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Brief report

Differences in white matter abnormalities between bipolar I and II disorders

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ABSTRACT

Background: Although patients with bipolar I and II disorders exhibit heterogeneous clinical presentations and cognitive functions, it remains unclear whether these two subtypes have distinct neural substrates. This study aimed to differentiate the fiber abnormalities between bipolar I and II patients using diffusion tensor images.

Method: Fourteen bipolar I patients, thirteen bipolar II patients, and twenty-one healthy subjects were recruited. Fractional anisotropy (FA) values calculated from diffusion tensor images were compared among groups using two-sample t-test analysis in a voxel-wise manner. Correlations between the mean FA value of each survived area and the clinical characteristics as well as the scores of neuropsychological tests were further analyzed.

Results: Patients of both subtypes manifested fiber impairments in the thalamus, anterior cingulate, and inferior frontal areas, whereas the bipolar II patients showed more fiber alterations in the temporal and inferior prefrontal regions. The FA values of the subgenual anterior cingulate cortices for both subtypes correlated with the performance of working memory. The FA values of the right inferior frontal area of bipolar I and the left middle temporal area of bipolar II both correlated with executive function. For bipolar II patients, the left middle temporal and inferior prefrontal FA values correlated with the scores of YMRS and hypomanic episodes, respectively.

Conclusions: Our findings suggest distinct neuropathological substrates between bipolar I and II subtypes. The fiber alterations observed in the bipolar I patients were majorly associated with cognitive dysfunction, whereas those in the bipolar II patients were related to both cognitive and emotional processing.

1. Introduction

In the Diagnostic and Statistical Manual of Mental Disorders (text revision; DSM-IV-TR), bipolar disorder is categorized into bipolar I, bipolar II, cyclothymia, and bipolar disorder not otherwise specified subtypes according to the clinical characteristics. Findings of aberrant neuroanatomy from neuroimaging studies on bipolar patients are sometimes inconsistent and even conflicting (Konarski et al., 2008). One possible origin is the pathophysiological heterogeneity manifested in bipolar patients (Haznedar et al., 2005; Simonsen et al., 2008). A recent neuropsychological study reported that bipolar I patients manifested more cognitive dysfunction in verbal learning, recall, recognition, and set-shifting compared to bipolar II patients (Simonsen et al.,

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2008). However, whether bipolar subtypes have distinct neural substrates remains unclear.

Diffusion tensor imaging allows us to detect abnormal white matter integrity by quantifying the degrees of fiber alignment, such as fractional anisotropy (FA) index (Mahon et al., 2009). Previous studies using diffusion tensor images as well as T1-weighted magnetic resonance imaging reported the white matter impairments of bipolar patients mainly in frontal areas (Adler et al., 2004; Beyer et al., 2005; Haznedar et al., 2005; McIntosh et al., 2005; Regenold et al., 2006; Stanfield et al., 2009; Yurgelun-Todd et al., 2007). Bruno et al. indicated the fiber alterations of bipolar patients in bilateral prefrontal, middle temporal, and middle occipital regions (Bruno et al., 2008). The analysis results of Versace et al. suggested that bipolar patients revealed anomalous white matter in uncinate fasciculus, optic radiation, and anterothalamic radiation (Versace et al., 2008). Wessa et al. showed the fiber abnormalities of bipolar patients in medial frontal, precentral, inferior parietal, and occipital white matter (Wessa et al., 2009). Mahon et al. reported that bipolar patients showed fiber impairments in the pontine crossing tract, corticospinal/corticopontine tract, and thalamic radiation fibers (Mahon et al., 2009). To date, most of the bipolar studies of diffusion tensor imaging adopted the region-of-interest (ROI) approaches (Adler et al., 2004; Beyer et al., 2005; Haznedar et al., 2005; Regenold et al., 2006; Yurgelun-Todd et al., 2007). Compared with ROI-based methods, voxel-wise whole-brain analysis is advantageous when the locations of abnormalities are difficult to predict and thus is more adequate to pathological investigation of bipolar disorders (Bruno et al., 2008; Mahon et al., 2009).

The goal of this study was to investigate whether bipolar I and bipolar II patients manifest different patterns of white matter abnormalities. FA indices of the recruited bipolar I and II patients were compared in a voxel-wise manner, without specifying ROIs. We hypothesized that white matter impairments exhibited in patients with bipolar I might be more related to cognitive functioning in contrast to patients with bipolar II.

2. Materials and methods

2.1. Participants

Twenty-seven right-handed bipolar patients (bipolar I = 14, bipolar II = 13) were recruited from the outpatients of Psychiatry Department, Taipei Veterans General Hospital. Clinical characteristics of bipolar patients were diagnosed by two psychiatrists according to Structured Clinical Interview for DSM-IV-TR. All patients, except one bipolar I and two bipolar II subjects, took a range of medications, including lithium, anticonvulsants, antidepressants, and antipsychotics. The mood symptoms were rated before image acquisition using the Young Mania Rating Scale (YMRS), 17-item Hamilton Rating Scale for Depression (HAMD17), Montgomery Åsberg Depression Rating Scale (MADRS), and Hamilton Anxiety Rating Scale (HARS). The demographic and clinical characteristics of all participated patients are listed in Table 1. Twenty-one right-handed healthy participants without history of psychiatric or neurological disorders were recruited from the community through advertisements. All the healthy subjects were evaluated using the Mini-International Neuropsychiatric Interview before the experiments to exclude those with psychiatric morbidity. No subject had history of substance misuse or abuse and everyone provided written informed consent to participate in the study according to the guidelines approved by the Institutional Review Board of Taipei Veterans General Hospital.

Table 1
Demographic characteristics.

Characteristic	Bipolar I patients (n = 14)	Bipolar II patients (n = 13)	Healthy subjects (n = 21)
Age, years (mean (std))	35.6 (10.9)	35.1 (9.8)	38.3 (11.9)
Gender, n (male/female)	7/7	2/11	8/13
Handedness, n (left/right)	14/0	13/0	21/0
Education, years (mean (std))	13.7 (2.0)	14.6 (2.1)	15.0 (3.2)
Duration of illness, years (mean (std))	7.3 (5.7)	9.4 (7.4)	–
(Hypo-)manic episodes (mean (std))	3.8 (2.8)[a]	2.8 (2.5)[b]	–
(Hypo-)manic/depression ratio (mean (std))	1.0 (0.6)[c]	0.6 (0.5)[d]	–
YMRS (mean (std))	0.9 (1.6)	2.0 (2.7)	–
HAMD17 (mean (std))	6.7 (5.8)	9.5 (6.6)	–
MADRS (mean (std))	5.6 (5.7)	11.5 (9.0)	–
HARS (mean (std))*	5.1 (4.7)	10.6 (7.9)	–
Medications, n			
Lithium[e]	2	0	–
Anticonvulsants[f]	12	10	–
Antidepresants[g]	12	10	–
Antipsychotics[h]	1	1	–

YMRS: Young Mania Rating Scale, HAMD17: 17-item Hamilton Rating Scale for Depression; MADRS: Montgomery Åsberg Depression Rating Scale; HARS: Hamilton Anxiety Rating Scale; std: standard deviation.
*Significant difference between bipolar I and II patients ($z = -2.32$, $p = 0.02$).
[a]Manic episodes; [b]hypomanic episodes; [c]manic/depression ratio; [d]hypomanic/depression ratio; [e]lithium, lithium carbonate, lidin; [f]lamictal, lamotrigine, rivotril, depakine, depakine chrono, ativan, topiramate; [g]wellbutrin, seroquel, erispan, stilnox, lexapro, effexor XR; [h]abilify.

2.2. Neuropsychological assessments

The neurocognitive functions of all participants were assessed using a neuropsychological test battery, including the Wisconsin Card Sorting Test for measuring the problem-solving ability, cognitive flexibility, and response maintenance; the word-list recall test from the Wechsler Memory Scale-III for evaluating the working memory capacity; and the Test for Attention Performance (version 1.02) for assessing the attention function. The assessment results are listed in Table 2.

2.3. Image acquisition and processing

All subjects were scanned on a GE Signa EXCITE 1.5 T system. A total of fourteen diffusion tensor images were acquired for each subject (spin-echo EPI, TR = 17000 ms, TE = 69.2 ms, matrix size = $128 \times 128 \times 70$, voxel size = $2.03 \times 2.03 \times 2.2$ mm^3), including thirteen images obtained by using diffusion gradients applied along thirteen nonparallel directions ($b = 900$ s/mm^2) and one image without diffusion weighting ($b = 0$ s/mm^2, B0).

Table 2
Performance of neuropsychological tests.

Test	Performance	Bipolar I patients	Bipolar II patients	Healthy subjects
WCST	Perseverative errors (%)	12.6 (5.3)	14.7 (10.2)	9.1 (3.8)
	Perseverative response (n)	15.9 (9.1)	18.8 (16.7)	9.8 (6.2)
	Non-perseverative errors (n)	23.6 (21.4)	20.8 (17.5)	11.8 (7.9)
	Failure to maintain set (n) [a]	0.9 (0.8)	0.5 (1.1)	0.7 (1.1)
WMS	Short-delayed recall (n)	7.9 (2.7)	8.8 (1.6)	9.2 (2.8)
	Recognition (n)	23.1 (1.1)	23.2 (0.8)	22.4 (5.5)
	Retention (%)	77.9 (18.4)	83.8 (17.1)	81.1 (22.8)
	Learning slope (n)	4.5 (2.0)	4.2 (1.3)	3.6 (1.6)
TAP	Go/no-go (ms)	496.2 (68.2)	488.7 (63.7)	485.8 (59.2)
	Divided attention (squares) (ms) [b]	590.1 (99.2)	597.4 (70.4)	851.3 (116.4)
	Divided attention (sounds) (ms)	951.4 (142.4)	926.3 (77.7)	604.4 (79.3)

Mean (standard deviation).
WCST: Wisconsin Card Sorting Test; WMS: Wechsler Memory Scale; TAP: Test for Attention Performance.
[a] Significant difference between bipolar I and II patients ($z=-2.00$, $p=0.05$).
[b] Significant difference between bipolar I/bipolar II/combined bipolar patients and healthy subjects ($z=-2.25$, $p=0.03$/$z=-2.36$, $p=0.02$/$z=-2.53$, $p=0.01$).

One additional T1-weighted image was acquired for each subject to provide a high resolution anatomical reference (3D-FSPGR, TR = 8.67 ms, TE = 1.86 ms, matrix size = 256 × 256 × 124, voxel size = 1.02 × 1.02 × 1.5 mm^3).

To reduce the head motion as well as the geometric distortion caused by eddy currents, diffusion tensor images of each subject were first aligned to the B0 image using affine registration. The aligned diffusion tensor images were then used to calculate the FA maps using FMRIB's Diffusion Toolbox[1]. The white matter regions in T1-weighted images were segmented using FMRIB's Automated Segmentation Tool[2] after removing the non-brain tissues (Liu et al., 2009). A customized white matter template was constructed by averaging the white matter images of all participants nonlinearly registered to a white matter template built from the local population. For each subject, a deformation field was estimated by combining the results of rigid registration between the B0 and T1 images and non-rigid registration between the segmented white matter image and customized white matter template. Subsequently, the FA map of each subject was spatially normalized to the customized white matter space by applying the individual deformation field. Before statistical comparison, all the normalized FA maps were smoothed by a Gaussian kernel with 6-mm full width at half maximum, which was determined according to the diameter of major fiber tracts in the human brain (Makris et al., 1997; Turken et al., 2008). In addition, the software of Brain Image Registration Tools (BIRT) was adopted to perform the affine and non-rigid registrations in this work (Liu et al., 2010).

2.4. Statistical analyses

A voxel-wise two-sample t-test analysis using Statistical Parametric Mapping (SPM2)[3] with age, gender, education, and total intracranial volume as covariates was performed to compare the whole-brain FA maps between the control group and three patient groups, including the bipolar I group, bipolar II group, and combined bipolar group (the pooled bipolar I and II groups). This analysis was also performed to directly contrast the FA maps between the bipolar I and II groups. To determine fiber alterations between groups, we first obtained the clusters which survived a threshold of $p<0.001$ (uncorrected, extent threshold = 50 voxels) from the whole-brain analysis and then applied small volume correction to each cluster by using an 8-mm-radius sphere centered on the peak location with a false discovery rate < 0.001. These survived clusters were reported as significant loci with structure and fiber labels indicated by Anatomical Automatic Labeling[4] and the probabilistic fiber tracts[5], respectively.

The Mann–Whitney U-test and Pearson χ^2 test were used to compare the demographic features and the neuropsychological performance, respectively, among the healthy, bipolar I, bipolar II, and combined bipolar groups. The Spearman's correlation analysis was applied to calculate the correlations between the mean FA value of each significant area and the clinical characteristics as well as the scores of neuropsychological tests for the patient and normal groups. Moreover, we also examined the relations between the demographic variables and neuropsychological performance of subject groups using Spearman's correlation analyses with significant level $p<0.01$.

3. Results

All the group pairs did not differ significantly in age, gender, handedness, education, and duration of illness (for patient groups only) ($p>0.05$). The comparison results of clinical rating scales showed that only the HARS values of the bipolar II patients were significantly higher than those of the bipolar I patients ($z=-2.32$, $p=0.02$). In the comparison of neuropsychological performance, the failure to maintain set

[1] http://fsl.fmrib.ox.ac.uk/fsl/fdt.
[2] http://fsl.fmrib.ox.ac.uk/fsl/fast4.
[3] http://www.fil.ion.ucl.ac.uk/spm/software/spm2.
[4] http://www.cyceron.fr/freeware.
[5] http://cmrm.med.jhmi.edu.

Table 3
Results of statistical analyses for FA comparison and correlation.

Comparison groups	Region	Side	Brodmann area	Fiber tract	MNI coordinate [a]	Cluster size (mm^3)	t
Combined bipolar<control	Thalamus	R	–	Anterior thalamic radiation	(13, −1, −8)	472	5.31
	Subgenual anterior cingulum	R	11	Corpus callosum forceps minor	(13, 38, −2)	149	4.55
Bipolar I<control	Thalamus	R	–	Anterior thalamic radiation	(13, −1, −9)	111	4.94
	Subgenual anterior cingulum *	R	11	Corpus callosum forceps minor	(12, 39, −3)	79	3.93
	Inferior frontal gyrus *	R	44, 6	Superior longitudinal fasciculus	(49, 2, 23)	303	4.86
	Rostral anterior cingulum	L	32	Cingulum	(−10, 37, 20)	79	5.00
Bipolar II<control	Subgenual anterior cingulum *	B	11, 25	Corpus callosum forceps minor	(13, 37, 0)	777	5.18
	Inferior frontal gyrus	R	48	Inferior frontal-occipital fasciculus	(41, 22, 21)	215	4.79
	Middle temporal gyrus *	L	37, 21	Superior longitudinal fasciculus	(−43, −52, 8)	118	4.52
	Inferior temporal gyrus	L	20	Inferior frontal-occipital fasciculus	(−30, −24, −1)	133	4.06
Bipolar II<bipolar I	Precuneus	R	–	Cingulum	(17, −53, 47)	206	5.58
	Inferior frontal gyrus	R	48	Superior longitudinal fasciculus	(30, 12, 28)	94	4.41
	Inferior prefrontal gyrus *	L	47	Anterior thalamic radiation	(−30, 37, 8)	77	4.21

L: left; R: right; B: bilateral.
[a] Peak location (FDR corrected, $p<0.001$, cluster threshold = 50).
* Significant correlation with the scores of neuropsychological tests.

scores measured from the bipolar I patients was higher than those measured from the bipolar II patients ($z=-2.0$, $p=0.05$). The healthy subjects had lower scores of divided attention (squares) than the bipolar I patients ($z=-2.25$, $p=0.03$), bipolar II patients ($z=-2.36$, $p=0.02$), and combined bipolar patients ($z=-2.53$, $p=0.01$).

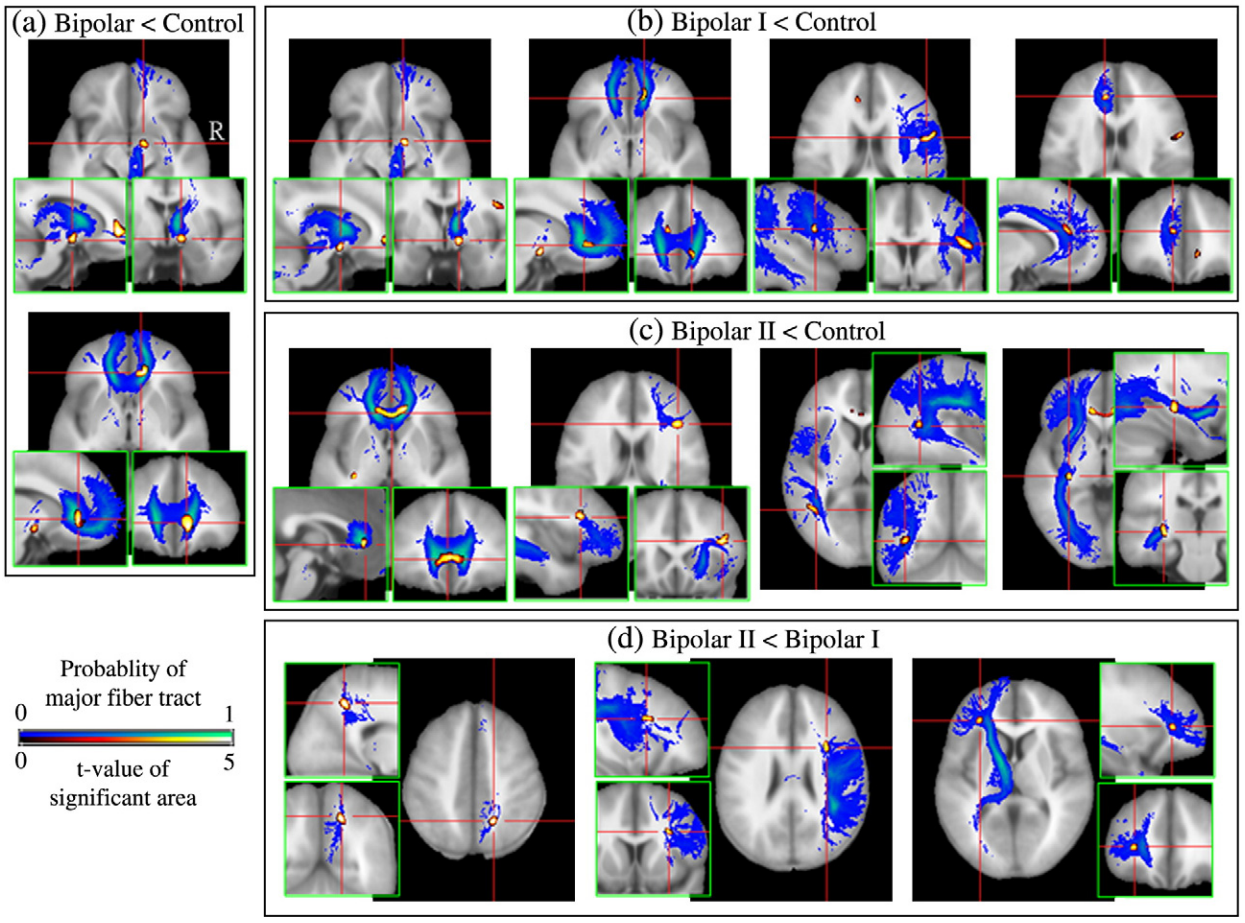

Fig. 1. Regions with significantly decreased FA values found in the (a) combined bipolar, (b) bipolar I, and (c) bipolar II groups compared to the controls; and (d) bipolar II group compared to the bipolar I group. The t-values of these areas are shown with "hot" color map (black–red–yellow–white) whereas the spatial probability maps of major fiber tracts covering these areas are shown in "winter" color map (blue–green), overlaid on the MNI-152 brain template. Detailed description of these regions can be found in the text and Table 3.

The regions with significantly decreased FA values found in group pairs are listed in Table 3. In contrast to the controls, the combined bipolar group displayed lower FA values in the right thalamus and right subgenual anterior cingulate cortex (Fig. 1a). For the bipolar I patients, significant decreases in FA were found in the right thalamus, right subgenual anterior cingulate cortex, right inferior frontal area, and left rostral anterior cingulate cortex, compared to the controls (Fig. 1b). The bipolar II patients showed lower FA values than the controls in the bilateral subgenual anterior cingulate, right inferior frontal, left middle temporal, and left inferior temporal areas (Fig. 1c). Compared to the controls, no areas with higher FA values were found in three patient groups. The bipolar II patients, compared to bipolar I, presented decreased FA values in the right precuneus, right inferior frontal gyrus, and left inferior prefrontal area (Fig. 1d). No areas with higher FA values were found in the bipolar II group compared to the bipolar I patients.

Compared to healthy controls, all the patient groups showed significantly decreased FA values in the subgenual anterior cingulate area. Both the bipolar I and combined bipolar groups manifested fiber alterations in thalamus, but this region was not revealed in the bipolar II group. The bipolar I group displayed lower FA values than the controls in the inferior frontal and rostral anterior cingulate areas, but these areas were not exhibited in the bipolar II group. On the other hand, the fiber alterations were observed at the temporal lobe in the bipolar II group, but not in the bipolar I group.

For the areas found in the comparison between the bipolar I and control groups, our correlation analyses showed that the mean FA value of the right subgenual anterior cingulate cortex was significantly correlated with the scores of short-delayed recall ($\rho = -0.83$, $p < 0.001$) and the mean FA value of the right inferior frontal area was significantly correlated with the performance of perseverative errors ($\rho = 0.56$, $p = 0.04$), perseverative responses ($\rho = 0.57$, $p = 0.03$), and word-list recognition ($\rho = -0.66$, $p = 0.01$). For the contrast between the bipolar II and control groups, the mean FA value of the bilateral subgenual anterior cingulate cortex was correlated with the scores of word-list retention ($\rho = -0.39$, $p = 0.05$) and YMRS ($\rho = 0.47$, $p = 0.01$), and the mean FA value of the left middle temporal region was correlated with the performance of perseverative responses ($\rho = 0.59$, $p = 0.04$). The mean FA value of the left inferior prefrontal area found in the comparison between the bipolar I and II patients was significantly correlated with the hypomanic episode ($\rho = 0.38$, $p < 0.05$). All the correlation analyses between the neuropsychological performance and the mean FA values for healthy controls were not significant ($p = 0.05$).

The correlation analyses between the demographic variables and neuropsychological performance indicated that the age/education of normal subjects was significantly correlated with the performance of learning slope ($\rho = 0.60$, $p = 0.006/\rho = -0.59$, $p = 0.008$), divided attention (squares: $-/\rho = -0.59$, $p = 0.008$), and executive function (perseverative errors: $\rho = 0.71$, $p = 0.001/\rho = -0.63$, $p = 0.004$; perseverative responses: $\rho = 0.67$, $p = 0.002/\rho = -0.66$, $p = 0.002$; failure to maintain set: $-/\rho = -0.62$, $p = 0.004$). The manic episode scores of the bipolar I patients were correlated with the performance of learning slope ($\rho = -0.73$, $p = 0.003$). For the bipolar II patients, the age was significantly correlated with the scores of short-delayed recall ($\rho = -0.71$, $p = 0.006$) and executive function (perseverative errors: $\rho = 0.72$, $p = 0.006$; perseverative responses: $\rho = 0.76$, $p = 0.002$; non-perseverative errors: $\rho = 0.69$, $p = 0.01$). Moreover, the bipolar II patients also showed significant correlations between the scores of HAMD17 and retention ($\rho = -0.77$, $p = 0.002$). For the combined bipolar group, the age was correlated with the performance of working memory capacity (short-delay recall: $\rho = -0.50$, $p = 0.009$; retention: $\rho = -0.51$, $p = 0.007$).

4. Discussion

In this study the fiber abnormalities of bipolar I and II patients were majorly located in the frontal lobe. The abnormal regions found in bipolar II patients were more bilaterally distributed, extending to the left temporal lobe, whereas the fiber alterations of bipolar I patients were more lateralized to the right hemisphere. Our results suggest that bipolar I and II patients present different neuropathological substrates in terms of the loss of bundle coherence or the disruption of fiber tracts.

Brain regions with significantly decreased FA indices found in the bipolar I patients majorly relate to the cognitive functions. The anterior cingulate cortex is highly involved in the network regulating both cognitive and emotional processing (Bush et al., 2000). Particularly, the rostral area found in this study locates in the cognitive division of anterior cingulate (Bush et al., 2000) and plays an important role in monitoring/signaling conflict or interference, decision making, and response to errors (Kelly et al., 2009). Thalamus is associated with the modulation of attentional processing and self-regulation of affective states. Its abnormalities were frequently reported in mood disorders, particularly in bipolar disorders (Konarski et al., 2008; Zubieta et al., 2000). The anterior region of the thalamus manifested in the bipolar I patients connects to the prefrontal and temporal areas (Behrens et al., 2003) and is important to affective and cognitive regulation (Aggleton and Brown, 1999). The inferior frontal area found in bipolar I, which locates in the superior longitudinal fasciculus III (Makris et al., 2005), participates in attention and executive functions (Lyoo et al., 2004) and plays an important role in working memory (Makris et al., 2005). Furthermore, this finding in superior longitudinal fasciculus III embraces Brodmann area 44 which belongs to the dorsal attention-cognitive system (Mayberg, 1997).

The brain areas with fiber deficits found in the bipolar II patients majorly associate with emotional processing. The observed bilateral subgenual anterior cingulate cortex locates in the affective division (Brodmann areas 11 and 25) (Bush et al., 2000) and is important to emotion regulation, such as affective responses and monitoring of rewarding or punishing results (Kelly et al., 2009). The middle and inferior temporal areas found in bipolar II patients were related to bottom-up emotional appraisal processing (Onitsuka et al., 2004). The middle temporal area located in the vertical part of arcuate fascicle, which links the frontal and temporal cortices, also modulates audiospatial information (Makris et al., 2005). The right inferior frontal area found in bipolar II patients relates to the emotional communicative processing based on facial emotions (Nakamura et al., 1999).

The FA indices of the combined bipolar patients were significantly lower in the right subgenual anterior cingulate cortex and the right thalamus compared to the controls. The right subgenual anterior cingulate cortex observed in both subtypes represents the common fiber abnormality in bipolar patients. This result is consistent with numerous previous findings in functional and volumetric aspects (Konarski et al., 2008). On the other hand, the thalamus area shown in the combined bipolar group only revealed in bipolar I group, but not in bipolar II group. This also supports the distinct neural substrates between the two subtypes.

For the contrast between bipolar I and II subtypes, the lower FA values of bipolar II patients in the precuneus implicate the impairments of the appraisal of emotionally salient visual perception as well as the subsequent preprocessing. As reported in (Malhi et al., 2004), the right precuneus of bipolar II patients manifested abnormal activation in response to positive vs. negative captioned pictures compared to healthy controls. The bipolar II patients also presented lower FA indices in the left inferior prefrontal and right inferior frontal areas, which were located in the superior longitudinal fasciculus and anterior thalamic radiation tract, respectively. These two major fiber tracts link to the orbitofrontal cortex and dorsolateral prefrontal cortex that participate in the process of emotion regulation (Phillips et al., 2008). The fiber abnormality of the right inferior frontal region was also reported in a previous diffusion tensor imaging study (Adler et al., 2004).

The results of this study indicated that the fiber alterations found in bipolar I and II groups were significantly correlated with the performance of working memory and executive function. However, the FA values of the bipolar I patients were correlated with more neuropsychological tests and these results support the findings of a recent neuropsychological study in which bipolar I patients presented cognitive dysfunction both in pattern and magnitude than bipolar II patients (Simonsen et al., 2008). The finding of the correlation between the FA values of the subgenual anterior cingulum and YMRS scores in the bipolar II group provides the neuroimaging evidence of the abnormal functionality in the subgenual anterior cingulum related to emotion regulation for the bipolar II subtype.

We also used the Tract-Based Spatial Statistics (Smith et al., 2006) method to investigate the fiber alterations between the bipolar I and II groups and between the control group and bipolar I, bipolar II, and combined bipolar groups. However, no areas with differences of FA values survived a threshold of $p<0.001$ (uncorrected).

The direction number of nonparallel diffusion gradients applied in diffusion tensor imaging could influence the resolution for differentiating fiber directions as well as the reproducibility of FA index. The experiments conducted by Heiervang et al. suggested that fiber tracts extracted from 12-directional DTI data were similar to those extracted from 60-directional data, particularly for the major bundles (Heiervang et al., 2006). For each subject, moreover, we acquired T1, T2, and MRS data, together with DTI data, for multi-modality investigation. Therefore, we decided to acquire DTI data along 13 nonparallel directions to meet the limited time constraint.

Treatments could affect the results of this study though the medication influences on neuropathological abnormalities are currently not certain. Chronic exposure to antipsychotics may alter the volume of thalamus (Haznedar et al., 2005). Antidepressant treatment could decrease the FA in frontal white matter (Alexopoulos et al., 2002). It was also reported that lithium may protect the anterior cingulate cortices of bipolar patients from volume loss (Sassi et al., 2004). Due to the variety of medication and the small numbers of patients taking each drug combination, analysis of the medication effects is difficult in this work. Moreover, the substance dependence and family history of participants are not considered in this study and the effects require further investigation.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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