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Keywords: Interoception, Eating Disorders, Functional Neuroimaging

Disclosure: Nothing to disclose.

T122

Intra-Cortical Myelination is Associated With 33 Impulsive and Compulsive Behaviors: A Latent Phenotyping Study of Disinhibition and Enriched Brain Gene Expression

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Background: Impulsive and compulsive symptoms are common, tend to co-occur, and collectively account for a substantive global disease burden. We previously found that approximately 70% of expressed variance in 33 impulsive and compulsive problems was accounted for by a single latent phenotype termed "disinhibition". Neurobiological mechanisms underpinning this novel trans-diagnostic phenotype have yet to be elucidated.

Methods: To study the neurobiology of this latent phenotype, we utilised the Neuroscience in Psychiatry Network (NSPN), a cohort of young people in the United Kingdom, who provided questionnaire data and Magnetic Resonance Imaging (MRI) scans. Partial Least Squares (PLS) was used to identify brain regions in which intra-cortical myelination (measured using Magnetisation Transfer, MT) was significantly associated with the trans-diagnostic disinhibition phenotype. We then identified genes whose expression was enriched in these disinhibition-associated brain regions, using data from the Allen Human Brain Atlas.

Results: The sample comprised 126 participants, mean (standard deviation) age 22.8 (2.7) years, being 61.1% female. Disinhibition scores were significantly and positively associated with higher MT in the following regions bilaterally: inferior frontal cortex, middle and superior frontal cortex, posterior cingulate cortex, superior parietal cortex, paracentral gyrus, post-central gyrus, supramarginal gyrus, and precuneus. Genes involved in receptor signalling pathways were significantly over-expressed in these disinhibition-related cortical regions, including noradrenergic receptors (ADRA1B, ADRA2C), opioid receptors (OPRM1, OPRK1), dopaminergic receptors (DRD5) and serotonergic receptors (HTR1E).

Conclusions: This study integrates and extends beyond established disease models of impulsivity and compulsivity using a trans-diagnostic, dimensional approach. These findings indicate brain regions and biological processes implicated in a multitude of related, impairing mental disorders characterised by disinhibition. Such a latent phenotyping approach could be used in future to quantify effects of pharmacological and other treatments, with the aim of ameliorating a range of disorders, including in their early stages.

Keywords: Trans-Diagnostic, Phenotyping, Impulsivity, Compulsivity

Disclosure: Cambridge Cognition, Promentis, Ieso Digital Health, Shire, Consultant, Elsevier, Honoraria, Wellcome Trust, Grant

T123

Event-Related Potential Neural Correlates of Aggressive Response Selection in Intermittent Explosive Disorder

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Background: Intermittent explosive disorder (IED) is a DSM disorder characterized by recurrent impulsive aggressive behavior. Research suggests that IED is characterized by abnormal functioning of the corticolimbic circuit. Specifically, IED has been associated with decreased orbitofrontal cortex (OFC) activity in response to angry faces relative to healthy research subjects, as well as heightened amygdala response to angry faces. Evidence for functional brain abnormalities in IED derive primarily from fMRI studies using static threatening stimuli. Accordingly, little is known about the temporally rapid functional neural correlates of aggressive retaliation to provocation in IED. The N2 component of the event-related potential (ERP) is associated with response selection and inhibitory processes. The current study investigates the functional significance of N2 during provoked aggression and compares healthy participants and participants with IED on task performance and the N2 ERP neural correlate of provoked aggression.

Methods: Adult men and women ages 21 to 54 (mean = 36, SD=10) were recruited from the community who: (1) currently met criteria for IED (N = 20; male=11, female=9); or (2) were healthy control subjects (N = 26; male=17, female=9). Participants were assessed for current and lifetime psychopathology using semi-structured diagnostic interviews. Participants completed an EEG session during which high-density EEG was recorded using 128 channels. During the session, participants completed a laboratory paradigm simulating a provocative aggressive interaction. Under the guise of competing in a reaction-time contest, participants were provoked by a (fictitious) opponent at varying levels of intensity across low and high provocation blocks. Provocations took the form of threats of electric shock to the fingertips, which were calibrated to participants' tolerance thresholds. Participants could 'retaliate' aggressively (or respond non-aggressively) by selecting a shock intensity for the opponent. The loser of each competitive trial received the shock selected by the other player. Following artifact correction, the data were epoched relative to the retaliation responses. The N2 ERP component was analyzed at the frontocentral midline (FCz) electrode. Provocation and retaliation effects on N2 amplitude (i.e., trial-provocation, block-provocation, retaliation intensity, and available responses) were assessed using generalized linear modeling.

Results: Provocation intensity and intensity of retaliation were not significant predictors of N2 amplitude (ps > .9). Average provocation intensity within task blocks also did not impact N2 amplitude (p = .18). Number of available response choices (Wald Chi-square=9.127, df=1, p = .003) and the interaction between available responses and block (low versus high provocation; Wald Chi-square=4.617, df=1, p = .032) significantly predicted N2 amplitude. N2 amplitude was larger when participants had more options for retaliation (3 versus 2). N2 was smallest when response options were limited and included the most aggressive (and the

least utilized) response option, indicating that N2 observed during the task is sensitive to subjects' subjective response space. Compared to other groups, female participants with IED retaliated the most intensely when provoked and showed corresponding higher amplitude of N2 (indicating the least constrained subjective response space) under high provocation.

Conclusions: In the current context, N2 amplitude appears to index subjective response space while retaliating to provocation. Rather than reflecting extent of inhibitory processing, N2 appears to index larger response space. Female participants with IED showed more aggressive responding to intense provocation than male participants with IED and healthy control subjects. Although IED is somewhat more prevalent in men, the current results suggest that women with IED may be more sensitive to intense provocation and show a pattern of neural activity associated with less constrained decision-making when responding to provocation.

Keywords: Irritability/Aggression, Intermittent Explosive Disorder, Threat Context, EEG, Event Related Potentials

Disclosure: Nothing to disclose.

T124

Safety and Efficacy of Esketamine Nasal Spray in a Depressed Patient Who was Being Treated With Tranylcypromine: A Case Report

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Background: Monoamine oxidase inhibitors are associated with a number of drug interactions, including antidepressants. Esketamine nasal spray is a newly FDA approved antidepressant which is unlikely to pose a drug interaction with MAOIs. However, MAOIs were not used in the clinical trials supporting the approval of esketamine nasal spray for the adjunctive treatment of individuals with treatment resistant major depressive disorder.

Methods: We describe a 61 year old woman with recurrent episodes of chronic major depressive disorder and multiple treatment failures to antidepressants of different classes as well as failure to respond to a course of ECT who was treated at our Center with esketamine nasal spray while taking tranylcypromine 60 mg daily. Initial mood and anxiety ratings were in the moderate range of severity. Because of concerns regarding safety, she was initially treated with half the usual starting dose (28 mg). This dose was increased to 56 mg for one session but lowered due to adverse effects, mainly dizziness.

Results: She responded well to treatment with esketamine nasal spray after the first treatment and mood and anxiety ratings were in the normal range after completion of the acute treatment phase (8 treatments over 4 weeks). Blood pressure tended to increase during treatment sessions but never reached levels of clinical concern. At baseline, blood pressure ranged from 91-108 mm Hg systolic and 56-70 mm Hg diastolic. Measurements at 40 minutes after dose administration ranged from 99-135 mm Hg systolic and 60-82 mm Hg diastolic. There were no indications of symptoms of a serotonin syndrome. Side effects were mild and included dissociation and sedation, which dissipated during the 2 hour post drug administration period. Her dose for the final 4 sessions was 42 mg.

Conclusions: Our patient was successfully treated with esketamine nasal spray and tranylcypromine for treatment resistant depression. There were no elevations of blood pressure outside the normal range and there was no indication of a serotonin syndrome. Our patient is likely the first to be treated with this combination, although there are reports in the literature of patients treated with MAOIs and IV ketamine or IV S-ketamine.

Keywords: Treatement Resistant Depression, Esketamine Nasal Spray, Tranylcypromine

Disclosure: Janssen, Honoraria

T125

Rapamycin Triples the Antidepressant Response Rate of Ketamine at 2 Weeks Following Treatment

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Background: Ketamine exerts rapid and robust antidepressant effects that are thought to be mediated by activation of the mechanistic target of rapamycin complex 1 (mTORC1). To test this hypothesis, depressed patients were pretreated with rapamycin, an mTORC1 inhibitor, prior to receiving ketamine.

Methods: Twenty-three patients suffering a major depressive episode were randomized to oral rapamycin (6 mg) or placebo, each was followed 2 hours later by intravenous ketamine 0.5 mg/kg in a double-blind cross-over design with treatment days separated by at least 2 weeks. Depression severity was assessed using Montgomery–Åsberg Depression Rating Scale (MADRS). Antidepressant response was defined as a MADRS improvement of 50% or more.

Results: Over the two-week follow-up, we found a significant treatment by time interaction ($F(8,245) = 2.02$, $p = 0.04$), reflecting prolonged antidepressant effects post rapamycin+ketamine treatment. At 2 weeks, we found higher response (41%) and remission rates (29%) following rapamycin+ketamine compared to placebo+ketamine (13%, $p = 0.04$, and 7%, $p = 0.003$ respectively). However, rapamycin pretreatment did not alter the acute effects of ketamine.

Conclusions: Rapamycin pretreatment failed in blocking the antidepressant effects of ketamine. Unexpectedly, pretreatment with rapamycin prolonged the antidepressant effects of ketamine. This observation raises questions about the role of systemic vs. local blockade of mTORC1 in the antidepressant effects of ketamine, demonstrates that rapamycin may extend the benefits of ketamine, and thereby potentially sheds light on mechanisms that limit the duration of ketamine effects. Registered at clinicaltrials.gov (NCT02487485).

Keywords: Depression, Ketamine, Rapamycin, Rapid-Acting Antidepressant

Disclosure: FSV7, Advisory Board, Lundbeck, Advisory Board, Janssen, Honoraria

T126

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of TS-121, a Novel Vasopressin V1b Receptor Antagonist, as an Adjunctive Treatment for Patients With Major Depressive Disorder

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