cost-effectiveness. We present the findings of a systematic review (SR) of published evidence on the clinical-effectiveness of PP1M for the treatment of adult patients with schizophrenia and other mental health disorders in the UK.

Methods: A literature search of UK-based studies in MEDLINE®, MEDLINE®-in-Process, Embase®, Cochrane library, and PsycINFO databases was conducted in March 2017. Conference proceedings and previous health technology assessment submissions were hand-searched. In August 2018, an updated search was conducted to identify and include relevant papers published post-March 2017.

Results: Twenty-one studies met the inclusion criteria (19 retrospective observational and two prospective studies). A mirror-image design was used in 10 studies. Sixteen studies were single-arm assessments of the efficacy or safety of PP1M, and five were multi-treatment comparisons. The proportion of patients with a diagnosis of schizophrenia ranged from 58% to 100% and follow-up time ranged from 16 weeks to 6 years. Hospital admissions and/or bed days were the most frequently reported outcomes (n = 14), followed by discontinuation rates (n = 13), CGI scores (n = 2), Positive and Negative Syndrome Scale (PANSS), Health of the
Nation Outcome Scales (HONOS), Crisis Resolution and Home Treatment Teams (CRHTT), and Medication Satisfaction Questionnaire (MSQ) (n=1 each). In six out of 14 studies hospital admissions and bed days were significantly reduced post-PP1M vs prior treatment (p<0.05). A further study showed significant decreases in inpatient admissions, but not bed days. Three studies reported reductions in admissions and/or bed days without providing statistical analyses. Three studies showed no difference in hospital admissions or bed days, and a single study showed an increase in admissions. Three different studies respectively showed, treatment with PP1M resulted in significantly improved psychotic symptoms, a numerical reduction in length of time spent under care of CRHTT, significantly improved HONOS scores over 2 years (p=0.0001) and MSQ scores over 1 year (p=0.0043) compared with baseline. Across all studies, PP1M discontinuation occurred most commonly due to lack of efficacy or adverse events.

Conclusions: The findings of the systematic review suggest that PP1M can be effective for the treatment of adults with schizophrenia and other mental health disorders in the UK setting. Available data shows a trend for PP1M treatment to decrease costly hospital admissions and bed days.

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B37
CLOZAPINE AND MYOCLONUS: SYSTEMATIC ANALYSIS OF THE EUROPEAN PHARMACOVIGILANCE DATABASE (EUDRAVIDELANCE)

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Introduction: Compared with other antipsychotics, clozapine appears to bear a great risk of inducing convulsions, including myoclonic seizures. However, reported evidence regarding clozapine-induced myoclonus is low, solely based on case series or literature reviews with up to 10 cases. This study aimed to evaluate incidence and characteristics of myoclonus associated with clozapine.

Methods: We searched for all suspected cases of “myoclonic epilepsy” associated with clozapine in EudraVigilance, the European pharmacovigilance database. All records of the database until October 2018 were included. To assess the association between myoclonus and clozapine, we calculated the Reporting Odds Ratios (RORs), a measure of disproportionality similar in concept to the relative risk ratio.

Results: Among 5,907,946 events of all types recorded in EudraVigilance, 634 cases of myoclonus were found. Out of these 634 cases, we investigated all 37 cases (5.8%) of myoclonus, which were associated with clozapine. The average dose of clozapine was 399±190 mg daily (13, dose not specified). The mean age of patients was 36.4±13.7 years (3, age not specified); 56.8% of them male (1, sex not specified). The mean duration of myoclonic epilepsy was only mentioned in 7 cases, resulting in an average of 47.9±77.2 days with a mean latency period of 137.9±269.5 days (8, time to onset not specified). In 16.2% of patients this adverse drug reaction led to discontinuation of clozapine (14, discontinuation not specified). The ROR for clozapine-induced myoclonic epilepsy was 6.02 (95% CI 4.37-8.29) compared to the remaining 597 cases not associated with clozapine. Therefore, clozapine fulfilled the safety signal criteria. Nevertheless, it is important to recall that this disproportionality should only be considered exploratory in the context of signal detection, as it does not allow quantification of the true risk.

Conclusions: To our knowledge, this study represents the biggest structured analysis of clozapine-induced myoclonus. Data from EudraVigilance confirm the existence of a safety signal for this adverse reaction. Thus, when prescribing clozapine, a careful approach is suggested in patients with potential risk factors for a lowered seizure threshold.

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EFFECT OF AGE ON THE RELATIVE EFFICACY OF Clozapine IN SCHIZOPHRENIA - A SYSTEMATIC REVIEW AND META-REGRESSION OF RANDOMISED CONTROLLED TRIAL DATA

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Introduction: Early and effective treatment of schizophrenia improves outcomes. Clozapine appears to have unique benefit when other antipsychotic medication has failed. This systematic review and meta-analysis aims to confirm clozapine's superiority over alternative antipsychotic medication and examine whether earlier use is associated with additional benefit.

Methods: Systematic retrieval, following PRISMA guidelines, of blinded, randomized controlled trials comparing clozapine with alternative antipsychotics in adults with schizophrenia. The effect of mean age on relative clozapine response was examined using random effects meta-regression, and multiple linear regression on available patient data.

Results: 276 studies were retrieved, of which thirty-nine met inclusion criteria. Thirty-four studies were included in the meta-analysis. Clozapine was significantly more effective than alternative antipsychotics in reducing psychotic symptoms and increasing response. However, meta-regression failed to show a more significant effect in younger patients: age on effect size (total psychotic symptoms p =0.79 CI -0.03 – 0.03).

Individual patient data was available for 2 studies, the larger of which showed a significant interaction between younger age and superiority of clozapine.

Conclusions: The results support clozapine's superiority over other antipsychotics. A convincing effect of age on this effect was not demonstrated, although this was suggested in one study. In the absence of additional effect by increasing age, there is no cause to delay clozapine. Future research should examine the relationship between length of illness and clozapine response.

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THE EFFICACY AND HETEROGENEITY OF ANTIPSYCHOTIC RESPONSE IN SCHIZOPHRENIA: A META-ANALYSIS

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Introduction: Antipsychotics are more effective than placebo in reducing symptoms in schizophrenia. However, response to treatment appears to vary, and as such it has been proposed that different subtypes of schizophrenia exist, defined by treatment-response. This has not been formally examined using meta-analysis.

Methods: Randomised controlled trials comparing placebo and antipsychotics in acute treatment of schizophrenia listed in PubMed, EMBASE and PsycINFO from inception until November 30, 2018 were examined. Mean change and variance of change in symptoms were extracted from each study, alongside publication year, participant age and gender, baseline symptom severity, antipsychotic dose, and use of placebo lead-in. Relative variability of symptomatic improvement in antipsychotic-treated individuals compared to placebo-treated individuals was quantified using coefficient of variation ratio (CVR). Mean difference in symptom change was quantified using Hedges’ g. The significance of potential moderating factors was assessed using meta-regression and sensitivity analyses. In addition, individual patient data
from two clinical trials was examined in terms of both the distribution of total symptom change, and the variability of individual symptoms and symptom factors.

**Results:** 11,006 articles were identified. 66 met inclusion criteria, reporting on 17,202 patients. Compared with placebo, antipsychotic-treated patients demonstrated greater symptomatic improvement ($g=0.47$, $p<0.001$) and reduced variability in symptomatic improvement for total ($CVR=0.86$, $p<0.001$), positive ($CVR=0.89$, $p<0.001$), and negative symptoms ($CVR=0.86$, $p=0.001$). Lower variability in antipsychotic-response was associated with studies published earlier ($z=3.98$, $p<0.001$), younger patients ($z=3.07$, $p=0.002$), higher dose treatments ($z=-2.62$, $p=0.009$), and greater mean-difference in symptom-change ($z=-5.70$, $p<0.001$). In the individual patient dataset (N=522 patients), antipsychotic treated patients did not show significantly increased variability for any individual symptom, and there was no evidence of a bimodal distribution of response.

**Conclusions:** Compared to placebo, antipsychotic treatment shows greater improvement and lower variability of change in total, positive and negative symptoms. This is contrary to the hypothesis that there is a subtype of antipsychotic non-responsive schizophrenia. Instead our findings, provide evidence for a relatively homogeneous effect of antipsychotic treatment in improving symptoms of schizophrenia.

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**B40**

**THE ROLE OF INFLAMMATORY BIOMARKERS IN PREDICTING TREATMENT RESPONSE IN PATIENTS WITH PSYCHOSIS: A SYSTEMATIC REVIEW**

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**Introduction:** Hyperactivation of the immune system in patients with psychosis is widely reported in the literature. Several studies are now emerging investigating the association between inflammatory biomarkers and response to antipsychotic treatment, detected by improvement in psychiatric outcomes (e.g. positive and negative symptoms), in psychotic patients. This systematic review aims to clarify whether inflammatory biomarkers, such as C-reactive protein (CRP) and tumour necrosis factor alpha (TNF-a), can be used as predictors of treatment response in psychosis.

**Methods:** We systematically reviewed the literature in PsychInfo, Ovid MEDLINE, and Embase databases to identify studies investigating the efficacy of inflammatory biomarkers in predicting treatment response in psychosis. Three categories of terms were used, including synonyms of each: 1) “inflammatory marker”; 2) “psychosis”; 3) “treatment response”. Furthermore, studies should have been conducted measuring psychotic or clinical symptom severity at least at two time-points. Only longitudinal studies on patients with psychotic disorder, published in English were included.

**Results:** Of the screened articles to date, we identified 17 studies investigating the association of inflammatory biomarkers together with changes in clinical symptoms and/or treatment response in psychotic patients. All 17 measured symptom severity, as indicated by a range of psychopathology scale scores, including the Positive and Negative Syndrome Scale (PANS), the Calgary Depression scale for schizophrenia (CDSS), the Scale for the Assessment of Positive Symptoms (SAPS), and Scale for the Assessment of Negative Symptoms (SANS). All 17 studies investigated correlations between changes in inflammatory biomarker (e.g. CRP, TNF-a, IL-6) levels and changes in the severity of the symptoms after treatment. Of these, eleven studies focused specifically on the efficacy of antipsychotic treatment and six studies investigated adjuvant treatments (e.g. antidepressants, anti-inflammatory treatment). From the overall sample, twelve studies found baseline or changes in one or more inflammatory biomarkers significantly correlated with changes in the severity of symptoms between at least two time-points; four had no significant findings, and one had not carried out relevant statistical analyses.

**Conclusions:** The heterogeneity among the selected studies, in terms of analysed biomarkers and treatments, suggests that the prediction power of biomarkers are highly dependent on the combinations
of treatments along with which markers are observed. However, our preliminary findings suggest that specific inflammatory biomarkers may successfully be implemented to guide treatment strategies in patients with schizophrenia.

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B41
METABOLIC CONSEQUENCES OF ANTIPSYCHOTIC TREATMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: Antipsychotic treatment is thought to be associated with metabolic disturbance, but the magnitude and extent to which metabolic alterations occur early in treatment remain unclear. Moreover, it is not known if baseline physiology and patient demographics predict metabolic disturbance, and how metabolic alterations relate to changes in psychotic symptoms. As such, we set out to determine whether short-term antipsychotic treatment leads to metabolic changes relative to placebo, to determine predictors of change, and to determine the relationship between metabolic change and psychopathology.

Methods: The Medline, EMBASE and PsychINFO databases were searched from inception until January 11, 2019. We selected double-blind randomised controlled trials (RCTs) comparing placebo and antipsychotics in acute treatment of schizophrenia and related psychoses. Random-effects meta-analyses for changes in body weight, body mass index (BMI) and metabolic parameters (fasting glucose, insulin, triglycerides, and total, Low Density Lipoprotein (LDL), and High Density Lipoprotein (HDL) cholesterol) were performed on antipsychotics combined, and, where data were available, for individual drugs. The quality of included studies was rated using the Cochrane Risk of Bias Assessment Tool. Meta-regression examined the relationship between metabolic changes and: 1) age, gender, ethnicity, weight, BMI, baseline metabolic parameter titre, and olanzapine-equivalent dose; and 2) changes in symptom severity.

Results: Of 11,186 citations retrieved, 65 RCTs met inclusion criteria, consisting of 13,554 antipsychotic-treated and 4,968 placebo-treated patients. Short-term antipsychotic use (median 6-weeks) was associated with significant increases in weight (g=0.39;p<0.0001), BMI (g=0.40;p<0.0001), total cholesterol (g=0.15;p<0.0001), LDL-cholesterol (g=0.06;p=0.04), HDL-cholesterol (g=0.09;p<0.001), triglycerides (g=0.12;p<0.0001), glucose (g=0.05;p=0.04), and insulin levels (g=0.12;p<0.001). Results did not change following exclusion of studies at risk of bias. On examination of separate antipsychotics, dopamine D2 receptor partial agonists were observed to have neutral/favourable metabolic profiles: cariprazine was associated with significant reductions in total (g=-0.15;p=0.01) and LDL-cholesterol (g=-0.19;p<0.01), while brexpiprazole was associated with a significant increase in HDL-cholesterol (g=0.19;p<0.001). Quetiapine and olanzapine were associated with the largest degree of metabolic dysregulation across all parameters (effect size range: g=-0.12 to -0.91, p<0.05). Greater increases in total and LDL-cholesterol were predicted by both younger age (p<0.05) and lower baseline BMI (p<0.01). Lower baseline total cholesterol also predicted greater antipsychotic-associated increases in total cholesterol (p=0.02). Improvements in symptom severity were significantly associated with increases in body weight (p<0.0001), BMI (p<0.01), total cholesterol (p<0.01) and LDL-cholesterol (p<0.01).

Conclusions: Antipsychotic treatment leads to rapid metabolic dysregulation relative to placebo. However, there are marked differences between antipsychotics. Metabolic changes accompany improvements in psychopathology. Findings indicate that early metabolic monitoring should accompany antipsychotic prescription, particularly in younger patients. Clinical decisions to preferentially use an antipsychotic with fewer metabolic side effects should consider that such treatments may be less effective in controlling psychotic symptoms.
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B42
CLOZAPINE USE IN EARLY INTERVENTION SERVICES: MANAGEMENT OF EARLY TREATMENT RESISTANCE.

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Introduction: Psychosis is a disabling disorder often presenting during pivotal developmental years for young adults. A ‘critical period’ in the development and treatment of psychosis is the basis of Early Intervention teams, with evidence to suggest that sustained and intensive intervention at this phase can improve outcomes (Birchwood, M. et al., 2014. Early Interv Psychiatry. 8(1), 59–67). Clozapine has superior efficacy in reducing symptom burden and in improving functioning in patients with treatment resistant psychosis (Thien, K. et al., 2019. Early Interv Psychiatry. 13(1), 18–23). This paper aims to explore the pathways to commencement of clozapine for patients with identified treatment resistance in Early Intervention Services in England.

Methods: Data was taken from 1027 participants in the National EDEN study which enrolled patients from Early Intervention Services across England over a 12-month period (Thien, K. et al., 2019. Early Interv Psychiatry. 13(1), 18–23). Data utilised included patient demographics, full medication history, Positive and Negative Syndrome Scale (PANSS) and Global Assessment of Functioning (GAF) symptoms and disability score measured at baseline, 6 months and 12 months. Prescribing patterns and pathways to clozapine were examined. Participants were identified as ‘treatment resistant’ by continuously raised PANSS positive sub score > 16 at baseline, 6 months and 12-month time points with prescription of two antipsychotic medications. Those eligible for treatment with clozapine but not prescribed clozapine (n=56) were compared to those who were identified as treatment resistant and prescribed clozapine (n=19) on functional outcome.

Results: A total 1746 individual medications were prescribed across the full EDEN sample (n = 1027) population. There were 1157 prescriptions for anti-psychotics. 143 (18.1%) participants, out of the 791 successfully followed up to 12 months, were identified as treatment resistant. 56 (7.1%) participants were identified as treatment resistant and eligible for treatment with clozapine, but not prescribed clozapine. 19 (1.9%) of participants, were prescribed clozapine. There were no significant differences in demographic details between the treatment groups. Paired sample T-test showed no significant difference in GAF disability in non-clozapine group (n=56) between baseline and 12months (p=0.271, CI = -8.45, 2.45). However, there was a significant difference in GAF disability in the clozapine group between baseline and 12 months (p=0.034, 95% CI = -16.41, -0.76).

Conclusions: This data examination has revealed high levels of treatment resistance in first-episode psychosis in early intervention services in England and low numbers prescribed clozapine, despite patient eligibility and efficacy in improving functional outcomes.

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**B43**

**HETEROGENEITY OF STRIATAL Dopamine Function IN Schizophrenia demonstrated BY meta-analysis of variance**

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**Introduction:** Dopamine function in schizophrenia is thought to display heterogeneity above and beyond that seen in the healthy population. While dopamine synthesis capacity has been reported to vary with treatment-response to antipsychotic medication, the broader hypothesis has not previously been systematically investigated.

**Methods:** We conducted a meta-analysis of variance (Nakagawa et al 2015 Methods Ecol. Evol 6(2), 143-152; Brugger & Howes 2017 JAMA Psych 74 (11), 1104-1111) to examine heterogeneity in molecular imaging indices of striatal dopaminergic function in patients with schizophrenia and healthy controls. We included 65 studies in 983 patients with schizophrenia and 968 controls, of dopamine synthesis or release capacities, D2/3 receptor (D2/3R) and transporter (DAT) availabilities, and synaptic dopamine levels. We quantified patient-control differences in inter-individual variability using variability ratio (VR) and coefficient of variation ratio (CVR).

**Results:** Inter-individual variability of striatal D2/3R (VR=1.26, p<.0001) and DAT availabilities (VR=1.31, p=.01), as well as synaptic dopamine levels (VR=1.38, p=.045) were found to be significantly greater in patients with schizophrenia. No differences in inter-individual variability of dopamine synthesis (VR=1.12, p=.13) or release (VR=1.08, p=.70) capacities were found. Findings were robust to choice of variability measure. Mean dopamine synthesis (g=0.65, p=.004) and release (g=0.66, p=.03) capacities, as well as synaptic dopamine levels (g=0.78, p=.0006) were greater in patients. Mean D2/3R (g=0.17, p=.14) and DAT (g=-0.20, p=.28) availabilities did not differ between patients and controls.

**Conclusions:** The results of this meta-analysis demonstrate significantly greater heterogeneity in striatal dopamine function in patients with schizophrenia, compared to matched healthy controls. The implication is that while elevated dopamine synthesis and release capacities may be core features of schizophrenia, changes in D2/3R and DAT availabilities, as well as in synaptic dopamine levels, occur in only a subset of patients. This heterogeneity may contribute to oft-remarked upon inter-patient differences in treatment response and side-effects to antipsychotic medication.

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**B44**

**The prevalence of treatment resistant psychoses in the community: a naturalistic study**

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**Introduction:** Treatment resistant schizophrenia is a major cause of disability. Clozapine is currently the only antipsychotic medication licensed for its treatment. However, the rate of treatment resistance among out-patients with schizophrenia or other psychoses, and the rate of use of clozapine among them, is not known. The main aims of this study are firstly to determine the point prevalence of treatment resistant psychosis in a community sample and, secondly, to determine the number of patients with treatment resistant schizophrenia who have never had a clozapine trial.
Methods: Clinico-demographic data were extracted from the case notes for 202 patients from two community mental health teams.

Results: We found that 56% (99/176) had a diagnosis of treatment resistant schizophrenia, and 52% (51/99) of these patients had never been treated with clozapine. Patients of non-white ethnicity were less likely to have had a clozapine trial (p=0.009). The point prevalence of treatment resistance within the Bipolar Affective Disorder (BPAD) sample was 19% (5/26).

Conclusions: These findings suggest that treatment resistant schizophrenia is common in the community mental health team and a large proportion of these patients have not received clozapine. These findings indicate that identifying and treating treatment resistance should be a focus of community services for schizophrenia.

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B45
A POST HOC ANALYSIS OF LONG TERM SAFETY AND TOLERABILITY OF LURASIDONE IN SCHIZOPHRENIA DISORDER: A 12 MONTH, DOUBLE BLIND, ACTIVE CONTROLLED STUDY
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Introduction: The aim of this post-hoc analysis was to evaluate the long-term safety and tolerability of lurasidone in patients with schizophrenia from a 12-month, double-blind, active controlled study.

Methods: This analysis was derived from a study of clinically stable adult outpatients who met DSM-IV criteria for chronic, stable schizophrenia and schizoaffective disorders (Citrome et al 2012). The schizophrenia population alone was studied in this post-hoc analysis. Patients were randomized in a 2:1 ratio, to once-daily treatment with flexibly-dosed lurasidone (40-120 mg), or risperidone (2-6 mg). Primary endpoints were safety and tolerability measures including adverse events (AEs), body weight, lipid parameters, prolactin, and ECGs. Secondary outcomes were assessments of efficacy.

Results: 427 patients were randomised to lurasidone and 202 patients to risperidone. Of these, 399 patients on lurasidone and 190 on risperidone were classified as having a diagnosis of schizophrenia. 35% (n=139) on lurasidone and 45% (n=86) on risperidone completed 12 months of treatment. Discontinuations due to AEs and insufficient clinical response were 17% and 8% for lurasidone, 10% and 6% for risperidone. The 3 most common AEs in the lurasidone group (vs. risperidone) were nausea (13.3% vs. 10.5%), insomnia (13.3% vs. 12.6%) and sedation (13.8% vs. 12.2%); in the risperidone group (vs. lurasidone) were increased weight (20.0% vs. 9.7%), somnolence (17.4% vs. 13.6%) and headache (14.7% vs. 9.0%). Clinically significant weight increase (≥7%) from baseline were 8% for lurasidone and 10% and 6% for risperidone. The 3 most common AEs in the lurasidone group (vs. risperidone) were nausea (13.3% vs. 10.5%), insomnia (13.3% vs. 12.6%) and sedation (13.8% vs. 12.2%); in the risperidone group (vs. lurasidone) were increased weight (20.0% vs. 9.7%), somnolence (17.4% vs. 13.6%) and headache (14.7% vs. 9.0%). Clinically significant weight increase (≥7%) from baseline were 8% for lurasidone and 14% for risperidone (NNH -16, 95%-CI, -9 to -120); clinically significant weight decrease was 13% for lurasidone and 6% for risperidone (NNH 15, 95%-CI, 9 to 44). Lurasidone and risperidone were associated with median endpoint reduction in cholesterol (-3.0 vs. -5.0 mg/dL; p=0.447) and triglycerides (-3.0 vs. -2.0 mg/dL; p=0.550) but remained unchanged for HDL in lurasidone vs risperidone group (0.00 vs. -2.0 mg/dL; p=0.007). Change in glucose was -1.0 for lurasidone vs. +2.0 mg/dL for risperidone (p=0.01). Prolactin change was minimal for lurasidone but significantly increased for risperidone (0.00 vs. +8.95 ng/mL; p<0.001). Least square mean change from baseline in PANSS total score was -4.8 for lurasidone and -6.6 for the risperidone (p=0.189) group.

Conclusions: Long-term treatment with lurasidone was well tolerated, with minimal effects on weight and metabolic outcomes. Comparable improvements in efficacy were observed with both agents and with...
comparable rates of relapse. Treatment with risperidone was associated with significantly greater effects on weight, plasma glucose and prolactin, but not on lipid parameters except for HDL change.

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**B46**

Efficacy and Safety of Haloperidol Intranasal in an Acute Psychiatry Unit

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Introduction: Background: Managing schizophrenic patients with agitation during psychiatric hospitalization by administration of intranasal haloperidol could be beneficial in terms of time to achieve sedation. The intranasal route bypasses the risk of needle-stick injuries and alleviates the distress that may occur from the intramuscular injections. Aim: to study the efficacy and safety of intranasal administration of haloperidol on mild-moderate agitated schizophrenic patients in a psychiatry inpatient unit.

Methods: Study design and methods: a randomized, open label observer-blind, single center, haloperidol-controlled trial on patients with diagnosed of schizophrenia, when they suffered a psychomotor agitation and followed for 60 min post agitation episode. The 16 patients were randomized to receive either (9) haloperidol intramuscular (IM) or (7) intranasal (IN). Clinical efficacy was measured as changes from the baseline minus 10, 20, 30, 60 minutes on Positive and Negative Syndrome Scale-Excited Component (PANSS-EC). Safety was assessed with changes in the electrocardiogram registered 5 minutes pre-treatment and 5 minutes post-treatment. Statistical analysis: Mann Whitney U test, significance: 0.05.

Results: PANSS-EC IM group IN group p-value median (percentile 25; percentile75) Baseline 17 (15.5; 20.5) 17 (16;2) Post-treatment change: 10 min 1 (0.5; 6) 6 (4; 7) p=0.042* 20 min 5 (3.0; 6.5) 6 (6; 1) p=0.091 30 min 6 (4.0; 6.5) 6 (5; 9) p=0.408 60 min 6 (2.0; 8.0) 6 (5; 1) p=0.470 ECG Heart Rate mean (SD) Baseline 70 (11.0) 73 (27.8) Post-treatment change: 0 (-6; 6) -7 (-18; 0) p=0.094 QTc mean (SD) Baseline 397 (41.0) 385 (27.8) Post-treatment change: -6.5 (-49.7; 31) -19 (-48; 10) p=0.463

Conclusions: Intranasal haloperidol was a non-invasive, rapid and effective alternative for reducing acute mild-moderate agitation on schizophrenic inpatients. It was well tolerated but a potential haloperidol related risk of mild tachycardia and minor QTc prolongation was observed, that needs due caution and further study.

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**B47**

Divergent Effects of Positive, Negative, and Disorganised Schizotypy in Probabilistic Reversal Learning: Controlling for Motivation, Metacognition, and Psychopathology

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Introduction: Performance on Probabilistic Reversal Learning Tasks (PRL) allows experimenters to assess how participants capitalise on environmental regularities. This may transfer to psychosis patients acting upon their preserved ability in real life. Therefore, factors predicting task deficits may be insightful targets
for novel interventions. However, assessments of PRL deficits in psychosis and how symptoms predict performance are currently mixed and the influence of drug treatment cannot be ruled out. Moreover, there are competing theories as to why deficits may occur. Aims were to: 1) be the first to investigate PRL deficits in schizotypy, 2) discern which schizotypy dimensions may predict performance, and assess 3) metacognition and 4) motivation as two additional explanations of performance. Metacognition and motivation were chosen due to being disrupted in psychosis.

Methods: PRL performance was assessed in 131 neurotypicals (18 – 25 years) varying on psychometrically defined schizotypy (O-LIFE). The task contained two learning blocks (L1, L3) and two reversal blocks (R2, R4), with rewarding and punitive stimuli reinforced at 80% probabilities. Participants completed the Becks Cognitive Insight Scale (BCIS), Depression Anxiety and Stress Scale (DASS-21), and a novel measure of motivation: Momentary Influences, Attitudes and Motivation Impact (MIAMI).

Results: All predictor variables entered a binomial multiple regression investigating their independent contributions (α=.01). Positive schizotypy did not predict overall performance, but predicted improved positive stimuli performance in the second reversal block (R4, p<.001) and poorer negative stimuli performance (p<.01). Conversely, negative (R4) and disorganised schizotypy (L1, L3, R4) predicted improved negative stimuli performance (all p<.01). Whilst self-reflectivity (metacognition) was consistently related to poorer reversal stage performance (p<.01), self-certainty was related to improved overall performance (p<.01). State stress levels predicted improved learning stage (L1) performance, but decreased reversal stage performance (R2, p<.01) – whereas anxiety had the opposite relationship. Finally, pre-task motivation predicted improved early task performance (L1), but poorer end task performance (R4).

Conclusions: This was the first study finding PRL deficits in psychometrically-defined schizotypy, demonstrating opposing effects of different psychosis-proneness dimensions on performance. Moreover, the effects of positive schizotypy were only apparent by analysis by stimuli type. Unexpectedly, higher self-reflectivity predicted poorer performance. It may be that those who report the higher level of metacognition, are in fact those that possess the least metacognitive abilities (e.g., lack of insight). This study also suggests that schizotypy, metacognition, and psychopathology all have their independent effects on performance, and should all be considered in interventions such as Metacognitive Therapy.

Funding: The presenting author receives a stipend and tuition fees from the Economic and Social Research Council

C01
AN AUDIT OF ELECTROCARDIOGRAM PROVISION FOR PSYCHIATRIC PATIENTS WITHIN 24 HOURS OF ADMISSION
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Introduction: Psychiatric patients have long been known to suffer from higher rates of cardiovascular disease. A physical health review is essential for new patients, as outlined by the Royal College of Psychiatrists (RCOP) in their standards for acute inpatient wards (Beavon et al, 2017. (AIMS-WA) – 6th Edition). Fundamental to this review is the electrocardiogram (ECG), which should be performed within 24 hours of admission and before the prescription of psychotropic medications. The risks of not doing so are significant, given the well-documented effects of some psychotropic medications in prolonging the QT interval, and in turn predisposing to cardiac arrhythmia. Aim: To improve the provision of electrocardiograms on psychiatric patients admitted to the Acute Assessment Unit (AAU) in the Cavell Centre in accordance with guidelines published by the RCOP.

Methods: Data was collected on all patients admitted to AAU in January 2018 (42 patients). Collection involved access to RiO notes; physical examination, investigation, and progress notes (and correlated with drug charts). Collection was focused on when during admission ECGs were performed, if they were performed before prescription of psychotropic medications, and if results were appropriately documented. These points of focus also formed the standards of the audit.
Results: 21/42 (50%) patients had an ECG performed during admission. 12/42 (29%) patients had ECGs performed within 24 hours. 8/36 (22%) patients who received psychotropic medication had an ECG before prescription. 11/21 (52%) ECGs had QTc recorded. 12/21 (57%) ECGs performed had clearly documented concerns/abnormalities - 1 of these was due to borderline QT prolongation. Of those who did not have an ECG, 5 were documented as having refused.

Conclusions: Clearly there is room for improvement in ECG provision. One significant inhibiting factor, patient consent, is non-modifiable. Other factors, however, such as the quality of handovers/documentation, inclusion of ECGs into a daily nursing checklist, time taken to repair/replace faulty machines, and the availability of more staff trained in ECG provision, are modifiable. Prevention of cardiac abnormalities, and early recognition of existing ones, are likely to improve the cardiovascular outcomes that have been a challenging aspect of psychiatric practice since the advent of psychotropic medication. The results from this audit have lead to the above modifications in local practice. The issues identified herein may also be relevant nationally.

Funding: No sponsorship received

C02
THE EFFECTS OF 12-WEEK PREBIOTIC ADMINISTRATION ON SLEEP IN ELEMENTARY SCHOOL-AGED CHILDREN: A RANDOMISED PLACEBO-CONTROLLED STUDY
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Introduction: Sleep plays a critical role in neuropsychological, neurocognitive and neurobehavioral development, especially in childhood (Hvolby, 2015, Atten Defic Hyperact Disord, 7, 1–18). It is known to be affected by stressors, diet, activity level and circadian rhythms. Recent evidence suggests that psychobiotics (pre- and probiotics) may have positive effects on sleep, but the number of studies available on gut microbiota and sleep is still limited, even more so in children. The aim of this study was therefore to investigate whether a 12-week intake of a prebiotic supplement (galacto-oligosaccharides, Bimuno®, B-GOS) influenced sleep in elementary school-aged children.

Methods: 35 children aged 7-9 received a 12-week treatment with prebiotic or a matched placebo in this randomised, double-blind, between-subjects, placebo-controlled study. Sleep was measured using both subjective (Child Sleep Habits Questionnaire CSHQ and sleep diaries; see Owens et al., 2000, Journal of Developmental and Behavioral Pediatrics, 21, 27-36 for details) and objective measures (actigraphy, MotionWatch8, CamNTech, Ltd, Cambridgeshire, UK). Mixed-design ANOVAs were used.

Results: For objective sleep, actual sleep time (F(1,29) = 10.336, p =.003) and immobile minutes (F(1,29) = 10.868, p =.003) decreased significantly over time for both treatment groups. There were no significant effects of treatment on any of the objective sleep variables. Subjective sleep, bedtime resistance (F(1, 27) = 27.313, p <.001), sleep onset delay (F(1,27) = 33.216, p <.001), sleep disorder breathing (F(1,27) = 4.596, p =.041), sleep anxiety (F(1,27) = 5.258, p =.030) and total sleep disturbance (F(1,27) = 6.666, p =.016) increased over time for both treatment groups. A significant interaction effect between time-point and treatment for Daytime Sleepiness (F(1,27) = 7.831, p =.009) was also found. Pairwise comparisons showed that this result was driven by higher scores for the treatment group at baseline, although this difference did not reach statistical significance (F(1,29) = 2.996, p =.094).

Conclusions: In this sample of children, the prebiotic did not influence sleep. Both objective and subjective measures of sleep showed a significant worsening over time for both groups, which could reflect either an age-related decrease in sleep (see Ohayon et al., 2004, Sleep, 27, 1255-1273, for a meta-analysis) or the effect of participating in the trial. Future studies should recruit children with sleep difficulties and consider differences in the methods and timings used for sleep recordings (e.g., school days vs. holidays/weekends).

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C03

MODULATORY EFFECTS OF AYAHUASCA ON PERSONALITY STRUCTURE IN A TRADITIONAL FRAMEWORK

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Introduction: Ayahuasca is a powerful psychoactive South American plant brew mix containing dimethyltryptamine (DMT) and monoamine oxidase inhibitors (MAOIs). It is used by certain communities within the Amazon basin and surrounding areas for ceremonial purposes. Westerners are now entering such communities primarily seeking alternative physical, psychological or spiritual healing. Glorified media representations have resulted in exponential growth in ayahuasca tourism, yet the brew itself is vastly understudied.

Methods: This paper assesses the impact of traditional ayahuasca use on human personality; typically deemed to be stable above the age of 30 and measured using the five-factor model (NEO-PI3), correlated with the extent of a perceived mystical experience (MEQ30) following ayahuasca ingestion. Rationale is based on Maclean et al (2011) which found a similar compound, psilocybin, caused long term increases in levels of Openness on the NEO-PI.

Results: Current study sample group N=24 found significant short-term (12 day) increases in levels of Agreeableness from pre-post ingestion (Mdiff = 10.13, 95% CI (2.34, 17.91), p = .012, d = 0.45), along with significant reductions in levels of Neuroticism (Mdiff = 17.08, 95% CI (10.12, 24.05) p < .001, d = 0.59). Long-term (six month) reductions in Neuroticism were sustained (M = 75.91, SEM = 4.26), Mdiff = 2.29, 95% CI (-5.16, 9.73), p = .539, d = 0.08), as were changes in Agreeableness (Mdiff = 6.14, 95% CI (-2.33, 14.62), p = .151, d = 0.26). Personality changes showed positive correlation with perceived mystical states within participants (rs(47) = -.56, p < .001).

Conclusions: These findings support the growing body of research that suggest therapeutic avenues for psychedelic compounds, and of mystical/peak experiences.

Funding: This study was independently funded.

C04

PSYCHEDELICS IN CONTEXT: PSYCHOLOGICAL, SOCIAL, AND ENVIRONMENTAL FACTORS IN GUIDED GROUP EXPERIENCES

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Introduction: Psychedelic ceremonies and retreats offer a structured, contextually rich, and supportive environment for individuals seeking healing, insight, or personal growth through the use of psychedelics (Tupper, K. W., 2008, International Journal of Drug Policy, 19(4), 297-30). Contextual extrapharmacological factors – set and setting – are regarded as fundamental to psychedelic drug effects (Carhart-Harris et al., 2018, Journal of Psychopharmacology, 32(7), 725-731). However, the specific ways in which psychological and environmental conditions affect acute experiences and long-term outcomes are unclear. Through a prospective online study using novel self-constructed and validated measures of set, setting, inter-, and intrasubjective drug experiences, we investigated the relationship of these variables with long-term psychological change following guided psychedelic group experiences.

Methods: Individuals who planned to participate in a guided psychedelic experience were recruited through facilitators and online fora. Questionnaires were sent out at multiple time points before and after the experience. Acute psychedelic experience measures included mystical-type experiences (MEQ), challenging experiences (CEQ), visual effects (ASC-VR), ego-dissolution and –inflation (EDI), emotional breakthrough (EBI), and social experience measures (Communitas, Fusion, Synchrony). Acute experience
measures were used to predict changes on the primary outcome well-being (WEMWBS). Psychological trait variables anxiety (STAI-SF), absorption (MODTAS), and suggestibility (SSS), state variables measuring set (PPS) and identity fusion, and items on intentions and environmental setting elements were used to predict the acute subjective experience in separate GLMs.

Results: The main outcome, psychological well-being, was elevated two and four weeks after the experience when compared to baseline (p < .001, η² = .399). This increase in well-being was more pronounced for individuals who had stronger ‘communitas’ (beta = 3.26, p = .038) and ‘emotional breakthrough’ experiences (beta = 5.80, p = .01) during the session. A positive mindset immediately before the experience and the perceived impact of ‘supportive individuals' were positively associated with emotional breakthroughs (p = .049, η² = .093; p = .019, η² = 0.79, respectively)

Conclusions: These results demonstrate the importance of sufficient preparation and emotional support in guided psychedelic experiences, as well as the capacity of environmental elements to shape responses. Challenging emotional processes mediated positive long-term change, putting into question the dichotomy between harmful challenging and beneficial mystical-type experiences. Anthropologically relevant intersubjective phenomena such as communitas may bear therapeutic relevance and should be considered in future research on psychedelic group experiences. This first quantitative examination of psycho-social and environmental factors in guided psychedelic settings is a significant step towards evidence-based guidelines for psychological harm-reduction and benefit-maximisation.

Funding: No funding was required for this research.

C05

EVALUATION OF THE UTILITY OF THE ASEX SCALE FOR ASSESSING SEXUAL DYSFUNCTION

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Introduction: Epidemiological studies indicate that approximately 40% of women and 30% of men report sexual difficulties. Recognition of sexual difficulties is sub-optimal, possibly due to difficulties in describing and eliciting problems relating to sexual function. Screening questionnaires may help to support this aspect of clinical practice. The Arizona Sexual Experiences Scale (ASEX) includes items that quantify sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. Total scores range between 5-30, higher scores indicating more severe difficulties. Although frequently used, its psychometric properties outside of North American populations and its utility in routine clinic settings are both uncertain.

Methods: We searched MEDLINE and EMBASE for articles published to March 2018, using the terms, Arizona Sexual Experiences Scale, Arizona Sexual Experience Questionnaire and ASEX. We then eliminated duplications, letters and papers not available in English. We grouped remaining papers into the three categories of validation, epidemiological, and outcome-based studies.

Results: We identified 236 records, 224 were screened, after excluding letters and duplicates. 219 were assessed for eligibility after 5 were excluded as not in English. 49 pre-clinical studies were excluded and 70 were excluded furthermore as were not obtainable or not specifically related to the subject. 100 papers were included. Cronbach's alpha analysis indicated that the ASEX had excellent internal consistency and scale reliability (α=0.9053) and strong test-retest reliability (for patients, r=0.801, p<0.01; for controls, r=0.892, p<0.01). Analyses of variance (ANOVAs) revealed significant differences in total ASEX scores between patients and controls (for males F=18.1, p<0.000; for females F=31.71, p<0.000) and between females and males (for patients F=5.22, p=0.026; for controls F=5.05, p=0.031). ASEX appears useful in a range of clinical situations including patients with primary sexual dysfunction (n=7), specific psychiatric disorders (n=9), specific physical illnesses (n=44) and treatment-emergent sexual dysfunction (n=42). Higher ASEX scores in populations with treatment-emergent dysfunction are associated with the 5-HT2A receptor -1438 AA genotype, and CYP2D6 poor metabolic status phenotype (n=2) in female patients.
Conclusions: The ASEX appears to be a reliable clinical instrument for identifying and quantifying sexual dysfunction across a range of populations in various clinical settings. Little is known about either the utility of ASEX in patients with anxiety disorders or possible relationships between ASEX scores and potential biological markers.

Funding: This study did not attract any external funding.

C06
DEEP BRAIN STIMULATION OF THE NUCLEUS ACCUMBENS IN SEVERE ANOREXIA NERVOSA: A CASE SERIES

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Introduction: Anorexia nervosa is one of the most debilitating psychiatric disorders, becoming severe and enduring (SE-AN) in a third of cases (Franko et al., 2013 Am J Psychiatry 170(8), 917-925). Few beneficial pharmacological Balestrieri et al., 2013 Eur Eat Disord Rev 21(5), 361-373) or psychological treatments exist (Watson and Bulik, 2012 Psychol Med 10, 1-24). DBS is a reversible, adjustable neurosurgical procedure, in which electrodes are inserted into specific neural targets, originally developed for movement disorders. Recently this has been trialled as a treatment for psychiatric disorders: OCD, depression and addiction. One trial applied DBS to the subcallosal cingulate in AN (50% responded) Lipsman et al., (2017). In this pilot study, we targeted the nucleus accumbens (NAcc), a centre for hedonic reward processing which is dysregulated in AN (Park et al., 2014 BRAT 62, 47-59).

Methods: A case series of four patients with repeated measures pre- and post- DBS electrode implantation to the NAcc with a 12 month follow-up period and double-blind on-off phase (protocol: Park et al., 2018 Front Psychiatry 9, 24). We used quantitative and qualitative measures of eating disorder psychopathology (EDE, YBC-EDS, CIA) and comorbid psychiatric disorders (YBOCS, HAMD, HAMA) following DBS. Our primary objective was to explore whether DBS has beneficial symptomatic effects in a group of SE-AN patients. We also aimed to explore ethical issues, capacity, consent and patients views pre- and post-DBS. As an exploratory pilot study, the small data set is not suitable for statistical analysis.

Results: Seven patients recruited, (four completed, three ongoing). Feasibility has been demonstrated with no major untoward events. Two of the Four completed patients have responded: with marked on-off improvement, and reduced psychopathology and increased quality of life by year 2. The participants who responded to DBS both had severe comorbid OCD which also improved. They continued to improve at annual follow up, patient 2 responded particularly well, BMI increasing from 14 to 18 at 28 months (19 at 32 months). In both, YBOCS and SHAPS scores at year 2 showed reduction in OCD symptoms and anhedonia. Patients 3 and 4 did not show significant change, both are still working towards recovery. All four elected to continue with the DBS stimulation.

Conclusions: A 50% response rate is in line with other studies of DBS in OCD and depression. Greater numbers are needed to further characterise those patients who most benefit and to optimise DBS as a treatment for SE-AN.

Funding: MRC CIC award, Charles Wolfson Charitable Trust , Swiss Anorexia Nervosa Foundation, Placito Bequest
C07
THE EFFECTS OF DEVELOPMENTAL STRESS AND TRAUMA ON REWARD PROCESSING: A SYSTEMATIC REVIEW

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Introduction: There is a substantial literature supporting the view that developmental trauma (DT) induces latent vulnerability for a range of mental illnesses including depression, psychosis, and substance use disorders (Teicher, M.H. et al./ 2016/ Nature Reviews Neuroscience/ 17/ 652-666). The reward processing system is a candidate neurocognitive latent vulnerability mechanism across these disorders (McCrory, E. J. et al./ 2017/ Journal of Child Psychiatry and Psychology/ 58/ 338 - 357). As alterations in reward processing have been implicated in the pathophysiology of numerous psychiatric disorders, we sought to systematically review the literature on the effects of developmental trauma on the adult reward system.

Methods: Following PRISMA guidelines, we conducted our systematic search electronically using search terms organised into two superordinate terms: a ‘developmental trauma’ term including ‘childhood maltreatment’, ‘developmental trauma’, ‘child abuse’, ‘child neglect’, ‘emotional abuse’, ‘sexual abuse’, and ‘physical abuse’, and a ‘reward processing’ term including ‘reward’, ‘punishment’, ‘reinforcement’, ‘striatum’, ‘basal ganglia’, ‘nucleus accumbens’, ‘monetary reward’, and ‘incentives’. We used MEDLINE and PSYCINFO. Reference lists of relevant abstracts were also screened. This review has been pre-registered with PROSPERO, ID number: 131950.

Results: 28 studies were included in final analysis. Animal studies (n=22) indicate that developmental stress exposure was related to reduced cell density and functioning in midbrain structures involved in reward processing alongside alterations in reward learning. In humans (n=6), developmental trauma was associated with altered reward anticipation, as well as blunted neural responses to reward in subcortical reward-related areas, such as the striatum. Several studies also reported dose-dependent effects whereby the extent of trauma was related to the degree of altered neural responses and behaviour.

Conclusions: From the studies reviewed, we conclude that DT can induce cross-species effects on the adult reward system in both animals and humans. Urgent research is needed to understand how developmental trauma-induced alterations in reward processing give rise to psychopathology.

Funding: No sponsorship was received for this study.

C08
ROLE OF DOPAMINERGIC NEUROTRANSMISSION IN ATTENTION AND IMPULSIVITY

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Introduction: Clinical and preclinical findings support a vital role for the dopaminergic system in attention and response inhibition; however, the mechanisms by which drugs that increase activity of the dopaminergic system improve cognitive function in individuals with ADHD are poorly understood. A better understanding in this area will facilitate drug discovery efforts for ADHD. The main objective of this study was to probe dopaminergic function in attention through measuring performance changes in the 5-choice continuous performance task (5C-CPT) during pharmacological manipulation of the dopaminergic system.

Methods: Thirty female Lister-Hooded rats (weighing 240 ± 5g at the start of training) were trained until they reached target parameters (>70% accuracy, < 30% omission and < 40% false alarms) in a standard 5C-CPT task in an adapted 9-hole operant chamber. 5C-CPT performance was then tested with either methylphenidate (0.5, 1.0 and 2.0 mg/kg) or atomoxetine (0.5, 1.0 and 2.0 mg/kg). Drugs were administered according to a Latin-square within subjects design.
Results: Results showed that there was a negative correlation between baseline vigilance after vehicle administration and the magnitude of improvement after administration of either drug. These results provide further support for the ‘inverted U’ model for modulators that act on the dopaminergic system.

Conclusions: Our next step is to investigate the effect of a range of dopaminergic agonists and antagonists on task performance to determine the receptor specify of our observed effects. Overall, these data will further clarify the contribution of dopamine receptors in attention and response inhibition and inform novel therapeutic strategies for ADHD.

Funding: I am a self funded PhD student

C09

OMEGA-3 FATTY ACIDS IMPROVE WORKING MEMORY AND BEHAVIOR IN CHILDREN WITH ADHD AND A HIGH HIGH-SENSITIVITY C-REACTIVE PROTEIN LEVELS (HSCRP)

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Introduction: Attention deficit hyperactivity disorder (ADHD) have higher comorbidity with inflammatory and autoimmune disorders. On the other hand, omega-3 polyunsaturated fatty acids (n-3 PUFAs) have been shown to have anti-inflammatory actions, particularly eicosapentaenoic acid (EPA), and to improve clinical symptoms in youth with ADHD. This study is aimed to investigate the effect of EPA on cognitive function in youth with ADHD.

Methods: We had enrolled 98 youth with ADHD (mean age of 9.32 ± 3.05 years, 85.7 % males) and randomized them into either n-3 PUFAs group (1.2 g EPA per day, n= 50) or placebo (1.2 g olive oil per day, n= 48) for 12 weeks. The youth were assessed with the Digit Span subtest of the Weschler Intelligence Scale for Children (WISCDS) for cognitive function and with the Strength and Difficulties Questionnaire (SDQ) for social behaviors before and after the trial. The blood sample was collected at baseline to assess the high-sensitivity C-reactive protein (hsCRP) level. The youth were categorized into low, moderate and high hsCRP groups according to the tertiles of the baseline hsCRP in an exploratory analysis.

Results: We found that in the youth with ADHD with a high baseline hsCRP (≥2.22 mg/L, n=29) level, the n-3 group has a greater improvement on the WISCDS total score (p< .05), the WISCDS backward score (p< .01), and the SDQ prosocial behavior scale scores (p< .05) when compared with the placebo group after 12 weeks; but such differences were not observed in the youth with ADHD with a low baseline hsCRP (<1.45 mg/L, n=29) (p= .329, .442, .663, respectively).

Conclusions: N-3 PUFAS, particularly EPA, improve working memory and prosocial behavior in youth with ADHD with high inflammatory status. EPA with its anti-inflammatory actions and a relative safety profile for adverse effects may have favorable effects on cognitive function and social behaviors in a subpopulation of ADHD with high inflammatory status.

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C10
ATTENTION DEFICITS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN A PRECLINICAL ANIMAL MODEL

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Introduction: Developing new treatments for attention deficit requires novel rodent behavioural paradigms with high translational value. Conventional rodent behavioural attention paradigms have low translational value compared to the human continuous performance test (CPT). In order to address this gap, we report here further validation of the recently developed rodent version of the human CPT.

Methods: C57BL/6J (n=40) female mice were trained in 8 touchscreen-based operant chambers (Campden Instr. Ltd, UK) to perform the rodent continuous performance test (rCPT). After reaching baseline performance criterion mice were tested on three different probes (variable stimulus duration, variable stimulus contrast and flanker distractors) to assess the effects of changes in these parameters on task performance. Finally, rCPT probe performance was tested 30 minutes after acute administration of methylphenidate (0.5 – 2 mg/kg, i.p.) or atomoxetine (0.5 – 2 mg/kg, i.p.), two compounds shown previously to modulate attention. Probe sessions were analysed by repeated-measures ANOVA with comparison of probe test performances using Tukey's multiple comparison test while one-way ANOVA were used for analysis of drug treatments. Statistical analyses were conducted with GraphPad Prism 7.

Results: Mice reached criterion baseline performance within a median of 17 sessions (min 16, max 23, M=17.75, SD=1.427). The rCPT performance of mice decreased with increases in attentional load during stimulus duration (F(2,39)=69.94, p<0.0001), stimulus contrast (F(3,39)=109.3, p<0.0001) while there was no significant main effect of flanker distractor. One-way ANOVA for all subjects revealed a near-significant main effect of atomoxetine treatment (F(3,29) = 2.844, p = 0.055, η2 = 0.227) and multiple comparison showed that accuracy was significantly improved by 1mg/kg atomoxetine for all animals in variable stimulus duration probe (p= 0.0266) whilst methylphenidate (MPH) had significant main effect (F(3,29)= 3.343, p<0.05) on accuracy and performance was significantly improved by 1mg/kg methylphenidate in variable stimulus duration probe (p<0.0299).

Conclusions: Our results provide further evidence that the rCPT can detect changes in attention performance. We also show for the first time that rCPT performance can be improved by atomoxetine. These findings further validate the value of the rCPT in both assessing pharmacological modulation of attention performance and increasing our understanding of the underlying mechanisms of attention deficit.

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C11
DEFINING THE EFFECTS OF OREXIN 1 AND 2 RECEPTOR ANTAGONISTS ON SLEEP ARCHITECTURE

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Introduction: The orexin receptors, OX1R and OX2R, contribute to sleep patterns differently. OX1R/OX2R knockout (KO) mice show severe sleep-wake fractionation and a narcolepsy-like phenotype; a mild phenotype is seen in OX2R KO mice and almost no phenotype in OX1R KO mice. Testing dual orexin receptor antagonists (DORAs) in OXr KO mice demonstrated that OX2R is essential for the hypnotic effects of DORAs. OX2R antagonists mainly enhance NREM sleep, whereas DORAs increase NREM and REM sleep;
OX1R antagonists alone do not affect sleep. These data led to the hypothesis that combined OX1R/OX2R antagonism increases REM sleep. The present study therefore investigated the dose-dependent effects of OX2R antagonism alone or combined with OX1R blockade on sleep-wake vigilance states in mice.

Methods: C57Bl/6J mice (males, n=6-12 per group) were surgically implanted with electroencephalogram (EEG) / electromyogram (EMG) head-mounts. The contribution of OX1R and OX2R on vigilance states was examined by administering different doses of the OX2R antagonist, MK1064 (10, 30, 100 mg/kg, p.o.) alone or in combination with the OX1R antagonist 1-SORA-51 (60 mg/kg), versus vehicle (20% TPGS) within animal. PSG recordings (23 hr for vehicle and drug treatments) were acquired using preamplifiers connected to a computer running Sirenia Acquisition software (gain 100X, high pass filter 0.5 Hz, low pass filter 100Hz, sampling rate 200Hz, Pinnacle Technologies Inc). Recordings were analysed using SomnivoreTM. Data were analysed using 2-way RM ANOVA with Fisher's LSD post hoc tests.

Results: MK1064 dose-dependently increased NREM sleep (from 10 to ~30 min per hour at 1 (P<0.001) and 2 (P<0.001) hours post-dose) without significantly affecting REM sleep. When MK1064 was co-dosed with 1-SORA-51, REM sleep was dramatically increased (~2-fold for 1-6 hours post-dose), but NREM sleep was also increased (from ~10-20 min per hour in the control condition to ~30-35 min per hour in the treated group for up to 6 h post-dose; P<0.001 for hours 1, 2, 3, 5 and 6, P<0.05 at hour 4 post-dose), such that the amount of NREM in the first 6 hours after dosing for the 30 mg/kg MK1064 + 1-SORA-51 group was not different from the 100 mg/kg MK1064 group (P>0.05). Furthermore, 1-SORA-51 converted a non-efficacious dose of MK1064 (10 mg/kg) into an efficacious dose for both REM and NREM sleep. Finally, rebound reductions in NREM and REM sleep in the early light phase (NREM: P<0.001 1 hour after lights-on, P<0.05 2 hours after lights-on; REM P<0.001, 2 hr after lights on), were seen when co-dosing MK1064 and 1-SORA-51, but not with MK1064 alone.

Conclusions: Co-administration of OX2R and OX1R antagonists amplified the sleep/wake effects of the OX2R antagonist alone and substantially increased REM sleep. In addition, the combination of OX1R and OX2R antagonism produced a rebound effect not seen with OX2R antagonism alone. These data indicate that although NREM sleep can be enhanced by antagonism of OX2Rs, both OX1R and OX2R antagonism are involved in the physiological control of NREM and REM vigilance states.

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DOE STRIATAL FUNCTION HAVE A ROLE IN PARKINSON’S DISEASE PSYCHOsis? - EVIDENCE FROM DAT IMAGING

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Introduction: The psychosis spectrum of Parkinson's disease (PD) is identified as a range of neuropsychiatric symptoms from illusions, formed hallucinations to delusions that occur during Parkinson's Disease (PD). Reduced Dopamine Active Transporter (DAT) binding in the striatum is often associated with motor symptoms of PD but previous studies show reduced striatal DAT binding PD patients who also develop psychosis. However, current theories about visual hallucinations focus on perception and attention deficits (PAD) (Collerton et al., 2005, Behav Brain Sci, 28, 737-57; discussion 757-94.), and the link between reduced DAT binding in the striatum and hallucinations is unclear. The aim of this study was to see if reduced striatal DAT binding is linked to the psychosis symptoms of PD, what mechanisms facilitate the onset and if the changes pre-date the onset of symptoms.

Methods: We conducted a retrospective cohort study by analysing data from 541 participants from the Parkinson's progression marker's initiative (PPMI) database. We analysed data from DAT scans of the overall striatum, regions of interest within the striatum, UPDRS and MoCA tests at the screening visit, 1, 2 and 4 years later. The primary outcome measure was striatal DAT binding. Analysis was conducted using a one-way ANOVA with post-hoc tests while controlling for age, cognition, and motor symptoms.
Results: Out of 541 participants, 21 developed formed hallucinations, 92 developed illusions, and 284 had no hallucinations or illusions and 144 were healthy controls. The formed hallucinations group had reduced DAT binding compared to the other two groups in the overall striatum at the screening visit (p=0.043) and particularly, in the right caudate at 1-year (p=0.019). When controlling for UPDRS, MoCA and age, the formed hallucinations group had reduced DAT binding in the right caudate at 1-year (p=0.046), although 61% of the participants had not yet had their first hallucination.

Conclusions: Even when controlling for motor symptoms, cognition and age, the formed hallucinations group had reduced DAT binding, particularly in the right caudate, compared to the other two groups. Reduced DAT binding in the right hemisphere caudate pre-dates the onset of visual hallucinations, implying it may be involved in the cause of hallucinations through its link to executive function, mainly inhibitory control. The findings suggest illusions have a different mechanism, providing avenues for research and treatment implications.

Funding: Data used in the preparation of this study were obtained from the Parkinson's Progress Markers Initiative database (http://www.ppmi-info.org/) funded by the Micheal J. Fox foundation. No sponsorship was received for this study.

D02
LOCATION PRIMING AS A MARKER OF COGNITIVE FUNCTION IN PARKINSON’S DISEASE AND ITS TREATMENT
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Introduction: Cognitive impairment in Parkinson's Disease (PD) is common, even in the early motor stages of the disorder, and has a substantial impact on quality of life and prognosis. There is intense interest in the development and discovery of drugs that enhance cognitive function in this patient group. An important limiting factor in the development of novel cognition-enhancing drugs is the lack of reliable and sensitive biomarkers to test the effect of pharmacological agents early in development. Given that implicit measures of cognition are less vulnerable to ceiling and compensatory strategy effects, they may be relatively more discriminative, and sensitive to pharmacological manipulation, than existing explicit measures. We assessed whether three implicit cognitive tasks were sensitive to cognitive change in prodromal and early-stage PD.

Methods: Patients within four years of PD diagnosis (n=30), REM Sleep Behaviour Disorder (RBD, n=31), and healthy controls (HC, n=30) completed a validated battery of computer-based implicit cognitive tasks. Groups were well matched for age and scored within the normal range on the Montreal Cognitive Assessment. Tasks included location priming, contextual cueing, and an implicit symbol location prediction task (ISLP). Motor and non-motor PD symptoms were also measured.

Results: Groups differed significantly in positive priming (F(2,88) = 6.8, p = .002), with RBD showing reduced positive priming relative to PD (p < .001) and HC (p = .026). Groups did not differ in negative priming. There was no evidence of a contextual cueing effect across the sample (p > .05). The ISLP demonstrated a main effect of congruency (p = .029), with participants significantly faster on predictive than catch trials, though there was no group interaction.

Conclusions: Results indicate location priming as a potential marker of early cognitive changes in PD. Reduced positive priming in RBD suggests the task is sensitive even to cognitive changes in prodromal PD, and could potentially be used prior to diagnosis. In contrast, PD patients showed slightly enhanced positive priming, though not significantly greater than HC. These findings are consistent with previous literature, and may reflect a pharmacological effect of existing dopaminergic medication which our future UCB-funded work will explore.
Funding: This research was funded by UCB Pharma and supported by the NIHR Oxford Health Biomedical Research Centre.

D03
DISRUPTED OUTCOME-RELATED BRAIN PATTERNS IN VISUAL AND PREFRONTAL CORTEX IN MEDICATED PARKINSON’S PATIENTS
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Introduction: Dopamine (DA) has been implicated in numerous cognitive processes, particularly in reinforcement learning and the ability to resist task-irrelevant information. DA is thought to play an important role in the resistance to distractors by stabilizing task-relevant representations in the dorsolateral prefrontal cortex (DLPFC) and making them less vulnerable to new inputs (Durstewitz & Seamans 2008). Impaired DA-related distractor resistance has been linked to reduced connectivity between the DLPFC and visual regions important for encoding task-relevant stimuli (Bloemendaal et al., 2015). The essential role of DA in signalling valence-based prediction errors when receiving feedback during RL has been well established (Schultz et al., 1997).

Methods: 24 Parkinson’s disease (PD) patients and 24 healthy controls (HCs) performed a reinforcement learning task while undergoing functional magnetic resonance imaging (fMRI), as well as a separate attentional capture behavioural task. PD patients were tested both ON and OFF dopamine medication. For each participant, brain activations related to positive and negative outcomes during reinforcement learning were extracted from visual and frontal regions of interest. Multivariate pattern analysis (MVPA) was carried out to assess DA-related differences in outcome-related representations in these regions, with classification accuracy capturing the accuracy with which the classifier could predict the correct outcome across trials. For the attentional capture task, resistance to distraction was calculated as the reaction time difference in responding to a target in the presence vs. absence of a salient distractor.

Results: In the attentional capture task, HC and PD ON showed greater distractor resistance than PD OFF. In the reinforcement learning task, MVPA results showed significant classification accuracy of good vs. bad outcomes in both object-selective cortex and DLPFC in all groups. PD ON had significantly lower classification accuracy than HC in both object-selective cortex (p=.045) and in the DLPFC (p=.035). There was a positive relationship in PD ON between distractor resistance in the large set size during the attentional capture task and outcome classification accuracy in both object-selective cortex (p=.007, r=.58) and DLPFC (p=.04, r=.43). In HC, the same correlation showed a negative relationship in object-selective cortex (p=.016, r=-.53).

Conclusions: DA levels (by health or medication) improves distractor resistance. Lower classification accuracy of outcomes in PD ON compared to HC suggests that DA medication does not lead to a healthy level of distinction between positive and negative outcomes in object-selective cortex or DLPFC. The opposite relationship between distractor resistance and classification accuracy in object-selective cortex for HC compared to PD ON suggests that DA medication perhaps does not operate in the same way across these cognitive processes as naturally-occurring DA.

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E01
SEROTONIN, COMPULSIVITY AND A NEW USE FOR MDMA?
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Introduction: The rodent spontaneous alternation behaviour (SAB) test in the Y-maze has a long history of use as a rat model of compulsivity (Yadin et al., 1991, Pharmacology, biochemistry, and behavior, 40, 311-315), but has recently been developed for use in mice (Arora et al., 2013, Behavioural brain research, 247, 146-152; Verma et al., 2018, Neuropharmacology, 138, 106-117). This model employs the use of 5-hydroxytryptamine 1A receptor (5-HT1AR) agonist (±)-8-Hydroxy-2-dipropylaminotetralin (8-OH-DPAT) to induce compulsive-like perseverance in the maze, possibly by producing a decrease in 5-HT neuron firing (Arora et al., 2013, Behavioural brain research, 247, 146-152).

Methods: 8-16 week old male C57BL/6J mice were tested in the Y-maze without the use of food baiting, following acute i.p. pre-treatment with 5-HT modulatory drugs or saline control. Spontaneous behaviour in the maze during 10 minutes was recorded by a treatment-blinded observer, and alternation ratio served as a measure of compulsive-like behaviour.

Results: 8-OH-DPAT dose-dependently induced compulsive-like perseverative behaviour at 0.5 (p<0.05), 1.0 (p<0.001) and 2.0 (p<0.001) mg/kg. Co-administration of 5-HT1AR antagonist, WAY100635, 2.0 mg/kg blocked the effect of 8-OH-DPAT (p<0.05) on SAB and confirmed that it was mediated by 5-HT1AR activation. The deficit produced by 8-OH-DPAT on SAB could be attenuated by acute pre-treatment with the 5-HT releasing agent, (±)-3,4-methylenedioxymethamphetamine (MDMA), 1.0 (p<0.05) and 10.0 (p<0.001) mg/kg but not by the 5-HT reuptake inhibitor, (±)-citalopram 2.5-7.5 mg/kg.

Conclusions: Our study further refined this rodent model of compulsivity to a non-baited version of the test that is less stressful to the animals and that does not require disruption of the animals by moving them during the test. The results suggest a new use for MDMA as a psychotherapeutic agent, but also raise questions related to validity of this rodent model of compulsivity.

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E02
CO-ADMINISTRATION OF MEPHEDRONE AND CAFFEINE ENHANCES STEREOTYPED BEHAVIOUR IN ADOLESCENT RATS, WITHOUT LONG-TERM CHANGES IN COGNITION OR HIPPOCAMPAL MICROGLIAL ACTIVATION
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Introduction: Recreational mephedrone use continues throughout Europe, often combined with caffeine (Gyarmathy et al. 2017 Int J Drug Policy 46:61-5). In rats, caffeine co-administration reverses mephedrone-induced anxiety and converts hypothermia to hyperthermia (Shortall et al. 2016 J Psychopharmacol 30:698-706). The current study examined longer-term consequences of repeated mephedrone administration, alone or with caffeine during adolescence, on cognition, anxiety and hippocampal microglial activation in adulthood.

Methods: Forty male Lister-hooded rats (Charles River, UK) were implanted with subcutaneous temperature-sensing microchips (idENTICHIP; Animalcare) on post-natal day (PND) 27-31. From PND34/35-42/43, they received repeated (i.p.) vehicle (saline 1mL/kg), mephedrone (7.5mg/kg), caffeine (10mg/kg), or mephedrone-caffeine co-injection (x3/day at 2h intervals on 2 consecutive days/week for 2 weeks; 12 injections) to mimic human weekend recreational use. Temperature and behaviour in the home cage were monitored throughout treatment. Open field exploration was examined 30min
after first injection each week. Starting 17 days after the final injection locomotor activity, novel object discrimination, elevated plus maze exploration, pre-pulse inhibition and conditioned freezing responses were examined (PND59-86) to detect any lasting changes in aversion or cognition. Brains were collected for immunohistochemical analysis of Iba1-positive microglia in the hippocampus. Data were analysed by 2-way, or 3 and 4 repeated measures ANOVA with Tukey/Bonferroni post-hoc, and Pearson's correlation. Results: Caffeine produced acute hyperthermia (+0.98±0.14°C above baseline). Mephedrone-induced hypothermia (-0.71±0.16°C below baseline) was attenuated or converted to mild hyperthermia in the second week following caffeine co-injection (+0.58±0.17°C; P<0.05-0.01 versus mephedrone). Mephedrone caused mild stereotypy (head weaving, forepaw treading) with increasing injection number, and increased distance moved in the open field (P<0.05 versus vehicle). Caffeine co-administration exacerbated this stereotypy (P<0.01-0.001 versus mephedrone), and increased central open field duration (P<0.05 versus mephedrone). Hippocampal Iba1-positive cell numbers remained unchanged.

Conclusions: Repeated caffeine and mephedrone co-administration enhanced short-term locomotor stimulation and produced anxiolytic-like effects, consistent with previous observations (Shortall et al. 2016). Weak induction of the serotonin syndrome by mephedrone was enhanced by caffeine, possibly because central 5-HT release induced by mephedrone was enhanced by adenosine receptor antagonism, as seen following MDMA and caffeine co-administration (Vanattou-Saitoudine et al. 2012 Br J Pharmacol 167:946-59). The altered temperature response associated with caffeine and mephedrone combination may reflect enhanced neuronal dopamine release by caffeine (Shortall et al. 2016). This dosing regimen did not reveal lasting cognitive deficits or altered hippocampal microglial activation, but alternative consequences including oxidative stress have been reported (Kaminska et al. 2018 Neurotox Res 34:525-37).

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E03
PROBING THE ‘BOUNDARY CONDITIONS’ OF CUE-ALCOHOL MEMORY RECONSOLIDATION: ARE SOME CONDITIONED MEMORIES TOO STRONG TO UNDERGO DESTABILISATION?

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Introduction: Following reactivation memories can be returned to a transient, labile state in which they are susceptible to modification. Reconsolidation thus presents an enduring mechanism by which the Pavlovian associations between cues and the reinforcing effects of alcohol can be modulated. The ability to modulate these memories is constrained by ‘boundary conditions,’ including memory strength. We explored whether the inclusion of prediction error (PE) at retrieval was sufficient to destabilise, naturalistic cue-alcohol memories such as those seen in clinical populations.

Methods: Sixty hazardous beer drinkers were randomised to receive N2O (a pharmacological blockade of reconsolidation) following the retrieval of cue-alcohol memories with (Ret-PE) or without PE (Ret-NoPE) or following PE without retrieval (NoRet-PE). History of personal alcohol use across the lifetime was obtained, and participants completed an alcohol Time Line Follow Back for two-weeks pre-treatment, and one-week post-treatment.

Results: A mixed 2 (time, baseline; test) x 3 (group) ANOVA revealed a significant Day x Group interaction (F2,54 = 4.489, p =.010, ηp² = .156) with beer consumption reducing in the Ret-PE group only (p=.001). Total Lifetime Drinks did not moderate the relationship between Group and change in beer consumption (ΔR²=-0.096, F2,53=0.325, p=0.724).

Conclusions: Destabilisation of naturalistic cue-alcohol memories is dependent on the inclusion of PE at retrieval. Change in beer consumption was not moderated by total cue-alcohol exposures, suggesting strongly conditioned memories can undergo destabilisation. Modulation of reconsolidation may therefore serve as an enduring treatment for alcohol dependence, and further study of the efficacy of N2O is warranted.

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E04
CANNTEEN: HOW DOES LONG-TERM CANNABIS USE AFFECT TEENAGERS’ AND ADULTS’ BRAINS? A PROTOCOL FOR OUR LONGITUDINAL MRI STUDY

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Introduction: Adolescence is a period in which the brain, and specifically the endocannabinoid system, continue to develop. It is thought that the harms associated with cannabis may be greater during adolescence than in later years. Changes in brain function and structure related to cannabis use may be more pronounced during adolescence than in adulthood. Despite these concerns, studies directly comparing teenage and adult cannabis users are scarce. Over the course of one year, we aim to examine changes in brain function, brain structure and white matter integrity in teenage and adult cannabis users and controls. We hypothesise that teenage cannabis users will show a significantly altered trajectory relative to teenage controls, compared to how adult cannabis users change relative to adult controls.

Methods: We use a longitudinal MRI design in which participants complete an MRI scan at 0 and 12 months. Participants come from a larger longitudinal behavioural study. We will recruit a total of 140 participants, split equally (n=35) between four groups: teenage cannabis users, teenage controls, adult cannabis users and adult controls. Cannabis users must use 1-7 days/week and controls must have not had more than 10 lifetime cannabis exposures. Adult cannabis users must not have been a regular cannabis user before turning 18. We measure blood oxygen level dependent (BOLD) response while participants complete a stop-signal task, a monetary incentive delay (MID) task and an n-back task, in order to measure the neural correlates of response inhibition, reward anticipation and working memory, respectively. Additionally, we take an anatomical T1-weighted scan for structural analysis and conduct diffusion tensor imaging to assess white matter integrity. We scan on a 3-T Siemens MRI scanner.

Results: We predict that there will be a significant interaction between age-group, user-group and time, on the following outcomes: (1) BOLD response during reward anticipation (relative to no reward anticipation) in the MID, (2) BOLD response during the 2-back condition (relative to the 0-back condition) in the n-back task, (3) BOLD response during a stop trial (relative to a go trial) in the stop-signal task, (4) grey matter volume in regions rich in cannabinoid CB1 receptors (e.g. medial temporal cortex, prefrontal cortex and basal ganglia), and (5) white matter integrity.

Conclusions: For the first time, we will be able to directly compare how teenage and adult cannabis users’ brains change over time, relative to matched controls. This will have important implications for cannabis policy, which aims to protect young people from the potentially harmful effects of cannabis.

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E05
BLUNTED NUCLEUS ACCUMBENS ACTIVITY IN BINGE DRINKERS DURING REWARD-GAIN EVENTS REVEALED BY EVENT-RELATED FUNCTIONAL MAGNETIC RESONANCE IMAGING

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Introduction: Alcohol and substance misuse enhances dopamine (DA) function by acting on midbrain DA neurons (Nestler, 2005, Nature Neuroscience, 8, 1445-1449). In animal studies, this effect is considered a causal mediator of multiple drug effects, behavioural and motivational. In humans, functional brain abnormalities have been more rarely studied, using event-related fMRI.

Methods: An instrumental learning task during fMRI and clinical ratings of alcohol misuse were used to
test hypothesised abnormalities. Forty binge drinkers and nineteen controls performed a reward-gain and loss-avoidance task, which was a modified version of the Pessiglione task (Pessiglione, 2006, Nature, 442, 1042). This task is highly sensitive to detect functional imaging abnormalities in addiction (Gradin, 2014, 39, 885) and in psychiatric disorder (Johnston, 2015, 138, 2766-2776). Diagnosis was made according to MINI-Plus. AUDIT was used to identify the diagnostic criteria for binge drinking. For each participant, functional whole-brain images were acquired using a 3T Siemens Time Trio scanner.

Results: As hypothesised, young binge drinkers exhibited blunted brain responses to non-alcohol-related, reward-gain events, in the nucleus accumbens (-10,8,-6) t=8.05, (12,8,-14) t=7.13. Significance was defined with a voxel threshold (P<0.05). AUDIT alcohol severity scale correlated negatively with bilateral nucleus accumbens (26, 20, -12) t=4.2, (-20, 22, -8) t=4.1.

Conclusions: These findings support an interpretation of progressive reward-processing dysfunction in binge drinkers. Functional imaging may be useful for identifying biomarkers of alcohol misuse and if so, could offer a novel target for treatment.

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E06
CANNABIDIOL AS A MODULATOR OF CUE REACTIVITY IN SMOKING CESSATION
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Introduction: Tobacco use disorder is a common addiction with high relapse rates - only 20% of ex-smokers remain abstinent six months after pharmacologically-aided smoking cessation (Hatsukami, et al., 2008, The Lancet,371,2027-2038). In recent years, an emerging treatment for substance use disorders has been the phytocannabinoid cannabidiol (CBD), one of the main active compounds in the cannabis plant. Previous research has found that CBD can reduce cigarette smoking (Morgan et al., 2013, Addictive behaviors,38,2433-2436) and attentional bias to smoking stimuli (Hindocha et al., 2018, Addiction,113,1696-1705), likely via its action on the endocannabinoid system. Preclinical research has suggested that CBD's effects are mediated via changes in cue induced craving (Ren et al., 2009, Journal of Neuroscience,29,14764-14769; Maldonado et al., 2006, Trends in neurosciences,29,225-232). The aim of this study was to examine whether CBD administration modulates reactivity to smoking cues.

Methods: This was a double-blind placebo-controlled study. Behavioural, biological, and fMRI data were collected. Dependent smokers (n=49) attended two study sessions scheduled two weeks apart and self-administered either CBD or a matched placebo using a vaporiser pen (‘e-cigarette’), as well as recorded their daily craving levels and the number of cigarettes smoked between study sessions. The fMRI component was a cue-reactivity task with a boxcar design where participants were exposed to smoking-related and neutral stimuli before and after treatment.

Results: Our main behavioural finding is that participants in the CBD group reported lower cigarette cravings during the two weeks between study sessions compared to the placebo group (t43= -2.18, p=.035, d=.654). The main fMRI findings were task-related activations in a network of regions that included the ACC (Tmax=1.95, uncorrected p=.030, peak voxelxyz=-10,-32,14), and insula (Tmax=2.14, uncorrected p=.020, peak voxelxyz=-36,-6, 14), as well as a reduction in reactivity to smoking stimuli, as measured by activation to smoking cues in the insula, for the placebo group (F1,27=7.18, p=.012, η2p=.210).

Conclusions: The main finding of this preliminary study is that compared to a matched placebo, CBD self-administration over a two-week period using a vaporiser pen was associated with lower levels of self-reported cigarette cravings over that period. This reduction in craving was not reflected in a reduced reactivity to smoking cues in an fMRI paradigm but in placebo two weeks of e-cigarette use reduced insula activation to smoking stimuli. Our findings suggest that CBD administration may produce therapeutic effects for individuals with tobacco use disorder, but further studies are needed to evaluate its mechanism.

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EXPLORING THE EFFECTS OF CIGARETTE SMOKING ON MULTIPLE PSYCHIATRIC OUTCOMES USING MENDELIAN RANDOMISATION.

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Introduction: Smoking is highly co-morbid with several psychiatric conditions, but understanding the causal nature of this relationship is complicated by confounding and reverse causation. Mendelian randomisation uses genetic variants to examine causal pathways between an exposure (e.g. smoking) and outcomes. Previous genetic instruments for smoking have only captured discrete aspects (e.g., initiation, heaviness), limiting power and requiring stratification on smoking status and therefore individual level data. To overcome these issues, we developed a novel genetic instrument for lifetime smoking exposure, which captures smoking duration, heaviness and cessation and includes both smokers and non-smokers, removing the need to stratify on smoking status. We also update previous instruments for smoking initiation using the most recent genome-wide association study (GWAS) from the GSCAN consortium.

Methods: We have triangulated evidence from multiple smoking instruments on four mental health outcomes: schizophrenia, major depression, bipolar disorder and suicide. For all mental health outcomes other than suicide, we have also tested bi-directional effects to investigate the self-medication hypothesis.

Results: We see consistent evidence for an positive effect of smoking on risk of depression (OR = 2.03, 95% CI = 1.74 - 2.37, P = 3.77 × 10^{-19}), schizophrenia (OR = 2.33, 95% CI = 1.71 - 3.18, P = 8.71 × 10^{-08}), bipolar disorder ( OR = 1.72, 95% CI = 1.29 - 2.28, P = 1.8 x 10^{-4}) and suicide attempts (OR = 2.42, 95% CI = 1.53 - 3.83, P < 0.001). Overall, there was weaker evidence for self-medication effects. There was evidence of stronger effects on suicide attempts than suicidal ideation suggesting we need to consider possible pleiotropic effects of impulsivity.

Conclusions: These findings indicate that the co-morbidity between smoking and psychiatric conditions is due, at least in part, to a causal effect of smoking on these outcomes. This provides further evidence for the detrimental public health consequences of smoking and the need to reduce smoking prevalence not only to reduce the burden of physical illness, but also to reduce the burden of mental illness.

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IMPAIRED EMPATHY AND PHYSIOLOGICAL RESPONSES TO SOCIAL EXCLUSION IN CHRONIC OPIOID USERS

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Introduction: Understanding the psychosocial factors involved in the opioid addiction is becoming an increasing priority in light of the current opioid epidemic. Social functioning in chronic opioid users may
become altered via changes to the endogenous opioid system. The ability to relate to others i.e. empathy, as well as sensitivity to social pain may be negatively affected by long-term opioid use. The current study aimed to assess both emotional and cognitive empathy, as well as subjective and physiological responses to social exclusion in opioid users who were either acutely intoxicated or recently withdrawn from using opioids.

Methods: Individuals on an opioid substitution medication (OSM) were divided into two groups: ‘Intoxicated users’ who had taken their OSM < 4 hours prior to testing (n=20), and ‘recently withdrawn users’ who took their OSM > 12 hours ago (n=20), and were compared with opioid-naïve controls (n=24). Emotional and cognitive empathy were assessed using a computer task (the Multifacetted Empathy Test) and self-report questionnaire. Participants also underwent a period of social exclusion (the Cyberball Game), following which they completed subjective mood measures and physiological markers of stress (salivary cortisol and heart rate).

Results: Recently withdrawn users had significantly lower emotional empathy (i.e. the ability to experience others’ emotional states) than the controls during the computer task (p=.048), as well as significantly greater anger after social exclusion (p=.016). Anger did not change in the intoxicated user group, and cortisol was lower over the duration of the study (p=.016). Impairments in empathy were not related to the duration of using opioids.

Conclusions: Impaired empathy and greater anger after social exclusion within the non-intoxicated opioid users may indicate an overarching impairment to emotional regulation. Attenuated anger after social exclusion in the intoxicated group as well as similar rates of empathy to the controls could suggest that opioids are used to regulate difficult emotional states, making it easier to socially relate and cope with difficult social scenarios. It is possible that increased anger is due to a depletion in endogenous opioids either caused by drug use as well as pre-existing factors such as social deprivation and marginalisation.

Funding: Funding was from the University of Exeter and the researcher’s studentship.

E09

EFFECTS OF HEALTH WARNING GLASSES ON ALCOHOL CONSUMPTION, ALCOHOL URGES AND ALCOHOL-RELATED ATTITUDES

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Introduction: It is estimated that around 10 million people in England regularly drink more than the recommended low risk guidelines. However, public knowledge about the health effects of alcohol are poor, with many drinkers not knowing the risks or believing the risks do not apply to them. There have been calls for alcohol product labels to include more comprehensive health warnings, but legislative changes are slow to implement. However, it is possible to develop other routes of health communication at the point of drinking. This study investigated whether drinking from a glass marked with an alcohol health warning affected the drinking experience of a single serving of beer and alcohol-related attitudes.

Methods: Regular beer drinkers (n=84, 50% male) were recruited and randomised to drink beer from either a glass marked with a (cancer) health warning or a standard (non-marked) glass (between-subjects design). Participants completed a drink ratings questionnaire during consumption to mask the nature of the study. Primary outcomes included measures of total alcohol consumed, alcohol urges and alcohol-related attitudes.

Results: There was no evidence of an effect of glass on consumption (p = .91) or urges (p = .48). There was evidence of differences in alcohol-related attitudes, with those drinking from the health warning glasses reporting more alcohol-related health concern (t = 5.22, df = 82, p < .001). There was also good support for health warning marked glasses with 66% and 64% of participants agreeing that health warning glasses “are a good idea” and “would make me think more about health effects of alcohol” respectively.

Conclusions: These findings suggest that using alternative communication methods to product labelling, such as health warning marked glasses could have positive population health benefit. In particular, it may
improve knowledge and consideration of the health consequences of drinking. While we saw no evidence of lower consumption across a single drink, this change in attitudes may be an important first step in encouraging people to consider the impact of alcohol on health, which in turn may impact intake over time.

Funding: Medical Research Council (MRC) - Public Health Intervention Development Award (MR/N027450/1)

E10
AUDIT OF PRESCRIPTION OF OPIATE-BASED ANALGESIA FOR INPATIENTS IN A PSYCHIATRIC UNIT
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Introduction: To identify and assess patterns of opiate prescribing in patients with a mental health diagnosis in order to avoid prescribed drug dependence To evaluate compliance with: Standard 1: Indication documented 100% of the time. Standard 2: Less than 1 year of usage of medication. Standard 3: Maximum equivalent morphine dose 120mg/24 hours.

Methods: Opiate prescriptions for the inpatients admitted during the 1st week of May 2018 in Taunton, Somerset. The sample consisted of a total of 11 patients who were prescribed opiates during this time frame.

Results: 1. The indication for giving opiates was documented in 73% of cases. The documented indication varied depending on the severity of the pain or a specific type of pain such as abdominal or back pain. 2. In just over half of the patients (55%) opiates had been used for less than one year. In this cohort 3 of the patients had been prescribed and using opiates for more than a year and were considered to be opiate dependent. 3. In the majority of cases (91%) the maximum dose of morphine was limited to 120mg/24hrs.

Conclusions: Opiates were prescribed infrequently in this group. The majority of prescriptions were for females over 50 years old and most patients were on the geriatric psychiatry unit. Codeine was the most commonly prescribe opiate in this cohort. Prescriptions over 120mg/24 hours were infrequent. The recommendations were to record the indication more often and to ensure that such a course of treatment is less than 12 months.

Funding: Nil

E11
ASSOCIATION OF PHYSICAL HEALTH WITH OPIATE SUBSTITUTION THERAPY PRESCRIBING
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Introduction: Opiate dependence is treated with opiate substitution therapy (OST), either methadone or buprenorphine, with psychosocial approaches. Guidelines for the management of opiate dependence list the optimal range OST as 60-120 mg/d for methadone, and 12-16 mg/d for buprenorphine. Given the negative long-term health effects of opiates, this project examined prescribing data from a London addiction service, to explore any association between physical health and OST dose.

Methods: Clinical records were examined and service users (SUs) were grouped by OST drug, SUs were given a score based on the number of the following physical health conditions recorded, each scoring 1 point: drug use other than primary opiate used at treatment start, alcohol listed as causing concern, chronic obstructive pulmonary disease, HIV-positive status, Hepatitis C-positive status, Smoking ≥7 days in last 28, and any recorded physical disability. Using all OST prescriptions over 12 months, averages were
calculated by subgroup for the single highest dose (SHD) recorded, and for the dose covering the most days of treatment (DMD). One-way ANOVA statistical analysis was used to compare the subgroups.

Results: 443 SUs were sorted into subgroups (Methadone n=330 buprenorphine n=113). Those scoring; 0: n=59 (methadone:44,buprenorphine:15), 1: n=172 (methadone:125,buprenorphine:47), 2: n=148 (methadone:108 buprenorphine:40), 3: n=52 (methadone 41 buprenorphine 11), ≥4: n= 12 (methadone:12 buprenorphine:0). Secondary drug use was the most common condition (n=291), followed by Smoking (n=215), and alcohol use (n=52). SHD increased with poorer physical health. Between the lowest and highest scoring subgroups dose rose from 43.3mg±2.9 to 57.5mg±6.0 of methadone (p=0.020;f=2.97) and from 5.8mg±0.9 to 13.2 mg±1.5.of buprenorphine(p=0.00003;f=8.81). DMD also increased with worsening physical health from 40.2mg±3.1 to 56.7mg±5.9 of methadone (p=0.016;f=3.10), and from 5.4mg±1.0 to 12.7mg±1.5 of buprenorphine(p=0.0001;f=7.68). OST drug choice also varied, of those scoring 0-2 72%-74% were prescribed methadone, this increased to 84% in the group scoring 3points. No SUs with over 3 conditions were prescribed buprenorphine.

Conclusions: The data indicate that prescribing patterns differ by SU’s physical health, both in choice of drug and dose prescribed, with poorer physical health linked to higher doses of methadone and buprenorphine, as well as a higher percentage of methadone prescriptions. It should be considered whether higher doses of OST are adversely impacting on physical health.

Funding: None

E12

BASELINE REPORTED CONCOMITANT SUBSTANCE ABUSE IN OPIOID SUBSTITUTION THERAPY: ASSOCIATION WITH TREATMENT OUTCOME AND PRESCRIBED MEDICATION DOSE

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Introduction: Opioid substitution therapy (OST) utilises methadone or buprenorphine across a range of different dosages to control and reduce illicit use of opioids and other substances. A challenge to successful OST is concomitant usage of other drugs, which has previously led to increased dropout rates and continued heroin use. [McCance-Katz et al, 2009,Am J Addict,19:47-52]. This study set out to determine the association between levels of concomitant substance abuse at baseline assessment, on maximum reached opiate substitute dose and treatment outcome.

Methods: Clinical records of 441 patients were extracted from an addiction clinic in Brent, London. Measures included dosages of prescribed methadone or buprenorphine, treatment outcome, and levels of polysubstance abuse at baseline, defined by substance use across different drug categories (Opiates, Stimulants, Depressants, Cannabinoids). Patients were grouped into single category users (opiate only), double category and triple category drug groups, before average maximum dose of prescription drug reached and treatment outcome (Successful, Dropout, Death) were determined for each. To determine statistical significance (p<0.05), a two-tailed T-test was performed for maximum dose, and a two proportion Z-test was used for treatment outcome.

Results: Patients on buprenorphine (N=111) had a significantly higher average maximum dose in the triple (12mg ±4.5) and double drug groups (10.4mg ±4.3) compared with the single group (7.5mg ±4.5), with P=0.0003 & 0.003 respectively. No significant difference for average maximum dose was observed between double and triple group patients on buprenorphine. For average maximum dose of methadone (N=330), no significant differences were seen between any of the drug use groups. Treatment outcome data was available for 161 patients. The % of opiate only patients with a successful drug free outcome (44%) was significantly higher than double (21%) and triple (20%) drug use groups (P=0.013 & 0.014 respectively). Furthermore, dropout rates in the double and triple groups were equal (52%), which was higher compared with the single use group dropout rate (38%). However, these differences were not significant.
Conclusions: These results indicate that for patients on buprenorphine, higher reported levels of polydrug use at initial assessment is associated with a higher maximum prescribed medication dose. For patients on methadone, however, there appears to be no effect on dosage. The results also show that higher reported polysubstance abuse at baseline may reduce the likelihood of successful treatment outcome. Future studies should further investigate drug specific influences on these treatment measures, and how frequency of concomitant substance abuse may impact OST.

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F01
RETROCUES FOR REWARD IMPROVE PRECISION OF WORKING MEMORY, FOR BOTH CONGRUENT AND INCONGRUENT ITEMS

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Introduction: Previous research has established that rewards and punishments influence the allocation of attention during perceptual encoding (Engelmann et al., 2009, Frontiers in Human Neuroscience, 3,4), but their effect on internally-directed attention is not well understood. This study aimed to address this discrepancy within the context of working memory, examining whether performance-based incentives presented during the retention interval of a working memory task (‘retro-cues’) can enhance recall, and if so, whether this can be attributed to a selective shift of cognitive resources.

Methods: We used a continuous-report working memory task based on that of Bays and Husain (2008, Science, 321, 851-4). Participants were briefly shown three arrows on a screen at random orientations; then, after a delay, were asked to recall one of them by rotating a central arrow to reproduce the correct orientation. In our experiment (n = 29), a retro-cue was presented during the delay period, and signalled the valence (reward/punishment/neutral) associated with one of the arrows; crucially, it did not indicate whether this arrow would actually be tested. Data was analysed with an ANOVA (congruence X valence) on participants' angular error for each trial. We also fitted a mixture model to the data, which decomposes errors into three sources: noisy recall of the target, noisy recall of a distractor and uninformed guessing (Bays et al., 2009, Journal of vision 9, 1-11).

Results: There was a main effect of reward (F2,56 = 4.30, p = .02), reflecting significantly increased accuracy in the reward condition compared to both the punishment (t28 = 2.52, d = 0.19) and neutral (t28 = 2.25, d = 0.17) conditions. However, there was no interaction between valence and congruence (F2,56 = 1.42, p = .25), indicating that the reward retro-cue benefited all stimuli. The results of the modelling were equivocal, with several of the parameters approaching, but none reaching, significance.

Conclusions: Our finding, that the reward retro-cue benefited all stimuli, could be seen as incompatible with the limited resource model of Husain and Bays (2008; ibid), if taken to mean that cognitive resources were increased across-the-board. Recently, Bays and Taylor (2018, Cognitive Psychology, 100, 43-52) have also reported that the mixture model can prove uninformative regarding retro-cue experiments and instead propose a neural model that has proven more successful. Efforts are therefore ongoing to examine whether this alternative model can account for our results, and hence how the mechanism of this effect can be better understood.

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F02
INVESTIGATION INTO THE BENEFICIAL EFFECTS OF AEROBIC EXERCISE ON COGNITIVE FUNCTION IN RODENTS

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Introduction: Cognitive dysfunction is an unmet clinical need in several psychiatric and neurological disorders. No drug has yet received a licence for cognitive impairment in schizophrenia (Talpos Drug Discov Today. 2017, 22(7):1017-1026). Aerobic exercise can improve cognitive function in schizophrenia patients (Falkai et al. Curr Opin Psychiatry. 2017, 30(3):171-175), potentially an important therapeutic approach. We are investigating pro-cognitive effects of exercise in the sub-chronic phencyclidine (scPCP) model for schizophrenia, and in normal animals. Our aim here is to evaluate the effects of aerobic exercise on object recognition memory pre and post dosing with scPCP. We have previously demonstrated that exercise (1h/day, 5 days/week for 6 weeks) reverses a robust scPCP-induced deficit in NOR, an effect which was sustained for 4-weeks (Neill et al, ACNP 2018).

Methods: Two groups of adult female Lister Hooded rats (n=20/group) were used: control and exercised. Rats were given access to running wheels in individual cages for 1h/ day, 5 days/ week, for 6 weeks, then tested in the 6h inter-trial interval (ITI) NOR test 48h after cessation of exercise. Then rats were dosed with PCP (2mg/kg twice daily for 7 days followed by 7 days washout) or vehicle and re-tested in the 1 min ITI NOR test. The wheel running data were analysed using linear regression, NOR exploration times were scored by a blinded experimenter and data were analysed by Student's t-test, the correlation analysis was performed using Pearson's r test.

Results: An overall significant (r=0.707, p<0.001) increase in mean running distance over time was observed. Following a 6h ITI, the non-exercised control rats failed to discriminate between the novel and familiar objects while exercised rats demonstrated a robust object discrimination (p<0.001). There was a positive correlation, r=0.514, n=20, p=0.0204, between rats that ran furthest over the 6 week period and NOR performance. Subsequent scPCP treatment did not impair object recognition performance (P>0.001 controls and P>0.01 scPCP), showing that exercise protected against the deficit. We have recently demonstrated this effect for handling (a form of environmental enrichment) prior to PCP dosing, see Watson et al, this meeting.

Conclusions: Aerobic exercise reverses a delay-induced deficit in object recognition memory and protects against the scPCP-induced deficit in female Lister Hooded rats. We show a positive relationship between the level of exercise and improved cognition. Further work to evaluate mechanisms of these effects could inform future therapeutic strategies in patients with cognitive impairments.

Funding: This work was funded by the University of Manchester and b-neuro at the University of Manchester.

F03
MICRODOSING OF 5-HT2A RECEPTOR AGONISTS PROMOTES CHANGES IN WELL-BEING, DEPRESSIVE SYMPTOMS AND PERSONALITY

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Introduction: Microdosing refers to the regular ingestion of sub-threshold or threshold level perceptible doses of classic psychedelic substances (5-HT2A receptor agonists) with the objective of causing subtle
changes in mood and cognition. Anecdotal reports suggest that microdosing induces minimal or no acute drug effects while promoting positive mood, creative thinking and well-being. There is sparse published scientific literature on microdosing however, and consequently little is known about its safety, efficacy and possible risks.

Methods: The present study prospectively collected web-based data and tracked the experience of individuals who planned to microdose over a period of four weeks. State and trait variables and dosing parameters were assessed at multiple time-points before, during and after individuals engaged in a microdosing protocol. Principal components, correlational, analysis of variance and regression methods were all employed.

Results: N= 150 participants completed the baseline measure and N=51 completed the key-endpoint measure at 4 weeks. In line with our main hypotheses, we found elevations in psychological well-being (p <.001; ηp2= .252), and reductions in trait anxiety (p <.001; ηp2= .232) and depressive symptoms (p <.001; ηp2= .232) at four weeks after microdosing compared with baseline. Furthermore, we found increases in the personality traits agreeableness (p =.021; ηp2= .103) and emotional stability (the inverse of neuroticism, p =.039; ηp2= .083 ), improvements in the ability to cope with stress (resilience, (p <.001; ηp2= .219 ), increases in social connectedness (p =.003; ηp2= .162) and nature relatedness and no increase in delusional Ideation (p .176; ηp2= .036) . Microdoses induced mild but noticeable subjective drug effects, that were more pronounced in individuals with higher baseline scores on trait absorption. The results provided little support for the inference that an expectancy bias (placebo effect) had driven the main effects because expectancy scores at baseline did not predict well-being changes over time (F(4,116.925) = .1.073, p =.373), .

Conclusions: This is one of the first quantitative and observational examinations of microdosing in a naturalistic setting. While mindful of design limitations such as the high rates of attrition and related data biases, these results suggest microdosing may indeed promote mental health benefits - although more rigorous placebo-controlled studies are very much required to tackle this matter properly.

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F04

EFFECTS OF LYSERGIC ACID DIETHYLAMIDE (LSD) ON PROBABILITY REVERSAL LEARNING IN HUMANS

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Introduction: Research into lysergic acid diethylamide (LSD) has been revitalised in recent years. Few studies, however, have focused on its behavioural effects in humans. LSD acts primarily on the serotonin 2A receptor (5-HT2A). Behaviourally, serotonin is critically involved in flexibly adapting behaviour as environmental circumstances change (Clarke et al., 2004, Science, 304, 878-880), as well as processing aversive outcomes (e.g. Chamberlain et al., 2006, Science, 311, 861-863). Both can be captured in a laboratory setting using probabilistic reversal learning (PRL) paradigms: Individuals learn by trial and error the most adaptive action in an acquisition stage, and this rule eventually changes in a reversal phase (Lawrence et al., 1999, Neuropsychologia, 37, 1359-1374). Severe serotonin depletion results in perseverative behaviour – an impaired ability to update action upon reversal (Clarke et al., 2004, Science, 304, 878-880; Walker et al., 2009, Cerebral Cortex, 19, 889-898). Milder reductions, meanwhile, result in an increased sensitivity to negative feedback (Bari et al., 2010, Neuropsychopharmacology, 35, 1290-1301; Chamberlain et al., 2006, Science, 311, 861-863). Here, for the first time, we tested the acute effects of LSD on PRL. We predicted LSD would modulate either sensitivity to negative feedback, or how learning affects subsequent perseverative behaviour.
Methods: Twenty healthy volunteers attended two sessions where they received either intravenous LSD (75μg in 10 mL saline) or placebo (10mL saline), in a double-blind within subjects design, before completing the PRL task.

Results: Simple linear regression showed that when on LSD, relative to placebo, a greater number of correct responses during the acquisition phase significantly predicted more perseverative errors in the reversal stage ($\beta = .558, p = .002$). Perseverative errors alone did not differ between conditions, nor did the number of correct responses during acquisition (both $p > .05$). In other words, with the same level of initial learning people perseverated more under LSD. Sensitivity to negative feedback, finally, was unaffected ($p > .05$).

Conclusions: Our findings suggest that LSD may more strongly stamp in learning, leading to a reduced ability to disengage from a stimulus once it is no longer rewarding. This effect is presumably a modulatory consequence of its 5-HT2A receptor agonist action. LSD appears to overweight prior experience, relative to new information, a hypothesis that we will formally test with follow-up computational modelling.

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F05

AYAHUASCA’S ‘AFTERGLOW’: IMPROVED MINDFULNESS AND COGNITIVE FLEXIBILITY IN NAÏVE AND EXPERIENCED AYAHUASCA DRINKERS

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Introduction: Introduction: There is a growing body of evidence demonstrating the therapeutic potential of ayahuasca for treating depression and anxiety. However, the mechanisms of action involved in ayahuasca’s therapeutic effects are unclear. Mindfulness and cognitive flexibility may be two possible psychological mechanisms. Like other classical psychedelics, ayahuasca also leads to an ‘afterglow’ effect of improved subjective wellbeing that persists after the acute effects have subsided. This period may also offer a window of increased therapeutic potential.

Methods: Objectives/Method: This research explored the effect of ayahuasca on mindfulness and cognitive flexibility in the afterglow period by comparing self report measures of mindfulness (Five Facets Mindfulness Questionnaire, FFMQ), decentring (Experiences Questionnaire, EQ) and cognitive flexibility (Cognitive Flexibility Scale, CFS), as well as neuropsychological task performance on the Stroop and Wisconsin Picture Card Sorting Task (WPCST). Participants were measured before drinking ayahuasca and again approx. 24 hours after ingestion, in a sample of 48 ayahuasca drinkers, whilst controlling for prior ayahuasca use.

Results: Results: We found mindfulness (as measured by the FFMQ total scores, $(F(1,46)=8.21, p=.003, \eta^2=.15)$) and decentring (measured by the EQ,$(F(1,46)=4.15, p=.025, \eta^2=.08)$) significantly increased in the 24 hours after use. Four of the five distinct mindfulness facets were also significantly increased (Observe $(F(1,46)=13.38, p<.001, \eta^2=.24$), Describe $(F(1,46)=3.76, p=.003, \eta^2=.08)$, Act with Awareness $(F(1,46)=7.08, p=0.01, \eta^2=.13$) and Non-reactivity $(F(1,46)=.02, p=.03, \eta^2=.10$). Cognitive flexibility (as measured by the CFS $(F(1,46)=8.25, p=0.006, \eta^2=.15)$ and the WPCST) was also significantly improved in the 24 hours after ayahuasca use. In the WPCST participants had a significantly higher number of correct responses 24 hours after ayahuasca relative to before $(F(1,46)=2.30, p=.14, \eta^2=.05)$ and there was no significant difference to response time suggesting accuracy improved without a significant slowing of response time. Changes in mindfulness and cognitive flexibility were not influenced by prior ayahuasca use.

Conclusions: Conclusions: The present study provides further evidence of an association between ayahuasca use and enhanced mindfulness, and highlights it as a potential psychological mechanism of the psychotherapeutic effects of ayahuasca. This was the first known study to measure cognitive flexibility in...
the ‘afterglow’ period and suggests it is worthy of further exploration as another possible psychological mechanism. Given psychological gains to mindfulness and cognitive flexibility occurred regardless of prior ayahuasca use suggests ayahuasca offers potentially therapeutic effects for both psychedelic naïve and experienced ayahuasca drinkers.

Funding: None

F06

COGNITIVE FUNCTIONS ASSOCIATED WITH CONSUMPTION OF TRADITIONAL VOLUMES OF KAVA (PIPER METHYSTICUM): A FEASIBILITY STUDY

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Introduction: Kava (Piper methysticum) is a traditional and culturally significant Pacific Island beverage, which contains active compounds called kavalactones that produce soporific relaxant effects similar to Benzodiazepine (Sarris et al, 2012, Human Psychopharmacology Clinical and Experimental, 27:262-9). Traditional kava drinkers frequently exceed the pharmacologically recommended amount of ≤300mg of kavalactones/day by 30 times (Aporosa & Tomlinson, 2014, Anthropologica, 56:163-75). Little is known about cognitive function at this high consumption rate. With Pacific peoples in New Zealand over represented in motor vehicle accidents, Police suspect traditional kava use may be a contributing factor. Previous research (Aporosa, 2017, Journal of Psychopharmacology, 31[8], A84) used an industry standard measure of drug driving to examine cognitive functions of kava users in a naturalistic setting. The industry standard measure revealed no statistical differences in cognitive functioning between kava users and control participants, despite observation of slowed movement and slurred speech by the kava users. Consequently, with full study utility as a goal, the feasibility of using a new psychometric measure of cognitive functioning – the Brain Gauge (BG) – was examined in a naturalistic setting.

Methods: Drawing on Eldridge et al’s (2016, PLoS One, 11[3]: p.15) definition of a feasibility study, experienced kava consumers (n=2 [males], mean age = 46.5) attended a 6 hour traditionally influenced kava session, each drinking 3.6 litres of kava equating to 5,220mg of kavalactones. At baseline, the participants completed BG (www.corticalmetrics.com [CM]) somato-sensory psychometric testing to measure six strategic, tactical and operational cognitive faculties including fine-motor-skills and fatigue. Each of the six domains are scored and compared against norms, which also informs a composite CM score. Re-testing was conducted following 3 and 6 hours of kava consumption.

Results: Consistent with subjective observations of the behavior of the participants, obvious negative changes over time were evident for reaction time, attention focus, time perception and temporal order judgement for one participant (CM composite score: 85 at baseline, 80 at 3 hours, 55 at 6 hours) but positive changes were evident for the second participant (CM composite score: 73 at baseline, 73 at 3 hours, 92 at 6 hours).

Conclusions: Unlike the industry standard measure of drug driving used in the previous study, use of the BG is feasible in a naturalistic setting. A full controlled study, aimed at understanding kava’s effects on driving following high consumption, is about to commence.

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**F07**
**COMPARING NOVEL SELECTIVE KV3.1/3.2 CHANNEL MODULATORS FOR EFFICACY TO RESTORE COGNITIVE AND SOCIAL BEHAVIOUR DEFICITS OF RELEVANCE TO SCHIZOPHRENIA IN AN ANIMAL MODEL**

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Introduction: We have established and thoroughly validated an animal model for cognitive impairments associated with schizophrenia (CIAS): Sub-chronic treatment of rodents with the NMDA receptor antagonist, phencyclidine (scPCP) leads to disinhibition of cortical circuitry and reduction in expression of the calcium binding protein, parvalbumin (PV) in fast spiking GABAergic interneurons (Gonzalez-Burgos & Lewis Schizophr Bull. 2012, 35:950-7). The voltage-gated potassium channel, Kv3.1 is predominantly localized in PV-positive interneurons, and has been shown to be reduced in un-medicated schizophrenia patients (Yanagi et al. Mol Psychiatry 2014; 19: 573-579). We previously demonstrated that the novel Kv3.1/Kv3.2 channel modulator, AUT6, could reverse cognitive and behavioural deficits in scPCP rats, and reverse the decrease in PV expression, confirming the importance of this target for the treatment for schizophrenia. Here we aim to compare the efficacy of other high potency Kv3.1/3.2 modulators in similar cognitive and behavioural tests in the scPCP rodent model.

Methods: Four cohorts of adult female Lister Hooded rats (240 in total) received PCP (2 mg/kg, i.p.) or saline i.p. for 7 days, followed by 7 days washout. Rats were then treated acutely with Kv3.1/3.2 channel modulators, AUT6 (3.0, 10, 30 mg/kg), AUT15 (1.0, 3.0, 10 mg/kg,), AUT16 (3.0, 10, 30 mg/kg,) or vehicle, orally 90 min prior to testing in novel object recognition (NOR), social interaction (SI) and reversal learning (RL) tasks. NOR exploration time was analysed by a paired Student t-test, SI and RL data were analysed by ANOVA and post-hoc LSD test.

Results: scPCP significantly impaired behaviour in these tests. Briefly, in NOR, scPCP rats showed deficits in the ability to discriminate between novel and familiar objects (p<0.05-p<0.001), reduced percent correct responding in the RL task (p<0.001) and in SI, scPCP significantly reduced sniffing following and increased avoiding (p<0.01-p<0.001). The minimum effective dose for each compound to reverse these scPCP-induced deficits was: NOR: AUT6 (10 mg/kg, p<0.001), AUT15 (3.0 mg/kg, p<0.001), AUT16 (10 mg/kg, p<0.01). RL: AUT6 (30 mg/kg, p<0.01), AUT15 (10 mg/kg, p<0.01). SI: (effective in one or more behavioural measure): AUT6 (10 mg/kg, p<0.05), AUT15 (1.0 mg/kg, p<0.001)

Conclusions: These in vivo results demonstrate superior potency of AUT15 compared to AUT6 and AUT16 in NOR and AUT15 compared to AUT6 in both RL and SI. In addition, the improvement of the in vivo potency from AUT6 to AUT15 is in agreement with the rank order of the in vitro activity of those compounds at both Kv3.1 and Kv3.2 channels. This work increases confidence that restoration of scPCP-induced social deficits and CIAS is via modulation of Kv3.1/Kv3.2 channels

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**F08**
**THE EFFECTS OF CANNABIS ON COGNITIVE BIASES, ANXIETY AND APPETITE IN INDIVIDUALS WITH PROBLEMATIC EATING BEHAVIOUR**

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Introduction: Cannabis has been found to increase appetite and reduce anxiety as well as maladaptive thinking patterns (Cuttler, Spradlin, & McLaughlin, 2018; Tchanturia et al., 2011; Beulaygue & French, 2017). This work examines the effects of cannabis on cognitive biases, anxiety and appetite in individuals with problematic eating behaviour.
Research on the effect of cannabis as a pharmacotherapy for eating disorders (ED) has been inconclusive. This study aimed to investigate whether cannabis can reduce weight-related cognitive biases and anxiety and increase appetite. These potentially therapeutic properties of cannabis may be valuable to psychological interventions.

Methods: Seventy-five frequent smokers were divided into high and low problematic eating behaviour (PEB) groups, in a repeated-measures design. The groups were determined using a median split of the Eating Attitudes Test (EAT-26) scores (Garner, Olmsted, Bohr, & Garfinkel, 1982). Participants’ eating behaviours, schizotypal symptoms, body perceptions and state-trait anxiety were recorded. A weight implicit attitude test (IAT) was employed to measure cognitive biases towards different body shapes. The participants were then requested to smoke their own cannabis until they felt sufficiently ‘high’. Participants were asked what type of cannabis they smoked (skunk, herbal, hash, resin or other), the estimated subjective strength of their cannabis and whether they smoked the cannabis with tobacco. Participants repeated the same state-related questionnaires, as well as the weight IAT post-cannabis administration. Visual analogue scales (VAS) were used to measure anxiety and hunger throughout the study.

Results: Results revealed that implicit biases towards body shapes reduced after cannabis administration, but only in the low PEB group \[t(72) = 2.59, p= 0.012, d=.61\]. Additionally, cannabis increased hunger in both high and low PEB groups \[F (2,146) = 20.69, p< .001, \eta^2 = .015\]. However, cannabis increased anxiety on VAS measures in both groups \[F(2,125)= 3.703, p=0.034, \eta^2 =.0472\].

Conclusions: These findings support evidence indicating cannabis increases hunger and changes implicit biases. However, the increase in anxiety scores may prevent full support for using cannabis to complement psychotherapies for ED. Theoretical and methodological implications will be expanded on further.

Funding: This research was funded by the Psychopharmacology and Addiction Research Centre (PARC) at the University of Exeter.

F09

ACUTE EFFECTS OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA) AND DELTA-9-TETRAHYDROCANNABINOL (THC) ON CIRCULATING ENDOCANNABINOID LEVELS IN HEALTHY HUMANS.

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Introduction: The endocannabinoid (eCB) system is involved in fundamental physiological and psychological processes. Circulating levels of eCBs in the periphery are an indirect marker of eCB tone and may also contribute to the regulation of emotional processes. eCBs are important signalling messengers known to improve mood, reduce stress and anxiety. Both MDMA and THC have been associated with distinct and reliable social and emotional effects in controlled laboratory studies. The aim of this study was to investigate the effects of MDMA and THC on circulating eCBs and their association with acute socially-relevant subjective effects.

Methods: Thirteen participants’ with previous experience with MDMA and THC, took part in three-session double-blind, double-dummy, placebo-controlled design to investigate the effects of oral MDMA (105mg/70kg) or oral THC (10 mg/70 kg) in comparison to placebo, on social processing. Circulating eCBs (anandamide (AEA), 2-arachidonoylglycerol (2-AG), Oleoylethanolamide (OEA) and palmitoylethanolamineane (PEA)) were taken 195 minutes post- THC/Placebo administration. Key subjective effects related to sociability and reward were assessed throughout using Visual Analogue Scales.

Results: MDMA (t(10)=2.6,p=0.03, d=0.79; % increase: 20%) and THC (t(12)=2.8, p=0.02, d=0.78; %increase: 11%) increased AEA levels in comparison to placebo. Both MDMA (t(10)=4.1 p=0.002, d=1.24; %increase: 32%) and THC (t(12)=4.7, p=0.001, d=1.29; %increase: 20%) also increased OEA levels compared to
placebo. Neither MDMA (p>0.05) nor THC (p>0.05) changed 2-AG or PEA levels in comparison to placebo. Exploratory correlations revealed a negative relationship between anandamide increase and feeling playful under MDMA in comparison to placebo (r(9)=-0.6, p=0.042).

Conclusions: MDMA and THC increased levels of circulating eCBs relative to placebo. These data provide novel biochemical evidence of an acute increase in eCBs, specifically anandamide and OEA, after MDMA or THC administration. The small sample size in this study precludes any strong conclusions being made about the relationship between plasma eCBs and subjective states. More research is required to disentangle this relationship.

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F10
TOWARD A NEURAL PROCESS OF PARANOIA: USING BIG DATA AND GAME THEORY TO MODEL LIVE HARM INTENT ATTRIBUTIONS FOR PHARMACOLOGICAL EXPERIMENTATION
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Introduction: Paranoia is the belief that harm is intended and will occur to the self. Understanding the mechanisms of paranoid belief is crucial for the prognosis and treatment of clinical syndromes such as psychosis. More specifically, understanding why harm intent attributions are made gives us useful insight into the dynamics of social cognition. However, paranoia is typically measured using static social questionnaires - these are unable to capture live harm intent attributions in real social situations. Here, we present a novel paradigm, the Helsinki Summit, that measures live social harm attribution across multiple partners. We use this paradigm to model how caffeine, sleep, pre-existing paranoia, and interpersonal sensitivity contribute to live social paranoia.

Methods: We include a large online cohort (n = 1740) and one double-blind, randomised experiment with caffeinated/decaffeinated coffee (n = 450), both drawn from the general population. We preregistered a number of predictions for the online experiments (http://aspredicted.org/blind.php?x=8cj8zk), and all scripts and preprints are available on osf.io . In each study participants answered a number of questionnaires and then played the Helsinki Summit – a multi-trial modification of the Dictator game used in previous studies to assess paranoia (Raihani & Bell, 2017, Scientific Reports). Each participant played six trials against three different partners in a random order.

Results: As predicted, pre-existing paranoia was found to predict increases in live harm intent attributions (b = 0.61, 95%CI: 0.36,0.88; p<0.001), but not selfish intent attributions (b = -0.04, 95%CI: -0.29, 0.21, p = 0.74). Pre-existing paranoia led to a ‘Jumping to Threat Bias’, with a higher chance of attributing high harm intent (>mean) in an earlier trial (b = -0.16, 95%CI: -0.28, -0.03, p = 0.01). Daily caffeine use, but not current caffeine intake, led to increases in harm intent attributions (b = 0.1, 95%CI: 0.03, 0.18, p < 0.01) but not selfish attributions.

Conclusions: Live social harm attribution using the Helsinki Summit replicated previous studies using single trials, confirming their utility in assessment of harm intent. We also confirm that paranoid beliefs are on a continuum throughout the general population, with putative ‘everyday’ factors such as caffeine use indexing variations in harm intent attributions. From this data we can derive mathematical parameters to test behavioural nuances in learning rate, uncertainty, and probability. Our multi-trial Dictator game is suitable for psychopharmacological studies to uncover dynamic processes underlying paranoid belief formation and maintenance.

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F11

THE DYNAMICAL INTERACTION BETWEEN ATTRIBUTION AND BELIEF: EVIDENCE FROM A NOVEL TASK

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Introduction: “Negative attributional style” is correlated with vulnerability to depression, but is not yet a convincing predictor of depression onset (Alloy et al., Oxford Handbooks Online, 2017). Bentall (Bental, 2003, Madness Explained, p.254-269) suggested that this is because attributional style is not fixed, but interacts with the dynamics of beliefs about the self. Detecting such interactions would require extended time series of both attribution and self-beliefs; such data do not yet exist. We therefore quantify the relationships between attributions and beliefs using a novel task.

Methods: Subjects (N=31) repeatedly played a game of skill or watch ‘another subject’ do so (actually their own previous trials), whilst making attributions about outcomes, and estimating how skilled they/the ‘other’ are. We used a variety of methods and reinforcement learning models to investigate the effect of attributions on skill estimates and the effect of reported skill on attributions – in both cases for beliefs about the self versus the ‘other’.

Results: We find that participants used outcome information to update their estimates of their own and ‘other’s skill, and they did so differently for losses attributed internally vs externally (KS test p self, other = 0, Hedges corrected d self = 0.19, other = 0.35 ), but not for wins. A model-based approach comparing different models of belief updating also favors models in which learning rates are different for internal vs external attributions. Conversely, we find that for both self and other, subjects are more likely to attribute wins, and less likely to attribute losses, internally in the case of high estimated skill (bottom vs top quartile skill responses repeated measures t-test self p = 0.03, Hedges d = 0.36, other p = 0, Hedges d = 1.05 ) and losses (self p = 0.003, d = 0.47, other p =0 , d =1.09).

Conclusions: Our task quantifies changes in, and interactions between, attribution propensities and beliefs about the self/‘other’. We found differences in such interactions when processing wins vs losses, consistent with positive belief maintenance plus sensitivity to sources of learning about negative avoidable outcomes. We find similar mechanisms for self and other, but stronger effects for the latter, which might stem from multiple sources of noise in the more emotionally salient self condition.

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F12

IMPACT OF VOLATILITY ON BEHAVIOUR IN TRANS-DIAGNOSTIC PSYCHIATRIC SYMPTOM DIMENSIONS

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Introduction: Computational models of learning suggest that uncertainty gates the extent to which new information is used to update current estimates of value. While this sensitivity to environmental volatility is beneficial for learning and is generally ubiquitous, previous work has shown that individuals with high levels of anxiety exhibit diminished sensitivity, with suggestions for a similar effect in depression owing to strong shared symptomology and heritability (Browning et al., 2015, Nat Neurosci. 18(4):590-596). As these aspects of psychopathology are highly correlated with one another, we tested if the effects would be best captured by an ‘Anxious-Depression’ dimension of psychopathology, or conversely other psychiatric dimensions, ‘Compulsive Behaviour and Intrusive Thought’ and ‘Social Withdrawal’, which have not been previously investigated in this context.

Methods: A general population sample (N = 437) completed a predictive inference task via Amazon's
Mechanical Turk. We manipulated the volatility of the task environment and examined how individuals used feedback to update their behaviour. We then investigated the extent to which there was an impairment in integrating evidence to adjust responses when the volatility of the environment changed in distinct dimensions of psychopathology, controlling for age, gender and IQ in our analyses.

Results: None of the psychiatric dimensions was significantly associated with impairments in adjusting learning based on environmental volatility. Instead, anxiety seemed to be linked a higher overall mean learning rate ($r=.10, p=0.03, \text{corr.}$), which was encapsulated by the ‘Social Withdrawal’ dimension ($r=.14, p=0.003, \text{corr.}$) and not the ‘Anxious-Depression’ dimension ($r=.004, p=1.00, \text{corr.}$).

Conclusions: We found that a failure in adjusting behaviour across stable and volatile environments was not linked to any of the psychiatric dimensions, which may be due to task differences from the previous study. Instead, high anxiety individuals showed an overall higher propensity for their response adjustments to be updated by new information. Surprisingly, ‘Social Withdrawal’ was the dimension which captured this increase in mean learning rate. These data underscore the potential pitfalls of examining a single clinical questionnaire drawn from a larger correlated space.

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F13

SELF-CONSCIOUSNESS AND NEGATIVE BIASES IN SELF-REFERENTIAL PROCESSING DURING ADOLESCENCE

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Introduction: Adolescence is associated with the onset of mental health disorders (Kessler et al., 2005, Archives of general psychiatry, 62(6), 593-602) and more frequent negative affect (Larson et al., 2002, Child development, 73(4), 1151-1165) compared with other ages. Adolescence is a period of development in which the concept of the self changes profoundly. The current study aimed to investigate how this emerging sense of self is reflected in memory and how it interacts with valence.

Methods: We recruited 211 female participants, split into four age groups: early adolescents (11.33-14.75, N=54), mid adolescents (14.83-17.67, N=58), late adolescents (18-23.75, N=49) and young adults (23.83-30.75, N=50). Participants completed a memory task in which participants first judge positive or negative adjectives in relation to the self (how well does the word MUSICAL describe you?) and in relation to a familiar other of their choosing (e.g. how well does the word SARCASTIC describe Hermione Granger?). After completing a distractor task, participants completed a recognition test for words judged in the first part of this task, alongside distractor words. This allowed us to investigate memory accuracy for positive and negative words judged in relation to the self (how well does the word MUSICAL describe you?) and in relation to a familiar other of their choosing (e.g. how well does the word SARCASTIC describe Hermione Granger?).

Results: We found a reference (self/other) by valence (positive/negative) by age group interaction in endorsement ratings, which appears to be driven by an increased willingness for the mid-adolescents to endorse negative words about themselves compared to other groups. This willingness to endorse negative words was significantly associated with social anxiety scores. We also found a reference by valence by age interaction in memory scores, with younger groups remembering more self-judged negative words than older groups. Memory score for self-negative words was not significantly associated with self-consciousness or social anxiety scores.

Conclusions: Our results may contribute to an understanding of how negative affect can interact with self-referential biases in adolescence and how this might relate to a negative sense of self.

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**F14**

**AN INTERACTION BETWEEN SOCIAL AFFECTIVE BIASES AND MONETARY OFFER AMOUNTS IN HUMAN INTERPERSONAL NEGOTIATIONS**

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Introduction: Negotiating the distribution of finite resources between parties who might have competing interests is an important part of human social interactions. Two key cognitive processes relevant to these social interactions are: (i) how people perceive their share of the resource distributions proposed by others, and (ii) the degree to which social affective biases (e.g. perceiving others' facial emotions more negatively than they actually are) influence these valuation mechanisms.

Methods: Participants (N=43) completed a brief facial emotion recognition task (bFERT) and rated various affective faces on a 9-point Likert scale (i.e. from negative to positive), allowing an assessment of social affective biases. Participants interacted with human confederates or a computerised opponent in a novel interpersonal monetary negotiation game which incorporates opponents' facial emotions, while undergoing pupillometry. All participants completed questionnaire measures of mood and social value orientation (e.g. Quick Inventory of Depressive Symptoms, Social Value Orientation Slider Measure). Affective biases were evaluated by fitting a 2-parameter weighting function to participant ratings in the bFERT. Participant choice behaviour was analysed using an ordinary least squares (OLS) regression model (e.g. regressors: opponent's facial emotion, offer amount, interaction term) as well as fitting formal computational models of the negotiation process. Pearson's correlation was used to evaluate linear relationships between psychological questionnaire scores and decision-making parameters.

Results: Regression analysis of acceptance probabilities suggested that unfair offers coming from proposers with positive facial emotions were more likely to be accepted (based on Bonferroni corrected t-tests on regression coefficients, all t>3.508, all p<.001). Model-based analysis suggested that social affective biases accounting for how people perceive others' emotional states are represented nonlinearly. Decision values, which guide participants' probability of accepting a condition in the negotiation game, are influenced by both the offer amount and an inequality term (i.e. difference between self and other's reward), which is further modulated by social affective biases. Pupillometry results suggested that pupil size encodes opponent's affective states, surprise associated with offers and the noisy fluctuations of the negotiation environment (all t> 2.01, p<.05).

Conclusions: The current study describes a computational model accounting for human social interactive decision-making. Central arousal systems (i.e. pupillometry indexing the firing of the central norepinephrine system) encode key elements of social interactive decision-making that influence participant choice behaviour.

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**F15**

**DEVELOPING A NOVEL STRESS INDUCTION PARADIGM FOR USE IN PHASE 1 CLINICAL TRIALS**

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Introduction: JNJ-55375515 is a compound currently in development for the treatment of depression. However, paradoxical increases in stress reactivity were highlighted in preclinical studies, which may limit its use as an antidepressant. Translation of such findings to humans is precluded by existing laboratory stress induction paradigms which rely heavily on confederate involvement, thus are difficult to standardise across study sites, and challenging to implement within clinical trials. The Oxford Cognition Stress Task (OCST) is a novel, web-based acute stress induction paradigm developed in collaboration with J&J. By building social evaluative threat and uncontrollability into a series of cognitive tasks, the OCST removes the need for confederate involvement.
ABSTRACTS

Methods: In a pilot study, 30 healthy male volunteers were randomised to complete the OCST or control task. Physiological and psychological measures of arousal were obtained at twenty-minute intervals. The OCST was subsequently implemented in a Phase 1 clinical trial, investigating the effect of JNJ-55375515 25mg (n=8), JNJ-55375515 12mg (n=8), and placebo (n=7) on arousal.

Results: Subjective stress (p=0.004), state anxiety (p<0.001), and negative affect (p=0.003), were significantly higher post-task relative to baseline for the OCST but not the control group. Increases in heart rate during the task (p=0.033), and the area under the curve with respect to the ground measure of salivary cortisol (p=0.044) were significantly greater for the OCST than the control group. Inferential statistics were not performed on phase 1 data due to the small sample size. Descriptive statistics revealed robust increases in self-reported stress, serum cortisol, and heart rate, coupled with reduced heart rate variability, in the JNJ-25mg group compared to placebo. In contrast, the 12mg group showed no task-induced increases in arousal.

Conclusions: Significant increases in both physiological and psychological measures of stress in a pilot study support the use of the OCST as an experimental stress induction paradigm, feasibly deliverable in a clinical trial setting. Implementation of the task in a phase 1 trial helped elucidate effects of a novel compound on arousal, with the JNJ-55375515 high dose group demonstrating a heightened reactivity to stress that is in line with preclinical studies.

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F16

INVESTIGATION OF 5-HT1A, 5HT2A AND 5-HT2C RECEPTOR INVOLVEMENT IN THE EFFECT OF OXYTOCIN ON RETENTION AND EXTINCTION OF FEAR-MOTIVATED MEMORY IN THE RAT

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Introduction: The neuropeptide oxytocin may have therapeutic potential for anxiety and post-traumatic stress disorders (PTSD). It exerts anxiolytic effects by enhancing 5-HT release onto 5-HT2A/2C receptors (Yoshida et al. 2009 J. Neurosci. 29:2259-71) and facilitates fear extinction (Triana-Del Rio et al. 2019 Psychopharmacology 236:339-54), although associated neurochemical mechanisms remain unclear. This study examined serotonergic contributions to oxytocin’s effect on conditioned freezing responses, and aversion-related 22kHz ultrasonic vocalisations (USVs) as an additional index of negative valence.

Methods: 80 male rats (165-250g; Envigo) were conditioned to associate three light and tone cue pairings with footshock (Watson et al. 2016 Eur. Neuropsychopharmacol. 26:208-24). Vehicle (saline, 1ml/kg i.p.) or selective antagonists of 5-HT1A (WAY-100635, 1mg/kg), 5-HT2A (MDL-100907, 1mg/kg) or 5-HT2C receptors (SB-242084, 0.5mg/kg) were administered immediately post-conditioning. Vehicle (saline, 1ml/kg s.c.) or oxytocin, at a dose (0.1mg/kg) that enhances prosocial behaviour and monoamine release without sedation or V1A receptor-mediated hypothermia (Kohli et al. 2019 Neuropsychopharmacology 44:295-305) were administered 15min later, to avoid anxiolytic confounds on acquisition (n=10 per combination). Respective treatments were repeated 60/45min before assessment of context- and cue-evoked freezing and USV (Watson et al. 2016) during retention (1d post-acquisition) and extinction (4d post-acquisition) trials. Frontal cortical oxytocin in vehicle+vehicle/vehicle+oxytocin-treated rats was measured by multiplex (Merck). Freezing duration and USVs were analysed by three-way repeated measures ANOVA (antagonist x oxytocin x time) with Tukey’s/Sidak’s post-hoc, and oxytocin levels by unpaired t-test.

Results: All groups learned to associate context/cue with footshock before treatment, shown by increased freezing (F(2,142)=84.83, P<0.0001) and USV (F(2,88)=103.1, P<0.0001) during acquisition (P<0.05-0.0001 first versus final footshock). Re-exposure to context/cue evoked freezing and USV, but neither retention
nor extinction were influenced by treatment (P>0.05 versus control). However, on a more subtle level
cue-evoked freezing during retention/extinction only reached significance (P<0.05-0.0001 versus context) after 5-HT receptor antagonists, whereas robust cue-evoked USVs (P<0.01-0.0001 versus context) occurred in all groups. By the time tissue was obtained (60min after the final injection) elevations in frontal cortical oxytocin were not statistically significant (vehicle+vehicle 5.8±1.4pg/mg, vehicle+oxytocin 11.2±2.3pg/mg; P=0.0593).

Conclusions: Post-acquisition oxytocin administration has relevance for PTSD, but did not influence fear memory retention or extinction in normal rats. This may be due to ceiling effects absent in PTSD models. Side-effects (Kohli et al. 2019) preclude higher systemic oxytocin doses, and suboptimal bioavailability after translationally-relevant nasal application (Leng & Ludwig 2016 Biol. Psychiatry 79:243-50) suggests improved delivery is needed for mechanistic insight and therapeutic predictions.

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F17
EFFECTS OF ACUTE ALCOHOL CONSUMPTION ON EMOTION RECOGNITION IN HIGH AND LOW TRAIT AGGRESSIVE DRINKERS
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Introduction: Recent research has suggested that acute alcohol consumption impairs processing of emotional facial expressions. As emotional processing plays a key role in effective social interaction, these impairments may be one mechanism by which alcohol changes social behaviour, including its link to increased aggression. This study investigated the effect of individual differences on this relationship by comparing emotion recognition performance after acute alcohol consumption in individuals with high and low trait aggression.

Methods: Regular non-dependent drinkers (n=88, 50% male) either high or low in trait aggression participated in a double-blind placebo-controlled experiment. Each participant attended two sessions. In one session they consumed an alcoholic drink (0.4 g/kg) and in the other they consumed matched placebo (order counterbalanced). After each drink participants completed two computer-based tasks: one measured global and emotion-specific recognition performance across six primary emotions (anger, sadness, happiness, disgust, fear, surprise), the other measured processing bias of two ambiguously expressive faces (happy-angry/happy sad).

Results: There was evidence of an effect of drink for global emotion recognition (F [1, 84] = 9.23, p = .003, ηp2 = .099), with poorer recognition after alcohol, but no evidence for an effect of trait aggression or an interaction (ps>.29). In addition, each emotion was analysed separately to explore any emotion-specific effects of alcohol using a signal detection approach. There was evidence for an effect of drink on sadness (F [1, 85] = 8.11, p = .006, ηp2 = .087) and fear (F [1, 85] = 4.81, p = .031, ηp2 = .054), with poorer sensitivity after alcohol. There was also evidence for a reduced bias towards happiness following alcohol (F [1, 85] = 4.45, p = .022, ηp2 = .060) and weak evidence for an increased bias towards sadness (F [1, 82] = 3.49, p = .065, ηp2 = .041).

Conclusions: These findings suggest that alcohol impairs global emotion recognition. They also highlight a reduced ability to detect sadness and fearful facial expressions. As sadness and fear are considered to be cues of submission and distress (i.e., function to curtail aggression), failure to successfully detect these emotion when intoxicated may increase the likelihood of aggressive responding to perceived provocation. This coupled with a reduced bias towards seeing happiness may collectively contribute to aggressive behaviour.

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KISSPEPTIN ENHANCES BRAIN PROCESSING OF OLFACTORY AND VISUAL CUES OF ATTRACTION IN MEN

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Introduction: Successful reproduction in mammals relies on the integration of sensory cues of attraction with emotions and behaviours. Kisspeptin (KP) is a potent activator of the reproductive axis with evidence that it may link reproduction with brain pathways controlling emotion and behaviour. KP receptors are expressed in brain regions related to olfaction, sexual function, and emotion but effects of KP on human sexual attraction are unknown.

Methods: We examined the effects of KP on brain activity during olfactory and facial attractiveness tasks using fMRI in 33 healthy heterosexual men. Participants received an infusion of KP or placebo (counterbalanced order), and brain responses were evaluated in response to a pleasant feminine scent and a viewing images of unfamiliar female faces from a validated database (facial attractiveness task). Imaging analysis was performed with FSL. Pre-processing: motion correction, smoothing (6mm), registration to a standard template, and high-pass filtering (0.01Hz). A GLM analysis modelled the occurrence of the stimuli, and included their temporal derivatives and head-motion regressors as confounds. Group analyses were random-effects (FLAME-1) models, with statistical maps thresholded at z=2.3, p<0.05 (cluster corrected). A set of a priori defined brain regions were used to extract data for region of interest (ROI) analyses.

Results: KP significantly enhanced brain activity in response to a pleasant feminine scent, in regions related to olfaction and emotion (including the amygdala, striatum and insula). ROI analyses showed KP increased brain activity in the main olfactory network (p=0.008) as well as in several limbic structures that express KP receptors and are associated with mood and olfaction: amygdala, hippocampus, thalamus, putamen, globus pallidus, caudate, insula and orbito-frontal cortex (p<0.05). When viewing female faces, KP significantly enhanced brain activity in the medial prefrontal cortex (mPFC), an established aesthetic brain region. ROI analyses also showed enhanced activity in the mPFC during KP administration to faces rated high, medium, and low attractiveness (p<0.01).

Conclusions: Collectively, we demonstrate for the first time that KP administration enhances brain responses to olfactory and visual cues of attraction in humans. These data have important implications for our understanding of reproductive physiology and the development of therapeutics targeting the KP neurotransmitter system.

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A FAILED REPLICATION: MDMA DID NOT INDUCE PROSOCIAL BEHAVIOUR UNDER LABORATORY CONTROLLED CONDITIONS

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Introduction: 3,4-Methylenedioxymethamphetamine (MDMA) is reported to promote prosocial behaviour in therapeutic and laboratory settings. Perceived trust and cooperative behaviour are two facets of prosocial behaviour. MDMA's effects on these may be mediated by the neuropeptide oxytocin. We aimed to test and replicate MDMA's prosocial effects. We hypothesised that (1) MDMA would increase prosocial behaviour; (2) MDMA would increase plasma oxytocin levels; (3) increased oxytocin would correlate with prosocial effects.

Methods: Twenty-five participants aged 21-58, (n=7 (28%) female), participated in this double-blind, balanced-order, repeated-measures, placebo-controlled study. Participants attended two acute sessions, one week apart. They received placebo (100mg ascorbic acid) during one session, and MDMA (100mg MDMA-HCl) at the other. Trust tasks required rating perceived trustworthiness of 66 faces and deciding how much money to invest in 20 faces. Cooperative behaviour tasks were ‘public good’, ‘dictator’, ‘ultimatum’ games. Participants self-rated subjective effects. Blood was taken pre-drug, two and four hours post-drug, tested for plasma oxytocin and MDMA levels.

Results: Plasma MDMA levels increased in all participants from zero to mean (+/-SD) of 213.83 ng/ml (66.13) and 211.25 ng/ml (86.80), two and four hours post-MDMA, respectively. A linear mixed-effects model on plasma oxytocin levels yielded a main effect of Time Time (F2,54=7.574, p=0.001), Drug (F1,54=19.992,p<0.001), Time x Drug interaction (F2,54=12.281, p<0.001) . Analysing the results for MDMA and placebo separately showed only a significant effect of time on plasma oxytocin in the MDMA condition (F(2,18)=14.867, p<0.001), reflecting an increase in plasma oxytocin levels post-MDMA. We found no significant difference between MDMA and placebo on any of the tasks. Self-ratings of ‘overall drug effect’ (p<0.001), ‘energy’ (p<0.001) were higher post-MDMA. There were no MDMA effects on ‘jaw clenching’, ‘euphoria’, ‘friendliness’ or ‘closeness to others’.

Conclusions: Despite augmentation in plasma oxytocin levels in response to MDMA, we found no increased prosocial behaviour. This contrasts with previous laboratory and naturalistic MDMA studies (Hysek et al, Soc Cog Affect Neurosci, 9, 2014, 1645–1652, Stewart et al 2014, J Psychopharmacol, 28, 1001-8). Similarly to Kuypers (Kuypers et al 2014, PLOS One, 9, e100719), we did not demonstrate an effect on trust tasks. Context may be key. Given that MDMA may improve psychotherapeutic relationships through increased trust when used for treatment of PTSD (Mithoefer et al, 2011, J Psychopharmacol, 25, 439-452), procedures assessing trust in ways mirroring the psychotherapeutic setting may yield different insights and allow delineation of mechanisms that lead to therapeutic benefit.

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CORTICOHIPPOCAMPAL CONSTRAINT OF OBSERVATIONAL FEAR LEARNING

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Introduction: Learning from others' experiences is a highly evolutionarily conserved mechanism providing necessary information about threat and safety. Recent studies have begun to reveal neural mechanisms underlying contextual observational fear learning (OFL) (Jeon et al., 2010; Ito et al., 2015; Keum et al., 2018), yet there has been little investigation into cued forms of OFL associating an unconditioned stimulus (US) and a discrete conditioned stimulus (CS) through observation. In the current study we define novel corticohippocampal mechanisms subserving cued-OFL.

Methods: We first established a behavioral assay to measure cued OFL in male C57BL/6J mice based on a contextual OFL procedure described previously by Jeon and Shin (2011). We then used in vivo optogenetics to assess the role of the dorsomedial prefrontal cortex (dmPFC) as well as ventral hippocampal (vHPC) inputs to the dmPFC during acquisition of OFL.

Results: Mice undergoing OFL displayed significantly more freezing to the CS during conditioning (unpaired t-test, p<0.05) and retrieval (unpaired t-test, p<0.05), as compared to CS-only controls. We then photosilenced excitatory CaMKII+ neurons in the dmPFC during either the conditioning or retrieval phase of OFL. We found that inhibiting the dmPFC during CS presentations produced a significant reduction in freezing to the CS during conditioning (eArch3.0 vs YFP, unpaired t-test, p<0.05) and subsequent retrieval (eArch3.0 vs YFP, unpaired t-test, p<0.05). By contrast, photosilencing dmPFC during CS presentations during retrieval did not alter CS-related freezing on retrieval (eArch3.0 vs YFP, unpaired t-test, p>0.05).

Lastly, we silenced vHPC inputs to the dmPFC during CS presentations on conditioning day. We found that silencing these inhibitory inputs augmented OFL during conditioning (eArch3.0 vs YFP, unpaired t-test, p<0.05) and persisted to retrieval (eArch3.0 vs YFP, unpaired t-test, p<0.05).

Conclusions: We show that mice form a lasting, stimulus-specific memory for a discrete environmental cue paired with footshock solely through observation of conditioning in an unfamiliar conspecific. These data demonstrate a critical role of the dmPFC in forming an association between a discrete cue and footshock through observation, but that once this association has been acquired the dmPFC is not necessary for the memory to be retrieved/expressed. Additionally, we reveal how vHPC inputs to the dmPFC are engaged and causally recruited to constrain this form of observationally-acquired learning. Together, our findings reveal a novel neural circuit underlying vicariously acquired fear, with therapeutic implications for PTSD and other anxiety disorders associated with abnormalities in socially learned threat.

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SYSTEMATIC REVIEW AND META-ANALYSIS OF BEHAVIOURAL RESPONSES THE OLFATORY BULBECTOMIZED (OB) RAT MODEL OF DEPRESSION

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Introduction: There is considerable concern across the biomedical sphere of reproducibility challenges of animal models across different laboratories (Begley, CG and Ioannidis, JPA 2015 Circ Res, 116: 116-126). In clinical research, the degree of consensus between experimental findings is evaluated using tools such as a systematic review and a meta-analysis (Leucht, S et al. 2009 Acta Psychiatr Scand, 119: 443–450). However, such approaches have only recently started to be examined preclinically (Hooijmans, CR et al. 2014,
The olfactory bulbectomized (OB) rat is an animal model that has been used extensively to evaluate antidepressants (Morales-Medina, JC et al. 2017 Behav Brain Res, 317: 562–575). Thus the objective of this study is to conduct a systematic review and meta-analysis in the OB rat model over the last 20 years.

Methods: Initially, a PubMed search was conducted from 1999-2018 using the keywords “rat”, “olfactory bulbectomy” and “behaviour” to find all primary research papers in the English language over this period. A range of experimental characteristics were recorded, as well as identifying the behavioural measurements that were conducted. A meta-analysis was conducted on the open field test, where the mean, standard deviation and group size were determined for the sham-operated and OB groups from each study. These data were then analysed using Comprehensive meta analysis® software to determine the individual and pooled effect sizes, which are depicted as standardized differences in means.

Results: Of the initial 120 publications, 110 were selected for the systematic review. Albino strains (Sprague-Dawley and Wistar) are used in 75% of studies, the vast majority of which used male rats exclusively with little change over the 20-year period. The open field was the most commonly used behavioural test, being used in over 50% of the studies. Although the parameters of the open field varied considerably, significant positive effect sizes were observed between OB groups and their sham-operated counterparts. The pooled standardized difference in means (95% confidence intervals) was 2.44 (2.11 to 2.77). A retrospective power analysis revealed that approximately 82% of the open field studies were overpowered, i.e. used more rats than were necessary to produce statistically meaningful results.

Conclusions: This investigation demonstrates that a systematic review and meta-analysis can be useful in evaluating preclinical data, drawn from a number of different laboratories using different methodological approaches. The hyperactive response of the OB rat, the most commonly used behavioural test for assessing antidepressant effects, is a consistent and robust parameter in this model.

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G03

RESCUE OF CYTOKINE-INDUCED REDUCTION OF HUMAN NEUROGENESIS AND INCREASE IN APOPTOSIS BY LONG CHAIN FATTY ACIDS

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Introduction: Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have increasingly been proposed as potential therapeutic agents in major depression. Both dysfunction in neurogenesis-related processes and overactivation of the immune system, particularly in treatment-resistant patients, have been shown in depression. While evidence suggests beneficial effects of both eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids on neurogenesis and in reducing the presence of pro-inflammatory factors (Borsini et al., 2017, Brain Behavior and Immunity, 65, 230-238), the differences between the two fatty acids remain poorly understood. On a molecular level, DHA has been suggested to increase differentiation more efficiently than EPA whereas clinically, EPA has been reported to reduce depression scores better than DHA. This study investigates the distinct protective effects of EPA and DHA on neurogenesis using our well-established model with the cytokine IL-1β to mimic the inflammatory status observed in depression.

Methods: Human hippocampal progenitor cells (HPC03A/07) were pre-treated with either EPA or DHA (10 µM) for 48 hours followed by 48 hours incubation with the cytokine IL-1β (10 ng/mL). Neurogenesis was then assessed with doublecortin (DCX), a marker for immature neurons, and microtubule-associated protein 2 (MAP2), a marker of mature neurons, and apoptosis was assessed with caspase 3 (CC3). The interaction and main effects were analysed using a two-way analysis of variance and a Bonferroni correction was used in the analysis of the simple effects.

Results: Consistent with previous findings, treatment with IL-1β was able to significantly decrease the number of DCX+ cells (-42%, F= 19.988, p<0.001) and of MAP2+ cells (-27%, F= 9.902, p= 0.002), as well as
increase apoptosis (CC3+ cells, +26%, F= 21.317, p<0.001), when compared with control condition. Both EPA and DHA prevented this decrease in neurogenesis and increase in apoptosis. Specifically, compared with IL-1β alone, both EPA and DHA prevented the decrease in DCX + cells (EPA: +34%, F= 37.585, p<0.001; DHA: +90%, F= 104.343, p<0.001) and MAP2+ cells (EPA: +61%, F= 71.306, p<0.001; DHA: +63%, F= 47.282, p<0.001) and the increase in CC3+ cells (EPA: -48%, F= 80.849, p<0.001; DHA: -53%, F= 84.857, p<0.001).

Conclusions: These findings demonstrate the ability of EPA and DHA to prevent the decrease in neurogenesis and neuronal differentiation caused by treatment with IL-1β, as well as the increase in apoptosis. This highlights the neuroprotective potential of EPA and DHA in depression, and each of those n-3 PUFAs should be further investigated in order to fully understand their specific molecular and therapeutic profile.

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G04
DOES EBSOLEN DECREASE SYNAPTIC GLUTAMATE AVAILABILITY?

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Introduction: In bipolar disorder, magnetic resonance spectroscopy has shown an elevation in glutamate in some brain regions. We have recently shown that ebselen, a potential new lithium mimetic, decreases glutamate in healthy volunteers (Masaki et al, 2016). However, if this change is reflective of glutamatergic neurotransmission changes, or is a consequence of metabolism alone, remains unknown. In this study, we used in vivo positron emission tomography (PET) to determine if ebselen reduced glutamate in the synaptic cleft, by using [18F]FPEB, an mGluR5 PET tracer. We hypothesised that ebselen, by virtue of inhibiting glutaminase (Thomas et al, 2013), should decrease brain glutamate levels and we should observe an increase in the uptake of [18F]FPEB in ebselen treated animals, compared to controls. Less glutamate at the receptor level implies more available sites for the tracer to bind to and consequently increased [18F]FPEB uptake. Aim: To determine whether brain uptake of [18F]FPEB increases after acute and chronic administration of ebselen in rats.

Methods: Rats were divided into four groups (N =4/group); ‘ebselen acute’, ‘vehicle acute’, ‘ebselen chronic’ (two weeks) and, ‘vehicle chronic’ groups. The acute treatment groups were administered 5 mg/kg ebselen or vehicle intravenously (IV) followed by an IV injection of [18F]FPEB 15 minutes later, and scanned for 45 minutes. The chronic treatment groups were at baseline, after one week, and two weeks of ebselen treatment (3 µg/mL in drinking water). The data was analysed using Logan graphical analysis with cerebellum as normative region and distribution volume ratio as the main parameter of interest.

Results: In the acute treatment group, there was an overall increase in [18F]FPEB brain uptake (p = 0.028, two-way ANOVA), as expected. In the chronic treatment group, there was an increased [18F]FPEB uptake using a two-way repeated measures ANOVA (p = 0.004), however, the vehicle group also showed an increase (p<0.001). On looking closer, there was a significant correlation between weight of the rat and brain uptake of [18F]FPEB (p = 0.03) and so the results were co-varied for weight. After corrected for weight, there was a significant increase in [18F]FPEB after 1 week of treatment, (p=0.004) but not after two weeks.

Conclusions: Acute administration of ebselen decreased synaptic availability of glutamate. However, chronic dosing offered a more complicated picture, where synaptic glutamate levels decreased after one week of treatment but then normalised after two weeks.

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G05
EFFECT OF R-(+)-METHANANDAMIDE ON NEURAL PROGENITOR PROLIFERATION IN STRESS CONDITION
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Introduction: The endocannabinoid system has been largely studied for its involvement in the regulation of cell fate. In particular, it has been shown that both CB1 and CB2 receptors are present in neural progenitor/stem cells and might control these cells proliferation, differentiation and survival (Galve-Roperh et al., 2013, Progress in Lipid Research, 52,633-650). However, previous data have reported both neuroprotective and neurotoxic effects of cannabinoid drugs in vitro, depending on the specific cannabinoid agonist, concentration and the neuronal cell line used (Bolgov et al., 2011, Cell and Molecular Neurobiology, 31,195-202). Moreover, these effects are also modulated by stress. For example, acute and chronic stress differently modulate the endocannabinoids levels in vivo (Morena et al., 2016, Neuropsychopharmacology, 41,80-102). Furthermore, in vitro studies of neuronal treatment with non-endogenous cannabinoid agonists produce different outcomes in the cell viability depending on the exposure to stressful conditions (Bolgov et al., 2011, Cell and Molecular Neurobiology, 31,195-202). Our study investigates whether incubation of human hippocampal progenitor cells (HPCs) with the selective CB1 agonist, R-(+)-Methanandamide (mAEA), influences human HPCs fate in the context of stress exposure (modelled by treatment with cortisol, as per our previous work (Anacker et al., 2013 Neuropsychopharmacology, 38,872-883)).

Methods: The multipotent human hippocampal progenitor cell line HPC03A/07 was used to evaluate the effects of mAEA and stress. Cells were incubated with cortisol at 100uM and/or mAEA at either 100nM or 1uM, under proliferating conditions, for 3 days. The number of proliferating cells was assessed with Ki67, whereas apoptotic cells were evaluated with caspase 3 (CC3) immunostaining. Two-way ANOVA with Bonferroni post-hoc test was used to assess differences among groups.

Results: Treatment with cortisol induced a reduction in the number of Ki67+cells, when compared with vehicle treatment (-6%, F=68.02, p<0.001), whereas treatment with mAEA (both 100nM and 1uM) did not significantly alter the number of Ki67+cells. Interestingly, co-treatment of cortisol with mAEA (both 100nM and 1uM) induced a larger reduction of Ki67+cells compared with cortisol treatment alone (-18%, p<0.001; -21%, p<0.001, respectively). With respect to apoptosis, treatment with cortisol induced an increase in CC3+cells when compared to vehicle (+68%, F=21.15, p<0.05). Interestingly, mAEA (both 100nM and 1uM) alone did not affect the number of CC3+cells; however, as per the decrease in Ki67, co-treatment of cortisol with mAEA (1uM only) significantly increased the number of CC3+cells with respect to cortisol treatment alone (+60%, p<0.05).

Conclusions: Our findings show that the distinct effects of mAEA on neuronal progenitor/stem cells fate depend on the physiological conditions (with or without stress) in which HPCs are proliferating. Indeed, in presence of stress, mAEA treatment caused a decrease in proliferation and an increase in apoptosis which was much stronger than treatment with cortisol alone. Future analyses should focus on the identification of distinct biological mechanisms characterising the effect of mAEA in presence of cortisol, ultimately aiming to a better understanding of the role of cannabinoids in the context of stress-related psychiatric disorders.

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G06
PRO- AND ANTI-INFLAMMATORY PROPERTIES OF INTERLEUKIN (IL-6): RELEVANCE FOR HUMAN HIPPOCAMPAL NEUROGENESIS

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Introduction: The cytokine interleukin (IL6), not only has disease-promoting inflammatory effects, but also exerts anti-inflammatory properties (Raison et al., Brain Behavior & Immunity, 2018). In particular, IL6 bimodal action seems to be dependent on its concentration levels, as well as on the concomitant presence of other pro-inflammatory cytokines (Felger and Lotrich, Neuroscience, 2013; Pedersen and Febbraio, Physiological Reviews, 2008). Here, using an in vitro model of human hippocampal progenitor cells we investigated whether co-incubation of cells with concentrations of IL6 and IL1beta found in depressed patients could detrimentally affect neurogenesis; and whether co-treatment with a higher concentration of IL6 could prevent such potential damages.

Methods: Cells proliferated for 3 days and differentiated for 7 days in the presence of IL-6 (1, 5 and 50000pg/ml) and IL1beta (1 and 10pg/ml) in co-incubation. Immunostaining of doublecortin (DCX)+ immature neurons and microtubule-associated-protein-2 (MAP2)+ mature neurons were performed. Two candidate cytokines, IL8 and IL13 were measured in supernatant with Meso Scale Discovery platform.

Results: Co-treatment of cells with IL-6 (5pg/ml) and IL1beta (10pg/ml), concentrations found in depressed patients, decreased the number of DCX+ and MAP2+ cells (-20% vs -1%, p<0.05 and -30% vs -2%, p<0.05, respectively), when compared with co-treatment with low concentrations of IL-6 and IL1beta (both 1pg/ml, as found in healthy individuals). In addition, IL-6 (5pg/ml) and IL1beta (10pg/ml) significantly increased the expression of the cytokines IL8 and IL13 in supernatant (+25% vs +10%, p<0.05 and +15% vs +5%, p<0.05, respectively), when compared with low IL-6 and IL1beta concentrations (1pg/ml). In contrast, co-treatment with IL1beta (10pg/ml) and a higher concentration of IL-6 (50000pg/ml) was able to prevent the decrease in both DCX+ and MAP2+ cells (from -20% to -2%, p<0.05 and from -30% to -4%, p<0.05, respectively) and significantly decreased the expression of the cytokines IL8, but not IL13 (from +25% to +9%, p<0.05 and from +15% to +13%, p=0.5 respectively), when compared with co-treatment with IL-6 (5pg/ml) and IL1beta (10pg/ml).

Conclusions: Our results demonstrate the ability of both IL-6 and IL1beta to detrimentally affect neurogenesis when used in concentrations similar to those found in depressed patients. Interestingly, this effect was prevented by treatment with a higher concentration of IL6, putatively via inhibition of IL8-mediated pathways. Further characterization of the underlying mechanisms of IL6 signaling will be of benefit towards future personalized medicine approach for patients with depression.

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G07
MOLECULAR PATHWAYS INVOLVED IN THE INTERFERON-ALPHA MODEL OF IMMUNE DEPRESSION

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Introduction: It is widely known that administration of the pro-inflammatory cytokine interferon-alpha (IFN-alpha) can induce depressive symptoms in patients who receive it as treatment for chronic viral hepatitis (Hepgul et al. (2016)/Neuropsychopharmacology/ vol. 41(10)/ 2502–2511). This supports the notion of a link between peripheral inflammation and depressive symptoms, although the molecular pathways involved in this link remain still unclear. The aim of our study is to understand how a single dose of IFN-
alpha regulates the expression of 2 candidate genes associated with the immune response in the whole blood mRNA of healthy individuals. We have chosen two genes found to be upregulated in peripheral blood of depressed patients, encoding for the purinergic receptor P2X7R and for the signal transducer and activator of transcription 1 (STAT1).

Methods: Using qPCR, gene expression of P2X7R and STAT1 was assessed in whole blood samples of 7 healthy male human volunteers at three different time points: 1 hour before, and 6 and 24 hours, after a subcutaneous injection of IFN-alpha 2a (3 million units). Repeated measure one-way ANOVA with Bonferroni post-hoc test was used to assess differences among groups.

Results: We found a significant increased expression in STAT1 gene at 6 hours (+ 660%; p=0.04) and 24 hours (+107%; p=0.038) after the injection of IFN-alpha. Moreover, P2X7R showed a trend towards an increase at both 6 and 24 hours after the challenge.

Conclusions: Possible molecular pathways involved in the IFN-alpha model of immune depression include upregulation of STAT1 and P2X7 expression.

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G08

AYAHUASCA INDUCES OPPOSITE CHANGES IN THE EXPRESSION OF GLUR1 AND GLUR2/3 AMPA RECEPTORS IN THE PREFRONTAL CORTEX OF WISTAR RATS

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Introduction: The consumption of Ayahuasca beverage is usual in several Brazilian syncretic religions that have expanded to countries in Europe and North America. Usually the ingestion of Ayahuasca occurs 3 times a week. This beverage is made from an Amazonian psychoactive plant containing the serotonin (5-HT) agonist N,N- dimethyltryptamine (DMT) and monoamine oxidase-inhibiting alkaloids (harmine, harmaline and tetrahydroharmine), resulting in enhanced serotonergic activation. Apart from 5-HT, Ayahuasca has been reported to affect glutamatergic processes in some brain areas including prefrontal cortex (PFC), which plays an important role in affective behaviour, attention, working memory, among others. This work aimed at investigating whether the ingestion of Ayahuasca might induce alterations in the expression of glutamate AMPA receptors (GluR1 and GluR2/3) in the dorsolateral PFC of rats.

Methods: Twelve groups of male Wistar rats (230-250g, n=5-8/each) were used. Six groups received 0.2 or 0.4ml/g of Ayahuasca beverage, only once (acute), 3 times/day for 3 days (subchronic) or once/day for 15 days (chronic). Six control groups received water at the same conditions. Sixty minutes after the last Ayahuasca ingestion the animals were anaesthetized, perfused and their brains sectioned (40um) for immunohistochemistry detection of GluR1 or GluR2/3 subunits. The number of immunopositive cells (IC) was quantified, separately, in the superficial and deep layers of the PFC, bilaterally. Comparisons between control and Ayahuasca groups used ANOVA followed by Bonferroni, DMS and Duncan tests (p≤0.05).

Results: For GluR1 either acute, subchronic or chronic ingestion of 0.2 or 0.4ml/g of Ayahuasca induced an increase in the number of IC in both superficial and deep layers of the PFC (6-21%, p<0.01) when compared to control groups. However, for GluR2/3 acute and subchronic treatments induced a decrease in the number of IC (7-15%, p<0.01) in both superficial and deep layers, while only the chronic ingestion of 0.2ml/g induced an increase (17-23%, p<0.01). No difference was found after chronic ingestion of 0.4ml/g. When the Ayahuasca groups were compared, the ingestion of 0.4ml/g always induced lower expression in both GluR1 and GluR2/3 than 0.2ml/g (7-18%, p<0.001).
Conclusions: Considering the involvement of the PFC in several neurodegenerative and psychiatric disorders, the results found here suggest that glutamate might be a potential therapeutic target for the treatment of disorders where the glutamatergic dysfunction is associated with serotonergic system activation.

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G09

HTR2A GENOTYPE INFLUENCES THE IMPACT OF CHILDHOOD ADVERSITY ON ADULTHOOD BROODING RUMINATION

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Introduction: Ruminative response style (rumination) is an inflexible cognition, a perseverative form of thinking about the person's own depressed mood, its possible causes and consequences. Rumination not only elevates the risk for future depression, but, via its maladaptive subtype, brooding, partly mediates the depressogenic effect of childhood adversity. The serotonin system has been implicated previously in the relationship of childhood adversity and rumination. Our recent results have also demonstrated significant gene-by-environment interaction effects between childhood adversity and two single-nucleotide polymorphisms (SNPs) of the serotonin receptor 2A gene HTR2A on rumination phenotypes. Our present aim was to go further, investigating SNP-by-SNP interactions (epistasis) between the same variables.

Methods: 1483 European white adults, recruited within the general population of Budapest, Hungary and Manchester, United Kingdom, provided questionnaire data on gender, age, childhood adversity and rumination, and were genotyped for two SNPs of HTR2A: rs6311 and rs3123. Stepwise linear regression was run in SPSS 25, with brooding score as the outcome variable, separately in the risk C allele carriers and in those with GG genotype of rs3125. Predictor variables were rs6311, population, gender, age, childhood adversity and reflection (the other, more adaptive subtype of rumination).

Results: Our results revealed no significant epistasis, since rs6311 did not emerge as a significant predictor in either rs3125 genotype group. However, an interesting difference could be detected between the two genotype groups in the order of emergence of predictors to explain the variance of brooding. In C carriers, the order was: 1.) reflection [ΔR²=0.195; F(1, 357)=86.241; p<0.001]; 2.) childhood adversity [ΔR²=0.110; F(1, 356)=56.443; p<0.001]; 3.) age [ΔR²=0.012; F(1, 355)=6.186; p=0.013]; 4.) population [ΔR²=0.016; F(1, 354)=8.749; p=0.003]; 5.) gender [ΔR²=0.010; F(1, 353)=5.464; p=0.020]. In contrast, in the GG group the order was: 1.) reflection [ΔR²=0.251; F(1, 1122)=376.921; p<0.001]; 2.) population [ΔR²=0.035; F(1, 1121)=55.331; p<0.001]; 3.) childhood adversity [ΔR²=0.017; F(1, 1120)=26.712; p<0.001]; 4.) age [ΔR²=0.017; F(1, 1119)=28.330; p<0.001]; 5.) and gender [ΔR²=0.009; F(1, 1118)=15.200; p<0.001].

Conclusions: We suggest a novel way to define gene-by-environment interaction: HTR2A rs3125 genotype modifies the importance of other variables that affect brooding. While reflection seems to play an important role (19.5% or 25.1% of variance) in explaining brooding irrespectively of genotype, additional variables in the GG group are much less important than reflection. However, in C carriers childhood adversity explains an almost tenfold of variance of brooding compared to GG carriers (11% vs. 1.7%).

G10

HAPPY AND SAD FACIAL EXPRESSION RECOGNITION AND DEPRESSIVE SYMPTOM SEVERITY IN A PROSPECTIVE COHORT STUDY

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Introduction: Negative processing biases are thought to play a causal role in the development of depressive symptoms and delay recovery from depression. People with depression may process facial expressions more negatively, or less positively, than healthy individuals. However, previous research has mostly been cross-sectional, making it unclear whether biases precede or follow depression. Many studies have also used small case-control designs prone to selection bias. We aimed to test whether processing of happy and sad facial expressions of varying intensities was associated with depressive symptom severity both cross-sectionally and longitudinally.

Methods: This was a prospective cohort study of individuals who had visited primary care services in the UK in the past year reporting depressive symptoms (n=509). Depressive symptoms were assessed using the Patient Health Questionnaire (PHQ-9) and Beck Depression Inventory (BDI-II) at four time-points, each two weeks apart. A computerised task measured recognition of emotional facial expressions at the first three time-points. We conducted analyses using multilevel models.

Results: More incorrect classification of faces as happy (a more positive emotion recognition bias) was associated with lower severity of concurrent depressive symptoms. For every additional incorrect happy response, PHQ-9 scores reduced by 0.05 of a point (95% CI =-0.10 to 0.002, p=0.06 after adjusting for confounders). This association was not replicated using the BDI-II. However, using both the PHQ-9 and BDI-II, there was strong evidence for a negative association between misclassification of ambiguous faces as happy and concurrent depressive symptoms (interaction term with facial expression intensity p<0.001). There was no evidence of an association with sad face recognition, and no longitudinal evidence for associations between happy or sad face recognition and subsequent depressive symptoms. Antidepressants were used by 69-71% of participants, but there was no evidence for associations between antidepressant use and happy or sad face recognition.

Conclusions: In this large prospective cohort study, depression was characterised by less positive processing and not more negative processing. When facial expressions were clear and identification easy, performance did not differ according to depressive symptoms. However, for more ambiguous facial expressions, misclassifying more faces as happy was associated with fewer depressive symptoms. Reduced positive biases when processing emotional facial expressions may be a cognitive marker of depression. Psychological therapies should therefore focus on reinstating positive biases that could be protective for mental health.

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G11

FK506 BINDING PROTEIN 5 GENETIC POLYMORPHISMS AND PHARMACOLOGICAL RESPONSE IN MOOD DISORDERS: A META-ANALYSIS

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Introduction: There is interest in identifying the association between genetic variability and treatment response in mood disorders. This is because a substantial number of individuals do not respond or don’t achieve full remission with sequential treatment algorithms. In the future, treatment approaches could
be guided by identifying genetic contributors to individual differences. FK506 binding protein 5 (FKBP5) gene polymorphisms have been investigated in relation to pharmacological response in mood disorder. The gene codes for a protein involved in the hypothalamic pituitary axis (HPA) feedback loop by acting as co-chaperone of the sensitivity of the glucocorticoid receptor. Research into FKBP5 originates from the link between HPA dysregulation and mood disorders and HPA normalisation following recovery. This meta-analysis expands on the work of Zou and colleagues on FKBP5 gene polymorphisms and treatment response in mood disorders (Zou et al, 2010, Neuroscience Letters, 484, 56-61).

Methods: A systematic search of the literature was conducted, and eleven studies were selected which investigated the relationship between single nucleotide polymorphisms Rs1360780, Rs3800373 and Rs4713916 and treatment response in mood disorders. Odds Ratio and 95% confidence intervals were obtained for each study and a meta-analysis was carried out by using Stata. Heterogeneity and publication bias were assessed.

Results: An association between Rs1360780, Rs3800373, Rs4713916 polymorphisms and treatment response was reported particularly in early studies. Eight studies investigating the interaction between Rs1360780 and treatment response were combined to carry out a meta-analysis. The results indicated that the association between Rs1360780 and treatment response did not reach statistical significance (Effect size=1.23, CI: 0.96 to 1.58). In this analysis the variation in effect size attributable to heterogeneity was 45.3% and not statistically significant (Heterogeneity chi square=12.79, p=0.077). There was no evidence of publication bias (Coef. 0.13, p=0.86).

Conclusions: This analysis suggests that Rs1360780 FKBP5 polymorphism might not be a strong candidate for predicting treatment response. Further research to fully establish the role of FKBP5 polymorphisms might be useful to help develop personalised treatment algorithms preferably by using genome wide association studies in view of the limitations in replicating results based on putative candidate genes.

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G12
REDUCED WILLINGNESS TO EXERT EFFORT IN CURRENTLY DEPRESSED AND REMITTED PATIENTS COMPARED TO HEALTHY CONTROLS AND FIRST-DEGREE RELATIVES

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Introduction: Anhedonia is a cardinal symptom of depression associated with poor clinical outcome, but its underlying cognitive mechanisms remain poorly understood. Although traditionally conceptualized as lack of pleasure, anhedonia appears to be related rather to lack of motivation which can be objectively measured with behavioural tasks as decreased willingness to exert effort for rewards. Here we aimed to examine whether decreased willingness to exert effort characterises not only depressed patients, as previously demonstrated, but also patients in sustained remission and unaffected first-degree relatives. We also aimed to test whether the impairment in motivation is driven by decreased reward sensitivity, increased effort sensitivity, or both.

Methods: Fifty unmedicated currently depressed (CD) and 46 remitted patients (REM) as well as 35 healthy first-degree relatives of depressed patients (HR) and 49 healthy controls (HC) completed a task in which they chose whether to exert physical effort (squeezing a hand dynamometer) in order to win monetary rewards. Levels of effort and reward were parametrically varied in each trial, and participants’ willingness to exert effort was analysed based on their choices using repeated-measures ANOVA. Reward and effort sensitivity were correlated with the degree of their motivational and general depressive symptoms, assessed with standardised clinical questionnaires.

Results: As expected, we found a significant interaction between effort level and reward magnitude on the willingness to accept an offer (F(4.91,863.81)=2.38, p<0.001): the willingness increased significantly
with increasing reward magnitude (F(1.63,287.18)=278.94, p<0.001) and decreased significantly with increasing effort level (F(1.72,287.18)=326.62, p<0.001). There was a significant overall group difference (F(3,176)=3.684, p=0.013) in the willingness to exert effort overall. This was due to the combined patient group (CD+REM) being significantly less willing to exert effort than the never-depressed group (HR+HC) (t(178)=3.208, p=0.002). There was no significant difference between CD and REM patients (t(94)=0.69, p=0.52), or between HR and HC (t(82)=0.64, p=0.52). In the combined patient group (CD+REM), low reward sensitivity was correlated with greater apathy and anhedonia scores (r>0.2, p<0.05), but not with general depressive symptoms.

Conclusions: These results suggest that decreased willingness to exert effort for rewards is a stable trait in depressed patients regardless of the presence of symptoms, which is consistent with the poor response of anhedonic symptoms to treatment. They also show that, in patients, high anhedonia scores are associated with low reward sensitivity. Together, these results help to elucidate the cognitive mechanisms underlying motivational impairment in depression.

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G13
IDENTIFYING DEPRESSION EARLY IN ADOLESCENCE (IDEA) PROJECT: A SYSTEMATIC LITERATURE REVIEW OF FMRI NEURAL RISK FACTORS FOR THE DEVELOPMENT OF DEPRESSION IN ADOLESCENCE

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Introduction: Major depressive disorder (MDD) is a leading contributor to the global burden of disease due to its early onset in adolescence, chronicity, and lack of sufficiently effective treatments. There is a crucial global health need to identify predictors of MDD for early detection and targeted intervention, specifically in adolescents across the globe. Therefore, we have conducted a systematic literature review to identify articles evaluating biopsychosocial risk and protective factors for MDD in youth aged 10 – 24 years across high-income countries (HICs) and low- and middle-income countries (LMICs). Here, the articles evaluating biological risk factors are considered, specifically neural risk factors from fMRI articles.

Methods: A systematic literature review adhering to PRISMA guidelines was conducted using comprehensive search terms across 7 databases (MEDLINE via Ovid, PsychINFO, Cochrane Database of Systematic Reviews, Web of Science, Lilacs, African Journals Online and Global Health) (PROSPERO registration CRD42018103973). Independent raters screened and retrieved articles for inclusion, extracted data, and rated quality with the Systematic Assessment of Quality in Observational Research (SAQOR).

Results: From a total of 4393 abstracts, 20 fMRI articles were eligible for extraction, representing over 1,500 adolescents, although only from the HICs USA and UK. 5 articles were longitudinal and 15 were cross-sectional / case-control, including samples of MDD (5 articles) or high-risk individuals (10 articles) by virtue of a family history of MDD, high neuroticism or early life stress (ELS), such as maltreatment, low socioeconomic status or peer rejection. A clear pattern of neural abnormalities in both MDD and high-risk individuals emerged. Reward-related activity (caudate, putamen, anterior cingulate cortex) is significantly reduced and negatively correlates with depression symptoms, except for medial prefrontal cortex activity to reward anticipation, which positively correlates with depression symptoms (corrected-p ≤ 0.01 in most). Conversely, negative emotion-related (passive viewing / matching of fear / sad / angry faces) activity in the bilateral amygdala is significantly increased and positively correlates with depression symptoms and vice versa in the dorsolateral prefrontal cortex (corrected-p ≤ 0.01 in most). Additionally, these abnormalities were consistently found to mediate the relationship between ELS and later depression (p ≤ 0.05 in most).

Conclusions: Reduced reward-related activity and increased limbic activity, alongside other psychosocial
factors, may be crucial predictors of the development of MDD specifically in adolescents, at least in HICs; however, most of the samples used were of Western Europe and North American descent thus limiting the generalizability of the findings, which need to be replicated in LMICs.

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G14

A SIMULATION META-ANALYSIS OF THE ROLE OF REINFORCEMENT LEARNING IN MOOD AND ANXIETY DISORDERS

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Introduction: In recent years, there has been increased interest in the use of reinforcement learning models to understand disorders involving enhanced negative affectivity, such as mood and anxiety disorders. These computational models can be exploited to produce testable, explicit predictions, and offer promise for identifying the mechanisms underlying symptoms dependent on reward- or punishment-learning processes. Here, we develop a new meta-analytic simulation modelling approach to exploit the increase in power gained by pooling samples from different research groups.

Methods: We extracted parameters from papers which a) used reinforcement learning models in b) mood and anxiety disorders with c) a case-control design and d) reported the mean and variance of all parameters in these models or e) made the individual participant-level free parameters available. Performance on a simple two-armed bandit task was simulated for each individual using the model specified in each paper, with both wins and losses varying according to a random walk with Gaussian noise. Model comparison was performed (8 models, fit using a Markov-Chain Monte-Carlo approach) over this meta-analytic simulated choice data and group comparisons were performed on the individual level parameters from the best-fitting model.

Results: Data from four papers (n=226, patients=126) were used (Chase et al. 2010, Psychological Medicine, 40, 433-440; Brown et al. 2018, eLife, 7, e30150; Kumar et al. 2018, Neuropsychopharmacology 43, 1581; Moutoussis et al. 2018, PLoS One 13, e0201451). The best-fitting model comprised two learning rate terms (one for reward, one for loss), a lapse term, and a sensitivity term. Group-level comparisons found no main effect of group on learning rate for rewards (F1,218=0.001,p=0.975), learning rate for losses, (F1,218=2.67,p=0.104), lapse (F1,218=1.11,p=0.294), or sensitivity (F1,218=0.001,p=0.970). There was also a main effect of study (all p<0.001).

Conclusions: This novel meta-analytic simulation approach to reinforcement learning allows us to capitalise on the increased power produced by analysing data from a greater number of participants. Our initial results indicate that there may not be a difference in reinforcement learning in those with mood and anxiety disorders compared to control participants. However, significant effects of study were found, indicating that individual effects reported in studies may depend on task design, participant group and other idiosyncratic features.

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G15

DOPAMINE RECEPTOR AVAILABILITY IN MAJOR DEPRESSIVE DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: Major depressive disorder (MDD) is a leading cause of global disability. Over a third of the patients do not respond to serotonergic treatments. Several lines of evidence implicate the dopamine system in the pathophysiology of MDD. However, the magnitude and nature of in-vivo dopaminergic changes has not been systematically appraised. Understanding the nature of dopamine dysfunction seen in MDD has the potential to aid the development of new therapeutics. Thus, we aimed to comprehensively review the in-vivo imaging evidence for dopamine receptor (D2/3) alterations in MDD.

Methods: The entire PubMed, EMBASE and PsycINFO databases were searched for studies from inception date to 30 March 2019. Out of the 1685 article searched, a total of 18 studies were identified that compared dopamine D2/3 receptor between 279 patients and 258 controls using positron emission tomography or single-photon emission computed tomography to measure striatal dopamine receptor availability. Demographic, clinical and imaging measures were extracted from each study, meta-analyses and sensitivity analyses were conducted in accordance with PRISMA guidelines. We determined the difference in dopamine D2/3 receptor availability in MDD and healthy controls using a random effect model.

Results: The I2 value was 48% (95% CI, 7%–76%), indicating moderate heterogeneity between studies. There was no significant difference in striatal dopamine receptor availability in major depressive disorder relative to controls (Hedge's g=0.18, p=0.15), or in the subgroup analysis with studies conducted using [11C] raclopride (Hedge's g= 0.33, p=0.14) and [123I] IBZM (Hedge's g= 0.13 p=0.42) did not reveal a significant difference in the D2/3 receptor availability between groups. The sensitivity analysis restricted to studies which had antidepressant free/naïve subjects did not show significant alteration in D2/3 receptor (Hedge's g=0.18, p=0.37).

Conclusions: Our data suggest that post-synaptic aspects of the dopamine system in the striatum are not altered in the MDD compared to healthy controls. The data contradicts preclinical and pharmacological literature on dopaminergic deficits in MDD.

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G16

CEREBRAL SEROTONIN RELEASE REDUCED AMONG PATIENTS SUFFERING SEVERE DEPRESSION: PILOT DATA FROM A PET STUDY WITH [11C]CIMBI-36 AND D-AMPHETAMINE CHALLENGE

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Introduction: The “serotonin hypothesis” of clinical depression is almost 50 years old and proposes that diminished serotonergic (5-HT) neurotransmission plays a causal role in the pathophysiology of depression. While finding some experimental support, it has not been possible to date to evaluate brain 5-HT fluctuations directly in the living human brain. We have recently demonstrated that the binding of the 5-HT2A receptor agonist radioligand, [11C]Cimbi-36, is sensitive to increases in extracellular 5-HT induced by an acute d-amphetamine challenge. In this study we aim to compare brain 5-HT release capacity in patients with major depressive disorder (MDD) to that of non-depressed healthy controls (HC), and to investigate the relationship between symptom severity and 5-HT release capacity among the MDDs.
Methods: Eight medication-free MDDs (3 female, 5 male, 39 +/- 10 y.o., BDI scores 30 +/- 7, range: 18-40) and 19 HC (2 female, 17 male, 32 +/- 9 y.o.), underwent [11C]Cimbi-36 PET before and 3 hours after an oral dose of d-amphetamine (0.5mg/kg). Dynamic PET data were acquired over 90 minutes and the total volume of distribution (VT) in the frontal cortex and the cerebellum was derived using the MA1 model with metabolite corrected arterial plasma input function. The frontal cortex binding potential (BPNDfrontal) was calculated as VTfrontal/ VTcerebellum-1, and 5-HT release capacity as Delta-BPND = 1- BPNDfrontal post-dose/ BPNDfrontal baseline. The severity of depressive symptoms among MDDs was rated at baseline using the Beck Depression Inventory (BDI). BPNDfrontal was compared between baseline and post-dose scans for each group using paired Student's t-test. Delta-BPND was compared between MDD and HC group using Students t-test, and linear regression was used to explore the association between BDI and Delta-BPND in the MDD group.

Results: Following d-amphetamine administration BPNDfrontal was significantly reduced in the HC group (17 +/- 13%, p<0.001), whereas no effect was seen in the MDD group (1 +/- 25%, ns). Delta-BPND was significantly higher in HC compared to MDD (p=0.036). Notably, the 3 MDDs with the highest BDI scores (>33) all had 5-HT release capacity below the range of the HC.

Conclusions: The first direct assessment of 5-HT release in the depressed brain provides support for the "serotonin hypothesis", demonstrating a reduced 5-HT release capacity in patients with MDD, with the amount of release correlating with the severity of depression. Further work will seek to confirm these pilot data and explore the tentative association seen between 5-HT release capacity and severity of depressive symptoms, as well as explore the relationship with clinical response to pharmacological treatment.

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G17

NEURAL CORRELATES OF MENTAL IMAGERY AND FUTURE SIMULATION IN THE BIPOLAR SPECTRUM

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Introduction: Growing evidence suggests that dysfunctional mental imagery contributes to emotional dysregulation in bipolar disorder and transdiagnostically (Di Simplicio et al., 2016, Bipolar Disorders, 18(8):669-683). Perceptual modification of dysfunctional imagery, delivered as part of a brief therapeutic intervention, has shown promising effects for reducing mood instability in bipolar disorder (Holmes et al., 2017, Transl Psychiatry, Jan 26;6:e720). This study is the first to investigate the neural underpinnings of the emotional impact of imagining negative future scenarios (future simulation) and perceptually modifying such mental imagery.

Methods: Euthymic participants with a bipolar spectrum (BP, N=19; criteria: bipolar disorder diagnosis or Mood Disorder Questionnaire (MDQ) scores ≥ 7 plus past major depressive episode) and healthy controls (HC, N =18; criteria: no lifetime psychiatric history and MDQ scores ≤ 3) recruited from the community underwent behavioural testing and an fMRI scan. During the task, participants were instructed to imagine negative future scenarios (Imagine), then to repeat the simulation of the scenarios, either as before (Repeat), or by perceptually modifying the imagery to black and white (B&W). Affect and imagery-based cognition were also assessed.

Results: BP participants rated the imagined scenarios as significantly more real and unpleasant compared to HC during the first and the repeated simulation (Imagine and Repeat: p < .05); while between groups differences were abolished after the imagery manipulation (B&W: p > .1). BP participants reported higher
sadness after the simulation task compared to HC (Group x Time: p < .05). Whole-brain analysis revealed a significant cluster of activation for the Group x Condition (Repeat vs. Imagine) interaction in a network of areas including the frontal pole, inferior frontal gyrus and insula: HCs showed a repetition suppression effect on neural activity during repeated future simulation, while this was not present in the BP group (p < .05). Independent Component Analysis revealed significant greater resting state functional connectivity in areas of the Default Mode Network (DMN) in BP vs HC across rest before and after the task.

Conclusions: Simulating negative future scenarios is subjectively more emotional in euthymic individuals with a bipolar spectrum compared to controls. This coincides with greater activity in emotion regulation prefrontal cortical areas and the DMN, both during simulation and rest, and identifies potential neural mechanism via which mental imagery amplifies emotions in BP. Perceptual modification of imagery successfully abolished differences in emotional impact between groups, indicating further promise as an intervention targeting mood instability.

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G18

TIME-VARYING FUNCTIONAL CONNECTIVITY REVEALS INCREASED BASAL GANGLIA META-STATE INTERCONNECTIVITY IN DEPRESSION WHICH IS REDUCED FOLLOWING TREATMENT WITH BUPROPION

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Introduction: Time-varying connectivity (TVC) analysis identifies functional networks which form for short periods of time (Allen et al., 2014, Cerebral Cortex, 24, 663-676). We present TVC analysis of resting blood oxygen level dependant (BOLD) activity recorded following a battery of emotional and reward processing tasks in patients with depression (n = 40) and healthy controls (n = 40), before and after six weeks of treatment with bupropion and placebo respectively. The results demonstrate the effects of depression and bupropion on emotion and reward related functional connectivity in the absence of explicit stimulation (Harmelech et al., 2013, J. Neurosci, 33, 9488-9497).

Methods: TVC analysis using the GIFT toolbox (http://mialab.mrn.org/software/gift/index.html) employs sliding window correlation between BOLD signals from spatially and temporally independent components. The patterns of connectivity in each window are then clustered to form prototypical meta-states which can be combined in a weighted manner to describe all other observed states.

Results: Four meta-states were identified: - Visual: High positive coupling within the visual regions and low coupling between all other regions; - Visual-cognitive: High positive coupling within visual regions and between ECN, precuneus and salience regions; - Default-executive: Positive coupling between DMN and executive control regions and negative coupling with salience, sensorimotor and visual regions; - Highly interconnected: Positive coupling between most regions but specific negative coupling with the basal ganglia (BG). There were statistically significant differences in meta-state composition between groups and across time-points. Patients with depression showed increased BG coupling compared to controls at baseline in the default-executive state (meta-state composition difference (MSCD) p = 0.029) and the highly interconnected state (MSCD p = 0.032). At follow-up patients showed decreased BG coupling compared to controls in the highly interconnected state (MSCD p = 0.040). Within-group analysis also identified decreased BG coupling in the visual state for patients after bupropion treatment (MSCD p < 0.001), but no significant differences in controls after placebo (MSCD all p > 0.340).

Conclusions: These results demonstrate a baseline increase in BG interconnectivity in depression compared to controls following a battery of emotional and reward processing tasks, which is reversed to
a relative decrease following treatment with bupropion. This observation is consistent with alterations in reward and emotional processing in depression, and the effects of bupropion (a norepinephrine–dopamine reuptake inhibitor) on the basal ganglia. Such meta-state descriptions may be informative in understanding depression treatment mechanisms of action and identifying novel biomarkers for diagnosis or personalised medicine.

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G19
THE DELAYED EFFECTS OF KETAMINE DURING AUTOBIOGRAPHICAL MEMORY RECALL. A NEUROIMAGING STUDY ON REMITTED DEPRESSED VOLUNTEERS
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Introduction: Depressed individuals as well as those who have remitted from the illness tend to recall more categorical and less specific AMs (Autobiographical Memories) (Haddad et al., 2014 J Behav Ther Exp Psychiatry. 45(2): p260-6). Moreover, those individuals experience difficulty in recalling positive AMs compared to negative or neutral experiences which could lead to or help maintain depressive mood (Young et al., 2016 Psychiatry Res, 248: p 159-61). In the last decade, ketamine has emerged as a potent, fast-acting antidepressant producing a detectable depressive symptom improvement as early as 2hours post drug administration (Zarate et al., 2006 Arch Gen Psychiatry, 63(8):p 856-64) . However, the drug's antidepressant effects in the brain remain largely unknown. Here we examine brain regions central for recall including the PCC (posterior cingulate cortex) and temporal areas, during a novel AM fMRI task 2 hours after ketamine.

Methods: 36 unmedicated, remitted depressed participants received placebo and ketamine (0.5mg/kg) during a 45min intravenous infusion in a cross-over design and were scanned 2hours after drug administration. The VAMP (Valenced Autobiographical Memory-Probe) task involves an interview prior to scanning when participants talk about recent positive, negative and neutral life experiences, which are then scored using a modified version of the LEDS (ref). During scanning 10 written statements of each event are presented and volunteers are given 12 seconds to think about each statement in as much detail as possible. A control condition requiring counting upwards was also included. Analysis of the imaging data was conducted using SPM-12.

Results: Whole brain analysis of the VAMP task in the placebo session (One Sample T-test) revealed that brain areas which have been previously implicated in AM recall are also significantly (p<0.05) activated during active AM recall compared to the control condition. These areas include the precuneus, the posterior cingulate cortex and temporal regions including the hippocampus. Moreover, the same set of regions seem to be involved in positive, negative as well as neutral AM event retrieval. When the ketamine and placebo sessions were compared (Paired T-test), the left PC presented with increased activation (p<0.05) under placebo compared to ketamine for positive recall.

Conclusions: The VAMP task showed similar activation in brain areas implicated in AM across all valence conditions which overlap with the Default Mode Network. Ketamine decreased activity only during the positively-valenced memory recall, which could reflect a facilitation in the recall of these memories.

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**G20**

**EFFECTS OF ACUTE FLUOXETINE ON EMOTIONAL REGULATION IN DEPRESSED ADOLESCENTS: AN FMRI STUDY**

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Introduction: Young people with depression have problems regulating their emotions, showing avoidance of unpleasant cues/situations and difficulties in cognitive reappraisal. Fluoxetine is the first line drug treatment for adolescent depression but the neural mechanisms underlying serotonergic antidepressants (SSRIs) in this age group are still poorly understood. Recent work from our lab showed that fluoxetine acts to decrease the rapid processing of anger cues in young people, but so far the effects of fluoxetine on the more complex regulation of unpleasant cues have not been previously characterised. The current study therefore aimed to assess the effects of fluoxetine on emotional neural regulation in depressed adolescents prior to changes in symptoms.

Methods: Twenty-nine depressed adolescents were randomised to receive their first, single dose of fluoxetine or placebo. Six hours later, participants completed an emotional regulation fMRI task, in which they were instructed to either view negative images naturally (‘maintain’), or to intentionally reinterpret the content of the pictures to reduce negative affect (‘suppress’). Significant whole-brain activations were identified using cluster-based thresholding (Z>3.1, p<0.05, corrected).

Results: Distress ratings were significantly lower in the suppress compared to maintain blocks (p<0.0001), hence showing that participants were able to decrease their negative affect via cognitive reappraisal, but there were no significant group differences in this behavioural measure. Neurally, participants on fluoxetine revealed increased activation in areas involved in visual processing (including the occipital pole and fusiform gyrus) in response to both maintain and suppress conditions.

Conclusions: These data suggest that fluoxetine increases the processing of negative stimuli regardless of the strategies used by the participants, which may reflect increased attention towards or less avoidance from such stimuli. Reduced avoidance from negative cues following antidepressant treatment has been previously reported in vulnerable populations at risk for depression, and could therefore reflect a key mechanism whereby participants engage with negative pictures which were previously avoided. Future research combining fMRI with eye-tracking is nonetheless needed to further clarify these effects.

Funding: This research study was funded by the John Fell Fund (111/124) and Medical Research Council (MRC) programme grant (85077) to Phil Cowen, and supported by the NIHR Oxford Health Biomedical Research Centre (OH BRC). Liliana Capitão was supported by the Portuguese Foundation for Science and Technology during most of the data collection period (doctoral grant code: SFRH/BD/64894/2009) and is now supported by the NIHR Oxford Health Biomedical Research Centre (OH BRC).

**G21**

**STRUCTURAL NEUROIMAGING OF ADVERSITY-PREDICATED RESILIENCE IN ADOLESCENT GIRLS**

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Introduction: There has been an increasing interest in structural brain correlates of resilience in adolescents and the emerging evidence suggests the involvement of the cortico-limbic neurocircuitry. Indeed, in adolescents, larger volumes in the right PFC have been implicated in adaptive functioning
following adversity (Burt et al, 2016. Child Psychol Psychiatry; 57 (11): 1287-96. Additionally, larger hippocampal volumes seem to indicate resilience (Dennison et al, 2015. Cogn Affect Behav Neurosci; 15(1): 80-94), although null findings have also been reported in a review (van der Werff et al, 2013. Front Behav Neurosci; 7: 39). Interestingly, in the few studies conducted, adversity as a precursor of resilience, or age and gender effects are often not taken into account. We were therefore interested in associations between resilience and brain structure in adolescent girls.

Methods: Adolescent girls who had been exposed to emotional trauma (N = 76) underwent high-resolution structural MRI scans, and brain structure was measured with FreeSurfer v6.0. Subjective resilience was measured with the Brief Resilience Scale (BRS) (Smith et al, 2008. Int J Behav Med; 2008; 15(3): 194-200, which assesses the ability to bounce back. To understand brain regions associated with resilience, we performed exploratory Spearman’s correlations between the BRS total score and the subcortical structures, the cortex and the cerebellum. We were also interested in age differences in these associations and therefore, considered separate age groups (12-13 years; N = 21); 14-15 years; N = 28; 16-18, N = 27). This was, however, a cross-sectional study.

Results: We observed overall negative associations between resilience and bilateral thalamus (left: ρ = -0.26, α = 0.02; right: ρ = -0.24, α = 0.03). When we consider age effects, the thalamic associations are seen in the older age group (16-18 years: left thalamus; ρ = -0.42, α = 0.03; right thalamus: ρ = -0.52, α = 0.006) but not in any of the younger age groups (all p-values > 0.36). In the 14-15-year group we observe negative associations with the left hippocampus (ρ = -0.46, α = 0.01) and the left nucleus accumbens (ρ = -0.46, α = 0.04).

Conclusions: The observed associations seem to be counterintuitive. The associations with resilience and the thalamus which has functional connections with the hippocampus may reflect a gender specific developmental aspect of resilience to adversity, that cannot be explicated from cross-sectional studies. Therefore, longitudinal investigations with large samples sizes will be helpful in elucidating developmental effects of adversity driven resilience on brain structure.

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G22
TRANS-DIAGNOSTIC PHENOTYPIC AND NEUROANATOMICAL MARKERS OF DEPRESSION
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Introduction: Depression is the most common co-morbidity seen with other mental disorders. Complex psychopathology presents clinicians with the challenge of correctly identifying comorbidities, avoiding misdiagnoses, and tailoring therapeutic options for the individual. There remains significant debate around the heterogeneity of depressive symptoms and their function as prognostic indicators. Our aim was to identify common and distinct neuroanatomical and clinical features of depression across diagnostic groups using supervised machine learning and provide a deeper understanding of the phenomenological profile of depression.

Methods: Cross-sectional data was taken from 245 subjects with recent onset depression (ROP) and recent psychosis (ROP) from the PRONIA study, an EUPF7 funded 8 centre study. A support vector machine (SVM) classification model was built using “pure” ROP and ROP groups and a battery of broad common clinical features seen in ROD and ROP and applied to subgroups with comorbidities (ROP with depressive symptoms (ROP+D) and ROD with psychotic symptoms (ROP+P) to determine the classification accuracy in
these groups based on their primary diagnosis. Models were then repeated using neuroanatomical (sMRI) data and finally both models were stacked together.

Results: Pure clinical classification model: Balanced accuracy: 80.8%, Sensitivity: 77.7%, Specificity: 86.7%, Area Under the Curve (AUC): 0.85. Positive Predictive Value (PPV): 70%, Negative Predictive Value (NPV): 88.6%. Application of model to the subgroups: Balanced accuracy: 61%, Sensitivity: 38%, Specificity: 84%, AUC: 0.66, PPV: 89.7%, NPV: 26.9%. Pure imaging classification model: Balanced accuracy: 62%, Sensitivity: 39.5%, Specificity: 84.4%, AUC: 0.67, PPV: 51.7%, NPV: 76.8%. Application of the model to the subgroups: Balanced accuracy: 50%, Sensitivity: 23.9%, Specificity: 76%, AUC: 0.45, PPV: 78.6%, NPV: 21.3%. Stacked Model: Balanced accuracy: 80.9% Application of the stacked model to the subgroups: Balanced accuracy: 60.5%

Conclusions: In this study we built a successful diagnostic classification model using both clinical and neuroimaging features. Our findings suggest that it may be possible to accurately identify depressive features in different diagnostic categories, including major depressive disorder and psychosis. This means that depressive features across diagnostic groups have a different clinical presentation. Interestingly, the clinical signature of the ROP+D group looks very much like the clinical signature of the “pure” ROD group and the ROD+P group. That finding suggests that depressive symptoms in psychosis hold a lot of weight and could mask the overall diagnosis. It also suggests that low level psychosis symptoms are of less importance than mood symptoms in ROD. Finally, while neuroimaging holds some potential to add to diagnostic accuracy in complex co-morbid disorders, the type of neuroimaging modality used should be carefully selected based on its potential to add value in diagnostic models.

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G23
THE EFFICACY OF ELECTROCONVULSIVE THERAPY (ECT): AN EVALUATION OF THE NATIONAL ECT ACCREDITATION SERVICE CLINICAL OUTCOME DATA 2017-2018

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Introduction: Introduction: Electroconvulsive Therapy (ECT) was first used to treat Depression in 1938, by Consultant Neurologist, Ugo Cerletti, and his assistant, Bini, in Rome, Italy. ECT remains the treatment-of-choice for patients who suffer with complex mental illnesses, such as treatment resistant depression (TRD), catatonia and clozapine-resistant psychosis. Increases in the volume of the hippocampus and the amygdala have consistently been observed in recent ECT studies. The major barrier stopping patients with TRD from receiving ECT in a timely manner, both historically and today, has been the stigma that the treatment has received from media outlets, films and newspapers, globally. Ten years ago, the Royal College of Psychiatrists (RCPsych), Centre for Quality Improvement (CCQI), set-up a quality assurance/quality improvement accreditation service, called the Electroconvulsive Therapy Accreditation Service (ECTAS). This was developed to try and reduce the stigma attached to ECT by standardising ECT Clinic regulation, operation and the delivery of ECT to patients in Ireland, Wales and England. All ECT Clinics were invited to sign-up to ECTAS to gain coveted accreditation status. To achieve accreditation, ECT clinics are expected to graduate through a rigorous course of self-review, peer-review and accreditation-review visits; where they are assessed against nationally-agreed, evidence-based standards of care, published by the RCPsych.

Methods: Aims and Methods: ECT clinics, which are part of ECTAS, are required to submit annual data surrounding their clinic outcomes. In this study, we aimed to evaluate the overall efficacy of ECT as a treatment for TRD. The Clinical Global Impression (CGI) Scale was chosen as the vehicle to measure the overall outcome of ECT; as this provided good overall face validity. Hence, the outcome data for acute ECT treatments for TRD patients between 2017 and 2018 was analysed.
Results: Results: Outcome data from eighty-two ECT Clinics was included. Sixty-six percent of ECT patients were female. The median number of ECT treatments administered was eight. The total number of patients receiving ECT has reduced six-fold since 1999. Ninety percent of TRD patients treated with ECT clinically improved, as per the CGI. Subjectively, cognitive side-effects remained the key area of concern for most patients.

Conclusions: Conclusions: ECT delivery has evolved and the treatment has become safer and more standardised. ECT is now largely given to patients with severe TRD. The total number of patients receiving ECT has fallen in absolute terms. Patient outcome scores have remained consistently high. This should encourage current/future clinicians to continue prescribing ECT in future.

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G24

ELEVATED INFLAMMATORY MARKERS IN CORONARY HEART DISEASE PATIENTS PREDICT ONSET OF DEPRESSION IN A THREE-YEAR PROSPECTIVE FOLLOW-UP.

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Introduction: Depression frequently co-occurs with coronary heart disease (CHD), worsening clinical outcomes (May et al., 2017, Eur. Hear. J. - Qual. Care Clin. Outcomes., 3:296-302). Given the pivotal role of inflammatory processes in both diseases, increasing attention is focusing on inflammation as a biological link between these two disorders (Halaris, 2013, Curr. Psychiatry Rep., 15:400). The aim of the present study was to investigate the role of inflammation in the development of depression among CHD patients during a 3-year follow-up. We examined two inflammatory biomarkers at baseline, the acute phase protein, C-reactive protein (CRP), and the neurotrophic factor, vascular endothelial growth factor (VEGF), as potential predictors of later insurgence of depression.

Methods: We recruited 96 CHD patients (male 78.1%, mean ±SD age 70.6 ±9.35 years), who were assessed at baseline and then every 6 months for three years. The sample included, at baseline, 26 depressed and 70 non-depressed, as confirmed by Clinical Interview Schedule Revised, CIS-R. Depressive symptoms were assessed at baseline by both the Patient Health Questionnaire-9 (PHQ-9) and the Beck Depression Inventory (BDI), and at follow-up by the PHQ-9 only. Biological assessments (serum CRP and plasma VEGF) were obtained at baseline, and measured by ELISA technique. Performing correlations, t-tests, and ANOVA, we investigated the association between elevated baseline inflammatory markers and measures of depression at baseline and during the follow-up, including onset and duration of depressive symptoms.

Results: In CHD patients, higher CRP and VEGF levels were associated with higher severity of depression at baseline (r=0.27, p=0.012 and r=0.35, p=0.012, respectively). During follow-up, n=22 subjects (of the 70 non-depressed at baseline) developed depression. Baseline CRP values were significantly higher in depressed patients vs. non-depressed, at each time-point from 18 to 36 months (percent difference ranging from 135 to 179%, p-values from 0.008 to 0.025). VEGF values were significantly higher in patients with an early-onset (≤6 months) depression vs. non-depressed (+168%, p=0.022). Both CRP and VEGF values were higher in patients who developed long-lasting (>18 months) depression (+133%, p=0.044 and +168%, p=0.022) vs. non-depressed, and with trend-level differences vs. those with shorter depression (p=0.051 for CRP and p=0.065 for VEGF).

Conclusions: Inflammation in CHD patients is associated with future development of depression. It is therefore crucial to identify reliable and ready-to-use biological markers of inflammation suitable for everyday clinical practice. The identification of depression high-risk phenotypes among CHD patients could allow targeted and patient-tailored interventions, finally improving clinical outcomes.
Funding: This research was funded by the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at South London and Maudsley National Health Service (NHS) Foundation Trust and King's College London; the UPBEAT Programme of research (which included this cohort) was funded by the NIHR Programme Grants for Applied Research Programme (PGfAR). These funders had no further role in study design, or in the collection, analysis and interpretation of data.

G25
A COMPARISON OF SHORT- AND LONG-TERM CORTISOL LEVELS IN MELANCHOLIC AND NON-MELANCHOLIC MAJOR DEPRESSIVE EPISODES USING HAIR AND SALIVA SPECIMENS
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Introduction: Inconsistencies remain in the research literature regarding cortisol concentrations in Major Depressive Episodes (MDE). Heterogeneity in symptom profiles, severity and the nature of cortisol specimens may underlie these diverse findings. Furthermore, some recent reports suggest that less severely ill outpatients with non-melancholic features of MDE (NM-MDE) may have a variation in the rhythm of cortisol secretion rather than in its concentration per se.

Methods: Cortisol measures were taken (1) over a short-term period (12 hours) by measuring daily salivary output using the area under the curve with respect to the ground (AUCg) and (2) over a long-term period (three months) in hair. In addition, cortisol reactivity measures in saliva – the cortisol awakening response (CAR) and the 30-minute peak cortisol secretion after awakening (PEAK) – were investigated in 19 patients with melancholic MDE (M-MDE, comprising DSM-5 psychotic and melancholic subtypes) and 52 with NM-MDE, and in 40 matched controls. Depression severity scores, from the 17-item Hamilton Depression scale (HAMD-17), were correlated with the cortisol measures to investigate the relationship between severity of depression and cortisol levels.

Results: The NM-MDE group showed a decreased daily salivary output in comparison to controls (p=0.01), but normal cortisol reactivity and long-term cortisol levels in hair. The M-MDE group did not exhibit any significant cortisol alterations nor association with severity scores. However, higher HAMD-17 score was linked with decreased long-term secretion (p=0.05) and higher early morning peaks (p=0.04) of cortisol levels in NM-MDE.

Conclusions: Cortisol alterations were more apparent in NM-MDE than M-MDE amongst moderately depressed outpatients. The contrasting findings in NM-MDE of reduced short term but normal long term cortisol output are compatible with an alteration in the rhythm of cortisol secretion.

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G26
MEASURING THE AVERAGE CORTISOL CONCENTRATION USING EARWAX
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Introduction: The depressive diagnostic is considered less than fully reliable. This may be explained by the large heterogeneity of this syndrome. One accurate biomarker may improve the consistency of this diagnosis. Cortisol has normally been measured aiming it since it is the most frequently found neurobiological alteration in Major Depressive Episodes (MDEs). However, cortisol levels using “short-term” specimens have been very diverging, due to the reactive hormone secretion profile. These specimens are not the most appropriate for reflecting the chronic cortisol concentration because several acute influences affect their levels. Currently, hair is used for measuring its long-term level. However, its widespread use appears unrealistic. Instead, earwax may be a more convenient and accurate specimen for reflecting the average cortisol concentration over different periods. Earwax analysis using Trears may be more expeditiously analysed than hair cortisol.

Methods: The right ear of 37 healthy participants were cleaned using a clinical procedure. One month after, earwax samples were extracted and analysed from the same ear using a self-cleaning outer ear device (Trears). During that visit participants also provided 1 cm of hair that represented the retrospective month of cortisol secretion. Earwax Cortisol Concentration (ECC) and Hair Cortisol Concentration (HCC) were correlated and compared between them. The time needed for analysing ECC and HCC was also compared.

Results: ECC was significantly larger than HCC (p<0.001). ECC and HCC were significantly associated (r=0.39; p=0.03). While males were associated with increased HCC in comparison to females (p<0.001), ECC was not affected by any covariate. Analysing HCC required 4 times more working hours than ECC, due to processing steps that, conversely to earwax analysis, hair sample analysis requires.

Conclusions: In comparison to hair, earwax accumulated more cortisol. Earwax was also a more stable specimen than hair. ECC using Trears was much more expeditiously analysed than HCC. ECC may constitute another accurate, but more affordable and suitable specimen for measuring the average cortisol concentration. ECC may be measured in MDE using Trears.

Funding: This research was funded by private funds generated by AHV and JB. Trears was designed by AHV and JB. The clinical research assistant, the research manager nor the laboratory analyst did not participate in the design of Trears. Similarly, the designers had no role in conducting the research or in the collection and management of the data. Finally, participants were not compensated for taking part in the research.
and the left was again collected using the clinical method. Both follow-up samples represented the same retrospective period of earwax secretion. The weight of both baseline samples and both follow-up samples were compared. Additionally, another comparison between the weight of both samples of each ear side was also conducted. Participants assessed their self-cleaning outer ear experience after the final assessment using a user survey.

Results: The weight of the baseline samples did not vary considerably between ear sides (p>0.05). Both external ear sides significantly increased their earwax production after the baseline cleaning procedure (both p<0.05). Trears was significantly more effective than the Reiner-Alexander syringe for removing earwax (p<0.001). Participants considered Trears as safer and more effective than most commonly used self-cleaning outer ear device, such as cotton swabs.

Conclusions: Trears may provide a more economical, convenient and efficient method for exploring the potential future diagnostic uses of earwax in depression. This device may also provide a safe alternative to cotton swabs.

Funding: This research was funded by private funds generated by AHV and JB. Trears was designed by AHV and JB. The clinical research assistant, the research manager nor the laboratory analyst did not participate in the design of Trears. Similarly, the designers had no role in conducting the research or in the collection and management of the data. Finally, participants were not compensated for taking part in the research.

G28
IDENTIFYING DEPRESSION EARLY IN ADOLESCENCE (IDEA) PROJECT: A SYSTEMATIC LITERATURE REVIEW OF INFLAMMATORY RISK FACTORS FOR THE DEVELOPMENT OF DEPRESSION IN ADOLESCENCE
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Introduction: Youth in low-and-middle-income countries (LMICs), who comprise 90% of the world’s child and adolescent populations, bear the greatest burden of depression (Kieling et al, 2011. The Lancet, 378:1515-25). Therefore, there is a crucial public health need to identify early predictors of depression among adolescents globally. Increasing evidence supports the role of inflammation in the development of depression. The aim of this study was to review existing evidence about association of increased inflammation in adolescent depression.

Methods: In accordance with PRISMA reporting standards, we conducted a systematic review to identify biopsychosocial risk and protective factors for the development of MDD in youth aged 10-24. We used comprehensive search terms across 7 databases (MEDLINE via Ovid, PsychINFO, Cochrane Database of Systematic Reviews, Web of Science, Lilacs, African Journals Online and Global Health) (PROSPERO registration CRD42018103973). Independent raters screened and retrieved articles for inclusion, extracted data, and rated quality with the Systematic Assessment of Quality in Observational Research (SAQOR).

Results: From a total of 4,393 abstracts, 5 articles were eligible for extraction: 3 were longitudinal, 1 cross-sectional, and 1 experimental. The total number of adolescents across all studies was 491, including MDD (1 article) and high-risk individuals (4 articles). High-risk was determined based on family history, cognitive vulnerability and early adversity. All studies came from high-income countries (HICs). Consistent across 4 out of 5 studies, interleukin-6 (IL-6) was measured in relation to depressive symptoms, with two studies reporting positive associations between peripheral levels of IL-6 and depressive symptoms. Interestingly, these effects were observed in adolescents with increased adiposity (b=.01, SE=.004, p=.01), or childhood trauma (CHT) (OR:1.50; CI 95%:1.10,2.06, p=.01). An increase in C-reactive protein in association with development of depressive symptoms was also reported and it was dependent on the higher score in
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CHT (b=0.57, SE:.23, p=.01). Other studies showed positive association between IkB mRNA and depression (r=.20, p<.05), and a negative correlation between depressive symptoms and natural killer cells activity (r=-.28, p=.01).

Conclusions: Increased peripheral inflammation may be important in predicting development of depression in adolescents, specifically in the context of adolescents with CHT or increased adiposity. However, the existing data is extremely limited in number and restricted to HICs. Therefore, the findings need to be replicated, in particular in LMICs, given the extent of adolescent depression burden in LMICs and the lack of research investigating early predictors of depression among adolescents in those countries.

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CHILDHOOD TRAUMA AND ANTIDEPRESSANTS RESPONSE IN PATIENTS WITH DEPRESSION: THE ROLE OF GLUCOCORTICOID RESISTANCE

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Introduction: Childhood trauma is among the most potent contributing risk factors for increased risk for major depressive disorder (MDD) and has been associated with poor treatment response (Williams et al., 2016, Translational Psychiatry, 6:e799). Hypothalamic-pituitary-adrenal (HPA) axis abnormalities and increased inflammation have been linked to both childhood trauma and depression (Nemeroff & Binder, 2014, J Am Acad Child Adolesc Psychiatry, 53:395-7), but the underlying mechanisms of these associations are poorly understood. The present study aimed to investigate the link between childhood trauma, HPA axis activity and glucocorticoid resistance in patients with depression and in relation to response to antidepressant treatment.

Methods: As part of the Wellcome Trust NIMA consortium, 163 depressed patients (42 treatment-responder, 80 treatment-resistant, 41 untreated) and 55 healthy volunteers were included in this study and assessed by Structured Clinical Interview for Diagnostic and Statistical Manual Version-5 criteria for MDD, 17-item Hamilton Rating Scale for depression, and Antidepressant Treatment Response and Childhood Trauma Questionnaires. Serum C-reactive protein and salivary cortisol were measured using turbidimetric detection and ELISA techniques, respectively. The presence of glucocorticoid resistance was defined as coexistence of hypercortisolemia and inflammation.

Results: Our results showed that treatment-resistant depressed patients had higher exposure to childhood trauma than treatment responders (U=1261.00, z=-2.259, p=0.024). No specific HPA axis abnormalities were found to be associated with treatment-resistance. Untreated depressed patients showed an increased diurnal cortisol level compared with those on antidepressant medication (U=1822.50, z=-2.595, p=0.009) and higher prevalence of glucocorticoid resistance than medicated patients and controls (χ²=15.948, p=0.001). The severity of childhood trauma was associated with increased diurnal cortisol levels only in individuals with glucocorticoid resistance (F=34.775, B=0.805, p<0.0001).

Conclusions: Our findings show that the severity of childhood trauma experience contributes to a lack of response to antidepressant treatment. The effects of childhood trauma in increasing cortisol levels are specifically evident in patients with glucocorticoid resistance and suggest glucocorticoid resistance as a target for the development of personalised treatment for the subgroup of depressed patients with a history of childhood trauma rather than for all patients with resistance to antidepressant treatment.
INVESTIGATING THE LINK BETWEEN PERCEIVED STRESS, OBJECTIVE STRESS AND BINGE EATING IN DEPRESSED AND NON-DEPRESSED BARIATRIC SURGERY PATIENTS

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Introduction: Binge Eating Disorder affects a high proportion of bariatric surgery patients in comparison to the general population (Shakory et al., 2015, Appetite,91:69-75). Emerging research suggests perceived stress may be linked to the development of binge eating in individuals across the weight spectrum (Thurston et al., 2018, Eating Behaviour,29:114-119), however only one study has confirmed this in a bariatric sample (Brown et al., 2018, Psychosomatic Medicine,80:A11). To further understanding of the risk factors associated with binge eating, we used a cross-sectional design to investigate the influence of perceived and objective stress on binge eating, in both bariatric surgery patients with depression and without depression.

Methods: Forty-two patients undergoing pre-surgical assessment for bariatric surgery took part in an ongoing study investigating the relationship between obesity and depression. Preliminary analyses have been completed on 19 patients with depression (mean age: 45.5 years; mean BMI: 49.4kg/m²; 58% female) and 23 patients without depression (mean age: 48.6 years; mean BMI: 51.3kg/m²; 48% female). All patients were assessed for depression using the Hamilton Depression Scale with Atypical Supplement (SIGH-ADS), and then completed self-report measures of acute stress (Perceived Stress Scale; PSS), binge eating (Binge Eating Scale; BES), and objective stress (number of negative life events experienced in previous 6-months; Brief Life Events Questionnaire; BLEQ).

Results: The depressed group of bariatric surgery patients had higher depression scores (mean±SEM: 21.00±2.0 vs. 1.71±0.5,p=0.00) and higher levels of perceived stress compared with the non-depressed patients (mean±SEM: 21.74±1.3 vs. 9.87±1.26,p=0.00). There were no significant differences between groups in scores of objective stress (mean±SEM: 0.78±0.2 vs. 1.05±0.3,p=0.64) or binge eating (mean±SEM: 28.39±1.8 vs. 30.84±1.8,p=0.33). Preliminary analyses showed no significant differences between patient groups, however when the whole group was considered, binge eating was associated with higher perceived stress (r=0.35, p=0.03). Binge eating was not associated with higher objective stress (r=0.01, p=0.93).

Conclusions: Our preliminary analyses suggest higher perceived stress is associated with increased binge eating in bariatric surgery patients. Patients with depression may not necessarily have higher levels of stress, but they seem to have an exaggerated response to stress, which could lead to their increased depressive symptoms. This may lead some bariatric surgery patients to participate in binge eating more often, as a coping mechanism for dealing with stress. Further analysis will be completed on a larger sample, providing more accurate insight into whether this link is only present in bariatric patients with depression or associated with perceived stress.

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TREATMENT-RESISTANT DEPRESSION, INFLAMMATION AND SEX DIFFERENCES: NEW INSIGHTS FROM THE BIODEP AND MINDEP STUDY

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Introduction: The incidence of depression is higher in women than in men, and sex differences also affect response to pharmacotherapy. A possible explanation could be the interplay between sex hormones and inflammation in depression. In fact, research has shown not only an association between inflammation and treatment response in depression (Chamberlain et al. 2019. The British Journal of Psychiatry, 214(1), 11-19), but also between inflammation and sex hormones, (Ford et al., 2004 Archives of internal medicine, 164(9), 1010-1014). In order to explore the relationship between inflammation and sex differences in treatment response, we investigated two groups of patients, responders and non-responders, with major depressive disorder (MDD) and have increased levels of inflammation (C-reactive protein, CRP >= 1 mg/L).

Methods: We merged data from two studies investigating inflammation in MDD population (n=132, BIODEP and MINDEP studies). A series of independent sample T-tests have been run to compare Log Natural transformed CRP means, firstly between non-responders (n= 100, Hamilton depression scale (HAMD) >= 14) and responders, (n= 32), and secondly between females and males, between and within groups.

Results: As expected, the analyses show significantly higher CRP levels in non-responders than responders (1.58 vs 1.27, t-value (130) = -2.24, p= 0.027). Specifically, female non-responders (n= 66) show a statistical trend for a higher CRP levels than females responders (n= 22), (1.69 vs 1.33, t-value (86) =-1.92, p=0.058). However, male patients did not show any difference in inflammation levels between non-responders and responders (1.38 vs 1.13, t-value (42) = -1.36, p= 0.181). Across the whole samples, females have higher CRP than males (1.60 vs 1.32, t-value (130) = 2.14, p=0.034). However, this effect is particularly present in non-responders, where females (n= 65) show higher CRP levels than males (n= 34), (1.69 vs 1.38, t-value (98) = 2.01, p= 0.047), while in responders there is no difference between females and males. This effect is stronger in the more depressed patients (HAMD >= 24), with female non-responders (n=5) have much higher CRP levels than male non-responders (n=12), (1.79 vs 1.12, t-value (15) = 3.12, p= 0.007), even though the sample size is small.

Conclusions: The increased inflammation levels in treatment-resistant depressed (TRD) patients may be driven more by females than males, bringing new insights in tailoring therapies for TRD population.

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INCREASED INFLAMMATION IS ASSOCIATED WITH MEMORY DYSFUNCTION IN FEMALE PATIENTS WITH COMMUNITY-TREATED DEPRESSION: PRELIMINARY RESULTS FROM NORTHERN FINLAND BIRTH COHORT 1966

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**Introduction:** Depression is associated with cognitive dysfunction. However, the underlying mechanisms are yet to be elucidated. Growing evidence suggested that inflammation may moderate the link between depression and cognition. Preclinical studies showed that the pro-inflammatory state could lead to infiltration of cytokines into critical brain structures for memory such as hippocampus (Tang et al. 2016). Depressed patients with high baseline inflammatory markers showed persistent cognitive dysfunction (Chang et al. 2012). Inflammation may be a potential target for treatment as a mediator of cognitive dysfunction in depression. In this study, we investigated the links between depression, memory, and inflammation in a population-based sample.

**Methods:** Data from Northern Finland Birth Cohort 1966 were used. CANTAB Paired Associates Learning (PAL) Test scores at the age of 46 were the main outcome. We used measures of C-reactive protein as the index of inflammation, and the self-reported depressive symptoms as measured by Symptoms Checklist-25. Psychiatric diagnosis data were obtained from National Register of Finland that were matched to the cohort data. Patients with confirmed diagnosis of depression were included in the analysis. We used regression models using PAL scores as dependent measures and CRP measures as the predictor.

**Results:** Patients with a history of depression showed poorer performance in CANTAB PAL test (first trial memory score) (p=0.007; df=1,4023; F=7.372). Self-reported depressive symptoms were also associated with more errors in the PAL (p=0.001; df=111,5227; F1,482). Elevated CRP levels were found in patients with a history of depression and in participants with higher depressive symptoms. Regression models showed that inflammation contributed to the association between depression symptoms and memory dysfunction only for female patients (p=0.028; df=2,3014; F=3.584) but not male patients (p=0.57; df=2,2265; F=0.563).

**Conclusions:** The results from an unbiased population-based birth cohort showed that depression was associated with poorer memory functions. Increased inflammation predicted the link between depression and memory in women only. The confounding factors such as medication and physical health will be examined in further analyses. These preliminary results indicated that pro-inflammatory state may be a contributory factor in cognitive dysfunction in depression.

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MATERNAL ANTENATAL DEPRESSION IS ASSOCIATED WITH SUBOPTIMAL FOETAL GROWTH AND NEONATAL NEUROBEHAVIORAL DEVELOPMENT

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**Introduction:** Maternal antenatal depression is associated with suboptimal neurobehavioural outcomes in the offspring as a neonate. As these effects are observed so early in life, they may be as a result of pre-birth factors. One proposed mechanism, which is possible to measure, is slower foetal growth. This could be an important method to identify children at-risk of neonatal neurobehavioural difficulties as early as at antenatal ultrasound scans. This study uses the Psychiatry Research and Motherhood-Depression (PRAM-D) cohort to first investigate the association between depression and slower foetal and neonatal
development, and then looks at associations between foetal and neonatal development.

Methods: Women recruited into the PRAM-D cohort were grouped according to depression diagnosis, using the Structured Clinical Interview for DSM-IV: no current or past history of depression (‘control’) or antenatal depression (‘case’). Foetal measurements were obtained from the routine ultrasound scan (20±3 weeks). Neonatal neurobehavioural development was measured using Brazelton’s Neonatal Behavioral Assessment Scale at around 6 days post-birth.

Results: In this sample, mothers with antenatal depression were routinely seen for their ultrasound scan around 1 week earlier than the control group, so this was included as a covariate in analyses. After controlling for gestational age at scan, the foetal head circumference measurement was significantly lower in those experiencing antenatal depression when compared with healthy controls [EM mean(SE): 192.34(0.86) vs. 195.53(0.90), F=3.12, p=0.047]. Post-birth, neurobehavioural scores were significantly lower in the infants of antenatally depressed mothers, on scales including social interaction [mean(SE): 6.33(0.20) vs. 7.47(0.16), X2=26.2, p<0.001], regulation of state [5.53(0.21) vs. 6.37(0.17), X2=8.69, p=0.013], and autonomic stability [5.24(0.13) vs. 6.13(0.15), X2=15.41, p<0.001]. Finally, foetal head circumference was positively correlated with neonatal social interaction scores [r=0.243, p=0.005; r=0.294, p=0.001], suggesting that the smaller the head circumference, the poorer the social interaction, and that this might be a potential mechanism linking antenatal depression to suboptimal neonatal function.

Conclusions: These data indicate that antenatal depression is associated with slower foetal growth at around 22 weeks and subsequent poorer early neurobehavioural functioning in the offspring, on a number of scales. We also show that foetal head circumference is associated with subsequent post-birth social functioning. This suggests that antenatal ultrasound scans might be an important timepoint at which babies at-risk of poor early neurobehavioural development might be identified, in order that resources and interventions are targeted at those most in-need.

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THE ROLE OF PSYCHOPHARMACOLOGICAL TREATMENTS IN THE RISK OF CONVERSION FROM LATE-LIFE DEPRESSION TO DEMENTIA: RESULTS FROM CRIS COHORT

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Introduction: It has been consistently demonstrated that depression increases the likelihood of dementia; however, factors contributing to this association are yet to be established. We evaluated the effect of various groups of psychotropic drugs, as well as other medications commonly prescribed in the elderly, on the likelihood of converting from late-life depression (LLD) to dementia.

Methods: Data was obtained from the Clinical Record Interactive Search (CRIS) system, which is a large database of mental health and dementia care in South London, and linked databases. Using first depression diagnosis after the age of 60, we followed patients until dementia diagnosis, death or censoring. We applied Cox proportionate hazard models to evaluate potential predictors, which were adjusted for baseline demographics, baseline cognition, and each item of the HoNOS 65+ scale.

Results: We identified 4297 cases of LLD, of which 1152 patients received a diagnosis of dementia during follow-up. Of our sample, 2165 (50.38%) were treated with SSRIs, 563 (13.10%) with SNRIs, 535 (12.45%) with TCAs, 968 (22.53%) with antipsychotics, and 161 (3.75%) with lithium. In fully adjusted models, only antipsychotics increased the risk of conversion (HR 1.23 (1.044-1.45), p< 0.013); no group of medication showed a protective effect. TCAs did not increase the risk of conversion in any of the models. When physical medication (antilipid, antihypertensive, anticoagulant/antiplatelet, antihyperglycaemic)
was included in the analysis, the effect of antipsychotics was no longer significant. At the same time, anticoagulant/antiplatelet medication (HR = 1.22, CI = 1.03, 1.44, p = 0.018) and antihyperglycaemic medication (HR = 1.35, CI = 1.08-1.7, p =0.01) increased the risk of dementia.

Conclusions: In the CRIS cohort, the risk of conversion from depression to dementia was only increased by antipsychotic drugs before adjusting for physical medication. TCAs or lithium did not influence the risk of conversion. Of physical medication, anticoagulant/antiplatelet and antihyperglycaemic medication increased the risk of conversion to dementia in a fully adjusted model. Further analysis may be needed to explore the role of physical conditions and combinations of medication on the likelihood of converting from late-life depression to dementia.

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A PATIENT-REPORTED MEASURE OF DEPRESSION REMISSION CORRELATES WITH A CLINICIAN-REPORTED MEASURE OF DEPRESSIVE SYMPTOMS IN A PIVOTAL MAJOR DEPRESSIVE DISORDER TRIAL OF SAGE-217

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Introduction: Major depressive disorder (MDD) is estimated to affect over 300 million people worldwide. In clinical trials, remission is typically defined based on clinician-reported symptom severity scales. Patients may have a broader conceptualization of treatment goals, including a return to usual level of functioning, improvements in positive mental health features, and a return to one’s normal self. To ensure quality care, it is important to confirm that clinicians’ perceptions of remission and patients’ perceptions of remission align. Correlations between symptom-based and patient-reported measures of remission were examined in post hoc exploratory analyses from a pivotal study of the oral GABA-A receptor positive allosteric modulator SAGE-217 in MDD.

Methods: Subjects of both sexes, ages 18–65, with unipolar depression and a Hamilton Rating Scale for Depression (HAM-D) total score ≥22 were randomized 1:1 to receive SAGE-217 or placebo for 14 days, with 4 weeks of follow-up. Efficacy measures, including HAM-D total score (remission defined as score ≤7) and the patient-reported Remission from Depression Questionnaire (RDQ; remission defined as score ≤27), were assessed. Pearson correlations were calculated between RDQ and HAM-D measures for all subjects. Adverse events (AEs) were reported through Day 42.

Results: The primary endpoint of the trial demonstrated a significant improvement for subjects treated with SAGE-217 (N=45) versus placebo (N=44) at Day 15 in HAM-D total score (p <0.001); the proportion of subjects achieving HAM-D remission was also significantly higher for SAGE-217 (p<0.001). At Day 15, SAGE-217 was associated with improvements in RDQ total score (p=0.004) and 6 of 7 RDQ domains (p<0.05), and RDQ remission rates were 45% and 24% for the SAGE-217 and placebo groups, respectively. Post-hoc analyses of all subjects (N=89) showed that change from baseline at Day 15 in RDQ total score was moderately correlated with change from baseline in HAM-D total score (0.662); at Day 42, the two were highly correlated (0.730). At Days 15 and 42, there was 73.2% and 84.6% overall concordance between subjects with HAM-D remission and RDQ remission (p<0.01, both time points). The most common AEs (≥5%) in the SAGE-217 group were headache, nausea, dizziness, and somnolence.

Conclusions: In this pivotal trial, SAGE-217 resulted in statistically significant improvements in depressive symptoms and patient-reported measures of depression and was generally well-tolerated. Patient-reported measures of remission were positively correlated with clinician-reported measures. High concordance between patient and clinician recognition of remission was observed, indicating consistency in recognition of improvement aligned with treatment goals.

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A SYSTEMATIC REVIEW OF PHARMACOLOGICAL AUGMENTATION TREATMENT GUIDELINES FOR UNIPOLAR DEPRESSION

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Introduction: Pharmacological augmentation is a widely recommended treatment strategy for depressed patients who have inadequately responded to antidepressant monotherapy. Clinicians may refer to a range of guidelines for advice on treatment selection, prescription, monitoring and discontinuation, each compiled by a different group or governing body, using varying methodologies. It is therefore plausible that the quality and content of recommendations may vary across guidelines, potentially limiting the ability of clinicians to offer objective, evidence-based care. This is of particular importance for augmentation, given the greater side effect burden associated with polypharmacy and poorer long-term outcomes associated with treatment-resistance. This systematic review sought to review the quality of all treatment guidelines for major depression and to compare the augmentation recommendations made by those deemed to be of a sufficient standard.

Methods: A systematic literature search was conducted to identify guidelines published in English between 26.07.2008 and 26.07.2018. Current versions of guidelines relating to the management of unipolar depression using pharmacological augmentation were quality assessed using the AGREE II tool. Data relating to the prescription of pharmacological augmenters were extracted from guidelines deemed to have been developed with sufficient rigour according to the AGREE II, and were narratively synthesised.

Results: 1467 records were identified by the search, 20 eligible guidelines were assessed for quality, 11 were sufficient for inclusion, with a mean domain score of 77% (SD=15.89) on the AGREE II. Guidelines differed in their definition of resistant depression and the stage at which they recommended the use of augmentation strategies, as well as the pharmacological agents recommended and the literature on which recommendations were based. Lithium and atypical antipsychotics were the only treatments to be recommended by all 11 guidelines, while ketamine was only recommended as a second-line option by one (the Maudsley Prescribing Guidelines) and as an experimental/specialist option in two (Institute for Clinical Systems Improvements and the Canadian Network for Mood and Anxiety Treatments).

Conclusions: There is a clear need for greater consistency in the quality and content of current guidelines for pharmacological augmentation in unipolar resistant depression. Although some inconsistencies can be accounted for by varying dates of guideline publication, and therefore differences in available literature, variation in the interpretation of research was also apparent. This was particularly evident for STAR*D study results, as the same reports were often used to support different levels of recommendation (i.e. first-line, second-line, or other) for one augmenter.

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AUGMENTATION THERAPIES FOR TREATMENT-RESISTANT DEPRESSION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: Depression is now considered to have the highest disability burden of all conditions. Although treatment-resistant depression (TRD) is a key contributor to that burden, there is little understanding of the best treatment approaches for those who do not respond adequately to first-line treatments and specifically the effectiveness of available augmentation approaches. We conducted a systematic review and meta-analysis aiming to quantify and qualify the evidence of psychological and pharmacological augmentation interventions for TRD.

Methods: Trials where patients with TRD were randomised to at least one augmentation treatment were included, where treatment-resistance was defined as insufficient response to at least two antidepressant treatments in the current episode. Pre-post analysis assessed treatment effectiveness, providing an effect size (ES) independent of comparator interventions.

Results: Of 28 included trials, only 3 investigated psychological treatments, while 25 examined pharmacological interventions. Assessing treatment classes, pre-post analyses demonstrated N-methyl-D-aspartate targeting drugs to have the highest effect size (ES=1.48, 95%CI 1.25–1.71). Other than aripiprazole (4 studies, ES=1.33, 95%CI 1.23-1.44) and lithium (4 studies, ES=1.05, 95% CI 0.83-1.26), treatments were each investigated in less than three studies. Overall, pharmacological (ES=1.22, 95%CI 1.10-1.33) and psychological (ES=1.08, 95%CI 0.48-1.69) therapies outperformed pill placebo (ES=0.78, 95%CI 0.65-0.91) and psychological control (ES=0.71, 95%CI 0.34-1.08).

Conclusions: Despite being used widely in clinical practice, the evidence base for augmentation treatments in TRD is sparse. This meta-analysis finds promising evidence across treatment modalities but indicates that the effectiveness of interventions less than four weeks (excluding ketamine) are similar to placebo.

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COGNITIVE REMEDATION THERAPY CONFERS BROAD BENEFITS TO EUTHYMIC PATIENTS WITH BIPOLAR DISORDER

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Introduction: A significant proportion of people with bipolar disorder experience cognitive impairments which hinder functioning and may increase susceptibility to relapses (Miskowiak et al., 2018). Bipolar disorder has been referred to as a “neuroprogressive” condition (Passos et al., 2016), but preliminary research suggests that cognitive function can be restored and even enhanced.

Methods: We present findings from a pilot randomised controlled trial of cognitive remediation therapy (CRT) for patients with bipolar disorder in a euthymic state (the “CRiB” trial; Strawbridge et al., 2016).
Patients were randomly allocated to receive a 12-week course of CRT in addition to treatment-as-usual (TAU), or to TAU alone.

Results: 60 patients participated in the CRiB trial (CRT+TAU n=29; TAU n=31). Fewer patients withdrew from the CRT than TAU arm (7% vs 16% respectively) and CRT satisfaction ratings were high, indicating that this therapy is both feasible and acceptable. Intention-to-treat analyses demonstrated improvements after the intervention period that were maintained 3 months later: Participants randomised to CRT improved more than the TAU group in domains of intellectual functioning (SES=0.71, 95% CI 0.29 to 1.13, p=0.001), working memory (SES=0.70, 95% CI 0.31 to 1.10, p=0.001), executive function (SES=0.93, 95% CI 0.33 to 1.54, p=0.003), everyday functioning (SES=0.49, 95% CI 0.18 to 0.80, p=0.002) and goal attainment (SES=2.02, 95% CI 0.89 to 3.14, p=0.001).

Conclusions: Cognitive remediation offers promising effects for enhancing cognition and functioning, although the trial was not powered to detect significant group differences. Effect sizes permit an informed power calculation to be undertaken for a future, more definitive trial.

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G39

SYMPTOM EFFECTS OF CAFFEINE INTAKE IN PATIENTS WITH BIPOLAR DISORDER: A SYSTEMATIC REVIEW

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Introduction: In healthy populations, caffeine appears to have beneficial effects on health; however, patients with bipolar disorder are routinely advised to limit caffeine use in psychoeducation programmes. We aimed to examine all literature reporting whether caffeine intake/withdrawal impacts the natural course of bipolar disorder, in terms of clinical outcomes.

Methods: Studies reporting data on individuals with bipolar disorder comparing a measure of caffeine use with illness severity (symptoms of mania, depression, psychosis, anxiety or suicidality) were included. PubMed, Embase and PsycINFO were searched (up to 01/12/2018) using the search terms: (caffeine or coffee or energy drinks or tea or soda or cola or coke or methylxanthine) and (bipolar or suicide or manic or mania or lithium).

Results: From 1845 articles identified, 17 were included in our systematic review (11 case reports, 5 case-control/cohort, 1 interventional study). Of the case studies, 2 reported patients with a diagnosis of bipolar disorder switching to a manic/mixed state after acutely increasing caffeine intake, 1 described an individual able to taper off psychotropic medications after stopping caffeine and 4 related increases in plasma lithium concentration after decreasing caffeine. The largest cohort study found that coffee drinkers were more than twice as likely to exhibit suicidal behaviour than non-drinkers, while a smaller study showed greater caffeine usage among bipolar patients with mixed states than those with uncomplicated clinical presentations. One further study showed no significant association between caffeine use and time to recover from a depressive episode, time to switch or time-to-relapse following recovery. The only interventional study found that a caffeine-free diet increased lithium blood levels, with 73% of patients showing a 24% increase in lithium blood levels.

Conclusions: The results of this systematic review are inconclusive, mainly due to a scarcity of studies and absence of trials assessing caffeine effects on clinical outcomes such as mania and suicidality, acutely and...
in the long-term. Most studies are case reports of acute manic episodes developing after a sudden increase in caffeine intake. A preliminary conclusion is that acute increases in caffeine consumption may precede the occurrence of manic episodes in patients with bipolar disorder, potentially through a direct stimulant effect and/or affecting the metabolism of lithium. Conversely, in light of the few long-term studies and inconsistency of results, further research is needed to determine whether caffeine use impacts the long-term prognosis of bipolar disorder.

Funding: This study represents independent research part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at South London and Maudsley National Health Service Foundation Trust (SLaM) and King's College London. The NIHR BRC had no involvement in study design, data collection, analysis or the decision to submit for publication. The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health.

G40

A META-ANALYSIS FOR THE ONSET OF ACTION OF QUETIAPINE IN THE TREATMENT OF BIPOLAR DISORDER

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Introduction: Bipolar Disorder is a major mental health problem and quetiapine is increasingly employed in its management. Rapid improvement in symptoms from episodes of illness is an important treatment goal. Here we evaluated evidence from randomised controlled trials to assess the extent of any early action of quetiapine on episodes of bipolar depression. This meta-analysis aimed to characterise efficacy of quetiapine as a treatment for bipolar depression, and by conducting weekly analyses, to determine when clinical effects are first observed.

Methods: Randomised controlled trials of quetiapine versus placebo in the acute treatment of bipolar depression were identified from a previous systematic review updated with searches of Medline, Embase, PubMed and Google Scholar. To conduct the meta-analysis, pooled effect sizes for the change in the primary efficacy variable, Montgomery-Åsberg Depression Rating Scale, were calculated using a random-effects model. Then, separate meta-analyses were conducted per week to determine by which week an effect was seen.

Results: Out of 467 papers identified, six studies met the criteria for inclusion. The number of patients taking a dose of 300mg or 600mg was 1991, with 886 patients randomised to placebo. At week one, using a random-effects model there was a pooled mean difference of -2.57 (95% confidence intervals of -3.33 and -1.81) between the quetiapine treatment group and placebo with a Cohen’s d of -0.32. After the treatment period, at week eight there was a pooled mean difference of -4.03 and a Cohen’s d of -0.37.

Conclusions: The use of quetiapine in the treatment of bipolar is efficacious, with a substantial effect experienced by the first week. This is significant in the treatment of bipolar as a viable treatment option. Moreover, this early benefit experienced by patients will contribute to their long-term physical and psychological well-being.

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EXPLORING WORKING MEMORY, IMPULSIVITY, AND EMOTION RECOGNITION AS POSSIBLE COGNITIVE BIOMARKERS IN ANXIETY AND DEPRESSION

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Introduction: Anxiety and depression have been shown to be associated with impairments in cognitive functioning. Understanding the nature of these deficits may allow for the identification of cognitive biomarkers and targets for clinical intervention. The aim of this study was to investigate the cross-sectional associations of anxiety and depression with three domains of cognition (impulsivity, working memory, and emotion recognition) in a large UK-based population cohort.

Methods: We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) to investigate associations between mental health and cognition at 24 years (n ~ 3380). Anxiety and depression were assessed through the Revised Clinical Interview Schedule (CIS-R; Lewis et al., 1992, Psych. Medicine, 22, 465-486). Working memory, impulse control, and emotion recognition were assessed using three computer-based tasks (the n-back, stop-signal, and 6 alternative forced-choice emotion recognition tasks, respectively).

Results: Linear regression analyses provided weak evidence for anxiety status being positively associated with impulsivity (b = 4.72, 95% CI = -0.59 to 10.02, p = 0.08) and strong evidence for being negatively associated with working memory ability (b = -0.11, 95% CI = -0.19 to -0.03, p = 0.005), after adjusting for age and sex. We observed a similar pattern of results for depression status: impulsivity (b = 5.47, 95% CI = -0.38 to 11.32, p = 0.07) and working memory (b = -0.08, 95% CI = -0.17 to 0.01, p = 0.07), although the evidence for working memory was considerably weaker than for anxiety. There was no clear evidence for an association between emotion recognition ability and either anxiety or depression.

Conclusions: Both anxiety and depression were associated with poorer performance on cognitive tasks assessing impulse control and working memory. However, performance on an emotion recognition task did not appear to be significantly disrupted. These associations will now be subject to prospective analyses and Mendelian Randomization analyses in order to investigate causality. Results will inform the development of targeted cognitive interventions for mood disorders.

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PATIENT OWN RATINGS OF SUPPORT IN FAMILY PRACTICES IN ENGLAND RELATED TO ANTIDEPRESSANT PRESCRIBING. IS THIS CHOOSING WISELY?

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Introduction: The interaction that people experience with the NHS in terms of management of mental health conditions is very variable. Using the UK National Patient Survey we previously showed in family (general practitioner) practices a strong link between positive patient ratings for long term condition (LTC) care and better glycaemic control (Heald AH, Stedman M, Farman S et al. Br J Gen Pract 2018; 68:320).

Methods: We examined at 5,700 practices serving a England population of 50 million, of these 800,000 patients completed the survey, of these 46% responded “Very Good” to overall experience, 43% Yes definitely to if enough support was provided, and 30% very confident manage the issues. The annualised Defined Daily Dose DDD of anti-depressants and anxiolytics were divided by practice population to give the average medication use. These were compared both uni-variately and multi-variately.
Results: 5,100,000 ADD of 28 anti-depressants (Citalopram and Sertraline made up 52%) and 690,000 ADD of 22 anxiolytics/hypnotics (Zopiclone and Diazepam made up 54%) were prescribed. Allowing for local practice situation demographics, locations and comorbidities, analysis showed that GP practices with higher ratings for patient overall experience prescribe upto 10% MORE anti-depressants while practices with higher ratings from patients on confidence in self management of long term conditions. prescribe upto 20% LESS antidepressant.

Conclusions: These findings raise important questions as to how the doctor/patient relationship and how patient perception of that relationship drives drug prescribing. Positive patient perception of clinical care seemingly links to higher levels of anti-depressants prescribing. While confident patients require Less Are physicians supporting their patients to choose their treatment wisely?

Funding: There was no external funding for this study.

**G43**

**COULD THE HIGH GROWTH IN THE USE OF ANTI-DEPRESSANT IN PRIMARY CARE BE LINKED TO THEIR REDUCING UNIT COSTS?**

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Introduction: In 3 years from 2014_15 to 2017_18 in GP practices in England there was a 37% rise in number being recorded on the depression register and 22% rise in total doses of anti-depressants. Total costs of anti-depressants have fallen 15%, a reduction in unit cost of 35%. The total number of different unique anti-depressants at different dose levels has increased from 94 to 107. Average anti-depressant prescribing rate (ADPR), Defined Daily Doses of anti-depressant /head population/day, was 0.10 and 90% of practices lie 40%-160% of this value. We used practice variation in ADPR to examine link to variations in practice situation and prescribing selection.

Methods: Collect the nationally public published population demographic, practice characteristics, and prescribing behaviour in each GP practice and year and use multivariate regression analysis to establish link to practice ADPR. Apply regression coefficients to the national change in level of each factor between the years to establish the level of their impact on the change in ADPR.

Results: The overall statistical model accounted for 80% of the variation in ADPR across the 6200 practices in 2017_18, with 2.1 billion doses of anti-depressant prescribed to a population of 52 million. Local location and demographics including age, gender, ethnicity, social deprivation, population density and latitude accounted for 62% of the variation, then including practice profile such as size and levels of comorbidity including depression brought this up to 71% of the variation. The remaining explained variation came from practice prescribing behaviour including number and mix and costs of different ADs being prescribed. Practices with higher cost / dose had lower ADPR; those using higher number of different antidepressants had higher ADPR. Applying the regression coefficient for these factors to the change in unit cost and mix of antidepressant over the last 3 years showed that 49% of the increase in ADPR could be linked to increasing use of lower costs and variety of anti-depressants.

Conclusions: This analysis highlights the opportunity to review the ADPR in each practice reducing variation by optimising their prescribing range. This has implication for local clinical behaviour and medicines management across a locality. These results represent a benchmark against which GP practices can establish their baseline ADPR incorporating their local demographic and practice profile; and then consider mix and relevance of the various anti-depressants so as to improve their relevant prescribing protocols.

Funding: No external funding was used for this project
H01
EVALUATION OF TSPO PET LIGAND BINDING CHARACTERISTICS TO DIFFERENT CELL TYPES IN NEUROINFLAMMATION

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Introduction: PET imaging with tracers binding to TSPO, or the 18kDa Translocator protein is a useful tool to assess neuroinflammation in the human brain. TSPO is commonly utilised as a biomarker of neuroinflammation or microglia activation. However, this is controversial as TSPO is present in various CNS and non-CNS cell types including microglia, astrocytes, endothelial cells, macrophages & platelets, which subsequently complicates the interpretation of data captured with TSPO PET imaging agents from a neuroinflammatory perspective (Turkheimer et al., 2015, Biochem Soc Trans, 43(4): 586–592). We have recently confirmed that [18F] DPA714 PET, one of the second generation TSPO PET tracers, is a useful tool for imaging the effect of subtle neuroinflammatory responses in the CNS. The aim of this study was to characterise the contribution of different cell types to the TSPO PET signal in a rat model of low level neuroinflammation induced by a systemic injection of LPS.

Methods: This study was ethically reviewed and conducted in accordance with Animals (Scientific Procedures) Act 1986 and the GSK Policy on the Care, Welfare and Treatment of Animals. Male Sprague Dawley rats were injected with either LPS (0.5mg/kg, ip., n=6) or vehicle (PBS, n=6) and 24 hours later quantitative RT-PCR was performed to measure the mRNA expression of different cell types specific genes (Iba1, P2ry12, Sall1, MCP-1, ICAM-1, Ly6c and CCR2) to assess the neuroinflammatory markers induced by systemic LPS. RNAscope technology for TSPO was used to co-localise TSPO to evaluate TSPO expression in the different cell-types and better understand the TSPO PET signal induced by systemic administration of LPS.

Results: Systemic administration of LPS significantly increased the expression of TSPO (p<0.0001) and PU1 (p=0.0104) in the hippocampus. In addition, a reduction of the specific resting microglia marker P2ry12 was found 24 hours after systemic LPS administration (p=0.0065). These results suggest that the increased TSPO overexpression in the hippocampus could be due to a proliferation or activation of microglia. TSPO was found to be co-localized in both Iba1+ cells and Iba1- cells in the vehicle-treated rats, however, LPS caused an increased number of TSPO+Iba1+ cells and TSPO+iba1- cells in the hippocampus. Sidak's post hoc multiple comparisons showed that this effect induced by LPS was only statistically significant in TSPO+Iba1- cells after LPS treatment compared to vehicle (p=0.0135).

Conclusions: We conclude that an important contribution of other glial and non-glial cells needs to be considered when assessing neuroinflammation with TSPO PET tracers.

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H02
EVALUATION OF [18F] DPA714 TSPO PET IN A RAT MODEL OF NEUROINFLAMMATION

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Introduction: The aim of the study was to evaluate the utility of in vivo TSPO PET imaging in a rat model of low level neuroinflammation induced by a systemic injection of LPS and increase our understanding of the cell types contributing the TSPO PET signal.

Methods: This study was ethically reviewed and conducted in accordance with Animals (Scientific Procedures) Act 1986 and the GSK Policy on the Care, Welfare and Treatment of Animals. To assess neuroinflammation we used the second generation TSPO tracer \([18F] \text{DPA714}\), first in the rat model of intracranial LPS (ic; which is known to induce a robust focal neuroinflammatory reaction; (Espinosa-Oliva et al., 2013, Methods Mol Biol, 1041:295-305) and secondly in a more physiologically relevant model of neuroinflammation, in rats systemically injected with LPS. For the intracranial LPS model, male Sprague Dawley rats were treated with unilateral stereotaxic injection of LPS (1ug) into the right striatum (n=3), and for the systemic LPS model, rats were injected with either LPS (0.5mg/kg, i.p. n=8) or Vehicle (PBS, n=8).

Results: Four days following ic. lesioning, in vivo nanoPET data demonstrated a significantly higher uptake of \([18F] \text{DPA714}\) in the LPS-injected side vs the non-injected side in AUC for TACs (p=0.0038). \([18F] \text{DPA714}\) nanoPET in the systemic LPS rat model showed an increased uptake in the LPS-treated group across all regions 24 hours after LPS. Sidak's Post-hoc multiple comparisons showed that olfactory bulb, hippocampus, mid brain, ventricles, white matter and cerebellum had a significant higher activity in LPS-treated rats compared to vehicle (>20%). No difference in peripheral distribution of the tracer was found between the LPS- and vehicle-treated groups. Ex vivo \([3H] \text{PBR28}\) autoradiography showed an increased binding in all the regions analyzed in the LPS-treated rats compared with vehicle. Two-way ANOVA showed a significant effect of ROI (F (7, 80) = 20.4; P<0.0001), treatment (F (1, 80) = 22.49; P<0.0001), however no significant interaction between ROI and treatment was found (F (7, 80) = 1.802; P=0.0982) on \([3H] \text{PBR28}\) binding.

Conclusions: In conclusion, imaging the effect of subtle neuroinflammatory responses in the CNS may be detected utilising \([18F] \text{DPA714}\) PET. Further analysis of the contribution of different cell types to the overall TSPO PET signal is ongoing to accurately characterize TSPO as an imaging marker in neuroinflammation.

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H03

MICROGLIA ACTIVATION FOLLOWING INTERFERON-ALPHA: A MODEL OF IMMUNE DEPRESSION? A TSPO PET STUDY IN HEALTHY HUMANS

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Introduction: Investigating the role of the immune system in the pathogenesis of depression, offers the opportunity to identify new therapeutic targets. Despite peripheral inflammation has been clearly associated with depression (Baumeister et al. 2014, Soc Psychiatry Psychiatr Epidemiol, 49: 841-9) its link with neuroinflammation remains unclear. We used the TSPO binding, Positron Emission Tomography (PET) tracer \([11C] \text{PBR28}\) to examine microglia activation, the core process of neuroinflammation, in 7 healthy males, following the peripheral immune challenge, Interferon-alpha (IFN-alpha). We then explored the association between microglia activation, peripheral inflammation and mood changes.

Methods: We recruited 7 (mean age: 30.1±6.4 years) high-affinity binders for the rs6971 polymorphism in the TSPO gene (Guo et al. 2012, Neuroimage, 60: 902-10). Each participant had 2 PET scans, before and ~24 hours after the IFN-alpha 2a, 3 million units, injection. The radioligand volume of distribution (VT)
across the brain was calculated with 2-tissue compartmental models (Rizzo et al. 2014, J Cereb Blood Flow Metab, 34: 1060-9). At different timepoints, we measured serum peripheral inflammatory biomarkers (inflammatory cytokines, high sensitivity C-reactive protein-hsCRP-and kynurenine pathway metabolites) and mood state profiles.

Results: Changes of brain PET signal were variable across subjects. From baseline to 24 hours after IFN-alpha, we found an average decrease in VT (whole brain DeltaVT =-20±11%, paired t test p=0.01). Interestingly, such decrease was no longer significant after correction for the portion of radioligand unbound to plasma proteins (fp) (paired t-test p=0.91). By contrast, in all subjects, hsCRP was steady from baseline to 6 hours after IFN-alpha (mean increase±SD: 0.3 ±0.5 folds) and increased significantly at 24 hours (mean increase±SD: 13.2±12.1 folds). There was no significant correlation between changes in hsCRP and changes in VT. Finally, inflammatory cytokines levels and depressive-like symptoms scores significantly peaked at 4-6 hours after the challenge.

Conclusions: In this study, IFN-alpha administration was associated with increased peripheral inflammation and with acute mood changes. By contrast, the neuroinflammatory response was heterogeneous. Moreover, changes of TSPO brain PET were sensitive to plasma tracer binding. Indeed, the Vt decrease in the second PET scan could be an artefact of the interaction between the radioligand and plasma proteins, increased following IFN-alpha. This could have wider implications for the field, especially for those studies measuring TSPO binding which have not controlled for this confounder. Further studies should clarify the link between peripheral and central inflammation, how TSPO relates to microglial activation state and how to measure in vivo neuroinflammation.

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**H04**

**EFFECTS OF DIFFERENT STRAINS OF CANNABIS ON BETWEEN-NETWORK INTEGRATION/SEGREGATION, EXAMINED USING RESTING-STATE FUNCTIONAL MRI**

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Introduction: Recent work on serotonergic drugs (psilocybin, and MDMA: Roseman et al., 2014, Frontiers, 8, 204; LSD: Carhart-Harris et al., 2015, PNAS. 113: 4853-4858) has shown that these compounds can have strong effects on the integration/segregation of the brain's Resting-State Networks (RSNs). Such effects are thought to underlie the profound changes in consciousness produced by the classical psychedelics. Cannabis is a widely used recreational drug and also produces alterations in conscious experience, via a different mechanism (CB1 receptors). Recent evidence (Wall et al., In press, Journal of Psychopharmacology) has shown that different strains of cannabis containing different levels of delta-9-tetrohydrocannabinol (THC) and cannabidiol (CBD) have dissociable effects on within-network connectivity in the brain's major resting state networks, however the effects of cannabis on between-network integration/segregation has never been examined.

Methods: This randomized, placebo-controlled, double-blind study assessed the acute effects of two strains of cannabis on inter-network connectivity among twelve RSNs using functional magnetic resonance imaging (fMRI). Seventeen healthy volunteers with previous cannabis experience received acute doses of cannabis (administered via vaporisation) containing THC (8mg THC), cannabis containing THC and CBD (8mg THC + 10mg CBD), or matched placebo, and completed a resting-state fMRI scan (among other assessments). Pre-processing of the functional data followed standard procedures (head-motion correction, spatial smoothing, high-pass filtering, and registration to a standard template), and also included a final step where nuisance variables (six head-motion regressors, plus the mean signal from white matter and
cerebrospinal fluid) were regressed out of the data. Twelve canonical resting-state networks were defined using Independent Components Analysis (ICA) on an independent data set sourced from the Human Connectome Project. Dual regression analysis was conducted to derive subject-specific time-series, and spatial maps of each network. Linear regression resulting in standardized beta values representing the strength of functional integration/segregation was performed on each pair of RSNs time-series, and the comparison between treatments was performed with paired t-tests (corrected for multiple comparisons).

Results: Neither strain of cannabis produced significant effects on between-network integration/segregation of the chosen RSNs, compared to the placebo treatment.

Conclusions: Despite the known effects of cannabis on within-network functional connectivity, acute administration of cannabis had no detectable effect on between-network integration/segregation. This suggests such effects may be unique to serotonergic compounds, particularly the classical psychedelics.

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H05

VISUOSPATIAL LEARNING RELATED BRAIN ACTIVATIONS MODULATED BY THE GLUCOCORTICOID AND PROGESTERONE RECEPTOR ANTAGONIST MIFEPRISTONE

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Introduction: Glucocorticoid receptor (GR) antagonism is a promising novel treatment for cognitive impairments in bipolar disorder. However, the effects of GR receptor antagonism on brain activity associated with cognitive processes are unknown. This study used the GR and progesterone receptor antagonist, mifepristone, to examine how GR antagonism effects the neural correlates of the visuospatial paired associates learning (vPAL) task using functional magnetic resonance imaging (fMRI) in healthy participants.

Methods: 20 right-handed healthy male participants without personal or familial psychiatric history were recruited to this placebo controlled, randomized, double-blind pharmacological fMRI study with a cross-over design. Each volunteer received 600 mg mifepristone or placebo on two separate imaging days. During each imaging session participants completed a vPAL fMRI task approximately 4 hours after taking mifepristone or placebo. fMRI data was analysed separately for the encoding and retrieval aspects of the vPAL task. SPM12 was used for pre-processing and whole brain voxel-wise analyses. Region-of-interest (ROI) analyses were completed using MarsBaR. ROIs were defined as angular and fusiform cortices for encoding, and angular and precuneal cortices for recall, using the peak coordinates of the most significant clusters generated by the main effect of the task. Signal change in the defined ROIs and behavioural data for recall were extracted to SPSS and paired t-tests were used for comparisons.

Results: Mean participant age was 27.3 ±7.7 and mean IQ was 114 ±5.2. Mifepristone administration did not significantly affect the number of correct responses made per recall level or task reaction times (p>0.05). The ROI analysis found that mifepristone administration was associated with significantly decreased fusiform cortex activations in first and second task encoding blocks (p=0.007, t=-3.03, df=19; p=0.031, t=-2.33, df=19). Additionally, mifepristone administration was associated with significant decreases in activation of the angular and precuneal cortices in the first recall block (p=0.017, t=-2.61, df=19; p=0.009, t=-2.88, df=19). There were no significant differences in fMRI brain activations between mifepristone and placebo conditions in the whole brain voxel-wise analysis (p>0.001 uncorrected).

Conclusions: Decreases in vPAL related brain activations associated with mifepristone administration for a similar task performance indicates that mifepristone may improve the neural efficiency of visuospatial encoding and recall.

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H06

EFFECTS OF DIFFERENT STRAINS OF CANNABIS ON THE CONNECTIVITY OF MAJOR SUB-DIVISIONS OF THE STRIATUM, EXAMINED USING RESTING-STATE FUNCTIONAL MRI

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Introduction: Delta-9-tetrahydrocannabinol (THC) is considered the principal psychoactive ingredient in cannabis and may be largely responsible for negative effects of cannabis use (addiction, psychosis). A second cannabinoid, cannabidiol (CBD), is non-intoxicating, may be therapeutically useful, and may buffer the user somewhat against the harmful effects of THC. Recent evidence (Wall et al., in press, Journal of Psychopharmacology) has shown that different strains of cannabis containing different levels of THC and CBD have dissociable effects on functional connectivity in the brain's major cortical resting state networks, but the effects of these different strains has not been examined in sub-cortical regions such as the striatum (where CB1 receptors are heavily expressed; Van Waes et al., 2012, Frontiers in Pharmacology, 3, 21).

Methods: Two strains of cannabis, delivered via vaporisation, were tested against placebo in a double-blind three-way crossover design (N=17). The three treatments were: cannabis containing THC (8mg THC), cannabis containing THC and CBD (8mg THC + 10mg CBD), or matched placebo. After dosing, participants undertook an MRI scanning session that included a 12-minute resting-state fMRI scan, among other assessments. Pre-processing of the data followed current best-practice procedures (head-motion correction, spatial smoothing, high-pass filtering, and non-linear registration to a standard template), and functional connectivity analyses were then conducted using three striatal seed-regions based on the definitions of Martinez et al. (2003, J Cereb Blood Flow Metab, 23, 285-300): the associative, limbic, and sensorimotor striatum. Mean white matter and cerebrospinal fluid signals were included in the analysis models as nuisance regressors, as well as head-motion parameters. Group-level analyses used FSL’s FLAME-1 model, and a threshold of Z=2.3, p<0.05 (cluster-corrected).

Results: All three striatal regions showed decreases in connectivity (relative to placebo) under the active treatment conditions. In the associative and sensorimotor striatum analyses, the two treatments produced broadly similar effects in a set of regions which included the mid-cingulate, pre-motor cortex, and the frontal operculum. In the analysis of the limbic striatum seed-region, no effect was seen for the THC+CBD treatment, while the pure THC treatment produced significant reductions in functional connectivity in the anterior insula and lateral frontal regions.

Conclusions: Cannabis has a strong effect on striato-cortical connections, with reductions in connectivity seen in all three sub-regions. However, dissociable results of the two treatments seen in the limbic striatum may suggest that CBD may mitigate somewhat the disruptive effects of THC, at least in this network.

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H07

KETAMINE, PSILOCYBIN AND LSD ENHANCE THE RESPONSIVENESS OF CORTEX TO INPUT - EVIDENCE FROM FIXED ORDER TIME-SERIES MODELLING OF HUMAN MEG DATA

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Introduction: There is a growing interest in understanding the neurophysiology of psychedelic drugs, including ketamine, psilocybin and LSD and their potential use in the treatment of mood disorders. These drugs each have complex pharmacology and distinct patterns of effects on the cortical M/EEG power
spectrum. Mean field modelling of cortical electrorhythmogenesis has demonstrated that the resting M/EEG can be regarded as arising from cortex linearly filtering white noise input (Liley et al 2003, Physics Review, 68, 051906). As such, the EEG can be modelled as an autoregressive moving average (ARMA) process where moving average parameter estimates can be used to provide estimates of the level of input entering each recorded area (Cortical Input). The autoregressive parameters can be used to estimate Cortical State, a measure of the responsiveness of cortex to input (cortical or subcortical) and also estimates regarding the main oscillations (poles) of the EEG, in particular, the alpha rhythm and its peak frequency and damping.

Methods: We re-analysed data from previously published MEG studies using psilocybin, LSD and ketamine. 275-channel MEG data were recorded in eyes-open resting state conditions on and off-drug. Data were pre-processed and projected into the source space at the 90 centroid locations of the AAL atlas using beamforming temporally downsampled and ARMA(8,5) parameter estimates were calculated for each channel and epoch of data. From these parameter estimates, measures of alpha peak frequency and damping, cortical input (CI) and composite cortical state (CCS) were obtained for both drug and no-drug conditions in each participant. At the group-level, differences were compared using nonparametric permutation testing, with significant results being considered as those where p<.05 after controlling the false discovery rate.

Results: Psilocybin was found to significantly increase CCS, reduce CI, damp alpha frequency poles but not affect their peak frequency. LSD was found to significantly increase alpha pole frequency by ~2Hz with only small damping effects and significantly increase CCS and CI. Ketamine was found to significantly decrease alpha pole frequency and increase damping and CCS but have no effect on cortical input.

Conclusions: Taken together, a common feature of the three psychedelic drugs investigated was to increase cortical state, that is, the responsiveness of the cortex to input. The increased cortical responsiveness to input, from either cortical or subcortical sources, could potentially explain some of the psychological effects of these drugs including, increased responsiveness to external stimulation, less constrained modes of thinking and potentially their ability to serve as therapeutic agents in mood disorders.

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GL01

KETAMINE AND NEXT GENERATION FAST ACTING ANTIDEPRESSANTS

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Introduction: In the last several decades, numerous preclinical and clinical studies have suggested that the underlying neurobiological basis of depression remains elusive due to the severity, complexity, and heterogeneity of the disorder. While the traditional monoaminergic hypothesis has largely fallen short in its ability to provide a complete picture of major depressive disorder, emerging preclinical and clinical studies suggest that dysfunctional glutamatergic neurotransmission may underlie the pathophysiology of mood disorders. Recent studies showing that a single intravenous infusion of the glutamatergic modulator ketamine elicits fast-acting, robust, and relatively sustained antidepressant, antisuicidal, and anti-anhedonic effects in individuals with treatment-resistant depression have prompted tremendous interest in understanding the mechanisms responsible for ketamine's clinical efficacy. These results, coupled with a new understanding of the mechanistic processes underlying ketamine's effects, have led to creative ways of investigating, repurposing, and expanding research into novel glutamate-based therapeutic targets with superior antidepressant effects but devoid of the side effects and abuse potential of ketamine. Ketamine's targets include noncompetitive NMDA receptor antagonism, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid throughput potentiation coupled with downstream signaling changes, and NMDA receptor targets localized on gamma-aminobutyric acid-ergic interneurons. Here, I review ketamine and other potentially novel glutamate-based treatments for treatment-resistant depression studies conducted over the past 15 years, including NMDA receptor antagonists, metabotropic glutamate receptor modulators, and glycine modulators including AV-101 a glycine partial antagonist. Both the putative mechanisms of action of these agents and clinically relevant studies are described.

Funding: Intramural Research Program, National Institute of Mental Health
PD01
MULTI-LEVEL INVESTIGATION OF ANTISOCIAL BEHAVIOUR ACROSS THE LIFESPAN: IDENTIFYING RISK AND TARGETS FOR INTERVENTION

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Introduction: Persistent antisocial behavior (AB) during development is thought to be associated with a number of social, psychiatric and cognitive difficulties across the lifespan. It has been proposed that there are two etiological pathways through which AB arises and persists: ‘adolescence-limited’ (AL) AB is relatively common, arising in adolescence as the result of a normative gap between biological and social maturity. ‘Life-course persistent’ (LCP) AB is less common, arising in childhood and often concurrent with elevated levels of psychopathic traits. LCP AB persists into adulthood, with its hypothesized origins in neurocognitive deficits. Thus, identifying predictors and risk factors for the development of persistent, severe AB is of great interest for targeting early interventions. However, multi-level research into developmental subtypes of AB is limited, and findings of neurocognitive abnormalities among these groups are mixed.

Methods: In this talk, I will discuss how complementary approaches utilising big data to measure relevant symptoms and risk factors can both improve our understanding of the way antisocial behaviour and associated problems develop, and also how these approaches can inform targets for intervention.

Results: Structural neuroimaging data from the age-45 assessment of the Dunedin Multidisciplinary Health and Development Study (N=861) show that signatures of reduced cortical thickness in executive control regions and broad signatures of reduced surface area are associated with the LCP subtype of AB. Moreover, statistical methods examining individual differences in symptom-level traits present promise as a way of classifying and targeting vulnerability in individuals with high levels of AB.

Conclusions: Findings support that the LCP subtype is associated with reduced cortical structure in regions hypothesised to relate to the presence of early-onset AB. Moreover, examination of individual differences in dimensional symptom measures can provide potential multi-level mechanisms that may serve as targets for intervention in individuals at a greater risk of developing severe, persistent AB and associated social, cognitive and psychiatric problems.

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PD02
CALLOUS-UNEMOTIONAL TRAITS PREDICT CHANGES IN CONDUCT PROBLEMS AND AMYGDALA MATURATIONAL TRAJECTORIES IN BOYS AGED 5-10 AFTER A BEHAVIOURAL INTERVENTION

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Introduction: Conduct problems (CP) have frequently been associated with structural abnormalities within the amygdala and insula. However, it is unknown whether these differences can be reversed or mitigated with successful intervention or whether they are ‘fixed’. We therefore used deformation-based morphometry (DBM) to assess whether behavioural changes after a well-validated parent training intervention (Incredible Years; IY) were associated with grey matter changes over the same period. As varying levels of co-occurring callous unemotional (CU) traits have been shown to a) have distinct neurobiological correlates and b) alter the efficacy of behavioural interventions, we examined the impact of CU traits on these neurobiological and behavioural trajectories.
Methods: 85 boys (age: 8.7±1.41) were scanned before and after (17±4.1 weeks) the IY intervention on a 3T GE Signa HDx and had their CP symptoms assessed at these two timepoints. MPRAGE T1w images (53 pre-post- pairs after QC) were analysed using an optimized longitudinal pipeline in SPM, with age appropriate tissue probability maps and a study specific DARTEL template. The Jacobian determinants of the warp between the two timepoints were multiplied by grey matter segmentations to provide maps of grey matter change over time. These images were analysed after coregistration and smoothing by an 8mm3 Gaussian FWHM kernel. Results were deemed significant at punc<0.005 and pFWE<0.05 after small volume correction within the amygdala and insula.

Results: Reduced CP symptoms between the two timepoints was associated with a pattern of decreasing volumes within the right amygdala (pFWE=0.039) and left insula (pFWE=0.002) and a trend within the left amygdala (pFWE=0.066). CU traits had a quadratic relationship with changes in both CP symptoms (p=0.003) and amygdala growth (Left: pFWE=0.019; Right: pFWE=0.025), such that those with the highest and lowest levels of CU traits showed the least improvement post intervention and the greatest levels of amygdala growth.

Conclusions: The structure of core regions involved in the pathophysiology of CP are amenable to behavioural intervention. Further, CU traits appear to play a key role in modulating this, with both highest and lowest levels of these traits conferring greater risk for increasing morphological abnormalities with the amygdala and poor response to treatment.

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PD03

WHAT CAN BIG DATASETS AND MULTIVARIATE MODELS TELL US ABOUT COGNITIVE PATHWAYS TO RESILIENCE IN PRIMARY EDUCATION?

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Introduction: Children grow up in environments that differentially affect and interact with individual abilities and attitudes. Cognitive ability, mental health, and socio-economic status have all been strongly linked with educational outcomes, but we know little about how they interact, or what factors help protect children against detrimental effects of growing up in relative poverty. Here, we present the results of the first wave of a longitudinal study that combines high-resolution cognitive assessment with an extensive inventory of mental health, attitude, and socio-economic status.

Methods: We tested 552 children aged 7-9 in their classrooms, using a custom tablet-based application. The battery included gamified cognitive tests of short-term memory, inhibition, fluid reasoning, executive function, processing speed, phonological awareness, numerical awareness, and educational outcomes (maths and reading fluency). The application also included questionnaires to assess mental health (RCADS depression and anxiety), attitude (growth mindset and conscientiousness), and socio-economic status (postcode-based deprivation and markers of family affluence). We employed decomposition analyses to establish the latent factors that shape our data, cluster analysis to identify sub-groups within our sample, a self-organising map to visualise how children are distributed across factor space, and network analysis to quantify the relationships between factors.

Results: The distribution of the data is relatively unimodal, with underlying factors being highly correlated. Beyond whole-sample trends, we observed subtle qualitative differences between self-organising map nodes, but no reliable sub-groups in a cluster analysis. Partial correlations revealed that cognitive factors like short-term memory, fluid reasoning, and processing speed explained a large amount of unique variance in educational outcomes (reading and maths fluency), whereas mental health did not. Instead, mental health related to attitude, which in turn related to cognitive processes. Socio-economic status had a direct effect on educational outcomes, but unexpectedly did not explain unique variance in mental health or attitudes.
Conclusions: Self-paced classroom-wide testing is efficient and effective. It is far quicker than traditional face-to-face testing. More importantly, our results suggest that low cognitive skills, poor mental health, and higher levels of socio-economic deprivation predict poor educational outcomes. Interestingly, these factors often overlap within the same individuals, suggesting that economic and mental well-being and cognition directly interact. The planned longitudinal data will be needed to unpack how these interactions emerge and persist over developmental time.

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PD04

BEHAVIOURAL AND COMPUTATIONAL SIGNATURES OF SOCIAL INFLUENCE ON DECISION MAKING IN ADOLESCENTS

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Introduction: Adolescence is a time of physical, cognitive and social growth and change.

Methods: I will present a series of behavioural experiments (cross-sectional as well as longitudinal) along with structural brain measures which shed light on social influence on decision-making from early adolescence to young adulthood.

Results: In cross-sectional studies as well as a large longitudinal cohort, we show that decision-making strategies as well as susceptibility to social influence changes as we grow up and find structural brain correlates, namely myelination markers, accompanying these changes. I will also show how this is related to past adversity as well as present (mal)adaptive real-life behaviours in a healthy cohort of teenagers and adults.

Conclusions: We provide mechanistic evidence as well as neuro-developmental correlates for the adaptive nature of susceptibility to social influences during adolescent development.

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PD05

TUNING OF EXCITATORY/INHIBITORY BALANCE—NEW INSIGHTS INTO THE NEUROPSYCHIATRIC DISORDER ASSOCIATED GENE-CYFIP1

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Introduction: Altered excitatory/inhibitory (E/I) balance is implicated in neuropsychiatric and neurodevelopmental disorders, but the underlying genetic etiology remains poorly understood. Copy number variations in CYFIP1 are associated with autism, schizophrenia and intellectual disability, but its role in regulating synaptic inhibition or E/I balance remains unclear. We show that CYFIP1, and the paralog CYFIP2, are enriched at inhibitory postsynaptic sites. While CYFIP1 or CYFIP2 upregulation increases excitatory synapse number and the frequency of miniature excitatory postsynaptic currents (mEPSCs), it has the opposite effect at inhibitory synapses, decreasing their size and the amplitude of miniature inhibitory postsynaptic currents (mIPSCs). Contrary to CYFIP1 upregulation, its loss in vivo, upon conditional knockout in neocortical principal cells, increases expression of postsynaptic GABAReceptorb2/3-subunits and neuroligin 3, enhancing synaptic inhibition. Thus, CYFIP1 dosage can bi-directionally impact inhibitory synaptic structure and function, potentially leading to altered E/I balance and circuit dysfunction in CYFIP1-associated neurological disorders.

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PD06
ANALYSIS OF GABAERGIC MOLECULAR MARKERS IN A MOUSE MODEL OF THE SCHIZOPHRENIA-ASSOCIATED 16P11.2 DUPLICATION

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Introduction: Duplications of chromosome 16p11.2 in humans dramatically increase risk for schizophrenia but the mechanisms involved remain largely unknown. Here, we provide a phenotypic analysis of GABAergic markers and behaviour in mice with an equivalent genetic mutation (16p11.2 duplication mice). Using in situ hybridisation, we show that expression of schizophrenia-relevant GABAergic cell markers (parvalbumin and calbindin) are selectively decreased in the orbitofrontal cortex of 16p11.2 duplication mice, while somatostatin expression is decreased in the lateral amygdala. To deepen our investigation of the 16p11.2 duplication mice as a model with relevance to schizophrenia, we tested them in cognitive tasks dependent on hippocampal-orbitofrontal connectivity. Performance was impaired in a rodent “N back” working memory task and in the touchscreen continuous performance task (CPT). Consistent with the hippocampal-amygdala GABAergic dysfunction, deficits in ethologically relevant social behaviours were also observed. Overall, the cellular, molecular and behavioural alterations in 16p11.2 duplication mice markedly mirror those observed in patients and suggests that GABAergic dysfunction in the hippocampal-amygdaloid-orbitofrontal circuitry may be an underlying mechanism of patients with schizophrenia, especially those with the 16p11.2 duplication. Moreover, our data further establish 16p11.2 duplication mice as an important translational rodent model with relevance to schizophrenia.

Funding: This work was supported by MRC grant MR/N012704/1 awarded to JA Pratt, BJ Morris and N Dawson.

PD07
THE EFFECTS OF CACNA1C VARIATION: INSIGHTS ON BIOLOGICAL MECHANISMS UNDERLYING RISK FOR PSYCHIATRIC DISORDERS

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Introduction: There is now consistent evidence from GWAS studies that variation in the gene calcium voltage-gated channel subunit alpha1C (CACNA1C) increases risk for psychiatric disorders. CACNA1C encodes the Cav1.2 subunit of voltage-gated calcium channels (VGCCs), which have been functionally implicated in a broad spectrum of neuropsychiatric syndromes. However, how variation in this gene contributes to the pathogenesis of psychiatric illnesses is currently not fully understood. My work endeavours to understand the molecular and behavioural consequences of variation in CACNA1C utilising rodent models and to determine how this may result in phenotypes consistent with psychiatric disease. I am particularly interested in the interaction of this gene with stress and how it may indicate a bridge between genetics and environment in certain cases.

Methods: Male Cacna1c+/- rats (n = 8 per genotype per test) were subjected to various forms of associative fear learning to probe potential deficits in learning and memory. Following learning, brains were taken for molecular analysis. To investigate the effect of stress on this gene, male wild-type rats (n = 12 per group) were subject to prepubertal stress (PND25-27), trained on similar associative learning platforms and brains taken in early adulthood (PND60).
ABSTRACTS

Results: Throughout both delay and trace fear conditioning, Cacna1c+/- rats froze significantly more than wild-type rats regardless of the cue presented to them, suggesting that Cacna1c heterozygosity results in aberrant fear conditioning to neutral stimuli. Molecular analysis revealed a decrease of PV interneurons (p = 0.0074), which have been shown to have a role in inhibitory learning processes. Following early life stress, a significantly reduced level of Cacna1c in comparison to a control group persisted until adulthood (mRNA: p = 0.01, protein: p = 0.04). These animals also show abnormal responses during delay and trace fear conditioning, although dissociable from the results seen in the heterozygote animals. Cacna1c+/- animals also show a trend to an increase in blood corticosterone levels (p = 0.07), further suggesting a possible link between Cacna1c and stress.

Conclusions: A reduced gene dosage of Cacna1c results in aberrant fear in response to irrelevant cues. This may suggest a wider indication of aberrant salience in these animals, consistent with models of psychosis. There is also a suggestion that Cacna1c may interact with stress, although to investigate this further a much larger gene x environment experiment would be required.

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PD08
INVESTIGATING ALTERNATIVE SPlicing OF CALCIUM CHANNEL GENES TO IDENTIFY NOVEL TREATMENT TARGETS FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

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Introduction: Identifying the cellular pathways underlying psychiatric disorders has great potential to improve patient lives. Genome-wide association studies have linked voltage-gated calcium channels (VGCCs), including CACNA1C and CACNA1D, to the risk of disorders including bipolar and schizophrenia. VGCCs are promising targets for new treatments, but as they are also important in the cardiovascular system any treatment must be brain-selective to avoid side effects. CACNA1C and CACNA1D have multiple annotated mRNA isoforms, and alternative splicing is crucial to determine protein function. Our aim is to identify brain-enriched VGCC isoforms as novel targets for new psychiatric treatments. We used innovative long-range Nanopore sequencing to characterise full length transcripts of CACNA1C and CACNA1D in human brain, and CACNA1C in mouse brain, heart and aorta. Our work has uncovered many novel mRNA isoforms that may influence protein function. In human brain, splicing of CACNA1C varied more between different brain regions than between individuals, suggesting splicing may be regulated according to cell type or function. In mouse, splicing of CACNA1C was clearly tissue-specific, with different isoform profiles in brain, heart and aorta. We expect that this underlying principle of tissue-specific splicing will be conserved between mice and humans. Our method uses targeted amplification of the transcript before sequencing, so could miss transcripts with alternative start or end sites. We performed 5’ RACE to identify the start sites of CACNA1C and CACNA1D in human brain. In addition to the CACNA1C start site currently annotated in the UCSC genome browser (Build Hg38), an unannotated start site was identified. Transcripts originating from this alternative start site are predicted to encode a protein with truncated N-terminus. Our data show that splicing of VGCCs in human brain is far more diverse than is currently appreciated. This information will be critical to reveal pathophysiological mechanisms, and to identify brain-enriched VGCC isoforms that may be novel drug targets for psychiatric conditions.

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PD09
WHAT WORKS FOR WHOM? AUGMENTATION STRATEGIES IN TREATMENT RESISTANT DEPRESSION

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Introduction: Despite the large proportion of the overall burden of depression being attributable to treatment-resistant depression (TRD), this substantial minority of patients has received relatively little attention in research. Reflecting this, TRD is inconsistently defined and discrepancies are apparent between research and clinical definitions. The majority of patients with definitive TRD are treated using augmentation pharmacotherapy but there is not consensus on which intervention strategies are most effective.

Methods: We have recently undertaken a number of systematic reviews aiming to ascertain: a) the effectiveness of any evidenced pharmacological or psychological augmenter interventions for individuals with TRD and b) to determine whether there are factors significantly predictive of response to augmentation treatments for this population. We have also explored whether clinical factors and/or biomarkers of inflammation could serve as predictors of subsequent treatment resistance, in order to target augmentation treatments to those at risk of non-response to commonly prescribed monotherapeutic treatments.

Results: Our work highlights the scarcity of high-quality evidence for augmentation interventions for TRD, particularly for psychological therapies. However, we find good evidence for lithium, lamotrigine and aripiprazole as well as early-stage promise for intensive CBT, ketamine and minocycline (amongst others). Early-response appears the most robust predictor of subsequent full response to augmentation treatments for this group of patients. There are a number of factors (such as elevated inflammatory profiles and complex clinical histories) which appear to precede the development of TRD and these data may be useful for targeting early augmentation treatment for patients at high-risk of non-response to monotherapies.

Conclusions: In spite of challenges, the evidence base for TRD is building and there are available treatments with evidenced effectiveness. Precision medicine approaches represent an exciting path for future practice to enhance treatment response and I outline how this might manifest in its early stages. Precision psychiatry could hold particular benefits for patients with TRD and ultimately reduce the burden of treatment-resistant depression, a challenge that is being tackled from multiple angles.

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PD10
CORTICO-LIMBIC HYPERCONNECTIVITY NORMALISES AFTER ELECTROCONVULSIVE THERAPY

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Introduction: Depression is a heterogeneous disorder, symptomatically and etiologically. Such pathophysiological variance may manifest in complex relationships between brain regions, termed functional connectivity. Based on patterns of functional connectivity, several depressive subtypes have been identified and related to specific symptomatologies (Drysdale et al, 2017, Nature Medicine 23: 28-38.). Treatment-resistant depression (TRD) may be particularly associated with hyper-connectivity of the left dorsal prefrontal cortex. However, corticolimbic circuits are also vital to the pathology of depression. Based on these observations, it is hypothesised that successful electroconvulsive therapy (ECT) in TRD will reduce corticolimbic hyper-connectivity.

Methods: Nine severely depressed, treatment-resistant individuals were recruited. This group of patients and the scanning parameters are detailed in Perrin and colleagues’ (2012) original paper (Perrin et al. 2012, Proceedings of the National Academy of Sciences of the United States of America 109(14): 5464-8). Participants underwent a resting state functional magnetic resonance imaging scan prior to and after
ECT. ECT was carried out twice weekly until symptoms remitted. A functional connectivity, seed-based, cluster size analysis was used to determine treatment-related effects. Seven seeds were placed in limbic and cortical regions in each hemisphere. A central seed was also placed in the posterior cingulate cortex. Paired-sample permutation t-tests were used to assess significance, using a family wise error correction (P<0.05) to control for multiple comparisons.

Results: After ECT treatment, the left amygdala had clusters of reduced connectivity with the right supramarginal gyrus, posterior cingulate gyrus, left superior parietal lobule, left postcentral gyrus, and left angular gyrus. Similarly, the right amygdala had reduced connectivity with the left superior parietal lobule, left postcentral gyrus, left supramarginal gyrus, posterior cingulate gyrus and the precuneus. Thalamic seeds presented with reductions with the left precentral gyrus and middle frontal gyrus.

Conclusions: ECT reduces corticolimbic connectivity in TRD. Specifically, amygdala connectivity with central posterior brain regions parallels the default mode network, which has been associated with self-referential thought. Meanwhile, reductions between thalamic and left prefrontal regions are involved in a cognitive control network. In contrast, treatment responsive depression has been associated with reduced functional connectivity, which increases with successful treatment. Therefore, hyperconnectivity may be specifically related to TRD or its subtypes.

Funding: This study was funded by the Chief Scientist Office of Scotland.

PD11

CONCEPTUALISING TREATMENT-RESISTANCE, UNDERSTANDING CURRENT TREATMENTS AND DEVELOPING NEW TREATMENTS FOR TREATMENT RESISTANT SCHIZOPHRENIA AND DEPRESSION

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Introduction: I will discuss 3 pieces of work into different aspects of treatment-resistance: 1) Resistant vs responsive schizophrenia (KCL): I will present the results of a systematic review aiming to address the issue of whether treatment-resistant schizophrenia reflects a categorically distinct disorder from responsive schizophrenia. 2) Longitudinal clozapine EWAS (KCL): I will then present the main results from my PhD - a longitudinal study examining changes in DNA methylation associated with response to clozapine in patients with treatment-resistant schizophrenia, based on rodent studies indicating clozapine's unique mechanism of action may be epigenetic. 3) Evaluating a novel treatment for resistant depression (Oxford): Finally, I will discuss the background and status of an ongoing study investigating the augmentative potential of a 5HT4 agonist in patients with depression who are not responding to SSRI/SNRIs.

Methods: 1) Resistant vs responsive schizophrenia: A systematic literature search was conducted to identify all studies which compared treatment-resistant schizophrenia (defined as either a lack of response to two antipsychotic trials or clozapine prescription) to treatment-responsive schizophrenia (defined as known response to non-clozapine antipsychotics). 2) Longitudinal clozapine EWAS: 22 participants with treatment-resistant schizophrenia, due to commence clozapine, were recruited. Clinical assessments (including PANSS) and samples of peripheral blood were collected before clozapine initiation and at six weeks, twelve weeks and six months after clozapine initiation. We used Illumina 450k arrays to assay epigenome-wide DNA methylation in 85 blood samples. 3) Evaluating a novel treatment for resistant depression: We are using a randomised, double-blind controlled experimental medicine study, in which participants who are showing inadequate response to SSRI/SNRIs are randomly allocated to either the novel 5HT4 partial agonist PF-04995274 (15mg daily) or matched placebo. After 7 days administration, cognitive biomarkers of response are assessed (e.g. facial expression recognition, emotional recall).

Results: 1) Resistant vs responsive schizophrenia: The most robust findings indicate that treatment-resistant patients show glutamatergic abnormalities, a lack of dopaminergic abnormalities, and significant decreases in grey matter compared to treatment-responsive patients. 2) Longitudinal clozapine EWAS: Differently methylated positions (DMPS) located on genes involved in glutamatergic and GABAergic systems, calcium signalling, glucose homeostasis, immune function, cell adhesion, glycine and neuronal development and transcription regulation were associated with clozapine exposure and/or within-participant symptom improvement. 3) Recruitment is ongoing.
Conclusions: 1) Tentative evidence supports conceptualising treatment-resistant schizophrenia as a categorically different illness to treatment-responsive schizophrenia. 2) Clozapine may normalise schizophrenia-associated disruption in glycine function, neuronal function and cell adhesion, reflected in changes in DNA methylation of associated genes.

Funding: The first two pieces of research were conducted while supported by a studentship from the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London. The longitudinal study of clozapine was supported by a UK Medical Research Council (MRC) grant (MR/ L003988/1) and CRESTAR, a grant from the European Union via the Seventh Framework Programme for Research and Technological Development. The current study of a 5HT4 agonist is funded by a UK Medical Research Council (MRC) grant (MR/P012604/1) and supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at Oxford Health NHS Foundation Trust and the University of Oxford.

PD12
PREDICTION OF TREATMENT-RESISTANT DEPRESSION BY COMBINING GENETIC AND CLINICAL RISK FACTORS
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Introduction: Treatment-resistant depression (TRD) affects 30% of patients with major depressive disorder (MDD) and a better understanding of the genetic pathways involved can contribute to precision psychiatry.

Methods: This study provided a deep coverage of inter-individual genetic variability by combining exome sequencing (rare variants) and genome-wide genotyping (common variants) in 1300 MDD patients. TRD was defined as lack of response to at least two drugs for depression of adequate duration and dose and it was compared to response to the first treatment, defined as a Montgomery-Asberg Rating Scale for Depression (MADRS) score<22 and a decrease of at least 50% after at least 4 weeks of treatment. The burden of rare and common genetic variants in functional genomic units (genes and groups of related genes, i.e. pathways) was compared between TRD and responders. Machine learning was used to develop models predicting TRD in 70% of the sample (training set) which were tested in the remaining 30% (testing set). The addition of clinical predictors of TRD selected in the training set was evaluated.

Results: Pathways and genes mediating neural plasticity and regulation of gene expression were associated with TRD. The predictive models developed in the training set showed promising prediction of TRD in the testing set in combination with clinical risk factors (chronic depression, number of previous episodes, suicide risk, MADRS pessimism and interest-activity scores) (AUC 0.75, 95% CI 0.68-0.81).

Conclusions: These results suggested relevant biological mechanisms implicated in TRD and a possible approach to develop predictors of TRD including genetic and clinical risk factors.

Funding: Chiara Fabbri is supported by a Marie Skłodowska-Curie Individual fellowship (EC grant agreement number 793526). The collection of the sample described in this abstract was supported by an unrestricted grant from Lundbeck to the GSRD (Group for the Study of Resistant Depression). Lundbeck had no role in the study design, in the collection, analysis, interpretation of data and decision to submit this abstract.
PW01
THE ROLE OF CANNABINOIDS IN THE DEVELOPMENT AND TREATMENT OF ADDICTION
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Introduction: The cannabis plant synthesises at least 144 cannabinoids including delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC and CBD have contrasting mechanisms of action on the endocannabinoid system and may have opposite effects on brain and behaviour. It is unclear how concentrations of THC have changed in street cannabis, and to what extent this might be associated with the development of addiction. The role of CBD as a treatment for cannabis use disorders has not yet been investigated.

Methods: Repeated cross-sectional studies were used to investigate changes in THC concentrations in street cannabis and associations between THC and treatment for cannabis use disorders. An adaptive Bayesian dose-finding clinical trial was used to estimate the effectiveness of four week CBD treatment (200mg, 400mg, 800mg) for reducing cannabis use compared to placebo in people with a cannabis use disorder. All volunteers received motivational interviewing in addition to CBD or placebo. Co-primary outcomes were cannabis use during treatment quantified by urinary THC-COOH/creatinine concentrations, and the number of days abstinent from cannabis.

Results: Concentrations of THC increased in herbal and resin cannabis (both p's <0.001) and changes in THC concentrations were associated with increased treatment for cannabis use disorders after adjusting for age, sex and non-cannabis treatment admissions (p<0.001). Bayesian analysis confirmed a dose-response relationship between CBD treatment and both co-primary outcomes of cannabis use, with 200mg found to be ineffective and 400mg and 800mg more effective than placebo for both co-primary outcomes; all p's (most effective dose I data) >0.9.

Conclusions: Concentrations of THC have risen in street cannabis and these changes are associated with increased treatment for cannabis use disorders. CBD can reduce cannabis use in a dose-dependent manner and may be an effective treatment for cannabis use disorders.

Funding: Medical Research Council, Society for the Study of Addiction

PW02
ENVIRONMENT X ENVIRONMENT INTERACTIONS IN RODENT DUAL-HIT MODELS FOR SCHIZOPHRENIA: RISK VERSUS RESILIENCE, AND IMPLICATIONS FOR DRUG DISCOVERY
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Introduction: Schizophrenia has a complex aetiology involving numerous genetic and environmental risk factors. Many of these have been replicated in rodents, in an attempt to understand disease mechanisms and evaluate novel treatments for poorly-managed negative and cognitive symptoms. Yet despite several compounds entering clinical trials few have progressed beyond Phase III; this is partly attributed to a need for improved preclinical models. A recent approach adopted within our laboratory therefore involves dual-hit combinations of early-life environmental contributors, like maternal infection, drug abuse and social adversity. Neonatal administration of the NMDA receptor antagonist phencyclidine (10mg/kg s.c. on postnatal days 7, 9 and 11), followed by post-weaning isolation rearing of male rats (from postnatal day ~22; PCP-Iso) produces more extensive cognitive impairment across a broader range of domains than either intervention alone. It also alters pro-social interaction and concomitant ultrasonic vocalizations in a manner more akin to negative symptomatology, consistent with a multiple hit hypothesis (Maynard et al. 2001 Schizophr. Bull. 27:457). Cognitive (but not social) deficits in PCP-Iso are reversed by the dopamine D₃-prefering D₂/D₃ partial agonist cariprazine (Watson et al. 2016 Eur. Neuropsychopharmacol. 26:208), which has since been approved for clinical use in the USA and Europe (Vraylar®/Reagila®). But neither memory impairments nor glutamate release from PCP-Iso hippocampal slices are influenced by the 5-HT6 receptor antagonist SB-399885, which may mirror the poor clinical outcomes with this class of compounds (Morozova et al. 2017 J. Clin. Psychopharmacol. 37:169). Surprisingly gestational administration of the viral mimetic
polyinosinic:polycytidylic acid (PIC; 10mg/kg i.p. on gestational day 15) actually protects against, rather than exacerbating isolation-induced changes in behavior, brain regional cytokine levels and mammalian target of rapamycin (mTOR) activation (King et al. 2017 J. Psychopharmacol. 31S:A112). Similar protection is reported for gestational PIC against an adolescent immune challenge (Clark et al. 2019 Prog. Neuropsychopharmacol. Biol. Psychiatry 89:286), or prior social stress (maternal separation) against isolation rearing (Ellenbroek & Cools 2002 Pharmacol. Biochem. Behav. 73:177). Recent attempts to understand developmental mechanisms contributing to the isolation syndrome include examination of the gut microbiome-immune-brain axis (Dunphy-Doherty et al. 2018 Brain Behav. Immun. 68:261). The resilience to isolation rearing conferred by gestational PIC points to possible adolescent involvement of the neuropeptide oxytocin. Current research is exploring options to enhance intranasal-brain delivery of oxytocin (via conjugation to novel cell-penetrating peptides), and future studies will examine the impact of oxytocin manipulation on emergence of neurodevelopmental deficits in our dual-hit models for schizophrenia.

Funding: Research in this summary presentation was funded by the University of Nottingham, Forest Research Institute, and an FP7 Marie Curie ITN award (r’BIRTH).

**PW03**

**DON'T GO BREAKING MY HEART: EXAMINING INTRINSIC AND EXTRINSIC CARDIOMETABOLIC RISK IN SCHIZOPHRENIA**

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**Introduction:** It is unclear if schizophrenia presents with intrinsic metabolic and immune dysregulation, and if immune alterations are typical of the condition, or only seen in a subgroup. Metabolic alterations are observed with antipsychotic treatment, but the relative severity of metabolic dysregulation with different antipsychotics is poorly defined. Pre-clinical evidence suggests that antipsychotics may be cardiotoxic, inducing myocardial inflammation/fibrosis. It is however unclear if these changes also occur in humans.

**Methods:** First, we describe meta-analyses of glucose, lipid, and immune parameters in first episode psychosis (FEP) compared with controls. We also consider if immune changes are typical in FEP or are only observed in a subgroup using meta-analysis of variability. Second, we consider the results of a network meta-analysis of change in glucose/lipid parameters in randomised controlled trials of acute antipsychotic treatment of patients with schizophrenia. Third, we consider the results of a cardiac MRI study which set out to examine for evidence of inflammation and fibrosis within the myocardium of patients compared with controls, with degree of fibrosis/inflammation indexed using native myocardial T1 time.

**Results:** At the onset of psychosis, patients present with increased fasting glucose, insulin, glucose post-OGTT, and insulin resistance (g=0.20-0.61, all p<0.05), but reduced total/LDL cholesterol (g=-0.22 - -0.19, p<0.05). Patients present with elevated immune parameters, although only interleukin-6 (IL6), interferon-g and interleukin-17 remain significantly elevated in sensitivity analyses that matched for lifestyle factors. Variability of IL6 was reduced in patients (CVR=0.64, p<0.0001), suggesting IL6 alterations are typical of psychosis rather than seen in a subgroup. Network meta-analysis of 18 different antipsychotics demonstrated that olanzapine and clozapine are the worst antipsychotics for increases in weight/BMI/cholesterol/triglycerides. Aripiprazole, brexpiprazole, cariprazine, and lurasidone are associated with best metabolic outcomes. In the cardiac MRI study, compared with controls, native myocardial T1 was significantly longer in patients with schizophrenia (d=0.89; p=0.02), suggestive of myocardial inflammation/fibrosis.

**Conclusions:** At the onset of illness and prior to antipsychotic treatment, patients with psychosis present with insulin resistance, which may point to an intrinsic vulnerability to diabetes mellitus. Findings do not support the presence of an immune subgroup in schizophrenia. Aripiprazole, brexpiprazole, cariprazine, and lurasidone are associated with the best metabolic outcomes, suggesting that, if all other factors are equal, clinicians and patients should choose these antipsychotics first-line. Cardiac MRI results are suggestive of an early diffuse fibro-inflammatory myocardial process in patients with schizophrenia. Future studies are required to determine if this is due to antipsychotic treatment.

**Funding:** MRC, Wellcome, BMA
PW04
TAKING CARE NOT TO BE SINGED BY THE WIND OF PSYCHOTIC FIRE-A DOPAINERGIC ROLLERCOASTER

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Introduction: In this presentation I will present research that I have conducted over the last 8 years or so, primarily using positron emission tomography (PET). These studies have focused on understanding the role of the presynaptic dopamine system in pharmacological challenge in healthy volunteers, as well as in psychosis (both bipolar psychosis and schizophrenia). I will also describe work I have completed in relation to treatment studies in affective and psychotic illness.

Funding: SJ is supported by a John, Margaret, Alfred and Stewart (JMAS) Sim Fellowship form the Royal College of Physicians (Edinburgh) and National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London.
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