

Widespread disruption of white matter myelin revealed from a relatively large scale of bipolar DTI study

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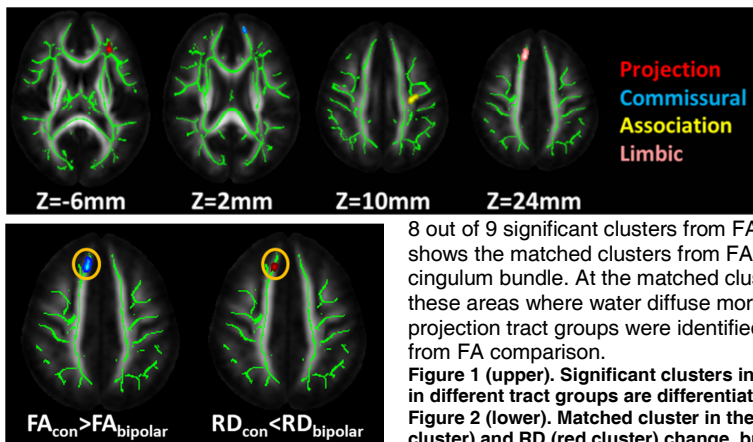
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Target Audience: Clinicians and MR physicists interested in identifying biomarkers of patients with bipolar disorder.

Introduction: Bipolar disorder (BD) is one of the most potentially disabling mental disorders, associated with high rates of psychological suffering, marked functional and economic impact, and elevated risk of suicide. Over the last two decades, neuroimaging studies have provided valuable information on the pathophysiology of this condition (e.g. 1, 2). White matter (WM) abnormalities are among the most consistent brain imaging findings in bipolar disorder. Metrics derived from diffusion tensor imaging (DTI), namely fractional anisotropy (FA), mean, axial and radial diffusivity (MD, AD and RD) are sensitive to microstructural changes of WM and can be used to infer the microstructural disruption of WM in various psychiatric conditions, including BD. Specifically, FA and MD are widely used to evaluate the integrity of WM microstructure. RD is sensitive to myelin changes and AD has been used to infer axonal damage [3]. Brain WM is often categorized into different tract groups including limbic, commissural, association and projection tracts. The WM tracts within a tract group perform similar functions. In this study, DTI has been applied to a relatively large sample (49 bipolar patients and 28 age-matched controls) to find if disruption of WM is widespread covering four functionally distinct tract groups and if demyelination constitutes the major neuropathology associated with BD.

Methods: Subjects and data acquisition: The sample consisted of 49 adult bipolar patients (age: 29.27 ± 7.92 years; 17 males, 32 females; 34 BD-I, 10 BD-II, and 5 BD-NOS) and 28 age-matched normal subjects (age: 29.19 ± 7.35 ; 10 males and 18 females). The subjects were recruited through local media advertisements and flyers posted in public areas. All patients met the DSM-IV-R criteria for BD. The diagnosis of BD among patients and the absence of mental disorders among controls were confirmed through the Structured Clinical Interview for DSM Disorders (SCID), which was administered to all participants by trained evaluators. Subjects with any significant medical conditions were excluded, as were those with neurological disorders or current use of illegal drugs. DTI scans were acquired using a 3T Siemens Allegra scanner using a spin echo-planar imaging protocol. Image acquisition parameters included; Repetition time=9200 ms, echo time=79 ms, slice thickness =2mm, imaging matrix=128x104, voxel size=2mm, b-value =1000 sec/mm². Group comparisons of WM microstructures with TBSS: DTI metrics were then computed and skull stripped for processing in TBSS (FSL4, <http://www.fmrib.ox.ac.uk/fsl/>) after correction of eddy current distortion. FA maps of both bipolar and control subjects were affine and then non-linearly registered to a MNI template FA map. FA, AD, RD, and MD were projected onto the skeleton from averaged FA map for group comparison and compared using voxelwise statistics. Prior to voxelwise statistics, the design test matrix was modified for removal of age and sex dependencies. Randomization was performed in FSL with 5000 iterations and a cluster threshold was used ($p < 0.001$). Only clusters with a minimum of 5 voxels were retained to reduce false positives due to noise.

Results: Widespread disruption of WM integrity: 9 significant clusters (5 in association, 2 in projection, 1 in commissural and 1 in limbic) spread across projection, commissural, association and limbic tract groups were identified from FA comparison. Table 1 lists the mean FA values of BD and control groups at these clusters. FA values in BD brains are significantly lower than those in control brains at these clusters. The largest cluster containing 32 significant voxels is located in limbic tract group. Fig. 1 demonstrates the four representative clusters covering all four tract groups. Disruption of myelination: 17 significant clusters (7 in association, 9 in projection and 1 in limbic) were also identified from RD comparison. Table 2 lists the mean RD values of BD and control groups at these clusters. RD values are significantly higher in BD brains than those of control brains at these clusters. The locations of



8 out of 9 significant clusters from FA comparison match to those from RD comparison. As an example, Fig. 2 shows the matched clusters from FA comparison (left of Fig. 2) and RD comparison (right in Fig. 2) in the cingulum bundle. At the matched clusters, the decreases in FA for BD patients are related to demyelination in these areas where water diffuse more freely radially. 4 significant clusters belonging to association and projection tract groups were identified from AD comparison and none of these locations matches to those from FA comparison.

Figure 1 (upper). Significant clusters in all four functionally distinct tract groups from FA comparison. The clusters in different tract groups are differentiated with different cluster colors.

Figure 2 (lower). Matched cluster in the cingulum bundle, highlighted with yellow circle, with significant FA (blue cluster) and RD (red cluster) change, but no significant AD change.

Discussion and Conclusion: With analysis of DTI data from a relatively large cohort of patients, it suggests that the WM integrity changes in BD are not restricted to a specific tract group such as commissural tract group [1] found previously, but are distributed to all four functionally heterogeneous tract groups. The matched locations for most of the significant clusters revealed from FA comparison to those revealed from RD comparison suggest that demyelination, rather than axonal damage, play an important role in WM microstructural changes of BD patients. These DTI metrics will be correlated to behavior test scores to facilitate understanding the relationship between behavior changes and the underlying WM microstructural changes.

Tract group	Commissural	Association					Limbic	Projection		
Tract	Fminor	SLF-L	SLF-R	IFO-L #1	IFO-L #2	UNC-L	CGC-R	CST-R	ATR-L	
FA(ctr)	0.321	0.406	0.358	0.356	0.420	0.405	0.388	0.573	0.379	
FA(BD)	0.270	0.365	0.270	0.306	0.355	0.347	0.328	0.537	0.320	

Table 1. The mean FA values at the significant clusters. FDR corrected $p < 0.001$ for all these clusters. Abbreviations: ATR/PT: anterior/posterior thalamic radiation; CGC: cingulum bundle in cingulate gyrus; CST: corticospinal tract; Fmajor/Fminor: forceps major/minor of CC; IFO: inferior fronto-occipital fasciculus; SLF: superior longitudinal fasciculus; UNC: uncinate fasciculus. L/R: Left/Right.

Tract group	Association							Limbic	Projection								
Tract	SLF-L #1	SLF-L #2	SLF-L #3	IFO-L	IFO-R #1	IFO-R #2	ILF-L	CGC-R	CST-L	CST-R #1	CST-R #2	CST-R #3	CST-R #4	CST-R #5	ATR-L #1	ATR-L #2	ATR-R
RD(ctr)	0.566	0.525	0.492	0.462	0.444	0.411	0.486	0.501	0.474	0.361	0.485	0.461	0.511	0.443	0.514	0.518	0.560
RD(BD)	0.647	0.563	0.540	0.552	0.485	0.465	0.549	0.570	0.511	0.397	0.515	0.498	0.563	0.481	0.566	0.586	0.603

Table 2. The mean RD values at the significant clusters. FDR corrected $p < 0.001$ for all these clusters. See legend of Table 1 for abbreviations.

References: [1] Wang et al (2008) Biol Psychiatry 64:730. [2] Pavuluri et al (2009) Biol Psychiatry 65: 586. [3] Song et al (2003) Neuroimage 17: 1429.

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