O3.3. REWARD PROCESSING AS A VULNERABILITY INDICATOR FOR PSYCHOSIS: RESULTS FROM A TWIN STUDY

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Background: Disturbances of the brain reward system is a common finding among patients with schizophrenia. Recent studies have found similar alterations in healthy relatives to patients with schizophrenia and reward disturbances have been suggested to be an endophenotype for schizophrenia. Here we compare brain reward activity between patients with schizophrenia, their healthy co-twin and a sample of matched healthy controls (HC). We hypothesize that patients as well as the healthy co-twins will show reward alterations compared to HC.
Methods: By coupling information from The Danish Twin register to the Danish Psychiatric Central Research Register, twins with a diagnosis of schizophrenia spectrum disorder were identified and invited to participate in the study. A sample of age and gender matched HC twins were invited as well. All participants went through a diagnostic interview, and psychopathology was characterized with the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI). Current level of function was estimated with Global Assessment of Function (GAF). The reward system was examined with a modified version of the monetary incentive delay task during functional magnetic resonance imaging (fMRI).
Results: A total of 219 participants were included in the study. Of these, 162 participants completed the fMRI scanning. For statistical reasons (independent observations), only one healthy twin from each HC couple was included in the analyses, which resulted in 116 participants: 42 patients with schizophrenia spectrum disorder, 34 healthy co-twins and 40 HC. Mean age for the whole group was 40.7(10.6) and 64 (55%) were males. There were no group differences in age and sex ($p>0.6$).
Psychopathology: Patients had a PANSS total score of 60(18.9), a CGI score of 4.1(1.5) and a GAF score of 55 (14.9). For the co-twins, PANSS-total was 36(7.1), CGI was 1.5(0.9) and a GAF was 78(11.1), whereas the HC had a PANSS total score of 31(1.6), CGI was 1(0.2) and a GAF was 86(5.6). One-way ANOVA showed a significant effect of group for PANSS total, all PANSS sub-scores, CGI and GAF. For all measures, post hoc t-tests showed significant group-differences between co-twins and HC (all $p<0.03$), co-twins and patients (all $p<0.001$) and HC and patients (all $p<0.001$).
Reward related fMRI activity: Whole brain group differences were analyzed in FSL by performing three pairwise comparisons: co-twins versus HC, co-twins versus patients, and HC versus patients. A corrected cluster significant threshold of $P=0.05$ was used.
During reward anticipation there were no group differences between co-twins and HC or co-twins and patients. Compared to HC, patients had a decreased contrast activity in the bilateral dorsolateral prefrontal cortex during anticipation of uncertain events. Likewise, patients showed decreased activity in left caudate during anticipation of loss.
During reward outcome evaluation, co-twins showed increased contrast activity compared to HC in the miss contrast and in the monetary loss contrast. Additionally, both co-twins and HC had increased contrast activity compared to patients in the miss contrast.
Discussion: Although the healthy co-twins were all without clinical diagnoses, they had a subtle but significantly higher level of psychopathology and a lower level of function compared to HC. Interestingly, the healthy co-twin had an aberrant increased activity during evaluation of negative outcome compared to the HC but also compared to their diagnosed twin. This may indicate that reward abnormalities can be observed along with even subtle psychopathology and thus may serve as vulnerability indicator of psychiatric conditions, whereas these abnormalities are partly normalized by medication in the diagnosed twin.

O3.4. INCREASED ENGAGEMENT OF THE FRONTO-PARIETAL NETWORK AND DECREASED ENGAGEMENT OF THE DEFAULT-MODE – CINGULO-OPERCULAR – SENSORIMOTOR BETWEEN-NETWORK CONNECTIVITY IN FIRST-EPISODE PSYCHOSIS PATIENTS

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Background: The brain basis of psychotic disorders is still inadequately understood; however, evidence strongly suggests a central role of the dysfunctional integration of signaling between brain systems, i.e. "dysconnectivity". Resting-state functional connectivity (FC) studies of chronic schizophrenia have revealed several illness-related, network-level changes. Patients have shown reduced modular structure, changes in the subcortical-cortical interactions, increased FC within the default-mode network (DMN) and reduced FC between fronto-parietal (FP) network components. Network-level changes in earlier stages of psychotic illnesses are less studied but DMN hyperconnectivity, loss of anticorrelation between task-positive and task-negative networks and both hypo- and hyper- corticostriatal connectivity have been reported in early and at-risk stages of psychosis. While studies using tasks and resting-state have yielded plenty of valuable information, regular fmri tasks capture only a narrow field of brain functioning and during rest, behavior may vary greatly between subjects. In this study we assessed subnetworks of first-episode psychosis (FEP) patients during processing of a movie stimulus that includes everyday-like rich variety of stimuli.
Methods: We recorded 3T fMRI of 71 FEP patients and 57 control subjects, recruited from the Helsinki Early Psychosis Study, while they watched scenes from the movie Alice in Wonderland (Tim Burton, 2010). We then constructed a network of 160 nodes based upon a meta-analysis of regions related to a wide range of cognitive and emotional processing, we extracted signal time courses from each node and created a 160x160 correlation matrix for each subject. Using GraphVar software, we first identified all pairs of nodes where FC was statistically significantly different between groups ($p < 0.05$, FDR-corrected for multiple comparisons) and then extracted Graph-Components, or subnetworks, in which all pairs of nodes are connected by significant links.
Results: We identified a statistically significant subnetwork of 49 nodes with mainly decreased but also some increased links of FC in patients. Nodes that had a high number of decreased FC links in patients were mostly situated bilaterally in the medial prefrontal (mPFC) regions of the DMN and subcortical regions of the cingulo-opercular (CO) network, concentrated in the basal ganglia. The decreased FC links of the DMN were relatively wide-spread, connecting to some nodes within the DMN and several nodes of the CO and sensorimotor (SM) networks as well as the cerebellum. The decreased FC links of the basal ganglia were mainly connected to nodes of the SM network and the cerebellum. Patients had nodes with several links of increased FC mainly in the FP network, connecting to nodes within the FP as well as nodes of the CO network and the cerebellum.
Discussion: Our results indicate that during naturalistic stimulus, network-level changes in FC are already present at the early stages of psychoses implicating similar networks and links as seen in earlier studies using resting state and simple stimuli in mainly chronic patients. However, we found the within FP as well as FP-CO connectivity to be increased in patients, seemingly contradicting earlier evidence of reduced FC between

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