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## Reduced white matter integrity and verbal fluency impairment in young adults with bipolar disorder: a diffusion tensor imaging study

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## Abstract

**Background**—Clinical evidence shows that bipolar disorder (BD) is characterized by white matter (WM) microstructural abnormalities. However, little is known about the biological mechanisms associated with these abnormalities and their relationship with cognitive functioning.

**Methods**—49 adult BD patients ((M±SD): 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 ((M±SD): 29.19 ± 7.35 years; 10 males and 18 females) underwent diffusion tensor imaging (DTI) imaging. DTI metrics were computed using whole-brain tract-based spatial statistics (TBSS) as part of the FMRIB Software Library. Measures of WM coherence (fractional anisotropy - FA) and axonal structure (mean, axial and radial diffusivity - MD, AD and RD) were employed to characterize the microstructural alterations in the limbic, commissural, association and projection fiber tracts. All participants performed the Brief Assessment of Cognition for Affective disorders (BAC-A).

**Results**—BD patients performed poorly on verbal fluency tasks and exhibited large clusters of altered FA, RD and MD values within the retrolenticular part of the internal capsule, the superior and anterior corona radiata, and the corpus callosum. Increased FA values in the left IFOF and the forceps minor correlated positively with verbal fluency scores. Altered RD parameters in the corticospinal tract and the forceps minor were associated with reduced visuomotor abilities.

**Conclusions**—The reported verbal fluency deficits and FA, RD and MD alterations in WM structures are potential cognitive and neural markers of BD. Abnormal RD values may be associated with progressive demyelination.

## Keywords

bipolar disorder; diffusion tensor imaging; cognitive; demyelination; TBSS

## Introduction

Bipolar disorder (BD) is a devastating illness with significant functional and social consequences for both affected individuals and their relatives [1, 2]. In BD the alternation of periods of euphoria and periods of depression is accompanied by significant cognitive impairment that persists during the euthymic and acute phases [3-6]. In particular, BD patients have been shown to present with deficits in visual motion perception [7], visuomotor speed, visual and verbal memory, sustained attention [5, 6, 8-11] and conceptual reasoning [12].

Microstructural abnormalities in white matter (WM) fiber tracts connecting to the limbic-striatal, cingulate, thalamus, corpus callosum and prefrontal regions have been observed in children, adolescents and adults with BD [13-20]. The corpus callosum and thalamic radiation of middle-aged and drug-naïve BD populations showed abnormal axial (AD) and radial diffusivity (RD) values [21-23]. Increased RD values have been observed in the cingulum, the superior and inferior uncinate fasciculus, the corpus callosum and the internal capsule of BD I patients when compared to their unaffected relatives and healthy controls [24]. Another study found similar abnormalities in the hippocampus, thalamus and caudate nucleus [25]. The reduction in WM integrity observed in BD has been linked to

processes of demyelination, cerebral hypoperfusion, neuroinflammation and reduced mitochondrial metabolism [25, 26] but there is little empirical evidence supporting either of these biological hypotheses.

Diffusion tensor imaging (DTI) is a non-invasive neuroimaging technique that enables visualization of the WM fibers, and characterization of microstructural changes based on the degree of water diffusion at a voxel and regional level. Traditional metrics derived from DTI are fractional anisotropy (FA) and mean, axial and radial diffusivity (MD, AD and RD). FA represents the proportion of water diffusion parallel to the axons compared to that perpendicular to the axons. AD and RD estimate water diffusivity along and across the axons, and MD is a linear combination of AD and RD where  $MD = (AD + 2 \cdot RD) / 3 = 1/3 \cdot AD + 2/3 \cdot RD$ . While a decrease in FA in projection fibers such as the thalamic radiation and the posterior corona radiata has been associated with disruptions in the overall WM organization, FA abnormalities in association tracts (e.g. longitudinal fasciculus) and commissural fibers (corpus callosum) have been linked to poor intra- or interhemispheric connectivity [27]. Further, findings from animal studies indicate that increased AD values may reflect axonal injury, and that RD values increase as a result of demyelination processes [28-30].

To date only a limited number of studies has investigated the relationship between DTI metrics and cognitive functioning in BD. A recent publication found WM alterations in the corpus callosum and the anterior thalamic radiation bilaterally in middle-aged BD I patients when compared to healthy controls [21]. Notably, the authors found a positive correlation between problem solving abilities and FA, MD and RD values in the thalamic radiation and fornix in BD but not in the HC group. In another study middle-aged BD I patients showed decreased FA values in the internal capsule, the right uncinate fasciculus and the corpus callosum along with decreased accuracy in set shifting and risk taking tasks [31]. In adolescents with BD I reduced mean FA values in fiber tracts connecting to fronto-temporal and cingulate regions were associated with psychomotor retardation on the Trail Making Test [32]. These findings show a link between WM abnormalities and reduced visuomotor processing speed and executive functions. It is, however, unclear whether this relationship is specific to BD I or represents a trait marker of the bipolar illness. Further, considering that the brain morphology changes considerably over the lifespan [33-35], it is difficult to compare the results of these studies as they included adolescents and middle-aged adults. Another potential confounding factor is related to the type of cognitive tests employed in previous studies as they may not be suitable for assessing cognition in BD.

Thus, the purpose of this study is to elucidate the relationship between WM integrity and cognitive functioning in young adults by using multiple parameters of WM integrity and the Brief Assessment of Cognition in Affective Disorder (BAC-A) – a well-validated cognitive battery designed specifically for BD [36]. Based on previous findings we expected to find WM abnormalities in the BD group when compared to HC. We also predicted to find positive correlations between indices of WM integrity and memory, visuomotor processing and executive scores, as these cognitive domains have been found to be impaired in BD.

## Materials and methods

### Participants

The sample included 49 adult BD patients ( $M\pm SD$ : 29.10 $\pm$ 7.86 years; 19 males, 30 females; 34 BD-I, 10 BD-II, and 5 BD-NOS) and 28 age-matched healthy controls (HC) ( $M\pm SD$ : 29.03 $\pm$ 7.34 years; 9 males and 19 females). Patients were recruited from inpatient and outpatient clinics of the University of North Carolina at Chapel Hill (UNC). HC 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 ascertained by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders Axis I (SCID I) [37], which was administered to all participants by an independent psychiatrist or trained research assistant. The interview also included the Montgomery–Åsberg Depression Rating Scale (MADRS) [38] and the Young mania Rating Scale (YMRS) [39]. Functional impairment was evaluated using the Global Assessment of Functioning (GAF) which is Axis V of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR) [40]. Participating BD patients and HC were aged between 18 and 48 years, had no history of substance abuse in the previous 6 months and no current medical problems. 41 of the 49 BD participants took psychotropic medication at the time of enrollment. HC with a history of any Axis I disorder in first-degree relatives and use of psychoactive medication less than 2 weeks prior to the start of the study were excluded. All female participants underwent a urine pregnancy test and urine drug screen to exclude pregnancy and illegal drug use. Subjects suffering from chronic medical issues including cardiovascular and neurological disorders were excluded. The study protocol was approved by the local Institutional Review board and informed consent was obtained from all the participants.

### Imaging data acquisition and image processing

All imaging was performed on a 3T Siemens Allegra scanner at the UNC imaging facility. Whole-brain diffusion-weighted images were acquired using a spin echo-planar imaging protocol. Image acquisition parameters included: repetition time=9200 ms, echo time=79 ms, slice thickness=2mm, imaging matrix=128 $\times$ 104, voxel size= 2mm, b-value =1000 sec/mm<sup>2</sup>. Two images without gradient loading (b-value =0 s/mm<sup>2</sup>) were acquired prior to the acquisition of 30 directions (each containing 80 slices) with uniform gradient loading (b<sub>0</sub> = 1000 s/mm<sup>2</sup>). To correct for eddy currents we used the first b<sub>0</sub> image as a template. In addition to diffusion-weighted images we also acquired T1-weighted structural images for the purpose of anatomical localization.

### DTI processing

The FMRIB's Diffusion Toolbox (FDT) within FSL (<http://www.fmrib.ox.ac.uk/fsl>) was used to preprocess diffusion weighted images and correct for eddy current distortions. FA maps of both BD and control subjects were affine and then non-linearly registered to an MNI template. FA images were created by fitting a tensor model to the raw diffusion data using the DTIFIT Reconstruct Diffusion Tensor tool. Brain Extraction Tool (BET) was used to remove non-brain tissue from images of the brain with a fractional intensity threshold of

0.3. DTIfit was then used to fit the diffusion tensor to each voxel thus creating voxel-wise maps of FA, AD, RD and MD.

Voxelwise statistical analysis of data was carried out using Tract-Based Spatial Statistics (TBSS) within FSL. All subject's FA data were affine-registered to MNI152 space using the FSL nonlinear registration tool FNIRT. The mean FA image was created and optimized to create a mean FA skeleton to represent common tracts among all individuals. Individual subjects' FA data was projected onto this skeleton. Voxelwise statistics across subjects (adjusted for gender and age) were carried out on each point of the FA skeleton using permutation-based non-parametric testing (RANDOMISE - as implemented in FSL), using 5000 permutations [40] to compare differences between BD patients and HC. A false discovery rate (FDR) correction was used to correct the threshold for multiple comparisons and the minimum threshold of statistical significance was set at  $p < 0.01$ . Based on the results of the voxel-wise analyses, we superimposed significant clusters containing 5 voxels on the Johns Hopkins University (JHU)-ICBM-DTI-81 WM labels atlas and extracted FA, RD, MD and AD values for each participant.

### Cognitive performance

All participants were administered the Wechsler Abbreviated Scale of Intelligence (WASI) a screener of verbal, non-verbal, and general cognitive ability [41] and the reading test of the Wide Range Achievement Test-4 (WRAT-4), which is a measure of premorbid intellectual quotient (IQ) [42]. Cognitive functioning was assessed by the Brief Assessment of Cognition in Affective Disorders (BAC-A) [36]. The BAC-A has been found to have strong psychometric properties in patients with BD Type I compared to HC and takes approximately 35 minutes to administer [36]. It assesses psychomotor speed, memory, attention and executive functions and comprises the following tests: Token Motor, Symbol Coding, List Learning, Digit Sequencing, the Category Instances/Controlled Oral Word Association Test and the Tower of London [43]. In addition to these 6 subtests the BAC-A includes the Emotional Stroop task [44] and the Affective interference test - a non-affective auditory verbal learning test similar in structure to the Auditory Verbal Learning Test (AAVLT) [45].

**Emotional Stroop test**—Participants are presented with sheets of papers with 4 columns of words of either neutral or affective polarity in colored (red, blue, green and yellow) or blank ink. They are then instructed to either read the words (Word naming) or the color of the words (Color naming) going down the columns. Participants are given 30 seconds to read as many words as they can on each page. The goal of this task is to determine the individual's ability to suppress irrelevant stimuli and read a word whose meaning identifies a different color from the color of presentation of the word (Interference). The Interference index is calculated by subtracting the number of correct responses to emotional words during the Color naming condition from the number of correct responses to emotional words during the Word naming condition. This index was adjusted for the number of correctly identified neutral words during the “Word” and “Color naming” conditions. The following formula was used: (Emotional Word Naming *divided by* Word Naming) *minus* (Emotional Color Naming *divided by* Color naming).

**Affective interference**—In this task participants are given three trials to learn 10 non-affective words (fruits and vegetables) and 10 affective words (.e.g. “cancer,” “triumphant,” “enraged”). After a 20-minute delay, recognition memory is tested by presenting the initial 20 words (10 emotional and 10 fruits and vegetables) along with 20 words that had not been presented earlier. This task evaluates components of short-term and delayed affective and non-affective memory.

The scores on the BAC-A were summarized in eight cognitive domains: *visuomotor* (number of correct responses on the Symbol coding and Token Motor tasks), *short-term affective memory* (number of correctly recalled words during the affective learning trials of the Affective Interference test), *short-term non-affective memory* (number of correct words during the non-affective learning trials of the List Learning and Affective Interference tests and number of correct answers on the Digit Sequencing task), *delayed affective memory* (number of correct words during the delayed free recall of affective words of the Affective Interference test), *delayed non-affective memory* (number of correct words during the delayed free recall of non-affective words of the Affective Interference test), *fluency* (number of correct responses on the Category and Controlled Oral Word Association tests), *inhibition* (Interference index of the Stroop task) and *problem solving* (number of correct responses on the Tower of London test).

## Statistical analyses

Statistical analyses were performed using IBM SPSS statistics (Version 21.0). Normality of each variable was investigated. Where appropriate, outliers were winsorised. Demographic, clinical and cognitive differences between groups were assessed with  $\chi^2$ -square and multivariate analyses of variance (MANOVA). Age and the WRAT-4 Reading score were entered as covariates in analyses on the BAC-A cognitive summary scores. Pearson's correlation coefficients were measured to explore the relationship between cognitive functioning and DTI metrics in the BD sample. Individuals with a MADRS score  $\geq 20$  (marker of moderate to severe depression) were excluded from the correlational analyses. This is based on previous evidence suggesting that measures of cognitive functioning collected during the severe phase of depression are not reliable indicators of individuals' mental abilities [46]. Demographic and cognitive results were considered to be statistically significant at a Bonferroni-adjusted *p-value*  $<.05$ .

## Results

### Group characteristics

Demographics and clinical features for BD and HC are reported in Table 1. There was no significant difference in age and gender between the two groups. Pre-morbid IQ (estimated by the reading score of the WRAT-4) was significantly reduced in BD patients compared to HC. The mean MADRS score of our BD sample was 16.82 (SD: 12.33) which is an indicator of mild to moderate depression. However, 15 subjects had a score  $\geq 20$ , a marker of moderate to severe depression.

## DTI metrics

As illustrated in Figures 1 and 2, BD patients exhibited reduced FA and increased RD and MD values in all major WM tracts. The largest clusters ( $> 10$  voxels) with abnormal FA values were located within the right corticospinal tract, the left superior longitudinal fasciculus (L-SLF), the left inferior fronto-occipital fasciculus (IFOF) and the forceps minor. Altered RD values were found within the right corticospinal tract and the IFOF bilaterally.

By superimposing these results on the JHU-ICBM-DTI-81 atlas clusters with reduced FA were found to be located in the right retrolenticular portion of the internal capsule and the right superior corona (see Table 1S). Clusters with increased RD were situated in the right posterior limb and the right retrolenticular portion of the internal capsule, the left anterior corona radiata, and the superior corona radiata bilaterally (Table 2S). Increased MD values were found in the body of the corpus callosum and the right superior corona radiata (Table 3S).

## Cognitive performance

Multivariate analyses showed a significantly reduced verbal fluency performance in BD patients [ $F(1,53)=7.19, p=.01, \eta^2=.12$ ]. Secondary analyses showed that BD patients generated a lower number of S-words [ $F(1,56)=6.09, p=.017, \eta^2=.09$ ] and names of animals [ $F(1,56)=6.61, p=.013, \eta^2=.106$ ] compared to HC (Figure 3).

## Cognitive performance and DTI metrics in BD

In the BD sample affective and non-affective short-term memory scores correlated negatively with the RD values in the left superior corona radiata ( $r=-.55, p=.017$  STM;  $r=-.49, p=.04$  STNM). The MD values in the right corticospinal tract were inversely related to short-term affective and non-affective memory ( $r=-.52, p=.02$ ;  $r=-.52, p=.026$ ), and delayed affective memory ( $r=.49, p=.04$ ) (Figure 4S).

## Discussion

The purpose of the current study was to examine WM integrity and its relationship with cognitive functioning in a group of young adults with BD. We performed unbiased whole-brain TBSS analyses and found that clusters with reduced FA and altered (increased) RD and MD values were predominantly located in the retrolenticular part of the internal capsule, the superior and anterior corona radiata, and the corpus callosum. These DTI abnormalities are consistent with previous results in BD [47] and provide valuable insight into the relationship between the integrity of WM pathways and the deficits in cognitive processing observed in BD. Indeed the internal capsule and the corona radiata are important WM nodes that facilitate the transfer of sensorimotor and cognitive information between the brain stem, the thalamus, and the fronto-striatal circuit [20, 48]. Further, the corpus callosum mediates the transfer of interhemispheric information, which is crucial for higher order cognitive functions, and exhibits morphological abnormalities in mood disorders [49, 50].

Increased FA values in WM fibers connecting to the frontolimbic and cingulate regions have consistently been reported in previous DTI studies in BD [47, 51, 52]. By contrast, only a

small number of studies has examined markers of water diffusivity such as RD and AD. These parameters are important as they provide information on the nature of the microstructural changes observed in BD [22, 51]. Animal models of WM injury show that elevated RD and MD values reflect a surge in brain water mobility and possibly reduced integrity of the axonal wall [53]. Other studies indicate that increased RD values are associated with myelin dysfunction [28-30]. Further, findings from postmortem brain studies in BD patients are consistent with the hypothesis that glial dysfunction and a reduced number of myelinating cells (e.g. oligodendrocytes) contribute to the pathophysiology of BD [54]. In addition, myelin genes have been found to be underexpressed in BD patients [55, 56]. Thus, the reported alterations in RD and MD values may be due to processes of myelin degeneration [57].

In this study cognitive functioning was assessed using the BAC-A, a comprehensive and well-validated cognitive battery for BD [36, 58]. Compared to HC, BD patients performed poorly on tests of verbal fluency and generated a reduced number of S- and animal words. Furthermore, in BD patients with a MADRS score < 20 reduced performance in affective and non-affective short-term memory tasks was associated with altered RD and MD values within the right superior corona radiata and corticospinal tract. Verbal fluency impairment has been previously reported in the literature on BD [5, 6, 10, 59-65] and has been linked to executive dysfunction [66], inefficient information retrieval techniques [67] and poor verbal skills [59, 60]. Given the participants' preserved vocabulary scores on the WASI, the present results suggest that poor planning and/or word retrieval skills may be potential explanations for the impaired verbal fluency skills observed in our BD sample. Further, the significant correlations between short-term memory and DTI metrics provide preliminary evidence for a potential association between white matter integrity and cognitive functioning in BD. In particular, the corticospinal tract is involved in semantic processing [68], an important mechanism underlying high order cognitive functions typically impaired in BD such as memory [6].

One of the strengths of the current study is the heterogeneity of the sample in terms of BD subtype as previous studies restricted their analyses to type I BD. Thus the reported changes in WM integrity and related cognitive deficits could be considered as being markers for BD. Furthermore, in this study cognitive functioning was assessed using the BAC-A, a comprehensive cognitive battery that has been recently validated in a sample of middle-aged depressed BD patients [36]. A potential confounder is that the majority of BD participants took one or more psychotropic medications. Psychotropic medications have been associated with volumetric changes in the fronto-limbic and hippocampal regions [69-71]. However their effects on the WM structure remain unexplored. It is noteworthy that we found significant differences in WRAT-4 scores, but not in WASI, between BD and HC. A possible explanation for the divergent results could be related to the smaller number of data points available for the WRAT-4 (42 BD /18 HC) compared to the WASI (45 BD/26 HC). In other words, it is possible that a larger number of WRAT scores in the HC group would have led to a less pronounced mean difference between HC and BD. Although our BD sample did not include rapid cyclers, at least 15 participants reported experiencing more than 30 manic or depressive episodes (up to a maximum of 100). This is the primary reason for the high mean lifetime number of mood episodes observed in Table 1 ( $20 \pm 34.02$  for



depressive episodes and  $7.108 \pm 11.83$  for manic episodes). However, given that these figures are based on self-report these findings should be interpreted with great caution and rather be viewed as “rough” estimates of illness chronicity in our sample.

It is noteworthy to mention that we chose the FDR correction over the more traditional threshold-free cluster enhancement (TFCE) because the TFCE correction would have required two optimization parameters to give proper weights to clusters depending on their height and spatial extent [70]. This cannot be known prior to analysis, thus different data may potentially require different parameters. To address this issue we used the FDR correction – a conventional correction method used in previous DTI studies [72, 73]. FDR clustering method may result in false positives located away from the cluster's “true” center. Despite this potential spatial error we were able to associate tracts to their cluster locations.

In summary, our findings provide evidence of the association between aberrant WM fiber integrity and cognitive deficits in young adults with BD. The reported impairment in verbal fluency and changes in WM integrity in fiber tracts connecting to the internal capsula, the corona radiata and the corpus callosum may serve as cognitive and neural markers of BD. The abnormalities in FA and RD observed in these regions could be related to mechanisms of progressive demyelination.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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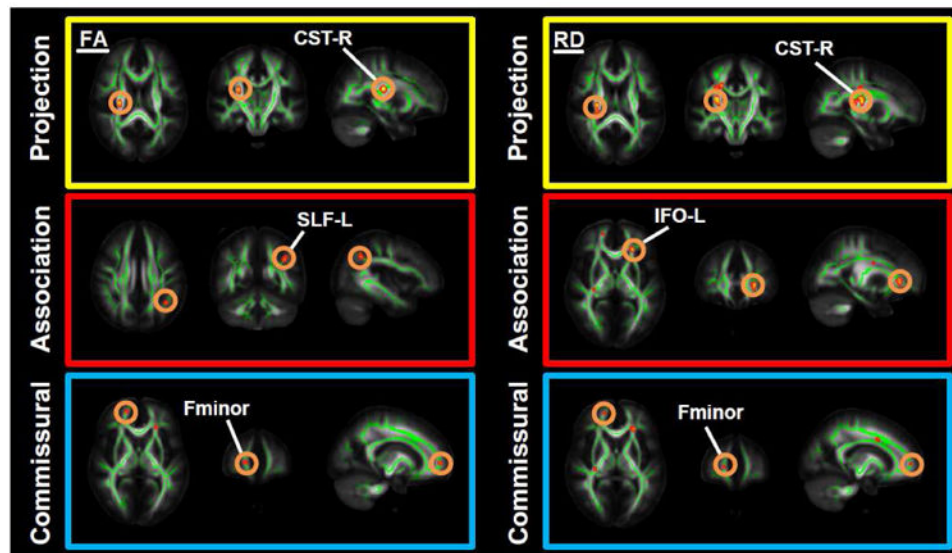
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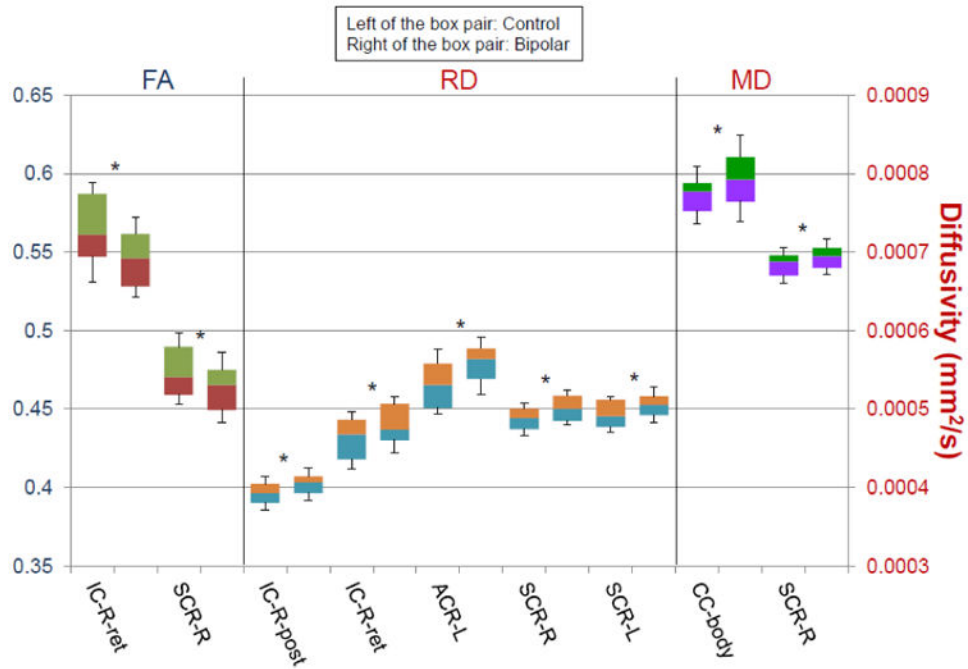
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### Highlights

- Tract-based spatial statistics for the whole-brain estimation of DTI parameters.
- BD patients displayed abnormal FA, RD and MD values in major white matter tracts.
- Cognitive functioning was assessed with the BAC-A.
- BD patients exhibited verbal fluency deficits.
- Abnormal DTI values were associated with reduced cognitive performance.



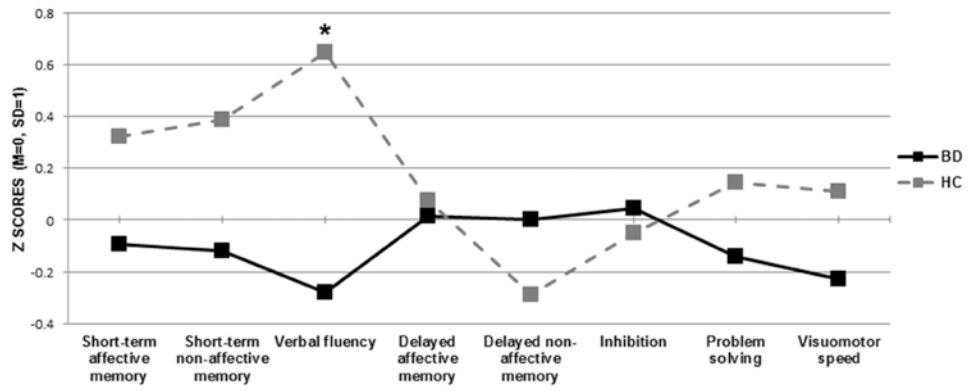
**Figure 1.** Results from TBSS analyses showing differences in fractional anisotropy (FA) and radial diffusivity (RD) in bipolar patients (BD) versus healthy controls (HC). Voxels are superimposed on the white matter skeleton (green). The background images are MNI152 template (MNI - Montreal Neurological Institute). Yellow-red clusters represent abnormalities in FA and RD in commissural, association and projection fibers (FDR-corrected  $p < 0.01$ ). Abbreviations: CST-R: right corticospinal tract, SLF-L: left superior longitudinal fasciculus, IFO-L: left inferior fronto-occipital fasciculus, Fminor: forceps minor.



**Figure 2.**

Mean fractional anisotropy (FA), radial diffusivity (RD), and mean diffusivity (MD) values in the retrolenticular part of the internal capsule (IC-ret), the posterior limb of internal capsule (IC-post), the superior corona radiata (SCR), the anterior corona radiata (ACR), and the body of the corpus callosum (CC-body) of BD patients (right of the box pair) and HC (left of the box pair). Tracts are labeled with reference to the JHU ICBM-DTI-81 white-matter labels atlas. L and R denote the left and right hemispheres. \*FDR-corrected  $p < .05$ .





**Figure 3.** Mean standardized scores of the eight cognitive summary scores of the BAC-A in BD patients and HC; Inhibition refers to the interference index of the Emotional Stroop test; \*Bonferroni-corrected  $p < .05$ .

**Table 1**  
**Demographic and clinical characteristics of the sample**

Group	N (BD/HC)	Bipolar disorder	Healthy Controls	$p/\chi^2$
		Mean (SD)		
Gender Male/female, N	49/28	19/30	9/19	.37
Age (years)	49/28	29.10(7.86)	29.03(7.34)	.97
WRAT Reading	42/18	104.57(15.18)	118.94(16.89)	.002
WASI Vocabulary	45/27	57.15(12.84)	59.59(11.5)	.42
WASI Matrix	45/26	54.13(7.50)	55.73(6.56)	.37
WASI Full Scale IQ	45/26	110.44(14.093)	114.46(13.27)	.24
YMRS	45/27	6 (5.68)	.40(.63)	.00
MADRS	35/16	16.82(12.33)	0	.00
GAF	37/15	60.32(12.59)	92.27(4.301)	.00
Age of onset of mood disorders (years)	41/0	20.85(6.87)	-	-
Lifetime number of manic episodes	46/28	7.108 (11.83)	-	-
Lifetime number of depressive episodes	43/28	20 (34.02)	-	-

Abbreviations: GAF: Global Assessment of Functioning, MADRS: Montgomery-Åsberg Depression Rating Scale, YMRS: Young Mania Rating Scale, WASI: Wechsler Abbreviated Scale of Intelligence, WRAT: Wide Range Achievement Test.