Anatomical Connectivity Changes Can Differentiate Patients with Unipolar Depression and Bipolar Disorders

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Abstract

Objective: Unipolar depression and depressive episodes of bipolar disorder have similar symptoms and their differential diagnosis is crucial because each disorder has different prognostic and therapeutic characteristics. The main aim of the current study was to investigate white matter alterations as measured by fractional anisotropy in individuals with bipolar disorder (BD) and unipolar depression (UD) using tract-based spatial statistics and to find out if these alterations can help to make a differential diagnosis between these two disorders.

Methods: Tract-based spatial statistics is a sensitive method of whole-brain analysis that relies on the voxel-based comparison. It uses nonlinear image transformation and permutation tests with correction for multiple comparisons. The study consisted of total number of 107 subjects; whom were diagnosed clinically at least by two different psychiatrists and their data were reviewed by another psychiatrist retrospectively. Whole-brain diffusion tensor images of 41 patients with bipolar disorder type 1, 43 patients with unipolar depression and 23 healthy controls were acquired using a 1.5 Tesla magnetic resonance imaging scanner. The results were analyzed with 1. Whole brain analysis, 2. Region of Interests (ROI) analysis followed by machine learning methods: Genetic Algorithm and Kernel Logistic Regression.

Results: Compared to controls, UD and BD subjects showed reduced FA in several white matter tracts (p<0.05). However, the age range of clinical groups was wider. To eliminate errors due to this difference in age ranges, we eliminated individuals from clinical groups and equalized the age ranges with that of the control group. However, even after restricting the age range of UD and BD subjects group, the results remained the same. As compared to UD group, BD group showed significant FA reductions (p<0.001, uncorrected) in the following white matter tracts: corticospinal tract, anterior thalamic radiation in the right hemisphere, and inferior longitudinal fasciculus in the left hemisphere. There were not any significant reductions in the UD group as compared to the BD group. Whole-brain analysis did not show significant group difference between patients diagnosed bipolar disorder and unipolar depression after statistical corrections were applied. However, ROI analysis followed by machine learning showed that patients with unipolar depression and bipolar disorder could be discriminated with a classification accuracy of 85.83% using logistic regression method.

Conclusion: Due to the small number of study in the literature, which directly compared patients with unipolar depression and bipolar disorder, the current study aims to improve the understanding of the etiology and pathogenesis of bipolar disorder and unipolar depression. The results of the present study are consistent with the current understanding of bipolar disorder neurobiology. This may mean that fractional anisotropy values can be used as a biomarker to differentiate bipolar disorder from unipolar depression if further confirmed by larger studies.

Keywords: Bipolar Disorder, Unipolar Depression, Tract-Based Spatial Statistics, White Matter

INTRODUCTION

Bipolar disorder (BD) is a chronic disorder, characterized by recurring depressive and manic episodes (1). Depressive episodes are seen more frequently and persists longer in the duration of the BD (2,3). Similarly, unipolar depression (UD) is associated with recurrent depression without manic episodes. In clinical settings, it may be difficult to distinguish the BD and UD group due to their similar clinical features. Already, 69% of individuals with BD are initially misdiagnosed with UD (4). However, the clinical course, prognosis and – most importantly – treatment of the two affective disorders significantly differ and therefore it is crucial to make a differential diagnosis between these two affective disorders. For example, this misdiagnosis may result in inadequate treatment, higher risk of suicidality and higher costs for treatment (5). Therefore, there is an increasing need for an adequate understanding of
the underlying mechanisms of these disorders and to determine biomarkers to establish a correct diagnosis at the initial presentation.

Biomarkers are important in that they can be quantitatively assessed independently from symptoms and therefore may provide an objective diagnostic accuracy. The first biomarker candidates were neuroimaging findings. The brain imaging techniques like functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), electroencephalogram (EEG) etc. provide new approaches to detect the functional and structural brain abnormalities. One of the promising non-invasive methods is DTI, which has allowed investigating the structural connectivity of neuronal tissue by measuring the diffusion of water in white matter tracts (6,7). For example, structural connectivity findings showed that BD is characterized with decreased anisotropy values in the frontal lobes, internal capsule, uncinate fasciculus and corpus callosum, while UD is associated more with white matter alterations in hippocampus and uncinate fasciculus (8,9). Based on the limited number of studies, more widespread alterations in white matter tracts have been reported in patients with BD compared to UD.

Although most of the above-mentioned studies used manually determined regions of interest (ROI) based approaches and the main limitation of these ROI studies is that they give information only about prespecified regions. However, recent advances in DTI analysis methods have allowed to compare the whole brains of patients with voxel-based statistics called tract-based spatial statistics (TBSS). TBSS uses nonlinear image transformation and permutation tests with a correction of multiple comparisons and does not require smoothing. Thus, TBSS provide sophisticated solutions for smoothness and alignment problems while evaluating white matter alterations (10). The whole brain approaches using more powerful statistics are more likely to identify the underlying neural basis of BD and UD (11).

Due to the fact that TBSS is a relatively new method, there are not many studies that used it to investigate white matter integrity in BD and UD. Relatively few studies compared directly the white matter pathways of individuals with BD and UD rather than comparing them separately with healthy controls (HC). The study of Versace et al. (2010) could be the first example, which compared the white matter integrity of individuals with BD and UD using TBSS and found that individuals with BD type 1 have reduced fractional anisotropy (FA) in the left superior longitudinal fasciculus (SLF) in the inferior temporal cortex compared to individuals with recurrent UD (12). Besides, there are a limited number of studies reporting consistently decreased FA values in individuals with BD in the following regions as compared to UD: in the anterior part of corpus callosum, left posterior cingulum (13), right corticospinal tract using whole brain analysis and the genu of the corpus callosum, posterior cingulum bundle using ROI analysis (14). However, there is a growing need for structural neuroimaging studies using whole brain analysis, larger samples sizes, and comparing individuals with BD and UD.

The aim of the current study is three-fold. First, connectivity alterations in BD and UD is investigated using whole brain analysis method, TBSS. As earlier studies showed reduced FA in white matter tracts in individuals with BD compared to UD, in this study we aimed to verify previous findings using a more sophisticated analysis method (TBSS). Our second aim was to obtain information about the pathophysiology of UD and BD by detecting white matter alterations in BD and UD as compared to controls. Our third aim was to determine discriminative ROI's for classification of UD and BD and the accuracy of machine learning methods for discriminating BD from UD patients. For these aims a two-fold analysis was made. 1. A whole-brain voxel-wise analysis to explore for group differences, 2. Machine learning analysis using FA values from individual ROIs.

**METHODS**

**Participants**

The study consisted of 107 subjects: 43 individuals with UD, 41 individuals with BD type 1 and 23 healthy controls. Patients were administered a structured interview and diagnosed based on Diagnostic and Statistical Manual of Mental Disorders fifth ed. (DSM-5), with a consensus of 2 psychiatrists (1). The UD group included 22 males and 21 females aged 14-62 years (mean age: 36.19±12.75 years) that met the DSM-5 criteria for UD. The BD group included 23 males and 18 females aged 15-60 years (mean age: 33.51±10.13 years) that met the DSM-5 criteria for BD. The control group included 14 males and 9 females aged 20-45 years (mean age: 30.52±6.50 years) with a negative history of the neurological and psychiatric disease. For selection of the clinical group participants, we retrospectively evaluated hospital records and included all participants that had a diagnostic interview and DTI data.
The study protocol was approved by the Üsküdar University Ethics Committee (27.09.2017, B.08.6.YÖK.2.ÜS.0.05.0.06/2017/234) and was performed in accordance with the Declaration of Helsinki. The control group provided written informed consent. However, the UD and BD patients were identified retrospectively based on hospital records and therefore informed consent was not taken.

**Data Acquisition**

The 1.5 Tesla Philips Achieva MRI scanner (Philips Medical Systems, Best, Netherlands) with a SENSE 8-channel head coil were used acquiring the whole brain images at NPIstanbul-Üsküdar University, Istanbul, Turkey. All DTI data were based on a single-shot spin-echo echo-planar imaging (EPI) sequence. The imaging parameters of DTI data were as follows: repetition time (TR): 9024.51 ms; echo time (TE): 66.752 ms; acquisition matrix: 128×128; flip angle: 90°; voxel size: 1.75 mm×1.75 mm×2 mm; slice thickness: 2 mm; slice spacing: 2 mm. One b0 image without diffusion weighting and 16 non-collinear gradient directions were acquired with a single b-value of 800 s mm⁻².

**Data Analysis of Imaging Data**

In the current study, we used tract-based spatial statistics for the whole-brain analysis (TBSS version 1.0, FMRIB Center, Oxford, United Kingdom), a software package implemented in FSL version 5.0 software (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl/) [10,15]. Eddy module is used for correcting original data for the effects of movements. After the eddy-current correction, brain was extracted using BET, and the diffusion tensor was calculated with the DTIFIT program for creating a single FA image from each subject in the study. Then, the standard TBSS procedure was applied on the data (10,16).

All individual FA volumes were registered to the FMRIB58 template using nonlinear registration. Then, the nonlinearly aligned images are merged into a single 4D image file and the mean of all FA images was created. All individual FA data were thinned to generate a mean FA skeleton. For the mean FA skeleton image, a standard FA threshold of 0.2 was chosen. Following these steps, the 4D projected FA data were fed into voxelwise cross-subject statistical analyses with following group comparisons; control vs. UD, control vs. BD and UD vs. BD. The threshold-free cluster-enhancement (TFCE) with the “3D” parameter settings was used for multiple comparisons (17). The null distribution was built up over 5000 permutations, and significance was tested at <0.001 levels, corrected (comparisons with the control group) and uncorrected (comparison between UD and BD) for multiple comparisons. Furthermore, significant voxels in white matter tracts were determined using the JHU White Matter Tractography Atlas (18,20).

**Statistical Analysis**

A t-test and the chi-square tests were used to compare age and gender variables respectively between the 3 groups. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 22) and p<0.05 was used for statistical significance.

**Machine Learning: Feature Selection and Classification**

The ROI data was used for discrimination of UD and BD based on 20 ROI’s. The ROI’s were ATR_L, ATR_R, Cingulate_L, Cingulate_R, Corticospinal_L, Corticospinal_R, Forceps_Major, Forceps_Minor, Hippocampus_L, Hippocampus_R, IFOF_L, IFOF_R, ILF_L, ILF_R, SLF_L, SLF_R, SLF_T_L, SLF_T_R, UF_L, UF_R. In this study we have used Genetic Algorithms along with Kernel Logistic Regression for feature selection and classification.

GA is an optimization algorithm that is inspired by natural evolution. GA works by having generations of populations where a population is composed of chromosomes that are candidate solutions to the optimization problem (21). Within the context of this study, GA was used for feature selection that is choosing the most discriminative and complementary features to be used in the classification model.

An initial population was created randomly, where each chromosome was composed of 1’s and 0’s namely the genes and each gene represented a feature in the feature vector (1 means the corresponding feature was used and 0 means it was unused). Each chromosome was evaluated using logistic regression classifier as a fitness function and the chromosomes with higher fitness values had higher probability of moving to the next generation. Next generation was then created by applying selection, crossover and mutation to the current population. The process of creating next generations was repeated either until a specific number of generations was created or the best solution in the population was not improved in last 10 generations. The maximum number of generation was set to 200.
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The Followings are The Steps of Genetic Algorithm:

- Generate a random population of n chromosomes, in this study n was set to 50. The length of each chromosome was 20 since we had 20 features (ROI’s). Evaluate the fitness of each chromosome in the population. The features selected by corresponding chromosome was fed into the classifier and the classification accuracy was used as the fitness of the chromosome.

- Create the next generation. Half of the next generation was created using non-dominated sorting selection, remaining half of the next generation was created using selection, crossover and mutation.

- In the selection process, two chromosomes are selected as parents. The chromosomes with higher fitness values has better chances of being selected. In the crossover process, two parents are used for producing two offspring’s. In this study we have used uniform crossover.

In the mutation process, each gene of offspring’s were changed from its initial state (0 is changed as 1 and vice versa) based on the mutation probability which was set to 0.01 in this study.

The offspring’s are placed in the next generation. Selection, crossover and mutation was repeated until n chromosomes are placed in the next generation.

If the maximum number of generations is reached or the best solution in the population was not improved in the last 10 generations stop the algorithm else go to step 2. The maximum number of generations was 200 in this study.

Logistic Regression is a modelling algorithm that is widely used for classification. LR model utilizes the logistic function to scale the model output between 0 and 1. The LR function is defined as;

\[ LR(x) = p(y|x) = \frac{1}{1 + e^{-(\beta_0 + \sum_{i=1}^{n} \beta_i x_i)}} \]

Here the \( \beta_0, \beta_1, \beta_2, ..., \beta_n \) are logistic regression coefficients and \( x_1, x_2, x_3, ..., x_n \) is the feature vector. The logistic regression function provides the probability of assigning particular input \( x \) to class \( y \) (22).

LR is a linear model but has the limitation of not being able to classify the data with nonlinear boundaries. Kernel logistic Regression (KLR) overcomes this problem by so called “kernel trick”, where the input data is transformed to a high dimensional space and linear modelling is used for classification of input data. This way a linear algorithm in the high dimensional feature space will operate like a nonlinear algorithm in original feature space. There are several kernel functions that are widely used in the literature such as linear, radial basis function and polynomial [23]. In this study, we have used Gaussian Combination (GC) kernel function. This kernel function was selected as it was providing the best discrimination ability amongst radial basis, polynomial and linear kernels. GC kernel function is defined as;

\[ K(x_i, x_j) = e^{-\frac{(x_i-x_j)^2}{\sigma_1}} + e^{-\frac{(x_i-x_j)^2}{\sigma_2}} - e^{-\frac{(x_i-x_j)^2}{\sigma_3}} \]

An exhaustive search approach was used for optimizing \( \sigma \) parameters where \( \sigma_1=0.1, \sigma_2=0.1 \) and \( \sigma_3=0.6 \).

RESULTS

As the age variable met the assumptions for normality, independent samples t-test was used to check for group differences. Gender differences were analyzed using c2 test. (see Table 1a and Table 1b). The results showed that there was no significant difference in age (t(82)=-1.06, p=0.29; Table 1) and gender(c2(1,84)=0.20, p=0.65) between the UD and BD groups. The genders of UD subjects were not significantly different from controls (c2(1,66)=0.57, p=0.45). Otherwise, there was a significant variation between the ages of controls and UD group (t(63.921)=2.39, p=0.02). Neither gender nor ages were significantly different between BD group and controls (c2(1,64)=0.14, p=0.71; t(62)=1.27, p=0.21).

Table 1a. The descriptive statistics for age in three groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
<th>Comparison</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD</td>
<td>33.51</td>
<td>10.13</td>
<td>BD-UD</td>
<td>1.06</td>
<td>0.29</td>
</tr>
<tr>
<td>UD</td>
<td>36.19</td>
<td>12.75</td>
<td>BD-Control</td>
<td>1.27</td>
<td>0.21</td>
</tr>
<tr>
<td>Controls</td>
<td>30.52</td>
<td>6.501</td>
<td>UD-Control</td>
<td>2.39</td>
<td>0.02</td>
</tr>
</tbody>
</table>

BD: Bipolar Disorder, UD: Unipolar Disorder

As compared to UD group, BD group showed significant FA reductions (p<0.001, uncorrected) in the following white matter tracts: corticospinal tract, anterior thalamic radiation in the right hemisphere, and inferior longitudinal fasciculus in the left hemisphere (Table 2, Figure 1). There were not any significant reductions in the UD group as compared to the BD group.
Compared to controls, UD (Figure 2) and BD subjects (Figure 3) showed reduced FA in several white matter tracts (p<0.05, corrected) (Table 3). However, as can be seen in the table, the age range of clinical groups was wider. To eliminate errors due to this difference in age ranges, we eliminated individuals from clinical groups and equalized the age ranges with that of the control group. However, even after restricting the age range of UD and BD subjects group, the results remained the same (Table 2).

**Table 2.** The significantly lower FA values in the individuals with BD compared with UD

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Voxels</th>
<th>p value</th>
<th>MAX X (mm)</th>
<th>MAX Y (mm)</th>
<th>MAX Z (mm)</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>0.001</td>
<td>-50</td>
<td>-15</td>
<td>-13</td>
<td>Inferior longitudinal fasciculus L</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0.001</td>
<td>23</td>
<td>-12</td>
<td>14</td>
<td>Corticospinal tract R</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0.001</td>
<td>1</td>
<td>-19</td>
<td>-4</td>
<td>Anterior thalamic radiation R</td>
</tr>
</tbody>
</table>

TFCE uncorrected results. Max X, Y, Z values describe the MNI coordinates of maximum group difference. BD: Bipolar Disorder, UD: Unipolar Disorder, L: Left, R: Right, TFCE: threshold-free cluster-enhancement

**Figure 1.** Significant TBSS FA results showing the contrast UD > BD (p<0.001, uncorrected). TBSS: Tract Based Spatial Statistics

**Table 3.** Clusters showing significantly reduced FA values in UD subjects and BD patients compared with age-matched and non-age-matched control subjects

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Voxels</th>
<th>p value</th>
<th>MAX X (mm)</th>
<th>MAX Y (mm)</th>
<th>MAX Z (mm)</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>C &gt; UD</td>
<td>166879</td>
<td>0.001</td>
<td>-3</td>
<td>-33</td>
<td>-43</td>
<td>Corticospinal tract</td>
</tr>
<tr>
<td>C &gt; UD (age-matched)</td>
<td>171266</td>
<td>0.001</td>
<td>8</td>
<td>-33</td>
<td>-42</td>
<td>Corticospinal tract</td>
</tr>
<tr>
<td>C &gt; BD</td>
<td>168311</td>
<td>0.001</td>
<td>11</td>
<td>-35</td>
<td>-39</td>
<td>Corticospinal tract</td>
</tr>
<tr>
<td>C &gt; BD (age-matched)</td>
<td>169969</td>
<td>0.001</td>
<td>13</td>
<td>-35</td>
<td>-39</td>
<td>Corticospinal tract</td>
</tr>
</tbody>
</table>

TFCE corrected results, Max X, Y, Z values describe the MNI coordinates of maximum group difference. BD: Bipolar Disorder, UD: Unipolar Disorder, FA: Fractional Anisotropy, TFCE: threshold-free cluster-enhancement

**Figure 2.** Significant TBSS FA results showing the contrast C > UD (p<0.05, corrected). TBSS: Tract Based Spatial Statistics

**Figure 3.** Significant TBSS FA results showing the contrast C > BD (p<0.05, corrected). TBSS: Tract Based Spatial Statistics
The results of feature selection and classification for discrimination of UD and BD based on ROI’s data is given in Table 4. Table 4 shows the confusion matrix as well as class recall and class precision rates. Using logistic regression method UD and BD patients were discriminated with an overall accuracy of 85.83%. The results of feature selection is also listed in Table 5. Using GA approach the features were either selected (marked 1) or not selected (marked 0). The table shows that 6 out of 20 features were selected as discriminative ROI’s for this classification task. The selected discriminative ROIs are as follows: Right cingulate, right inferior frontooccipital fasciculus, right superior longitudinal fasciculus, forceps major, left corticospinal tractus and left uncinated fasciculus.

Table 4. Confusion Matrix, Class Recall and Class Precision for KLR classification

<table>
<thead>
<tr>
<th></th>
<th>UD – Actual</th>
<th>BD – Actual</th>
<th>Class Precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>UD – Predicted</td>
<td>35</td>
<td>6</td>
<td>85.37%</td>
</tr>
<tr>
<td>BD – Predicted</td>
<td>6</td>
<td>37</td>
<td>86.05%</td>
</tr>
<tr>
<td>Class Recall</td>
<td>85.37%</td>
<td>86.05%</td>
<td></td>
</tr>
</tbody>
</table>

BD: Bipolar Disorder, UD: Unipolar Disorder, KLR: Kernel Logistic Regression

Table 5. The list of selected features with GA approach

<table>
<thead>
<tr>
<th>ROI</th>
<th>Selected (marked 1)</th>
<th>Not Selected (marked 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATR_L</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>ATR_R</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Cingulate_L</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Cingulate_R</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Corticospinal_L</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Corticospinal_R</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Forceps_Major</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Forceps_Minor</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Hippocampus_L</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Hippocampus_R</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>IFOF_L</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>IFOF_R</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>ILF_L</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>ILF_R</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>SLF_L</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>SLF_R</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>SLF_T_L</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>SLF_T_R</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>UF_L</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>UF_R</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>


DISCUSSION

The present study used voxel-based TBSS method to compare the FA values of individuals with BD and UD. The results demonstrate that the UD and BD groups showed lower FA levels in similar white matter tracts, as compared to the control group. Moreover, the individuals with BD has lower FA values in several tracts in both hemispheres. These tractus differences successfully discriminated UD and BD patients with high accuracy.

Cingulate bundle belongs to the well-known Papez circuit and involved in core cognitive processes such as memory, pain, and emotion (24).

Reduction of this tractus in BD as compared to UD, may be related to more severe emotional control problems seen in BD. Similarly several studies reported trait-related difficulties in BD involving emotion recognition and regulation. Uncinate fasciulus is a bundle that connects temporal lobe and frontal lobe. Studies suggest that it is involved in episodic memory, language and emotional processing (25). Forceps major is the posterior part of the corpus callosum that connects occipital lobes. Abnormalities of corpus callosum is frequently reported in bipolar disorder, along with schizophrenia and autism spectrum disorder (26). The corpus callosum FA reduction bipolar disorder might be responsible for commonly reported inter-hemispheric connectivity differences (27). IFOF connects occipital lobe with key structures in frontal lobe involved in language processing and cognitive control (28). The reduction of IFOF in bipolar disorder may be associated with impaired top down control on sensory and face processing areas and this may further result in delusions (29). The same speculation also applies to the finding of reduced SLF in bipolar, which connects superior frontal areas with temporal and occipital lobes. The corticospinal tract (CST) is starting from the cerebral cortex, terminates on the interneurons and motor neurons in the spinal cord, and has many functions such as voluntary movements and regulation of spinal reflexes (30,31). The current study found decreased FA in the left CST in BD patients compared to UD. There is not a large number of studies showed a difference in CST between UD and BD. One study using TBSS demonstrated the same results as the present study (14).

The primary limitation of the study is that the present study included BD patients in all the phases of the illnesses. However, previous literature showed that there was a different pattern of white matter alterations (12,32,33). While the BD patients were in a depressed phase, they showed largest white matter reductions. In the manic phase, they showed an intermediate reduction in FA values and there was only small FA reductions in...
euthymic patients. Another limitation is that most of the patients were under medication effect during the scanning and this might produce a confounding effect. However, the course of chronic psychiatric conditions usually does not allow strict experimental inclusion criteria due to the long course of illness and problems in reaching drug-naïve patients. The medications used in BD and UD are slightly different and the effects of different drugs in the white matter integrity is still unclear (34). Future studies should focus on drug-naïve samples; however, as most UD and BD patients are prescribed medications immediately after diagnosis, it might be difficult to find such patients.

Although, individuals with BD and UD share common symptomatic and functional impairments; the results of the present study demonstrate that tract-based spatial statistics and subsequent machine learning approach may discriminate between UD and BD patients. If these results are confirmed in further studies, FA values in cingulum, corpus callosum, CST, IFOF, SLF and uncinated can be used as a biomarker for differentiating BD and UD patients. In addition, future studies should attempt to explore the effects of medications on connectivity.

REFERENCES


