Differences between bipolar disorder patients and control subjects using a new SPM Toolbox for Track-Based Spatial Statistics

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Introduction: A growing body of research findings has implicated aberrant white matter connectivity in the neuropathophysiology of bipolar disorder (BD). While the extent to which such abnormalities are related to disease onset and course is yet uncertain, recent findings support the validity of Diffusion Tensor Imaging (DTI) as a means of exploring the relationship between white matter connectivity and bipolar disorder. Multiple abnormal fiber tracts connecting frontal-limbic brain regions have been identified in BD, including the uncinate fasciculus and the cingulum [1]. The purpose of this study was to examine the differences in diffusion tensor imaging data between bipolar patients and healthy control subjects using the methodology of Track-Based Spatial Statistics (TBSS) [2-4] and our newly developed SPM TBSS Track Toolbox. We chose to examine one white matter fiber tract, the cingulum given its potential role in the pathophysiology of BD.

Methods: Twenty-four euthymic bipolar subjects (mean age 34.13, s.d. 11.9, 13 males and 11 females) and seventeen healthy control subjects (mean age 29.5, s.d. 7.9, 7 males and 10 females) were used in the study. All subjects were screened for a history of neurologic disorder, medical illness and psychiatric illness other than bipolar disorder. Images were acquired using a 3.0T Siemens MR scanner. DTI data were acquired in the axial plane using a diffusion weighted standard single shot, double spin echo, echo planar protocol. Multiple diffusion-weighted images were acquired using a single diffusion "b" weighting value of 1000 sec/mm2. MRI acquisition parameters were: TE/TR = 81ms/5sec; matrix = 128 x 128 on a 20cm FOV; slice thickness = 5mm with no gap. Images were analyzed in the new SPM TBSS Track Toolbox, which consists of four main processing steps: (1) preprocessing (motion correction of diffusion data, estimation of diffusion tensor and fractional anisotropy FA maps in SPM Diffusion Toolbox, and erosion on FA maps, (2) normalization using SPM's nonlinear registration algorithm based on cosine basis functions, (3) calculation of mean FA skeleton using FSL's TBSS "thinning" algorithm based on non-maximum suppression, and (4) projection of individual FA maps onto the mean skeleton. The group differences were analyzed using the individual subjects' FA skeletonized images and the two-sample t-test in the second-level SPM analysis ($p < 0.001$, with a minimum cluster-size threshold k set at 20 contiguous voxels). The region of interest (cingulate gyrus) was selected using WFU Pickatlas utility (Maldjian et al 2003), and significant clusters of group differences were determined according the statistical threshold of $p<0.001$, and k=20.

Results: TBSS analysis was performed in SPM for the contrasts comparing healthy control subjects with the bipolar patients. The t-tests were calculated for all subjects' FA data projected onto individual skeletons. These results indicate that bipolar disorder patients had significantly lower FA within a focal region of the cingulate gyrus compared to control subjects. Statistically significant voxels (77 voxels , $p<0.001$) were identified for all skeletonized data and are illustrated in red on Figure 1. Four clusters within the cingulate gyrus were found to have significantly lower FA (T=4.51 at x=11, y=-31, z=31; T=3.79 at x=16, y=24, z=43; T= 3.71 at x=8, y=-4, z=37; and T=3.36 at x=-17, y=-10, z=50). Data were superimposed on the FA skeleton images in the coronal, sagittal and axial planes.
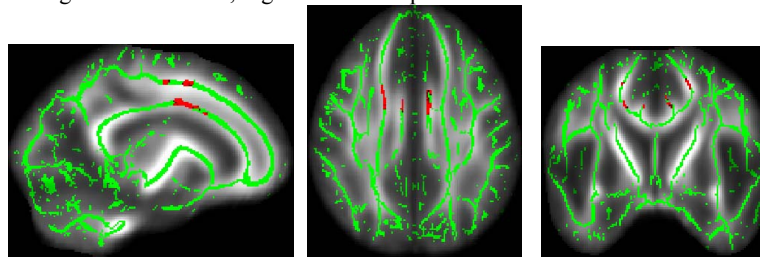

Figure 1. TBSS in FSL for contrast: Controls>Bipolar Patients. Statistically significant voxels for skeletonized data in cingulate gyrus are displayed in red, while the mean FA skeleton for all subjects is displayed in green.

Conclusions: In this study we applied automated tract-based analysis to DTI data to investigate white matter changes in the cingulate gyrus in patients with bipolar disorder. We found significant differences in the cingulate when patients were compared with normal controls. Voxel-wise differences in DTI indices were assessed using TBSS, which increases the sensitivity and the interpretability of the results compared with voxel-based approaches based purely on non-linear registration [2]. These findings contribute to a growing literature reporting white matter abnormalities in bipolar disorder [5] and suggest that DTI techniques can highlight microstructural abnormalities in the brain, not evident on conventional MRI, which may be associated with the neuropathology of this disorder.

References
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