T163. STRUCTURAL AND CONNECTIVITY CHANGES IN THE CEREBELLUM CONTRIBUTE TO EXPERIENCING AUDITORY VERBAL HALLUCINATIONS

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Background: Auditory verbal hallucinations (AVH) have been explained in the context of the forward model, giving the cerebellum a prominent role. However, research utilizing multiple neuroimaging modalities has rendered results on the specificity of cerebellar contribution to AVH unclear.

Methods: To examine the reliability and regional specificity of cerebellar changes in AVH, a systematic search of electronic databases through October 2019 was conducted to identify neuroimaging studies of the cerebellum in psychotic patients or nonclinical participants reporting AVH, focusing on structural MRI, diffusion tensor imaging, and resting state functional connectivity studies. Twenty-two studies were included, including 892 participants with AVH (792 psychotic patients; 100 at-risk subjects) and 775 healthy controls. Activation likelihood estimate analysis (ALE) examined the reported coordinates for reduced volume, fractional anisotropy (FA) or connectivity (control participants > participants with AVH) and increased volume. FA or connectivity (participants with AVH > control participants). The consistency of cerebellar changes and their relationship with sociodemographic and clinical measures were meta-analyzed.

Results: The ALE meta-analysis revealed changes in both anterior and posterior cerebellar lobes, with opposite patterns: whereas decreased volume or connectivity was identified in the right anterior cerebellum (lobule IV/V), increased volume or connectivity was identified in the bilateral posterior cerebellum (Crus I and II). A random-effects model with small sample corrections identified consistent changes in both volume and functional connectivity of the cerebellum in participants with AVH (g = 24; SE = 11, 95% CI [33, 1.34]), which were enhanced in Crus I (g = 1.52, SE = .28, p = .006, 95% CI [.73, 2.31]) but not moderated by age, sex, medication, or illness duration.

Discussion: The ALE meta-analysis confirms cerebellar structural and connectivity changes in psychotic and nonclinical participants reporting AVH. These changes may contribute to AVH due to altered sensory feedback and consequently to erratic prediction as described by the forward model. The current findings also indicate that not all cerebellar regions are equally affected by AVH: the most pronounced changes were observed in Crus I. Specifically, altered communication between Crus I and neocortical network nodes, including the prefrontal cortex, may contribute to ineffective cognitive control in AVH, leading to external misattributions of auditory feedback and a reduced sense of control over events in the environment.

T164. NETWORK CONNECTIVITY SUPPORTING REWARD LEARNING DIFFERENTIALLY DISRUPTED IN TREATMENT RESISTANT SCHIZOPHRENIA

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Background: It is estimated that one third of patients with schizophrenia fail to adequately respond to antipsychotic medication, termed ‘treatment-resistance’. This occurs despite adequate blockade of D2 receptors in the brain. The parsimonious options are that treatment resistance could arise through a failure of cognitive control over the dopaminergic dysfunction in the striatum; or has a different primary non-dopaminergic mechanism that isn’t targeted by current antipsychotics. Contemporary models suggest that schizophrenia is associated with reduced reward prediction errors (RPE) and consequent aberrant salience driven by increased dopamine levels that ‘drown out’ phasic signals. This causes positive symptoms and impaired reward learning. However, RPE signalling in treatment-resistant patients appears intact despite sub-optimal behavioural performance. It is therefore unclear how reward learning is impaired in these patients.

Methods: We investigated how reward learning is disrupted at the network level in 21 medicated treatment-responsive and 20 medicated treatment-resistant patients with schizophrenia compared with 24 healthy controls (HC). Participants learnt to associate one of two emotional faces with a reward during a reinforcement learning task in an MRI scanner. Functional MRI BOLD signal was extracted from four brain regions (fusiform cortex, amygdala, caudate and anterior cingulate cortex (ACC)) activated in response to face cues and RPEs. These formed a network of interacting brain regions supporting reward learning. Dynamic Causal Modelling assessed how effective connectivity between regions in this cortico-striatal-limbic network is disrupted in each patient group compared to HC. Connectivity was also examined with respect to symptoms and salience. Finally, cognitive control and the role of glutamate were assessed by relating top-down...
connectivity from the ACC with glutamate levels measured from the same region of the ACC.

**Results:** In responsive patients, there was enhanced top-down connectivity from the ACC to sensory regions (fusiform and amygdala) and reduced input to the caudate compared to HC. Increased top-down connectivity was inversely correlated with symptom severity and sensory-salience. This suggests the presence of an effective compensatory mechanism for unreliable sensory information in responsive patients. Resistant patients however showed normal network connectivity compared to HC except abnormal connectivity within the ACC. This supports an alternative, non-dopaminergic mechanism disrupting reward learning in this refractory group. Increasing connectivity from ACC to caudate was related to positive symptom severity and salience in this group. Moreover, ACC glutamate levels were related to key top-down connections in HC and responsive patients but were not related to any connections in resistant patients. This suggests that glutamate may not be modulating connectivity effectively in this network to exert cognitive control and update reward predictions.

**Discussion:** In summary, differential mechanisms underlie disrupted reward learning between responsive and resistant groups. Resistant patients show similar RPE signalling and network connectivity to HC suggesting their dopaminergic functioning is intact. Impaired glutamate function may present a key mechanism that disrupts reward learning – and why dopaminergic drugs are ineffective. This finding is important for developing new drugs (e.g. glutamatergic targets) and guiding treatment strategies (e.g. giving clozapine earlier) in resistant patients. Future research probing cognitive control mechanisms and glutamate function will be useful to elucidate this putative pathology in treatment resistance.

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**T165. ANTI-Glutamatergic Property of N-Acetylcysteine Documented in Vivo with 1H MRS**

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**Background:** Deficits of brain glutathione (GSH), the primary antioxidant in living tissue, and associated redox imbalance are postulated to be implicated in schizophrenia. However, due to poor blood-brain barrier permeability of GSH, direct supplementation is ineffective in restoring its brain levels. Therefore, there has been great interest in investigating N-acetylcysteine (NAC), as a prodrug that can be deacetylated to supply cysteine (Cys), which crosses the BBB and is the rate-limiting substrate in brain GSH synthesis and restoration. Once inside the cell, Cys combines with glutamate (Glu) to initiate GSH synthesis in a reaction that is catalyzed by the enzyme gamma-glutamylcysteine ligase (GCL), the rate-limiting enzyme.Likely due to the in situ reaction of NAC-supplied Cys with Glu in the brain, GSH synthesis, NAC is believed to have anti-glutamatergic properties. However, direct in vivo evidence of NAC as an anti-glutamatergic agent is currently lacking. In this study, we used 1H MRS to monitor changes in brain levels of both GSH and Glu in response to 4 weeks of daily supplementation with NAC in healthy volunteer subjects. We postulated that 4 weeks of NAC treatment would elevate GSH and decrease Glu levels.

**Methods:** Subjects: Participants recruited for this study consisted of 12 mentally and physically healthy human volunteer (HV) subjects. NAC Supplementation: To investigate the effects of dietary NAC supplementation on cortical GSH and Glu levels, each HV subject underwent 1H MRS scans at baseline. Then a 4-week supplement of 900mg NAC tablets was provided, to be taken 2 per day for a daily NAC dose of 1800mg. Finally, each subject was brought back after 4 weeks for the post-NAC 1H MRS scans to assess the effect of the treatment on cortical GSH and Glu levels.

**Brain 1H MRS:** In vivo cortical GSH spectra were recorded in 15 min on a 3.0 T GE MRI system from a 3cmx3cmx2cm occipital cortex voxel, using the standard J-editing technique, with TE/TR 68/1500ms and 290 interleaved excitations (580 total). Levels of Glu, uncontaminated with glutamine, were obtained from the same occipital cortex voxel in 6 min using the CT-PRESS method, with TE/TR 139ms/1500ms, and 129 chemical shift encoding steps in increments of 0.8ms in 11 dimension. Peak areas for both GSH and Glu were derived by frequency-domain fitting of the recorded spectra. The resulting peak areas were then expressed as ratios relative to the area of the unsuppressed tissue water signal in the voxel.

**Results:** GSH Levels: The effect of 4 weeks of NAC supplementation on GSH levels was a numerical increase that did not reach statistical significance relative to baseline (p=0.33).

Glu Levels: Following 4 weeks of NAC supplementation cortical Glu levels decreased significantly compared to baseline (p=0.04).

**Discussion:** This study has shown that following 4 weeks of taking NAC, brain Glu levels in HV decreased significantly, even though a numerical increase in GSH levels did not reach statistical significance. The observed Glu decrease at 4 weeks suggests a net increase in the consumption of intracellular Glu reserves in the GCL-catalyzed reaction that combines NAC-supplied Cys with Glu in GSH synthesis. The failure of GSH levels to increase significantly after NAC likely reflected the established “feedback inhibition” mechanism whereby GSH synthesis is shut off in a tissue with normal levels, with de novo synthesis due to NAC occurring only in a subset of subjects with “low” GSH levels (i.e., below the sample mean) at baseline. In summary, the results of this study support the role of NAC as an anti-glutamatergic agent, which may seem to modulate Glu levels by increasing the availability of intracellular Cys that then combines with Glu to initiate GSH synthesis, leading to a lowering of total Glu levels as measured by MRS.

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**T166. Visualization of AMPA Receptors in Patients with Schizophrenia and Depression: The First PET Imaging Study**

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**Background:** Evidence on physiological roles of AMPA receptors in psychiatric conditions, including schizophrenia, has been accumulated, which mainly derives from psychiatric disease model animals as well as post-mortem brain tissues. However, its clinical translation was limited due to lack of any tool to visualize AMPA receptors in living human brain. We have recently developed a new positron emission tomography (PET) probe for AMPA receptors (Miyazaki et al. Nature Medicine, in press). Here, we used the first PET probe that specifically binds to AMPA receptors and successfully visualized these receptors in living human brain of patients with schizophrenia.

**Methods:** We developed a novel PET probe for AMPARs, named [11C] K-2 (Miyazaki et al. Nature Medicine, in press). Male patients aged 30–49 with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) underwent a [11C] K-2 PET scan and an MRI scan for co-registration of the PET image and received clinical assessments for symptomatology, including the Positive and Negative Syndrome Scale (PANSS) (registration number: UMIN000025132).

[11C]K-2 was synthesized at Yokohama City University Hospital in accordance with GMP ordinance and was certified by the Japanese Society of Nuclear Medicine. PET imaging was performed with a TOSHIBA Aquiduo scanner (TOSHIBA Medical), which provided an axial FOV of 240 mm, and 80 contiguous 2.0 mm thick slices. Standardized uptake value ratio (SUVr)30–50 min with the whole brain and white matter as a reference was calculated, respectively.