

Functional Connectivity Correlations in the Cortical-Thalamic Network of Patients with Schizophrenia using fMRI and DTI

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Hypotheses of functional disconnection (lack of communication) between different brain regions attempt to explain several psychiatric disorders. In the case of schizophrenia, it has been proposed that the cortical-thalamic pathways are disrupted. This disconnect can be due to a damage to the connecting pathways (white matter tracts) or due to an imbalance of neurochemistry. In the past these two mechanisms of disconnected communication have been investigated 'indirectly' using synchronous analysis of functional brain imaging data (e.g. PET & fMRI) or directly by looking at the integrity of white matter tracts using Diffusion Tensor Imaging (DTI) [1,2]. Here we sought to investigate the nature of this disconnect by simultaneously looking at the relationship between two schizophrenia abnormalities: 1) the synchronous activation signal in two functionally connected areas in the brain; with 2) the integrity of the interconnecting white matter fibers.

Methods: Schizophrenic subjects (n=9) between the ages of 20-68 were recruited from outpatients psychiatric facilities. The diagnosis of schizophrenia was confirmed by a structured diagnostic interview (Comprehensive Assessment of Psychiatric Symptoms and History; CASH). Drug testing and medical screening was performed to exclude patients with substance abuse and cardiovascular disease that might affect MRI results. All imaging were performed on a 3T Allegra MRI scanner (Siemens, Erlangen, Germany). DTI was acquired using a pulsed-gradient spin-echo sequence with EPI-acquisition (TR=4100ms, TE=80ms, FOV=21cm, matrix=128x128, 32 slices, thickness=3mm skip 1mm, b-factor=1250 s/mm², 12 gradient directions, 5 averages). Whole brain Diffusion Tensor data was obtained and fractional anisotropy (FA) indices were computed using in-house software [3]. Functional MRI BOLD images were acquired with a gradient echo-planar sequence in the same slice locations as the DTI using the following protocol: 32 axial slices, 3mm skip 1mm, TR=2s, TE=30 ms, flip angle=90°, FOV=21 cm, matrix size=64x64. The N-Back working memory task using letters from the English alphabet was implemented on using the E-Prime software (Psychology Software Tools, Inc.). Three Bold scans were obtained on each subject using the 0,1 and 2-back conditions. fMRI data was analyzed using SPM2 (Wellcome Department of Cognitive Neurology, London). Images were motion corrected, smoothed (6mm x 6mm x 6mm) and coregistered to a matching T2 weighted image. Functional synchrony was accessed using in-house developed software using Matlab 7.0 (The MathWorks, Inc Natick MA). The software allowed the user to trace an arbitrary region of interest (ROI) and then compute the product-moment-correlation coefficient of all the other voxels in the brain with respect to the time series of the selected ROI. Significant voxels are then super imposed on the anatomical MRI. To investigate the cortical thalamic connection we traced the thalamus as the reference ROI. Correlation coefficients in the voxels in the dorso-lateral-prefrontal-cortex (DLPFC) that were significantly correlated with the activity of the reference ROI was then obtained (Fig. 1). These then serve as a measure of the functional synchrony between those two regions. To access the structural component of the connectivity between these two ROIs we obtained the FA index of the white matter between these two ROIs. The FA values were obtained in portions of the ipsilateral internal capsule (Fig 2).

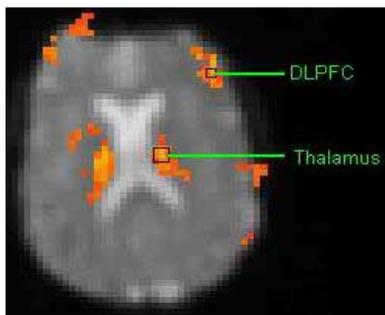


Figure 1. Significant BOLD correlation coefficients with respect to thalamic activation time course.

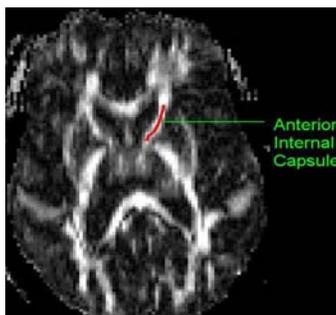


Figure 2. Fractional Anisotropy ROI in the internal capsule.

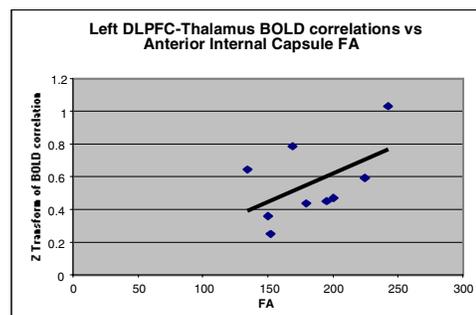


Figure 3. Correlation between FA of internal capsule and thalamo-DLPFC BOLD synchrony.

Results: The Bold correlation values were first Z-transformed to generate a normal distribution. Subsequent analysis was performed by computing the correlation between the transformed functional BOLD correlation values and the FA indices. The r-value of this correlation was 0.53 with $p < 0.09$ for the two hypothesized region (Fig 3).

Conclusion: Here we have presented a novel analysis approach to functional connectivity study by using fMRI and DTI as complementary modalities. The findings show that the functional disconnection in the cortical-thalamic pathways may be the result of defective wiring (white matter) between these two regions.

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2. Ardekani, B.A., Nierenberg, J. et al., Neuroreport, 2003. **14**(16): p. 2025-9.
3. Basser, P.J., et al. NMR in Biomedicine, 1995. **8**: p. 333-344.