Results: There were no between-group differences in socio-demographic or clinical characteristics (Tab 1). Participants did not differ on WM task performance during online tDCS (Tab 2). However, there were significant between-group differences in manipulation of information with the real tDCS performing significantly better than sham, controlled for baseline (b=0.68, CI 0.14 - 1.21; p=0.044) after consolidation [6].

During WM the ROI analysis demonstrated increased activation underneath the site of the anode in the medial frontal gyrus in the real tDCS group, as compared to sham. There was a positive correlation between with consolidated performance and the activity in the medial frontal gyrus. Further, tDCS demonstrated significantly reduced activation in the left cerebellum. During EF task, increased performance was associated with decreased activity in the ACC [5].

Discussion: This is the first tDCS study to examine the brain activity during WM and EF assessment in individuals with schizophrenia using fMRI. This data suggests that biasing the membrane potential of neuronal populations in the frontal cortex seems to improve their response to other inputs i.e. decreased BOLD activation in the WM and EF network. Although the mechanism of action of tDCS is not clear yet [6], one may speculate that if the BOLD response represents synaptic activity [7], including input from other areas, then tDCS might increase the probability that a synaptic input will generate a response in an output neuron, without the need of any additional energy expended by the cell. tDCS offers a potential new therapeutic approach to the treatment of cognitive deficits.

F156. LONGITUDINAL WORKING MEMORY FUNCTIONAL DISCONNECTIVITY REFLECTS HETEROGENEITY IN INDIVIDUALS AT ULTRA HIGH RISK FOR PSYCHOSIS

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Background: Variation in trajectories of Ultra high-risk (UHR) psychosis mental state posts challenge to schizophrenia prevention or onset delay intervention. Our previous work described the heterogeneity at this prodromal stage of schizophrenia in both brain structure changes and resting-state functional network differences. Functional dysconnectivity can be one of the altered brain substrates underlying clinical symptoms. Lower resting-state functional connectivity (FC) within the salience network (SN) in schizophrenia was detectable at the UHR stage. FC between the fronto-parietal network (FPN) and the SN was disrupted when network integration fell apart in the UHR state.

FPN and SN are important for working memory (WM), which is largely compromised in schizophrenia and lesser in UHR group. Our previous work showed that WM task-related activation in the FPN and SN differed between the UHR and controls. Importantly, such differences varied with WM demands. Evidence has demonstrated that compared to resting-state FC, task-based FC may better predict behavioral performance. However, the WM-related FC in UHR group and its longitudinal changes are still largely unknown. To cover the gap, we sought to examine the heterogeneity in the WM task-related FC changes in a group of UHR participants over time. We expected WM-related FC would link to individual differences in clinical trajectories.

Methods: Based on the longitudinal changes of UHR state within 2 years, participants were divided into 3 groups: 42 controls, 34 UHR remitters (UHR-R) and 42 UHR non-remitters (UHR-NR). We acquired fMRI (TR/TE = 2000/30 ms, 3 x 3 x 4 mm3, 28 slices) when participants performed WM task at different WM demands, varying from information maintenance alone (low) to requiring both maintenance and manipulation (high). We used seed-based approach (gPPI) to compare task-related FC of the FPN and the SN among groups. Voxel-wise FC with six seeds (bilateral anterior insula, parietal, and dorsal lateral prefrontal cortex, identified based on task activation) was regressed on WM demands and groups, controlling for age, gender, education, ethnicity, handedness and task accuracy. Linear mixed modeling methods were used to test longitudinal FC changes and the association between FC and clinical syndromes.

Results: Task performance was worse at high WM demand as expected, but no significant difference was found between groups or over time. Compared to controls, higher FC between the FPN (superior parietal gyrus) and the SN (insula) at low demand was observed in the UHR-NR group at baseline. Within the SN, WM-demand related FC between right insula and thalamus varied among 3 groups: low FC at low demand and high FC at high demand in controls; high FC at low demand but low FC at high demand in the UHR-R group. In contrast, UHR-NR group had high thalamus-insula FC in both WM demands. Moreover, longitudinal FC increase only occurred within the SN at high WM demand in the UHR-R group, while other task-related baseline group differences of FC remained stable over time. Importantly, the rate of intra-SN increase of FC over time at higher WM demand was associated with decline of the positive psychosis syndromes in the UHR-R group.

Discussion: In support of the functional dysconnectivity hypothesis, our study indicated that UHR state was accompanied by altered brain FC during WM task performance. In contrast to lower SN FC at rest, UHR state showed SN hyper-connectivity in task with low WM demand, suggesting the importance of studying UHR both at resting and in task. Importantly, intra-SN FC increase at high WM demand was linked to positive psychosis syndrome reduction in remitters, while no FC changes if UHR state persisted. We argued that task FC could reflect the clinical heterogeneity of the UHR group.

F157. HIERARCHICAL PREDICTION ERRORS DURING AUDITORY MISMATCH UNDER PHARMACOLOGICAL MANIPULATIONS: A COMPUTATIONAL SINGLE-TRIAL EEG ANALYSIS

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Background: A central theme of contemporary neuroscience is the notion that the brain embodies a generative model of its sensory inputs to infer on the underlying environmental causes, and that it uses hierarchical prediction errors (PES) to continuously update this model. In two pharmacological EEG studies, we investigate trial-wise hierarchical PEs during the auditory mismatch negativity (MMN), an electrophysiological response to unexpected events, which depends on NMDA-receptor mediated plasticity and has repeatedly been shown to be reduced in schizophrenia.

Methods: Study1: Reanalysis of 64 channel EEG data from a previously published MMN study (Schmidt et al., 2012) using a placebo-controlled, within-subject design (N=19) to examine the effect of S-ketamine. Study2:64 channel EEG data recorded during MMN (between subjects, double-blind, placebo-controlled design, N=73), to examine the effects of amisulpride and biperiden. Using the Hierarchical Gaussian Filter, a Bayesian learning model, we extracted trial-by-trial PE estimates on two hierarchical levels. These served as regressors in a GLM of trial-wise EEG signals at the sensor level.
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Results: We find strong correlations of EEG with both PEs in both samples: lower-level PEs show effects early on (Study1: 133ms post-stimulus, Study2: 177ms), higher-level PEs later (Study1: 240ms, Study2: 450ms). The temporal order of these signatures thus mimics the hierarchical relationship of the PEs, as proposed by our computational model, where lower level beliefs need to be updated before learning can ensue on higher levels. Ketamine significantly reduced the representation of the higher-level PE in Study1. (Study2 has not been unblinded.)

Discussion: These studies present first evidence for hierarchical PEs during MMN and demonstrate that single-trial analyses guided by a computational model can distinguish different types (levels) of PEs, which are differentially linked to neuromodulators of demonstrated relevance for schizophrenia. Our analysis approach thus provides better mechanistic interpretability of pharmacological MMN studies, which will hopefully support the development of computational assays for diagnosis and treatment predictions in schizophrenia.

F158. FUNCTIONAL CONNECTIVITY DIVERSITY OF THE INSULA CORTEX IN SCHIZOPHRENIA: SUBREGIONS OR CONTINUOUS?
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Background: The function, cytoarchitecture and connectivity of the insula cortex are diverse. Cluster analyses have been applied to functional magnetic resonance imaging (fMRI) connectivity data to parse this diversity and subdivide the insula into discrete subregions. However, the number of subregions comprising the insula remains vexed and whether these putative subregions are disturbed in neuropsychiatric illness are unknown. The present study aimed to (i) rigorously evaluate the number of subregions (if any) into which the insula can be subdivided based on topographic variation in whole-brain patterns of insula functional connectivity; and, (ii) establish whether the connectiological topography of the insula is altered in schizophrenia.

Methods: Two alternative models explaining the heterogeneity of insula connectivity were tested: (Model i) insula comprising discrete subregions, each associated with a distinct connectivity fingerprint; and, (Model ii) connectivity varying as a continuum across insula, without marked boundaries. Cluster analysis was used to delineate discrete subregions, and a novel gradient-based method was developed to evaluate whether connectivity varied continuously across the insula. These models were tested in a sample of individuals with schizophrenia (N=49), healthy comparison participants in right temporal regions, but an increase in spectral power in the left superior temporal cortex. A significant effect of hemisphere was found, reflecting higher 40 Hz ASSR power in the right hemisphere in schizophrenia patients (P<0.02).

Discussion: This is the first study that comprehensively investigate the potential differences in connectional pathology of insula between its anterior and posterior aspects. We conclude that the connectional diversity of the insula inferred from resting-state functional connectivity should be conceptualized as continua of variation, rather than discrete subregions. We posit that the reduced differentiation between the anterior and posterior insula in schizophrenia may impact on the ability in discriminating self-generated from externally-generated sensory information, possibly contributing to hallucinations in the disorder.

F159. NEUROMAGNETIC 40 HZ AUDITORY STEADY STATE RESPONSES AND AUDITORY CORTICAL GABA AND GLX IN CLINICAL HIGH RISK AND FIRST EPISODE OF PSYCHOSIS INDIVIDUALS
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Background: Robust impairments in the power and phase of 40 Hz auditory steady state responses (ASSR) have been reported in chronic schizophrenia patients. This could reflect changes in the balance between inhibitory GABAergic and excitatory glutamatergic neurotransmission in auditory cortex. However, the direct link between the ASSR and alterations in these neurotransmitter systems has not been systematically explored. Furthermore, it remains unclear whether 40 Hz ASSR impairments are present in early and at-risk stages of psychosis. The current study aims to explore the 40 Hz ASSR in first-episode of psychosis patients and individuals at clinical high risk (CHR) of psychosis, and the possible relationship of deficits in gamma-band entrainment to a dysfunctional excitation inhibition balance, as reflected by alterations in cortical GABA and glutamate.

Methods: Data from 80 CHR, 11 FEP and 40 age-matched healthy control participants were collected as part of the MRC-funded Youth Mental Health Risk and Resilience study. MEG data were recorded on a 4D Neuroimaging Magnes 3600 Whole Head 248 Channel system, while participants were passively presented with a series of 1000 Hz carrier tones amplitude modulated at 40 Hz. Data were analysed at sensor and source-level in the frequency-domain for spectral power and intertrial phase coherence (ITPC). For source-reconstruction, an eLoreta source-analysis algorithms was employed. Auditory regions of interest (ROIs) were defined using 98 nodes defined from the AAL-atlas. Levels of right auditory GABA and Glx (glutamate + glutamine) were measured using 1H-MRS at 3T and 2*2*2 cm voxels and were estimated relative to water. GABA levels were further corrected for grey and white matter and cerebrospinal fluid levels within the voxel. Finally, 40 Hz ASSR power in right auditory cortex was explored in relation to neurotransmitter levels in the same region.

Results: Across groups, the ASSR stimulus activated temporal regions, including bilateral heschl’s gyrus and superior temporal cortex. A significant effect of hemisphere was found, reflecting higher 40 Hz ASSR power in the right hemisphere across groups. CHR and FEP participants showed attenuated 40 Hz ASSR power and ITPC compared to healthy control participants in right temporal regions, but an increase in spectral power in the left hemisphere. A moderate positive correlation was found between right auditory GABA and 40 Hz ASSR power in the right superior temporal gyrus in CHR, but not in controls.

Discussion: These results provide a link between MRS measures of GABA and 40 Hz ASSR power impairments in CHR individuals. Furthermore, these preliminary findings indicate that slight alterations in the 40 Hz