Title

83. Ventricular Enlargement and Progressive Reduction in Cortical Gray Matter Are Linked in Prodromal Youth Who Develop Psychosis

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based on interviews with patients and their families. Patients were followed during treatment and response to treatment was defined, a priori, based on minimal psychotic symptom items of the Brief Psychiatric Rating Scale. We generated functional connectivity maps from 6 regions of interest (ROIs) within the striatum in each hemisphere. Group level analyses were performed for each ROI, independently, with log transformed DUP as a covariate. Significance was defined at $P < 0.05$, cluster corrected. Post-hoc mediation analyses were performed on a composite measure of corticostriatal connectivity derived from the significant results of our DUP analysis.
Results: We included 85 patients in our analyses (mean age 21; 61 males, 24 females), who had a mean DUP of 102 weeks (SD=77; median=35 weeks). We found that increased DUP correlated with decreased functional connectivity between striatal nodes and frontal and parietal regions, some of which are within the central executive network. In post hoc analyses, a primary explanatory factor within these significant connections showed a mediation effect between DUP and treatment response.
Conclusion: Our results indicate that variation in corticostriatal circuitry may play a role in the relationship between longer DUP and worsened response to treatment. Future prospective studies are necessary to further characterize potential causal links between DUP, striatal circuitry and clinical outcomes.

82. ASSESSING FIDELITY OF OBJECT REPRESENTATIONS IN VISUAL CORTEX IN SCHIZOPHRENIA AND BIPOLAR DISORDER USING MULTIVARIATE PATTERN ANALYSIS

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Background: People with schizophrenia show impaired performance on specific tests of visual perception, such as visual masking tasks that assess perception of objects, and these impairments have been linked to functional outcomes. People with bipolar disorder also show deficits on some visual masking tasks to a lesser degree than in schizophrenia. Visual masking deficits are linked to abnormalities in the Lateral Occipital Complex (LOC), an object-selective region of visual cortex, but the precise nature of functional abnormalities in LOC remain unclear. We hypothesized that neural representations of objects in LOC are degraded in schizophrenia, rendering visual masking tasks more difficult.
Methods: We assessed the similarity of object representations (i.e., machine learning classification accuracy) in LOC using Multivariate Pattern Analysis (MVPA) of functional MRI (fMRI) data in 51 patients with schizophrenia, 53 patients with bipolar disorder, and 50 healthy controls. Each participant completed one run of a standard localizer task for LOC as well as five runs of an unmasked object perception task in which images of different categories of objects appeared. We defined a region of interest (ROI) for each subject using the LOC localizer, then used MVPA to assess how similar patterns of activity were in that ROI for the different categories of objects presented during the main task. In a separate testing session outside the scanner, we assessed each participant's performance on a visual masking task involving pictures of household objects, and we computed a threshold level of masking performance for each subject using standard psychophysical analysis techniques. We evaluated the relationship between pattern similarity and masking thresholds using a correlational analysis in each group.
Results: All groups showed above-chance classification accuracy. Overall, the similarity of activation patterns in LOC for different object categories did not differ significantly across groups. However, there was a significant correlation between classification accuracy and masking performance in the schizophrenia group that was not evident in the other two groups. In the participants with schizophrenia, higher classification accuracies, indicative of well-differentiated patterns of activity in LOC for different objects, were associated with better visual masking performance.
Conclusion: These results suggest that, on average, object representations in LOC are not unusually degraded in schizophrenia or bipolar disorder. However, normal variations in the fidelity of object representations in LOC are linked to abnormal visual masking performance in schizophrenia. Thus, we find evidence of a novel neural correlate of impaired visual masking performance in schizophrenia.

83. VENTRICULAR ENLARGEMENT AND PROGRESSIVE REDUCTION IN CORTICAL GRAY MATTER ARE LINKED IN PRODROMAL YOUTH WHO DEVELOP PSYCHOSIS

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Background: In a recent prospective longitudinal neuroimaging study, clinical high-risk (CHR) individuals who later developed full-blown psychosis showed an accelerated rate of gray matter thinning in superior and medial prefrontal cortex (PFC) and expansion of the ventricular system after applying a stringent correction for multiple comparisons. Although cortical and subcortical volume loss and enlarged ventricles are well characterized structural brain abnormalities among patients with schizophrenia, no prior study has evaluated whether these progressive changes of neuroanatomical indicators are linked in time prior to onset of psychosis. Therefore, we investigated the relationship between the changes in cortical gray matter thickness and ventricular volume using the longitudinal neuroimaging data from the North American Prodrome Longitudinal Study (NAPLS) at the whole-brain level.
Methods: MRI structural data were acquired at baseline and 12-month follow-up, and follow-up scans for those who developed fully psychotic symptoms were assessed at the point of conversion. In total, 37 CHR cases who converted to psychosis, 230 CHR cases who did not convert (nonconverters), and 132 healthy comparison subjects had usable baseline and second time point scans. Imaging measures were first transformed to annualized rates of percent change (ARCH) in each cortical vertex. Interval is the time between BL and FU scans in years. Relationships between ARCH of total ventricle volume and ARCH of cortical gray matter values were tested vertex-wise using the general linear model. Among the subjects with BL and 12-FU data available, 125 CHR cases and 66 controls were followed to an additional third time point for a 24-month MRI assessment. For the purpose of testing the replicability of our main hypotheses, neuroanatomical ARCH measures between the 12 and 24 month follow-ups were also computed with a parallel set of statistical tests as described earlier.
Results: The results showed that ventricular expansion is linked in time to progressive reduction of gray matter, rather than to structural changes in proximal subcortical regions, in a broadly distributed set of cortical regions among CHR youth, including superior, medial, lateral, and inferior PFC,

superior temporal gyrus, and parietal cortices. In contrast, the healthy controls did not show the same pattern of associations. The main findings were further replicated using a third assessment wave of MRI scans in a subset of study participants who were followed for an additional year.
Conclusion: In summary, expansion of the ventricular spaces is linked in time with an accelerated rate of widespread cortical thinning prior to psychosis onset. The cortical regions experiencing altered maturation during the psychosis prodrome may be more widespread than the regionally specific clusters that have been identified in previous case–control studies

84. NEUROMETABOLITE HERITABILITY AND CORRELATION WITH SCHIZOPHRENIA IN ANTERIOR CINGULATE AND LEFT THALAMUS: AN MRS TWIN STUDY

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Background: Aberrant glutamate levels have been found in frontal and thalamic areas of unmedicated schizophrenia patients early in the disease, although differences were not pronounced in more chronic patients (1,2). Genes coding for glutamate receptor subunits have been related to schizophrenia (3), but to our knowledge heritability of glutamate levels has not been established. This is the largest twin study to investigate heritability and correlation with schizophrenia liability of glutamate and other brain metabolites.
Methods: 21 monozygotic (MZ) proband (diagnosis in the schizophrenia spectrum) pairs, 16 dizygotic (DZ) proband pairs, 22 MZ healthy control (HC) pairs and 19 DZ HC pairs were included along with 11 twins included without their sibling. All were recruited by combining the Danish Twin Register and the Danish Psychiatric Central Register. 3T [1H]-MR spectroscopy (MRS) was used to obtain spectra from anterior cingulate cortex (ACC) and left thalamus for assessment of glutamate (Glu), N-acetyl aspartate (NAA), choline (Ch), creatine (Cr) and myo-inositol (mI). Spectra were analyzed using LCModel. Structural equation modeling implemented in OpenMx was used to estimate additive genetic (A), common environmental (C) and unique environmental (E) effects on metabolite levels. The best fitting model was determined by the Akaike Information Criterion.
Results: The AE model showed heritability estimates in the AC of Glu 36%, NAA 9%, Ch 43% and mI 38%. The CE model showed estimates of common environmental influence in the thalamus of NAA 26%, Ch 52%, Cr 33%, and in the AC Cr 26%. NAA, Ch and Cr concentrations in the AC were negatively correlated with schizophrenia liability. No other associations were found.
Conclusion: Establishing heritability of Glu in AC of 36%, is a new discovery that further ties the glutamatergic circuitry to genetic variations. In our cohort, no correlation to disease liability was found for Glu, which is in accordance with Glu levels decreasing with illness duration (4). Taken together with previous findings of altered Glu levels in unmedicated patients early in the disease (1,2), it suggests Glu as a possible endophenotype for the early stages of schizophrenia.
Both NAA and Ch levels in AC were found to be heritable and correlated to schizophrenia liability. This indicates a genetic component influencing these metabolites in relation to schizophrenia, and as such NAA and Ch in the AC could be an endophenotype for schizophrenia.
1. Theberge et al., 2002
2. Kegels et al., 2012
3. Ripke et al., 2014
4. Marsman et al. 2013

85. DIFFUSION IMAGING OF WHITE MATTER PATHWAYS IN SCHIZOPHRENIA: ARE ILLNESS-LINKED CHANGES PROGRESSIVE?

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Background: The presence of altered white matter microstructure in disorders involving psychosis is well established, but the nature and developmental course of these changes are not well understood (Peters & Karlsgodt, 2015). It is not clear whether the presence of attenuated frontal white matter anisotropy at any phase of illness indexes a pathophysiological change that occurs only within the prodromal and/or first episode phases, or whether early white matter changes are part of a lifespan trajectory of accelerated white matter degeneration in patients (Schwehm et al., 2016; Wright et al., 2014). It also remains to be determined whether schizophrenia-linked anisotropy changes are the result of axon damage or if they also reflect organizational changes.
Methods: Diffusion MRI data were collected in 81 schizophrenia patients (54 First Episode and 27 Chronic), and 65 controls (Mean age = 26, 98 males, N = 146). Tract Based Spatial Statistics (TBSS; Smith et al., 2006) were performed to examine group differences in Fractional Anisotropy (FA; a widely used measure of white matter coherence) on a whole-brain voxel-based level. Average FA was extracted from a whole-brain-derived ROI, and subsequently used to examine whether the association between Age and FA differed as a function of illness. Fiber density ("fixel-based") analysis was also performed (Raffelt et al., 2016). Fixel-based analysis leverages anatomical and crossing-fiber information to assess whether group differences are likely to be attributable to loss of white matter fiber bundle density or cross-section.
Results: Compared to controls, the schizophrenia group displayed a pattern of reduced FA in the bilateral frontal lobes and the corpus callosum (FWE-corrected, $P < .05$). ROI analysis indicated a lack of significant interaction between Group and Age on FA in whole-brain significant regions ($P = .81$). Preliminary results from whole-brain analyses of fiber density indicate a trending inverse association between fiber density in the postcentral corpus callosum (FWE-corrected $P = .08$), but no such trend was evident in the frontal regions identified by TBSS analysis of FA.
Conclusion: These results replicate the oft-reported finding that frontal and callosal FA is lower in schizophrenia. Cross-sectional analysis of Age and FA indicates that patients do not display a steeper rate of age-related FA decline compared with controls, suggesting that the group difference in FA manifests before the onset of psychosis, but does not progress across phase of illness. Preliminary assessment of fiber density raises the possibility that axon loss within postcentral callosal fiber bundles may be partly responsible for FA changes in postcentral callosal fibers. The lack of group differences in frontal fiber density supports the notion that schizophrenia-linked FA changes in these white matter regions are unlikely to be due to axon loss, but rather, to organizational changes.

86. THE IMPACT OF CHILDHOOD TRAUMA ON BRAIN STRUCTURE AND STRESS RESPONSE: DIFFERENCES BETWEEN FIRST-EPISODE PSYCHOSIS PATIENTS AND HEALTHY CONTROLS

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