06.4. AUDITORY AND LANGUAGE AREAS DISTINGUISH CONVERTERS FROM NON–CONVERTERS AT BASELINE IN SHARP CLINICAL HIGH-RISK SUBJECTS FOR PSYCHOSIS STUDY

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Our recent studies investigated whether changes in brain glutamate are present in healthy individuals with high psychometric schizophrenia, and whether these are related to changes in cortical connectivity response to emotion and (2) gray matter volume (GMV).

**Methods:** Forty-eight healthy participants were recruited based on their score on the O-LIFE questionnaire (Mason et al., 2005), after pre-screening 250 respondents to online advertisement. Participants with high levels of unusual experiences (HS group; that is, scored >7 on the Unusual Experiences (UE) subscale of the O-LIFE), and participants with low UE (LS group; that is, <2 on O-LIFE UE subscale), were invited to participate. Groups were matched by age, gender and IQ. A structural MRI scan, glutamate proton magnetic resonance spectroscopy in the anterior cingulate cortex (ACC), and functional magnetic resonance imaging (fMRI) measuring corticolimbic response during emotional processing were acquired at 3T in a single session. Glutamate levels were analyzed using LCModel 6.3-1L. Voxel-based morphometry was applied to quantify GMV and both GMV and fMRI group level analyses were run using SPM12. Standalone imaging results as well as fMRI/gray matter interactions were considered significant after voxel-wise P<0.05 family-wise error correction.

**Results:** While viewing emotional pictures, HS individuals showed greater activation than did subjects with LS in the caudate, and marginally in the ACC, hippocampus, medial prefrontal cortex (MPC) and putamen. Although no between-group differences were found in glutamate concentrations, within the HS group ACC glutamate was negatively correlated with striatal activation (bilaterally in caudate and in left putamen at P < 0.05) and marginally with MPFC (P = 0.052) and amygdala (left: P = 0.062; right: P = 0.079), correlations that were not present in LS subjects. Structurally, subjects with HS showed GMV decreases in the rolandic operculum/superior temporal gyrus (P < 0.05) at the whole-brain level, and significantly increases in GMV were also detected using ROI in the prefrontal ACC (both P < 0.05). Furthermore, in HS subjects ACC glutamate levels were negatively correlated with GMV in the ACC (P < 0.05). Such association was absent in LS. These findings provide, to our knowledge, the first evidence that brain glutamate levels are associated with emotional hyper-responsivity and volumetric changes in HS in brain regions thought to be critical in the pathophysiology of psychotic symptoms.

**Discussion:** Collectively, these results are in line with a dimensional view of psychosis by suggesting that interactions between brain structure, neurochemistry, and functional response to emotion within a cortical circuit are involved in the expression of psychotic-like experiences at non-clinical and clinical levels. These findings may also serve as evidence of potentially protective mechanisms, as our studies involved high-functioning individuals with HS and some of the observed effects are opposite to what would have been predicted from studies in clinical groups.

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**O6.3. PATTERNS OF GRAY MATTER ABNORMALITIES IN PATIENTS WITH FIRST-EPILOGUE AND TREATMENT-NAÏVE SCHIZOPHRENIA**

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**Background:** To detect schizophrenia-related anatomical changes that are not confounded by antipsychotic treatment and to establish clinically identifiable subgroups that differ in underlying neuroanatomical patterns.

**Methods:** This case-control study was conducted at West China hospital in China, and analysis was undertaken in Robarts Research Institute, London, Canada. 206 patients with schizophreniaform psychosis and schizophrenia and 170 healthy controls were scanned on a Sigma 3.0-T MR scanner; 137 patients with schizophreniaform psychosis and schizophrenia and 172 healthy controls were scanned on a 3.0 T MR scanner. All the patients were first-episode and treatment-naïve. Source based morphometry (SBM) performed to analyze the gray matter (GM) concentration. Latent class analysis used to identify clinical subtypes of patients using the scores of symptom dimensions. GMC component-based connectomes were constructed to study the graphic organization of structural brain network of subtypes of schizophrenia.

**Results:** Patients showed prominent reduction in GM in two components; one including anterior insula, inferior frontal gyrus, anterior cingulate and another with superior temporal gyrus, and precuneus, inferior/superior parietal lobule, cuneus, and lingual gyrus. Increased GM was seen in one component of cerebellar tonsil and inferior semi-lunar lobule, and the other component of middle temporal gyrus, superior temporal gyrus, middle frontal gyrus and putamen. Greater GM of latter component was associated with less severe positive symptoms and better performance on cognitive tests. Reduced global efficiency only existed in a subgroup of patients with severe negative and disorganization symptoms.

**Discussion:** These findings delineate a common pattern of gray matter changes in schizophrenia, and a subgroup of patients with robust cortical reorganization suggestive of compensatory plasticity after first episode.

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**O6.4. AUDITORY AND LANGUAGE AREAS DISTINGUISH CONVERTERS FROM NON– CONVERTERS AT BASELINE IN SHARP CLINICAL HIGH-RISK SUBJECTS FOR PSYCHOSIS STUDY**

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**Background:** Frontal and temporal lobes abnormalities are often reported in schizophrenia. In the present study, we tested whether or not these abnormalities exist in individuals at clinical high risk for psychosis (CHR), and whether they distinguish between those CHR who convert to psychosis versus those who do not convert to psychosis at one year. We analyzed both corticolimbic and sub-threshold psychotic symptoms, we also explored the relationship between cognition and symptomatology and the two brain regions.

**Methods:** Magnetic resonance images, clinical and cognitive data were acquired in 130 CHR who did not convert to psychosis (CHR-NC), 22 CHR who converted to psychosis (CHR-C) and 92 healthy controls (HC) at the Shanghai Mental Health Center, in Shanghai, China, who were tested as part of a NIH funded China and Harvard Medical School collaboration. An internal pipeline developed at the Psychiatry Neuroimaging Laboratory (PNL), Brigham and Women’s Hospital, Harvard Medical School, was used to process the scans. The pipeline includes several quality controls, which are designed to ensure the reproducibility of results.
control steps and FreeSurfer 5.3 (FS) processing, the latter modified to include an automated PNL developed masking methodology, the MABS. FS output was 9 temporal and 11 frontal regions in the left and right hemisphere. All data were Z-scored to the mean and standard deviation of HC. Gender and group differences were investigated using multivariate analyses, and Spearman’s correlations were employed to investigate the relationship between brain measures and cognitive and clinical measures.

Results: SA analysis of the frontal and temporal lobes showed no significant differences among the three groups, while specific and significant group differences were found in CT. More specifically, for the temporal lobe a main effect of Group (p=0.021) and a significant interaction of Region x Group (p=0.01) were found. Post hoc analyses showed that CT of Heschl’s gyrus and of the posterior region of the superior temporal sulcus distinguished CHR-C from CHR-NC (p=0.027) and from NC (p=0.002), with CT of CHR <CHR-NC=NC. For the middle temporal gyrus (MTG) CT was also significantly smaller in CHR-C than in NC (p=0.004) and at trend level in CHR-NC (p=0.098). With respect to the frontal lobe, no significant main effect of Group was found but a significant region X Group interaction was identified. Post hoc analyses showed smaller CT of the pars triangularis in CHR-C with CHR-C<CHR-NC (p=0.02) and NC (p=0.012). The CT of the pars opercularis was smaller in CHR-C compared to NC (p=0.036). In CHRC, the CT of MTG was significantly and positively correlated with the Verbal Learning test and with the Hopkins Verbal Learning test (rho=0.64; p=0.005), with strength of correlation decreasing with task repetition. Further CT of MTG was correlated with the Brief Visual Memory Test (rho=0.6; p=0.004). A significant and positive correlation was also found between CT of the pars opercularis (rho=0.7; p=0.002) and the Brief Visual Memory test. The same correlation was also present with the pars triangularis. None of these correlations were present in NC or CHR-NC.

Discussion: These results indicate that specific CT abnormalities in circumscribed areas of the frontal and temporal lobes at baseline distinguish between CHR individuals who convert to psychosis versus those who do not at one-year follow-up. The brain regions involved belong to language circuits and their CT abnormalities correlate with verbal learning suggesting that these brain circuits are among the first affected by processes leading to frank psychosis.

O6.5. LINKING CORTICAL AND CONNECTIONAL PATHOLOGY IN SCHIZOPHRENIA

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Background: Schizophrenia is associated with cortical thinning and breakdown in white matter microstructure. Whether these pathological processes are related remains unclear. We used multimodal neuroimaging to investigate the relationship between cortical thinning and breakdown in adjacent infracortical white matter as a function of age and illness duration.

Methods: Structural magnetic resonance and diffusion images were acquired in 218 schizophrenia patients and 167 age-matched healthy controls to map cortical thickness (CT) and fractional anisotropy (FA) in regionally adjacent infracortical white matter at various cortical depths.

Results: Between-group differences in CT and infracortical FA were inversely correlated across cortical regions (r=−0.5, p<0.0001), such that the most anisotropic infracortical white matter was found adjacent to regions with extensive cortical thinning. This pattern was evident in early adulthood (20 years: r=−0.3, p=0.005) and middle life (30 years: r=−0.4, p=0.004, 40 years: r=−0.3, p=0.04), but not beyond 50 years (p>0.05). Frontal pathology contributed most to this pattern, with extensive cortical thinning in patients compared to controls at all ages (p<0.05); in contrast to initially increased frontal infracortical FA in patients at 30 years, followed by rapid decline in frontal FA with age (rate of annual decline: patients: 0.0012, controls 0.0006, p=0.001).

Discussion: Cortical thinning and breakdown in white matter anisotropy are inversely related in young schizophrenia patients, with abnormally elevated white matter myelination found adjacent to frontal regions with extensive cortical thinning. We argue that elevated frontal anisotropy reflects regionally-specific, compensatory responses to cortical thinning, which are eventually overwhelmed with increasing illness duration.

O6.6. LACK OF ANTIPSYCHOTIC MEDICATION EFFECTS ON WHITE MATTER MICROSTRUCTURE IN SCHIZOPHRENIA

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Background: A number of studies have reported decreased white matter integrity in patients with schizophrenia, but little is known about the relationship between white matter integrity and antipsychotic medications.

Methods: We enrolled 42 unmedicated patients (thirty were medication-naive) with schizophrenia in a longitudinal trial with risperdone. Symptom severity was assessed with the Brief Psychiatric Rating Scale (BPRS). We obtained diffusion weighted images before medication was started, and after six weeks of treatment. Healthy controls matched 1:1 on age, gender, and parental socioeconomic status were also scanned twice six weeks apart. 30 diffusion sampling directions spanning the whole sphere were acquired twice and concatenated (in plane resolution 2.2mm, slice thickness 2.2mm, b-value 1000 s/mm2, 5 b0 images). After visual inspection of raw images we used TORTOISE for correction of bulk motion, eddy currents and susceptibility artifacts using a single interpolation step in DIFF_PREP. For each dataset, the first B0 image was selected as the reference for registration. Prior to registration, diffusion weighted and structural images were upsampled at a factor two and smoothed with a Perona-Malik anisotropic edge favoring gradient based filter to compute the transformations from moving to fixed images. After computation of transformations, original images were used to create the registered images. Bspine correction was done with the T2 weighted image (approximated from a T1 image using AFNI’s FATCAT). Diffusion and structural images were resampled to 1.5mm isotropic voxels. Gradient tables were rotated along with motion correction. To obtain a summary measure of motion, the root-mean-square (RMS) was calculated both for absolute (RMSabs) and relative (RMStrel) movement. Datasets with RMSabs of greater than the voxel edge length were excluded from further analysis. Tensors were computed with DIFF_CALC using a linear fitting algorithm. To spatially normalize diffusion images to the Illinois Institute of Technology atlas (IT2) space, we implemented an optimized non-linear image registration using a modified version of 3DQwarp in AFNI. The warping optimization implements an iterative refinement, where an input image is repeatedly processed through an optimizer in smaller and smaller patches, incorporating convergence criteria at each patch level to better resolve artifacts, with a final patch size of 3x 5x 3 mm. To assess whole brain voxel-wise group differences and changes over time in scalar indices used AFNI’s 3dttest++ (age, sex, and RMSstdev as covariates) with clustsim, a bootstrapping method used to correct for multiple comparisons.

Results: Mean age of patients was 26.62 years, 62% of subjects were male. Of the 42 patients included here, 33 completed the study. BPRS total scores decreased significantly after six weeks of treatment, average risperdone dose at that time was 3.73±1.72mg. Fractional anisotropy (FA) was significantly decreased in a small area of the medial temporal lobe and mean