Abnormality of variance of resting state fMRI signal in white matter for schizophrenia

Hu Cheng[1], Jerillyn Kent[1], Mallory Klaunig[1], Dae-Jin Kim[1], Brian O'donnell[1], William Hetrick[1], and Aina Puce[1]
[1]*Indiana University, Bloomington, IN, United States*

Introduction: White matter abnormality in Schizophrenia (SZ) has been demonstrated by both structural MRI and diffusion tensor imaging (DTI)[1,2]. Studies have shown decreased fractional anisotropy and increased diffusivity in frontal, parietal, occipital, and temporal lobes, as well as abnormalities within the fiber bundles connecting these regions (e.g. uncinate fasciculus). In addition, wide-spread disruption of functional connectivity among different brain regions has been shown in SZ patients by evaluating the correlation of time courses from resting state functional MRI[3]. Recently, abnormalities in the amplitude of low frequency resting state fMRI signal have been observed in SZ patients[4]; notably, variance of BOLD amplitude in task fMRI has been correlated with task performance and decreases with aging[5]. Besides thermal noise, the variance of MRI signal can be induced by physiological activities (e.g. respiratory movement, neurovascular circulation) and neuronal activity. Therefore, the variance of resting state MRI signal carries diverse information related to the tissue properties, physiological conditions, and cognitive states. To date, studies of BOLD variance have been applied only to gray matter; however, an extension to the whole brain analysis holds promise. In this report, we examined the variance of the signal in resting state fMRI across the whole brain, and found significant differences between schizophrenia patients and non-patient controls (NC).

Methods: 1. Subjects recruitment: 13 SZs (8 male, mean age 36.7 ± 9.9 years) and 8 NCs (5 male, mean age 26.6 ± 6.0 years) were recruited and completed the study protocol. Diagnosis was determined using the Structured Clinical Interview for the DSM-IV (SCID-IV) and medical chart review. The SCID-IV for non-patients was used to confirm that there was no history of Axis I disorders in the NCs. Participants were excluded for neurological illnesses of loss of consciousness lasting more than 5 minutes. Alls NCs were given and passed a urine screen for illicit substances. MRI scans: subjects were scanned on a Siemens TIM Trio 3 T scanner using a 32-channel coil. The resting fMRI scan was first performed with EPI sequences (TR/TE = 2500/30 ms, FOV = 220 mm, 128×128 matrix, iPAT2, 200 volumes), during which the subjects were at rest with eyes closed. Then the high resolution (1 mm^3) anatomical scan was performed with MP-RAGE sequence. Data processing: the functional images were motion corrected, coregistered with the anatomical image, and then normalized to the MNI standard template using FSL (http://www.fmrib.ox.ac.uk/fsl/). Gaussian smoothing with 8 mm kernel was then applied to the normalized images. The smoothing can effectively reduce the thermal noise but has little effect on the physiological noise, which is spatially correlated. After that, the slowly varying drift from the scanner was removed from the time series of each voxel using quadratic detrending. Then, the temporal noise was computed as the standard deviation of the voxel-wised time course. The temporal noise is dominated by physiological noise, but can be dramatically influenced by the sensitivity of the coil. The coil sensitivity varies with distance between the imaged brain and the coil. Those voxels closer to the coil tend to have higher signal and noise because physiological noise is proportional to the signal strength. To get rid of this confounding effect for multi-subject comparisons, the temporal signal-to-noise ratio (TSNR) was computed for each voxel by dividing the signal intensity to the standard deviation. Statistics: the TSNR image of both SZ patients and controls were input to SPM5 (Wellcome Department of Cognitive Neurology, London, UK) for two-sample t-test. We used $P < 0.05$ (uncorrected) with a cluster size of > 50 voxels and $P < 0.001$ (uncorrected) with a cluster size of > 20 voxels as statistical thresholds for the final results.

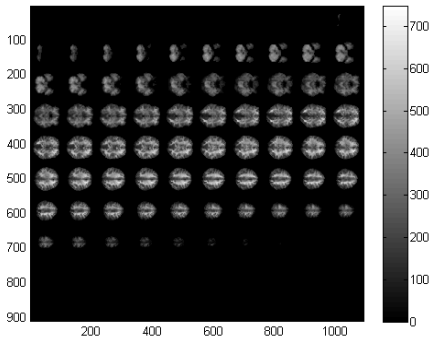

Fig. 1. An example of the TSNR map.

Results: A TSNR map from one subject is shown in Fig. 1 as an example. The TSNR map shows very good contrast between the white matter and gray matter/CSF because the physiological noise is much lower in the white matter. The results of two-sample t-test of TSNR between SZ patients and controls are displayed in Fig. 2. The controls showed higher TSNR mainly in the white matter, clustered in several regions including temporal, frontal, and parietal lobes, cerebellum, anterior cingulate, and major white matter tracts. White matter abnormalities in these regions have been previously reported in SZ. On the other hand, only few small regions show higher TSNR for SZ. As a more conservative threshold was used, the difference in temporal lobe remained significant.

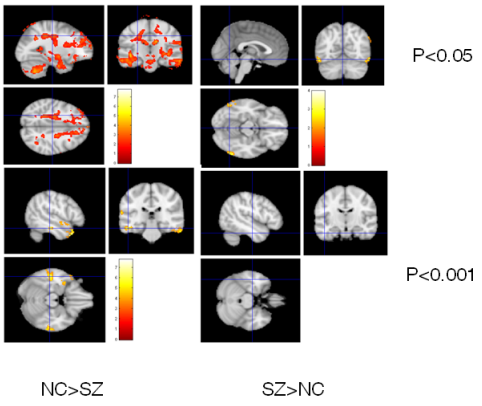

Fig. 2. Regions showing significant difference between SZ and NC

Discussion: Although the underlying mechanism is far from clear, application of this new analysis method revealed pronounced differences between schizophrenia patients and normal controls. The differing regions converge with those found to be impaired in DTI studies of SZ[2]. Volumetric changes of white matter or aberrant white matter microstructure could account for increased variance of the resting state signal in white matter, but other factors such as neuronal activity may also contribute to the variance. Because of the rich information in the variance of resting fMRI signal across time, the TSNR analysis approach could complement existing methods such as voxel-based morphology analysis, diffusion tensor imaging, and functional connectivity.

References: 1. Whitford T., Am J Psychiatry. 2007; 164:1082-89. 2. White T. et al, Schizophr Bulletin. 2011, 37:222-232. 3. Liang M. et al., NeuroReport. 2005; 17:209-213. 4. Hoptman M. et al., Schizophr Res. 2010; 117:13-20. 5. Garrett D., et al., J. Neurosci. 2010; 30:4914-21.