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Similarities and differences of white matter connectivity and water diffusivity in bipolar I and II disorder

Tae Hyon Ha[a], Ju Young Her[a], Jae Hyoung Kim[b], Jae Seung Chang[a], Hyun Sang Cho[c], Kyooseob Ha[a,d,*]

[a] Mood Disorders Clinic & Clinical Affective Neuroscience Laboratory, Department of Psychiatry, Seoul National University Bundang Hospital, 166 Gumiro, Bundang-gu, Seongnam-si, Kyeonggi-do 463-707, Republic of Korea
[b] Department of Radiology, Seoul National University Bundang Hospital, 166 Gumiro, Bundang-gu, Seongnam-si, Kyeonggi-do 463-707, Republic of Korea
[c] Department of Psychiatry, Severance Mental Hospital, 696-6 Tanbeol-dong, Gwangju-si, Kyeonggi-do 464-100, Republic of Korea
[d] Department of Psychiatry, Seoul National University College of Medicine and Institute for Human Behavioral Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Republic of Korea

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ABSTRACT

Differences and similarities in microstructural white matter alterations between bipolar I and bipolar II disorder were investigated. Twelve patients with bipolar I disorder, 12 patients with bipolar II disorder and 22 healthy controls underwent diffusion tensor imaging. Fractional anisotropy (FA) and mean apparent diffusion coefficient (ADC) maps were compared between groups using voxel-based whole brain analyses. Both bipolar I and II groups had a FA decrease in the corpus callosum, cingulate and right prefrontal regions, and a ADC increase in the medial frontal, anterior cingulate, insular and temporal regions, compared to controls. The bipolar I group had a FA decrease in the right temporal white matter and a ADC increase in the frontal, temporal, parietal and thalamic regions, compared to the bipolar II group. The results suggest disrupted integrity of commissural fibers and white matter in the anterior paralimbic structures in bipolar disorder. Relative sparing of the dorsal system and long association fibers may differentiate bipolar II from I disorder.

1. Introduction

Bipolar disorder is a chronic disabling psychiatric disorder characterized by recurrent episodes of mania or hypomania and depression. Recent evidence suggests the role of white matter abnormalities in the pathophysiology of the disorder. A loss of glial cells in the cingulate and dorsolateral prefrontal cortices [27,33], and a reduction of myelination-related genes expression [26] have been observed in postmortem brains of patients with bipolar disorder. These microscopic findings, along with results from in vivo studies using neuroimaging techniques, support the hypothesis that communications between neural nodes involved in emotional regulation are disrupted in bipolar disorder. In vivo investigation of structural white matter abnormalities includes measurements of white matter hyperintensities and regional white matter volumes using magnetic resonance (MR) imaging. The white matter hyperintensities, however, do not seem to be specific to bipolar disorder [7], and the underlying causes and clinical correlates are largely unknown. Volumetric studies that had measured total white matter volumes in bipolar disorder yielded mixed results [18,30]. Findings from analyses of volumes of white matter subregions are mixed as well. Among them, callosal areas were found to be reduced in a meta-analytic study [3].

Given the characteristic architecture of white matter that consists of fibers and supporting glial cells, studying the coherence and integrity of tubular structures rather than volume may provide a more sensitive measure for studying white matter alterations in a psychiatric disorder. Diffusion tensor imaging (DTI), a technique tracing the diffusion of water molecules that is restricted in fiber structures, thus enables detection of subtle changes in tissue microstructural organization through indices such as fractional anisotropy (FA) and apparent diffusion coefficient (ADC). DTI studies of adult patients with bipolar disorder have explored FA alterations in large fiber tracts in widely distributed brain regions to yield mixed results [1,6,8,9,13,20,22,25,28,31,32,35,36]. Heterogeneity of the samples, besides methodological differences, may be a factor contributing to the inconsistent findings. Previous DTI studies included only patients with bipolar I disorder (BD I) or mixed groups of patients with BD I and bipolar II disorder (BD II), and little attention has been given to BD II.

BD II is characterized by recurrent episodes of depression interspersed with short periods of hypomanias but not mania. BD II may

* Corresponding author at: Department of Psychiatry, Seoul National University Bundang Hospital, 166 Gumiro, Bundang-gu, Seongnam-si, Kyeonggi-do 463-707, Republic of Korea. Tel.: +82 31 787 7431; fax: +82 31 787 4058.
E-mail address: kyooha@snu.ac.kr (K. Ha).

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Table 1
Demographic and clinical characteristics of bipolar I, bipolar II, and control subjects.

	Bipolar I ($N = 12$)	Bipolar II ($N = 12$)	Controls ($N = 22$)
Age	37.3 ± 10.59	35.6 ± 7.56	34.7 ± 7.12
Gender (M/F)	3/9	2/10	5/17
Education years	14.9 ± 1.78	15.5 ± 2.15	14.2 ± 2.14
Age at onset	24.0 ± 10.31	22.3 ± 8.06	
Illness duration	13.3 ± 9.63	13.3 ± 6.28	
HAMD scores	5.5 ± 6.90	4.2 ± 4.43	
YMRS scores	1.4 ± 1.51	1.3 ± 1.53	

HAMD, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale.

represent the most common phenotype of bipolar disorder and the most frequently encountered subtype of mood disorders in a clinical population who is presenting depression [2,24]. Patients with BD II have a more chronic course with more frequent depressive episodes [17], higher suicidal risk [23], and poorer quality of life [21] than patients with BD I. Despite its clinical significance, the neurobiology of BD II has been poorly investigated. In our previous report exploring differences in gray matter abnormalities between the BD I and BD II groups, compared to widespread gray matter reductions in the BD I group, those deficits in the BD II group were limited within the anterior paralimbic regions [11]. Thus, we have suggested that the anterior paralimbic circuits including ventromedial prefrontal cortices are common neural substrates for BD I and BD II, and that the involvement of the dorsolateral prefrontal, temporal and parietal regions may differentiate BD I from BD II. Based on our previous findings, we hypothesized that disrupted white matter integrity in patients with BD II would be restricted to the anterior paralimbic regions, while regional changes in indices of DTI would distribute widely in BD I.

2. Materials and methods

The patient samples were recruited from the outpatient units of the Mood Disorders Clinic at Seoul National University Bundang Hospital and consisted of 12 patients with BD I (2 male and 10 female) and 12 patients with BD II (3 male and 9 female) meeting the DSM-IV criteria, according to the Structured Clinical Interview for DSM-IV axis I Disorders (SCID). Demographic and clinical variables were assessed on a clinical interview form designed for an imaging study. 22 healthy controls (5 male and 17 female) were recruited by leaflet advertisement. Absence of axis I psychiatric disorder in the control group was confirmed with the SCID, Nonpatient Version. Exclusion criteria were age less than 18 years or more than 60 years, any lifetime history of neurological or significant medical illnesses, history of substance abuse, and left-handedness. Patients being in a severe mood episode were excluded. There were no significant differences in regard to age, gender ratio and education years among three groups. The onset age, illness duration, depressive symptom severity measured by Hamilton Depression Rating Scale [12], and manic symptoms severity measured by Young Mania Rating Scale [34] did not differ between the BD I and BD II groups (Table 1). All the patients were taking medications at the time of scan. In the BD I group, 8 were on lithium, 5 were on divalproex (2 were on combination of lithium and divalproex), 6 were on combination of lamotrigine and mood stabilizers, and 11 were on atypical antipsychotics (all were on combination with mood stabilizers except one who were on clozapine monotherapy). In the BD II group, 5 were on lithium, 8 were on divalproex (2 was on combination of lithium and divalproex), 7 were on lamotrigine (6 were on combination with mood stabilizers), and 10 were on combination of atypical antipsychotics and mood stabilizers. The number of patients who were taking lithium, divalproex, lamotrigine and atypical antipsychotics, respectively, and the mean dose of these medications was not different between the BD I and BD II groups. This study was approved by the institutional review board at Seoul National University Bundang Hospital, and written informed consent was obtained from all subjects after the procedures had been fully explained.

Diffusion tensor imaging and three dimensional T1-weighted fast-field echo imaging were acquired on a 1.5T scanner (Intera, Philips Medical Systems, Best, The Netherlands). Single-shot spin-echo EPI was utilized for DTI with following parameters: $b = 600\,s/mm^2$ with 15 different directions, repetition time/echo time = 7228/70 ms, field of view = 224 mm × 224 mm, matrix = 112 × 112, 55 transverse sections with 3 mm thickness without a gap, and voxel dimensions = 2 mm × 2 mm × 3 mm. T1-weighted fast-field echo imaging was obtained using the following parameters: repetition time/echo time = 25/4.6 ms, flip angle = 30°, field of view = 240 mm × 240 mm, matrix = 256 × 256, 175 sagittal sections with 1 mm thickness without a gap, and voxel dimensions = 0.94 mm × 0.94 mm × 1 mm.

The imaging data were processed using the FMRIB Software Library (FSL) [14], as well as the statistical parametric mapping software (SPM8) (Wellcome Department of Cognitive Neurology, London, UK). Each raw data set for motion and eddy current distortions was corrected by affine registration to a reference volume using the FSL Diffusion Toolbox (FDT). Diffusion tensor matrices from sets of 15 diffusion-weighted images were generated using a general linear fit algorithm, and the three eigenvalues ($\lambda_i = 1, 2, 3$) and eigenvectors ($\varepsilon_i = 1, 2, 3$) were calculated by matrix diagonalization. Using FDT software, the FA and ADC were determined for every voxel, according to standard methods [5]. The T1 images, as source images, were coregistered to the B0 images without diffusion weighting. The transformed T1 images were then normalized into T1 Montreal Neurological Institute (MNI) template and resliced to 2 mm × 2 mm × 2 mm isotropic voxels in SPM8. Then, the yielded normalization parameters were applied to the FA and ADC maps. Finally, these normalized FA and ADC data were smoothed using a Gaussian kernel of 10 mm full width at half maximum. The kernel size was determined empirically to best demonstrate group differences.

The preprocessed FA and ADC maps were compared between groups using a two-sample *t*-test in SPM. Significance was set at a *p*-value less than 0.001 with extent threshold of 40 contiguous voxels. To specify white matter fiber tracts that pass through significant clusters from comparisons of FA maps, clusters were transformed as regions of interest into naïve spaces and an explorative tractography was performed using MedINRIA software (http://www-sop.inria.fr/asclepios/software/MedINRIA/).

3. Results

Compared to controls, the BD I group had a FA decrease in the corpus callosum including the genu, body and spenium, left anterior and posterior cingulum, right frontal white matter constituting superior longitudinal fasciculus, right prefrontal white matter constituting inferior fronto-occipital fasciculus and uncinate fasciculus, right temporal white matter constituting inferior longitudinal fasciculus and in the left parietal associations fibers region. Compared to controls, the BD II group had a FA decrease in the right anterior and posterior cingulum, body and slpenium of corpus callosum, and in the right medial prefrontal white matter. The both patients groups had no regional FA increases compared to controls. Direct comparison of two patients groups revealed that the BD I group had a lower FA in the right temporal white matter constituting inferior longitudinal fasciculus than the BD II group (Table 2, Fig. 1A).

Compared to controls, both the BD I and BD II groups had an ADC increase in the bilateral frontal, anterior cingulate, insular and