Abnormalities in fronto-parietal white matter microstructure may be associated with increased risk for schizophrenia.

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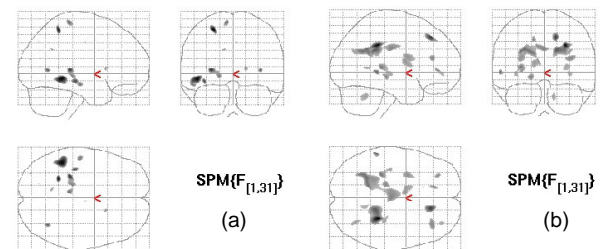
Introduction: Morphometric analyses of structural MRIs have revealed widespread abnormalities of gray matter in young first-degree relatives of schizophrenia patients [1]. These results suggest that abnormal neurodevelopment may characterize increased vulnerability for schizophrenia in individuals at genetic risk for the illness. However, it is unknown whether white matter abnormalities also characterize vulnerability in this high-risk population (HR-S). This question is of importance because cortico-cortical dysconnectivity is presumed to be a key feature of schizophrenia [2]. One approach to understanding dysconnectivity in HR-S is to assess microstructural alterations in white matter tracts in key areas of the cortex. Such alterations may assume functional significance if they are associated with impaired performance on tasks that depend on intact connections between key heteromodal areas of the brain. The oculomotor delayed response task (ODR) is a task of spatial working memory that depends on intact fronto-parietal communication. Subjects must maintain memory for a spatial location in the periphery of vision for a brief delay period; at the end of the delay, they are required to make an eye-movement to the location. In this task, tonic frontal lobe activity to maintain information occurs in collaboration with spatial encoding in the parietal lobe [3]. The ODR task provides a window into neurodevelopment, and its performance is impaired in HR-S subjects [4]. Our goal was to use voxel-based morphometry (VBM) [5] to assess the relationship between alterations in white matter microstructure and ODR performance in HR-S subjects compared to a healthy control (HC) sample. Particularly, we were interested in whether impaired performance on the ODR task would be correlated with abnormalities in fronto-parietal white matter microstructure.

Methods: Subjects were 19 young first-degree relatives of schizophrenia patients (mean age=15.4 yrs, 8 females) and 18 healthy control subjects (mean age=14.6 yrs, 9 females) with no family history of mental illness. Eye movement studies in HR-S were conducted using infrared (IR) recordings in a dark room. During a trial subjects were instructed to maintain fixation at a central cue. Memory targets were presented briefly (100 ms) in the horizontal plane toward the left or right of center of fixation. Subjects were instructed to remember the peripheral target's location while continuing to fixate their gaze at the fixation cue. After a delay period (8 s), subjects were cued to direct their gaze to the remembered location of the target in the periphery. The principal dependent variable of interest was the distance in visual angle (°) between the location of the final resting eye-position and the actual target location (lower ° indicates higher accuracy). HR-S were separated into high performing (HR-S$_{HP}$), and low-performing (HR-S$_{LP}$) groups based on a median split of error performance in the ODR task. HR-S$_{HP}$ (n=9) performed significantly more accurately than HR-S$_{LP}$ (n=10), (2.51° vs. 5.82°, t_{17}=6.32, p<.0001) but did not differ in terms of age or gender (p>.25). T$_1$-weighted SPGR images (124 1.5 mm thick contigual coronal slices) were collected on a 1.5T G.E. system for all 37 subjects. VBM analyses were conducted using SPM 99 [6]. The T$_1$-weighted images were spatially normalized into stereotactic space and segmented into gray, white and CSF compartments using probabilistic classification. White matter images were subsequently smoothed by convolving with a Gaussian smoothing kernel (12 fwhm). Initial contrasts were established to compare each of the two HR-S sub-groups with HC (with age and gender used as covariates). This analysis assessed whether white matter abnormalities were more extensive in HR-S$_{LP}$ than HR-S$_{HP}$. Further analyses were conducted to investigate correlations between ODR performance and white matter concentration in the entire HR-S sample. A preset threshold (p=0.005, uncorrected) was employed to identify suprathreshold voxels in all the analyses.
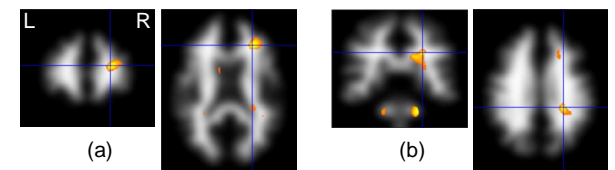
Results: Figure 1 depicts maximum intensity projections of suprathreshold clusters ($F_{(1,31)}$>9.13) visualized on orthogonal glass brain views. As can be seen, compared to HC, reductions in white matter concentration were more extensive in the HR-S$_{LP}$ (Figure 1b) than the HR-S$_{HP}$ (Figure 1a) sub-group. These results suggest that increased fronto-parietal white matter deficit is associated with impairment on the ODR task. The nature of this relationship was further investigated within the HR-S group by regressing ODR errors against white matter concentration for all 19 subjects. Significant negative correlations were observed in frontal, parietal and cerebellar white matter indicating that reductions in white matter concentration were highly correlated with the degree of impairment on the ODR task. Significant clusters in frontal cortex (Figure 2a) and parietal cortex (Figure 2b) are projected on the coronal and axial planes of a smoothed white matter map.

Figure 1. Whole-brain reductions in white matter concentration for each HR-S sub-group are depicted in glass brain orthoviews. (a) HR-S$_{HP}$ < HC (b) HR-S$_{LP}$ < HC.

Figure 2. Significant negative correlations between ODR errors and white matter concentration are visualized on coronal and axial planes of an individual white matter map (left=left). (a) Cross hairs are centered on the significance peak in right middle frontal white matter, t_{16}=4.82, Talairach coordinates (x=27, y=35, z=17 mm). (b) Cross hairs are centered on the significance peak in right parietal white matter, t_{16}=5.13, Talairach coordinates (x=27, y=-34, z=35 mm).

Discussion: Reductions in white matter concentration measured from MRI images may reflect aberrant tissue microstructure resulting from processes such as abnormal myelination [7]. White matter abnormalities have increasingly been associated with schizophrenia reinforcing the idea of the illness being characterized by cortico-cortical dysconnection [8]. The current results provide suggestive evidence of emergent fronto-parietal dysconnection during adolescence in individuals at risk for schizophrenia (Figure 1). This dysconnection may be an important characteristic of vulnerability to the illness and may be expressed in impaired performance on neurobehavioral tasks (such as the ODR) that rely on fronto-parietal function. The resultant negative correlations between the degree of task impairment and white matter pathology (Figure 2) indicate that morphometric techniques and neurobehavioral tasks may be conjunctively used to probe abnormal structure and function relationships that may underlie risk for neuropsychiatric illnesses such as schizophrenia.

References: 1. Job DE, Whalley HC, McConnell S, Glabus M, Johnstone EC, Lawrie SM, *Schiz Res* **64**, 1-13 (2003). 2. Friston KJ, *Acta Psychiatr Scand Supp.* **395**, 68-79 (1999). 3. Chafee MV, Goldman-Rakic PS, *J Neurophysiol* **83**, 1550-1566 (2000). 4. Diwadkar VA, Sweeney JA, Boarts D, Monstrose DM, Keshavan MS, *CNS Spectrums* **6**, 899-903 (2001). 5. Ashburner J, Friston KJ, *NeuroImage* **11**, 805-821 (2000). 6. Wellcome Dept. Cogn. Neurol, London, http://www.fil.ion.ucl.ac.uk/spm. 7. Flynn SW, Lang DJ, Mackay AL, Goghari V, Vavasour IM, Whittall KP et al., *Mol Psychiatry* **8**, 811-820 (2003). 8. Lim KO, Helpern JA, *NMR Biomed* **15**, 587-593 (2002).