FP components. It would seem that during movie viewing patients engage more regions involved in attentional control (perhaps for compensatory purposes) whereas control subjects have stronger involvement of regions related to spontaneous cognition and high-order integration.

O3.5. TESTING THE DOPAMINE HYPOTHESIS OF PSYCHOSIS USING POSITRON EMISSION TOMOGRAPHIC IMAGING IN FIRST EPISODE BIPOLAR AFFECTIVE DISORDER AND SCHIZOPHRENIA

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Background: The dopamine hypothesis of psychosis suggests that dopamine abnormalities are present in psychotic illness, irrespective of diagnostic class. Meta-analyses of Positron Emission Tomography (PET) studies of the dopamine system have shown elevated dopamine synthesis capacity in schizophrenia, though there is a dearth of studies examining this in other psychotic disorders.
We therefore sought to answer the question of whether abnormalities of the presynaptic dopamine system are seen in bipolar psychosis, how this compared to schizophrenia, and whether positive psychotic symptoms were associated with dopamine synthesis capacity, irrespective of diagnostic class.
Methods: Cross-sectional, case-control 18F-DOPA Positron Emission Tomography (PET) study in people with first episode bipolar psychosis, schizophrenia and control subjects. Clinical measures included the Positive and Negative Syndrome Scale (PANSS), Young Mania Rating Scale and Global Assessment of Functioning (GAF).
Results: Mean (SD) ages were 23.6 (3.6) years in 22 people with bipolar psychosis (13 male), 26.3 (4.4) years in 16 people with schizophrenia (14 male), and 24.5 (4.5) years in controls (14 male). There was a significant group difference in striatal dopamine synthesis capacity (Kicer) ($F_{2,57} = 6.80$, $P = .002$), post-hoc tests indicating Kicer was significantly elevated in both the bipolar group (mean [SD], 13.18 [1.08] × 10–3 min-1; $P = .002$) and the schizophrenia group (mean [SD], 12.94 [0.79] × 10–3 min-1; $P = .04$) compared with controls (mean [SD], 12.16 [0.92] × 10–3 min-1). Kicer was positively correlated with positive psychotic symptom severity in the combined bipolar and schizophrenia sample currently experiencing psychosis, explaining 27% of the variance in symptom severity ($n = 32$, $r = 0.52$, $P = .003$).
Discussion: This is the first study to examine the presynaptic dopamine system in bipolar psychosis, finding an elevation compared to controls, equivalent to schizophrenia, from first onset of illness. A relationship was found between dopamine synthesis capacity and positive psychotic symptoms, across diagnostic classes, indicating a transdiagnostic role for dopamine synthesis capacity and positive psychotic symptoms.

O3.6. DEFICITS IN CONTEXT-DEPENDENT ADAPTIVE CODING IN EARLY PSYCHOSIS AND HEALTHY INDIVIDUALS WITH SCHIZOTYPAL PERSONALITY TRAITS

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Background: Adaptive coding of reward values is a fundamental principle of brain functioning to efficiently represent a theoretically infinite range of rewards in the natural environment with the limited coding range of reward-processing neural machinery. Patients with schizophrenia show impaired neural adaptation to the current reward context. However, it is unknown if and how generally this impairment extends across the psychosis spectrum.
Methods: We studied 27 patients with first-episode psychosis, 26 individuals with schizotypal personality traits and 25 healthy controls using functional magnetic resonance imaging in combination with a variant of the monetary incentive delay task. We assessed adaptive reward coding in two reward conditions with different reward ranges.
Results: Compared to healthy controls, patients with first-episode psychosis and individuals with schizotypal personality traits showed less efficient neural adaptation to the current reward context in the caudate. The two groups therefore showed a similar deficit in reward representation as patients with schizophrenia. In addition, we find impaired adaptive coding of reward in the caudate and putamen to be associated with total symptom severity across the psychosis continuum.
Discussion: Deficits in adaptive coding were prominent across the psychosis continuum and even detectable in unmedicated healthy individuals with schizotypal personality traits. In addition, the association between total symptom severity and impaired adaptive coding in the right caudate and putamen suggests a dimensional mechanism underlying imprecise neural adaptation. Our findings support the idea that impaired adaptive coding may be a general information-processing deficit across the psychosis spectrum and not limited to schizophrenia.

O3.7. EFFECT OF N-ACETYLCYSTEINE ON BRAIN GLUTAMATE LEVELS AND RESTING PERFUSION IN SCHIZOPHRENIA

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Background: Schizophrenia may be associated with elevations in glutamate levels in the anterior cingulate cortex (ACC), and this may be particularly apparent in patients who have not responded well to conventional antipsychotic treatment (Egerton et al., 2012; Mouchliantis et al., 2016). This suggests that compounds that can decrease ACC glutamate levels may have therapeutic potential for this group. N-acetylcysteine (NAC) is one such compound, currently under investigation as an adjunctive therapy for schizophrenia. The effects of NAC on brain glutamate levels and physiology in schizophrenia have not been previously evaluated. The primary aim of this study was to examine whether a single oral dose of NAC can alter brain glutamate levels in schizophrenia. The secondary aim was to characterise the effects of NAC on regional brain perfusion.
Methods: In a double-blind placebo-controlled crossover study, twenty patients with a diagnosis of schizophrenia underwent two 3 Tesla MRI scans, performed one week apart, and following administration of a single oral dose of 2400mg NAC or matching placebo. Proton magnetic resonance spectroscopy (1H-MRS) was used to investigate the effect of NAC on glutamate and Glx (glutamate plus glutamine) levels scaled to creatine (Cr) in the anterior cingulate cortex (ACC) and in the right caudate nucleus. Pulsed continuous arterial spin labelling (pCASL) was used to measure the effects of NAC on resting cerebral blood flow (CBF) in the same regions. 1H-MRS spectra were analysed using LCModel version 6.3-0I using a standard basis set. Individual CBF maps were pre-processed in the Automatic Software for ASL Processing (ASAP) toolbox running in SPM-8 in Matlab 6.5. The effects of NAC on 1H-MRS metabolite levels were determined using paired

samples t-tests. Changes in rCBF were determined using within-subjects, second-level analysis implemented in SPM-8.
Results: In the ACC, Glx/Cr was significantly reduced in the NAC compared to placebo condition (t(17) = 2.40; P = .03, d = 0.64). There was no significant effect of condition on Glu/Cr in the ACC, or on Glx/Cr or Glu/Cr in the right caudate nucleus, or on any of the other metabolites quantifiable from the 1H-MRS spectra. There were no significant differences in CBF in the ACC (mean (SD) placebo = 47.22 (8.81); NAC = 46.83 (7.29); t(18) = .349, P = .73) or in the right caudate nucleus (mean (SD) placebo = 37.51 (7.48); NAC = 37.77 (6.71); t(18) -.310, P = .76) in the NAC compared to placebo condition. There was also no significant difference in global CBF between conditions (mean (SD) placebo = 39.64 (10.02); NAC = 40.03 (9.13); t(18) = -.398, P = .70).
Discussion: These results provide preliminary evidence that NAC may reduce ACC glutamate metabolites in schizophrenia. Future studies will need to determine the extent to which reductions in glutamate metabolites following a single dose of a glutamatergic compound are indicative of longer-term efficacy in improving symptoms.

O3.8. DORSOLATERAL PREFRONTAL CORTEX IN DRUG-NAÏVE FIRST EPISODE SCHIZOPHRENIA: DYNAMIC PHASE COHERENCE OF INFRASLOW OSCILLATIONS

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Background: Dorsolateral Prefrontal Cortex (DLPFC) has been identified as the seat of many synaptic changes in schizophrenia. Functional neuroimaging studies indicate inefficient recruitment of DLPFC, often termed as hypofrontality, that appears in conjunction with disrupted connectivity of DLPFC with other brain regions. Very Low Frequency Oscillations (VLFO or infraslow oscillations) stem from AMPA currents, and are thought to represent a slow, cyclic modulation of cortical gross excitability. These oscillations are phase-synchronised enabling long-distance communication. This synchrony fluctuates across time (dynamic), indicating state-shifts. Dynamic synchrony can be captured using variance of phase coherence (vPC). We aimed to isolate the brain regions showing abnormal vPC with right DLPFC in drug-naïve first episode schizophrenia compared to healthy controls. Based on our prior work indicating fronto-insular dysconnectivity, we hypothesized that anterior insula would show the most disrupted dynamic phase coherence with DLPFC among all other brain regions.
Methods: 129 drug-naïve patients with first episode of schizophrenia (FES) and 197 age- sex- and education-level matched healthy controls (HC) were recruited. Based on Dosenbach's atlas applied to 7.67 minutes (230 timepoints with TR=2 s) of eyes-open resting fMRI scan, we extracted timeseries of 160 functional network nodes, and identified right DLPFC with MNI coordinates (x=40,y=36,z=29). Wavelet-transformation was done to enable time-frequency analysis that decomposed the timeseries data into 3 bins of very low frequency oscillations (0.02–0.04 Hz, 0.04–0.06 Hz, 0.06–0.08 Hz). We then estimated phase coherence between DLPFC and other 159 regions at each timepoint, and the variance (vPC) across the entire acquisition. Regions showing aberrant vPC with right DLPFC were identified using FDR corrected 2-tailed $p<0.05$ as the threshold of statistical significance in a two-sample t test comparing HC and FES groups. A two-step clustering procedure using likelihood-distance measure was employed to stratify sub-groups of FES with or without vPC disruption. The resulting subgroups were compared based on clinical symptom scores using van der Gaag's 5-factor PANSS model.
Results: The FES group showed a significant reduction (FDR corrected p = 0.03) in vPC between right DLPFC and left anterior insula within the frequency band: 0.02 - 0.04 Hz. The rDLPFC-lAI path can be termed as a long-distance connection based on anatomical distance measure (82.6 mm, compared to a median of 75mm) when compared to HCs. FES group was split into 2 subgroups using the clustering procedure. FES-2 (n=51) had higher vPC of rDLPFC-lAI connectivity compared to HC (Hedges' g: -2.0, p=0.001) while FES-1 (n=78) had lower vPC compared to HC (Hedges' g: 0.47, p=0.009). FES-1 had more 'emotional' and 'positive symptoms' but had similar symptom loadings in other PANSS domains compared to FES-2.
Discussion: Reduced variability of phase coherence between anterior insula and DLPFC in schizophrenia confirms our prior hypothesis of Salience Executive Loop dysfunction in this illness. Current results indicate that aberrant connectivity with anterior insula is the major lateral prefrontal disruption even in a drug naïve state at rest. Further, this aberration seems to be specific to infraslow rather than other frequency bands, raising the possibility that this may be a key mechanism of modulating overall cortical excitability in schizophrenia. It is possible that this dysfunction is specific to a subgroup with more psychotic symptoms at first presentation.

O4. Oral Session: Genetics

O4.1. GENETIC VULNERABILITY TO DUSP22 PROMOTOR HYPERMETHYLATION IS INVOLVED IN THE RELATION BETWEEN IN UTERO FAMINE EXPOSURE AND SCHIZOPHRENIA

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Background: Epigenetic changes may account for the doubled risk to develop schizophrenia in individuals exposed to famine in utero.
Methods: We therefore investigated DNA methylation in a unique sample of patients and healthy individuals conceived during the great famine in China. To further examine the causality of the identified DNA methylation differences we also exposed human fibroblasts to nutritional deprivation and analyzed changes in expression and DNA methylation.
Results: In the famine exposed schizophrenia patients we found significant hypermethylation of the dual specificity phosphatase 22 (DUSP22) gene promoter (Chr6:291687–293285) (N=153, p=0.01). The presence of a direct link between famine exposure and DUSP22 transcription was supported by increased methylation (p=0.048) and expression (p=0.019) in response to nutritional deprivation in the cultured human fibroblasts (N=10). These findings are in line with previous research that implicated hypermethylation of DUSP22 in the environmental risk to neuropsychiatric disorders. In postmortem brain samples from schizophrenia patients, variation in DUSP22 methylation was genetically regulated across chromosomes by a region on chromosome 16. This cross chromosomal regulation of variability in DUSP22 methylation is consistent with new 3D genome interaction data obtained using Hi-C capture in brain and previously published data on lymphocytes.
Discussion: Together our results identify an epigenetic locus at which the response to prenatal famine exposure is genetically regulated across chromosomes and that is relevant for a major psychiatric disorder.