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REVIEW ARTICLE

Neurobiological underpinnings of bipolar disorder focusing on findings of diffusion tensor imaging: a systematic review

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Objective: To review the available data on diffusion tensor imaging (DTI) of subjects with bipolar disorder (BD), with a particular focus on fractional anisotropy (FA) in white matter (WM) tracts.
Methods: The PubMed/MEDLINE database was searched for relevant articles, which were included in a systematic review of the literature. FA reductions and WM abnormalities were divided anatomically into three groups: commissural tracts, association tracts, and projection tracts.
Results: Eighteen studies met the inclusion criteria. The corpus callosum was the main impaired commissural tract as demonstrated by FA reductions. Five studies reported FA reductions in the cingulum. Two studies reported decreased FA in the anterior thalamic radiation, and one in the corticospinal tract. Conversely, three studies found increased FA values in WM tracts involved in BD pathophysiology.
Conclusion: Despite considerable heterogeneity, these results indicate a direct link between executive cognitive functioning and abnormal WM microstructural integrity of fronto-limbic tracts in patients with remitted BD, providing further evidence of the neuronal disruption that underlies BD symptomatology.

Keywords: Bipolar disorder; diffusion tensor imaging; neuroimaging; diffusion tractography

Introduction

Bipolar disorder (BD) is a severe psychiatric disorder that affects approximately 1.5% of the world population[1,2] and remains one of the leading worldwide causes of disability, morbidity, and mortality.[3,4] The progression of BD is frequently associated with an increased number of episodes,[5-8] subclinical symptoms in the interepisodic period,[9,10] higher rates of comorbidities,[11] increased risk of suicide,[12] a higher number of hospital admissions,[13] and poorer response to treatment.[6] Furthermore, several studies have shown a strong association between number of mood episodes and unfavorable clinical outcomes, especially cognitive and functional impairment.[14,15]

In BD, neural substrate reactivity is changed by repeated mood episodes, which ultimately promote a brain rewiring that leads to increased vulnerability to life stress.[16-18] Changes in brain structure have been widely reported in BD patients.[19] Over the past decade, substantial effort has been made in neuroimaging research to understand the neural system abnormalities that underlie BD, and significant progress has been made in identifying regional brain differences that could contribute to the symptoms of acute episodes.[20]

Morphometric studies have demonstrated that patients with BD exhibit enlargement of the third and lateral ventricles; a reduction in the gray matter volumes of the orbital and medial prefrontal cortex, ventral striatum, and mesotemporal cortex; and enlargement of the amygdala. Such neuroanatomical changes tend to be more pronounced in patients who have experienced repeated episodes. With respect to neuropathological findings, recent data suggest that changes in neuroplasticity, particularly in cell resilience and connectivity, are the main findings associated with BD.[21-25]

Other studies suggest that structural brain changes are found mainly in the frontal, temporal, and limbic white matter (WM) regions.[26-31] WM abnormalities have been widely detected in subjects with the pathophysiological features of BD, especially with diffusion tensor imaging (DTI) techniques.[29]

Diffusion imaging principles are based on measurement of the motion of water molecules within tissues.[32] Free water usually moves equally in all directions in an isotropic fashion. When the movement of water molecules is restricted, however, preferential directions are taken, and movement consequently becomes anisotropic.

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Therefore, water mobility in the brain is markedly reduced in compact tissue, such as WM, is reduced to a lesser extent in gray matter (GM), and is almost free in the cerebrospinal fluid (CSF). Pathological processes that alter the normal brain structure may affect water motion and thereby affect the resulting diffusion indexes.[33]

Diffusion images can be acquired from a minimum of three gradient directions that yield two different types of sequences: diffusion-weighted imaging (DWI) and DTI. The use of more than six encoding directions improves the accuracy of tensor measurement for any arbitrary orientation (Figure 1).[34]

WM tracts can be divided anatomically into three groups: commissural tracts, projection tracts, and association tracts. Commissural tracts are fibers that interconnect the hemispheres of the brain, such as the corpus callosum (CC). Association tracts are groups of fibers that interconnect cortical areas within the same hemisphere, and projection tracts are efferent and afferent fibers that interconnect the cortex to subcortical structures.[35-38]

Previous investigations have hypothesized that microstructural changes in the WM of frontal-subcortical circuits leads to a disconnection syndrome between the frontal and subcortical regions.[30] These network alterations have been associated with clinical symptoms of BD, which suggests that DTI is a promising technique for evaluation of the underpinnings of neuropathology in BD.[39]

The aim of this paper is to conduct a systematic review of studies that have used DTI in patients with BD, with particular emphasis on fractional anisotropy (FA) findings, and discuss the relevance and connection of these findings to BD pathophysiology.

Methods

Systematic review

The recorded variables for each article included imaging technique (magnetic resonance imaging [MRI], DTI), imaging analysis (whole-brain/region of interest [ROI]), field strength, gender, mean age, exposure to medication, brain regions analyzed, and principal findings (BD vs. controls).

Selection procedures

The inclusion criteria were: a) English-language original articles published in peer-reviewed journals, in which study participants were diagnosed with BD type I (BD-I) or BD type II (BD-II), and which employed structural or neurochemical imaging techniques. Studies were independently assessed for eligibility by two researchers.

Search strategies

The PubMed/MEDLINE database was searched using the following queries based on Medical Subject Headings (MeSH) descriptors: "imaging, diffusion tensor and bipolar disorder," "diffusion tractography and bipolar disorder," and "tractography, diffusion and bipolar disorder." There were no limits regarding year of publication, and the search included papers published through January 2015.

Results

The search yielded 127 articles. Search strategies and exclusion criteria are summarized in Figure 2. We found 18

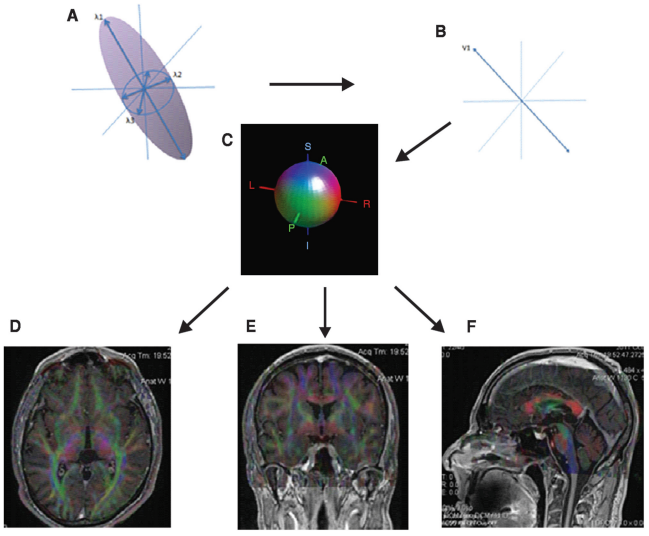

Figure 1 Diffusion measurements along multiple axes. The shape and the orientation of a diffusion ellipsoid is estimated. From the estimated ellipsoid (A), the orientation of the longest axis can be found (B), which is assumed to represent the local fiber orientation. This orientation information is converted to a color at each pixel. By combining the intensity of the anisotropy map and color, a color-coded orientation map is created (C). The diffusion tensor image map is rendered in the axial (D), coronal (E), and sagittal (F) planes. The color coding depicts the local fiber orientation, i.e., the principal eigenvector of the diffusion tensor, with red indicating mediolateral, green denoting anteroposterior, and blue representing superoinferior. Color coding is also indicated by the red-green-blue sphere (C).

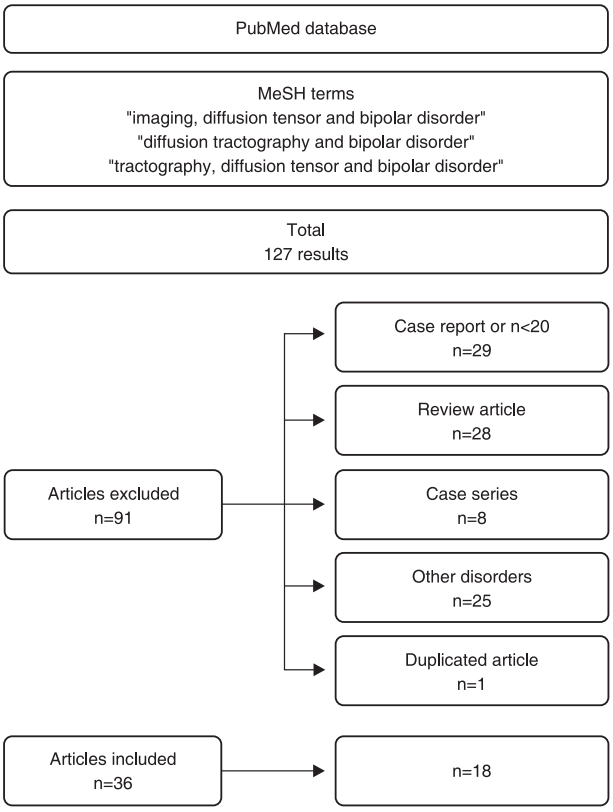

Figure 2 Flowchart of identification and selection of studies for a systematic review of diffusion tensor imaging in bipolar disorder.

published DTI studies that identified WM changes in subjects with BD. We assessed FA in three different anatomical groups: commissural tracts, projection tracts, and association tracts. Tracts for which FA findings were reported in the included studies are presented in Figure 3.

Results are highly heterogeneous, and most published papers have reported decreased FA values in WM tracts (Table 1). Overall, the most common finding is decreased FA values in commissural and association tracts, particularly in the fronto-limbic tracts (Table 2).[43,53,54]

FA and WM tracts

With respect to the commissural tracts, most authors found decreased FA values in the CC.[29-31,40,43-46,49]

Regarding association tracts, five studies found decreased FA values in the cingulum.[29,43,45,48,49] With respect to the projection tracts, two studies noted decreased FA in the ATR, and one study found decreased FA in the corticospinal tract (CST) (Table 2).

Conversely, three studies reported increased FA values. Wessa et al.[55] found increased FA values in the medial frontal, precentral, inferior parietal, and occipital WM. Mahon et al.[56] observed higher FA levels within the right and left frontal WM, while Versace et al.[42] observed increased FA in the left uncinate fasciculus (UF) (reduced radial diffusivity distally and increased longitudinal diffusivity centrally), left optic radiation (increased longitudinal diffusivity), and right anterior thalamic radiation (ATR).

Discussion

Most studies reported decreased FA values in regions involved in emotion processing, such as the commissural tracts, especially the CC, and the association tracts.[43,53,54,57-60] The latter include the UF,[47,61-63] the ATR,[62,63] and the cingulum.[45,61]

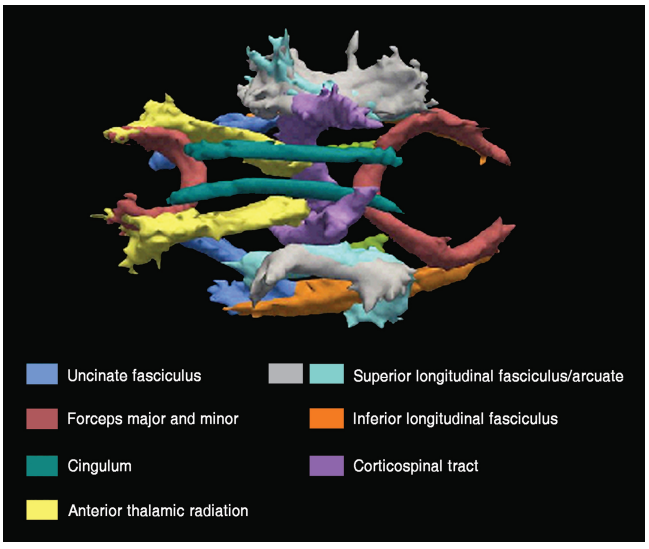

Figure 3 White matter tract reconstruction based on reported findings of decreased fractional anisotropy on diffusion tensor imaging: uncinate fasciculus,[40-42] corpus callosum/forceps,[29,31,40,43-48] cingulum,[29,43,45,48,49] anterior thalamic radiation,[31,42] superior longitudinal fasciculus,[29,31,40,43,50] inferior longitudinal fasciculus,[40,43,50,51] corticospinal tract.[52]

Table 1 Diffusion tensor imaging studies in bipolar disorder

Study	Patients	Age	BD type I/II/ other	Disease duration (years)	Mood state	Substance use	Drugs	Tesla | direction	B-value	Software	Voxel size (mm^3)	Measures	Results
Maller[43]	31 BD 31 HC	43.29±9.13 39.58±10.7	16/15/0	N/A	N/A	N/A	7 drug users (6.288) with BD-I/10 (5.738) with BD-II	1.5 | 12	0/1,000	FMRI Diffusion toolbox/TBSS	0.9x0.9x3	FA, AD, RD	Widespread, significant FA differences between controls and all BD subjects, primarily along the CC, cingulum bundles, fornices, SLF, ILF/FOFs, thalami, and UF. Significant differences in FA and all its constituent values between controls and BD-I and BD-II subjects separately.
Oertel-Knöchel[31]	21 BD 20 HC	35.67±10.6 36.90±11.0	21/0/0	7.62	Euthymic	N/A	Mood stabilizers (n=21), antidepressants (n=9), neuroleptics (n=12), anxiolytics (n=3)	3 | 60	0/1,000	TBSS FSL 4.1	3x3x3	FA, MD, RD, AD	Patients with BD showed significantly higher MD, RD, and AD scores in comparison with HCs in the left superior longitudinal fascicle. FA scores were not significantly different between groups.
Sarrazin[29]	118 BD 86 HC	36.32±10.4 37.26±11.2	118/0/0	15.57	Euthymic	25 alcohol	Lithium (n=39), other mood stabilizers (n=64), antipsychotics (n=52), antidepressants (n=54)	3 | 41	0 /1,000	Connectomist 2.0 and BrainVisa 4.2	2x2x2	GFA	Compared with controls, BD-I patients had significant reductions in mean GFA values along the body and splenium of the CC, the left cingulum, and the anterior part of the left arcuate fasciculus when controlling for age, gender, and acquisition site. Patients with a history of psychotic features had a lower mean GFA value along the body of the CC than those without such a history.
Oertel-Knöchel[30]	30 BD 32 HC	39.22±12.3 39.22±10.3	30/0/0	10.2	Euthymic	N/A	8.30 (7.40) years of medication use	3 | 60	0/1,000	FMRIB/MRIST/ TBSS	1x1x1	AD, RD, FA, MD	Significantly lower FA values in BD patients than in controls. The CC tended to show lower FA and higher RD in BD patients compared with controls. The splenium and truncus showed significantly lower FA and the truncus showed higher RD in BD patients compared with controls. FA values were significantly reduced in BD patients in the right thalamic radiation and showed trend-level significance in the left ATR.
Canales-Rodríguez[44]	40 BD 40 HC	40.6±8.9 40.4±9.3	40/0/0	15.9	Euthymic	Excluded	39 mood stabilizers (n=39) or lithium alone in combination with others (n=30), valproate (n=2), lamotrigine (n=2), others (n=5); antidepressants (n=9). antipsychotics (n=22), combination (n=1)	1.5 | 55	0/1,500	Brain Extraction Tool (FSL)	2x2x3	FA, MD, PTO, GFA	Significant reductions in FA were observed in the splenium of CC and right insula. There was a widespread pattern of increased MD in gray and WM tissues including anterior cingulum, left insula, and subcortical nuclei, without significant decreases in BD patients. Three of the contrasts (FA, mean diffusivity, and GFA) revealed abnormalities in subcortical structures, including the hippocampus, thalamus, and caudate nucleus.
Ambrosi[40]	20 BD 21 HC	41.95±13.1 34.61±10.8	0/20/0	12.6	Euthymic	Excluded	19 lithium (n=7), anticonvulsants (n=10), antidepressants (n=8), antipsychotics (n=10)	1.5 | 12	N/A	FSL/FMRIB/ TBSS	N/A	FA	Significant, widespread FA reduction in patients with BD-II compared with controls in all major WM tracts studied, including cortico-cortical association tracts, i.e., uncinate, inferior fronto-occipital, inferior longitudinal, and superior longitudinal fasciculi, interhemispheric tracts, as well as limbic tracts and parahippocampal tract.

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Study	Patients	Age	BD type I/II/ other	Disease duration (years)	Mood state	Substance use	Drugs	Tesla | direction	B-value	Software	Voxel size (mm^3)	Measures	Results
Emsell[45]	35 BD 43 HC	44±10 42±10	35/0/0	12	Euthymic	7 alcohol users	10 (7) years' lithium use	1.5 | 64	0/1,300	Explore DTI	2.5x2.5x2.5	FA, MD, AD, RD	Significant differences between patients and control subjects in FA, MD, and RD in the CC. In the fornix, significant differences were found in MD, AD, and RD. In all cases, anisotropy decreased and diffusivity increased in patients compared with controls.
Leow[46]	25 BD 24 HC	41.6±12.7 41.6±10.6	25/0/0	20.8	Euthymic	N/A	Valproic acid (n=7), carbamazepine (n=1), lamotrigine (n=3), antipsychotic (n=14), SSRI (n=8), antidepressants (n=5), benzodiazepines (n=3)	3 | 64	0/1,000	DTI Studio	1x1x1	FA, MD	Statistically significant group differences in FA, in including the genu, body, and splenium of CC. There was no significant between-group difference in MD for any WM structure, as the genu exhibited higher MD values in the bipolar group.
Torgerson[52]	27 BD 26 HC	44.2±12.9 41.5±12.1	27/0/0	23.2	Euthymic	13 alcohol users, 7 drug abusers	Antipsychotics (n=16), anticonvulsants (n=15), antidepressants (n=14), benzodiazepines (n=5)	3 | 64	0/1,000	TrackVis	2x2x2	FA	No differences in fiber FA between BD subjects and healthy controls, except for reduced FA in one of the corticospinal tracts (CST-R2).
Benedetti[49]	40 BD 21 HC	47.79±13.2 39.86±11.0	40/0/0	13.54	Euthymic	Excluded	Lithium (n=14)	3 | N/A	0/900	TBSS	1.88x1.87x2.3	MD, FA, DI, RD	Compared with control subjects, patients showed lower FA in the genu of the CC and in the anterior and right superior-posterior corona radiata. Higher radial diffusivity values were found in WM tracts of the splenium, genu and body of CC, right mid-dorsal part of the cingulum bundle, left anterior and bilateral superior and posterior corona radiata, bilateral SLF, and right posterior thalamic radiation.
Wessa[55]	22 BD 21 HC	45.41±12.6 42.95±13.1	14/08/2	22	Euthymic	Excluded	Lithium (n=10), anticonvulsants (n=11), atypical antipsychotics (n=5)	1.5 | 41	0/700	BrainVisa 3/ TBSS	1.88x1.87x2.3	MD, FA	FA was significantly increased in BD patients relative to healthy controls in medial frontal, precentral, inferior parietal, and occipital WM. No group differences in mean diffusivity were found.
Wang[41]	33 BD 31 HC	30.4±10.8 31.8±9.6	33/0/0	N/A	10 manic/ hypomanic, depression, 16 euthymic	17 (13 alcohol and/ or nine other substances, four other substances)	Lithium (n=9), anticonvulsants (n=16), antipsychotics (n=14), antidepressants (n=12), benzodiazepines (n=7)	3 | 32	0 /1,000	WFU Pick Atlas tool	1.5x1.5x1.5	FA	An association was found between pACC-amygdala functional connectivity measurements and the structural integrity of ventro-frontal WM, including the UF, where FA was significantly decreased in the BD group.
Zanetti[50]	37 BD 26 HC	34.1±9.1 28.8±9.5	37/0/0	11.6	16 depressed/21 remission	Excluded	Depression: lithium (n=6), valproate (n=6), lamotrigine (n=5), antipsychotics (n=8), antidepressants (n=7), benzodiazepines (n=6). Remission: lithium (n=6), valproate (n=2), carbamazepine (n=3), antipsychotics (n=11), antidepressants (n=9), benzodiazepine (n=4)	3 | 6	0/850	BioImage Suite 2.0	1.6x1.6x3	FA, MD	Significantly decreased FA and increased MD in bilateral prefronto-limbic-striatal WM and right inferior fronto-occipital, superior, and inferior longitudinal fasciculi were found in all BD-I patients vs controls and in depressed BD-I patients compared both to controls and to remitted BD-I patients. These findings suggest that depression in BD-I may be associated with acute microstructural WM changes.
Mahon[56]	30 BD 38 HC	33.4±8.7 31.9±8.6	25/2/3	N/A	N/A	11 alcohol or other substances	All treated with antidepressants and/or mood stabilizers	1.5 | 25	0/1,000	DTI Studio	N/A	AD, RD, FA	Voxelwise analysis of WM revealed three regions with higher FA in the right and left frontal WM and one region of lower FA in the left cerebellum in BD patients compared to healthy volunteers.

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Table 1. (Continued)

Study	Patients	Age	BD type I/II/ other	Disease duration (years)	Mood state	Substance use	Drugs	Tesla | direction	B-value	Software	Voxel size (mm^3)	Measures	Results
													These findings suggest that, compared to healthy volunteers, adult patients with BD have higher FA in the bilateral frontal WM, corresponding approximately to fibers of the corticopontine/ corticospinal tract and SLF, as well as superior thalamic radiation fibers. In addition, FA was lower in the left cerebellar WM, thus corresponding approximately to the pontine crossing tract, in patients compared to healthy volunteers.
Versace[42]	21 BD 25 HC	35.9±8.9 29.48±9.4	31/0/0	12.29 depressed/ 11.82 remitted	14 depressed/17 remitted	10 alcohol or other substances	All medicated	3 | N/A	0/850	FSL/TBSS	N/A	N/A	Subjects with BD had significantly greater FA in the left UF (reduced radial diffusivity distally and increased longitudinal diffusivity centrally), left optic radiation (increased longitudinal diffusivity), and right ATR (no significant diffusivity change), as well as significantly reduced FA in the right UF (greater radial diffusivity), vs. controls. Decreased FA was observed in the left optic radiation and in the right ATR among subjects with BD taking mood stabilizers vs. those with BD not taking mood stabilizers, as well as in the left optic radiation among depressed vs. remitted subjects with BD.
Wang[48]	BD 42 HC 42	32.6±10.1 28.7±9.1	42/0/0	N/A	11 manic/ hypomanic, 9 depressed, 22 euthymic	N/A	Lithium (n=11), anticonvulsants (n=20), antipsychotics (n=19), antidepressants (n=17), benzodiazepines (n=8), levothyroxine sodium (n=5)	3 | 32	0/1,000	BioImage Suite	N/A	FA	FA was significantly decreased in the anterior cingulum in the BD group compared with healthy controls; however, FA in the posterior cingulum did not differ significantly between groups.
Wang[48]	BD 33 HC 40	32±10.1 29.2±9.2	33/0/0	N/A	7 manic/ hypomanic, 7 depressed, 19 euthymic	11 alcohol, 6 substance abuse, 3 other substances	No medication (n=6), lithium (n=8), anticonvulsants (n=17), atypical antipsychotics (n=17), benzodiazepines (n=8)	3 | 32	0/1,000	BioImage Suite	N/A	FA	Using complementary ROI- and voxel-based DTI methods, the authors found decreased FA values in participants with BD compared to HCs in the anterior and middle CC subregions encompassing the genu, rostral body, and anterior portion of the mid-body.
Bruno[51]	BD 36 HC 28	39	25/11/0	13.8	N/A	N/A	Lithium (n=23), sodium valproate (n=3), carbamazepine (n=4), lamotrigine (n=3), neuroleptic (n=9)	1.5 | 7	0/700	SPM2	N/A	MD, FA	In the patient group, mean diffusivity was increased in the right posterior frontal and bilateral prefrontal WM, while FA was increased in the inferior, middle temporal, and middle occipital regions.

AD = axial diffusivity; ATR = anterior thalamic radiation; BD = bipolar disorder; BD-I = bipolar I disorder; BD-II = bipolar II disorder; CC = corpus callosum; FA = fractional anisotropy; FMRI = functional magnetic resonance imaging; FOFs = fronto-occipital fasciculi; GFA = generalized fractional anisotropy; HC = healthy controls; ILF = inferior longitudinal fasciculi; MD = mean diffusivity; N/A = not mentioned in text; PTO = probability of return to the origin; RD = radial diffusivity; ROI = region of interest; SLF = superior longitudinal fasciculi; SPM = statistical parametric mapping; SSRI = selective serotonin reuptake inhibitors; TBSS = tract-based spatial statistics; UF = uncinate fasciculus; WFU = Wake Forest University School of Medicine PickAtlas; WM = white matter.

The findings of decreased FA values are consistent with the description of BD as a disconnection syndrome.[64,65] The two major symptom domains in BD are mood instability and poor cognitive control over executive functions.[57] Historically, the aforementioned regions have been found to be involved in emotional processing. In 1937, Papez[66] proposed that emotion regulation is enabled through rich reciprocal connections between parts of the prefrontal cortex with the amygdala, anterior temporal regions, subgenual anterior cingulate cortex, striatum, and thalamus.

Contrary to the predominant findings, Wessa et al.,[55] Mahon et al.,[56] and Versace et al.[42] found increased FA values in different WM tracts. Despite a lack of support in the literature, a number of variables may explain these results. For example, most of these studies were performed before 2009 and used either fewer DTI directions or older versions of reconstruction software, or involved patient selection bias.

The main region exhibiting decreased FA values was the CC, the major interhemispheric WM connection that integrates emotional, cognitive, motor, and sensory information. The anterior CC regions integrate all right and left prefrontal cortex, anterior cingulate, and insula regions implicated in emotional deregulation, a core symptom of BD.

With respect to the association tracts, several studies have reported impairment in WM connection in patients with BD, with most indicating impairment in the cingulum[29,43-45,48] and the UF.[40,42,43] The cingulum is a complex fiber system that forms a central component of the entire limbic network where the UF carries association fibers between the medial prefrontal cortex and the anterior temporal lobe, including the amygdala. These regions have been extensively related to the pathophysiology of BD.[67-69]

In projection fibers, three studies described decreased FA values in the ATR. The ATR connects the dorsomedial and anterior thalamic nuclei with the prefrontal cortex, and the anterior part of the ATR is connected with the hippocampus through the fornix. Alterations in the connections between the thalamus and limbic areas may be relevant to cognitive processing and to clinical symptoms observed in patients with BD.[49,70] Alterations in ATR fiber integrity have been previously reported in BD patients, consistent with functional magnetic resonance imaging (fMRI) and structural findings.[19]

Certain important pathways could also be related to the pathophysiology of BD. The fornix is a projection tract that is located underneath the CC and connects the hippocampus with the mammillary body as well as with other cortical and subcortical structures.[30] Both structures are part of the limbic system and known to be involved in memory processes. The lack of previous reports regarding fornix alterations in BD may be due to the anatomic characteristics of the fornix and to the spatial resolution of current MRI methods.[49]

Previous investigations have hypothesized that microstructural changes in the WM of the frontal-subcortical circuits lead to a disconnection syndrome between the frontal and subcortical regions.[39] These results suggest a direct link between executive cognitive functioning and abnormal WM microstructural integrity of the fronto-limbic tracts in remitted BD patients, and provide further evidence of the neuronal disruption that underlies the residual symptomatology of BD.

It is not clear whether number of episodes, duration of illness, and other clinical progression characteristics are associated with decreased FA values. However, BD has a poorer long-term outcome than previously thought, with persistent cognitive impairment and functional decline.[71,72] Cognitive impairment has been found to affect executive functions predominantly, while moderate cognitive deficits have been observed in other cognitive tests, such as verbal memory, response inhibition, sustained attention, psychomotor speed, abstraction, and set-shifting.[73] These cognitive impairment domains seem to have a close correlation with WM and brain connectivity deterioration.[74-76]

Recently, a neuroinflammatory component has been implicated in the pathophysiology of certain psychiatric disorders,[77] and offers a plausible explanation as to why WM lesions are present in patients with BD.[78] Of note, WM is particularly vulnerable to the inflammatory neurotoxic

Table 2 White matter tracts with decreased fractional anisotropy values on diffusion tensor imaging studies

White matter tracts/studies	Main results
Commissural tracts	
Maller[43]	Corpus callosum, fornix
Sarrazin[29]	Corpus callosum
Oertel-Knöchel[31]	Corpus callosum, fornix
Emsell[45]	Corpus callosum
Leow[46]	Corpus callosum
Canales-Rodríguez[44]	Corpus callosum
Ambrosi[40]	Interhemispheric tracts
Benedetti[49]	Corpus callosum
Wang[48]	Corpus callosum
Association tracts	
Maller[43]	Cingulum bundles, superior longitudinal fasciculi, inferior longitudinal fasciculi, fronto-occipital fasciculi, uncinate fasciculi
Sarrazin[29]	Cingulum, arcuate fasciculus
Emsell[45]	Cingulum
Ambrosi[40]	Uncinate, inferior fronto-occipital, inferior longitudinal, superior longitudinal fasciculi
Canales-Rodríguez[44]	Cingulum bundle, superior fronto-occipital fasciculus
Zanetti[50]	Prefrontal-limbic-striatal white matter, inferior fronto-occipital, inferior longitudinal, superior longitudinal fasciculi
Versace[42]	Uncinate fasciculus
Wang[48]	Cingulum
Bruno[51]	Inferior longitudinal fasciculus
Projection tracts	
Maller[43]	Thalami (not specified)
Canales-Rodríguez[44]	Corona radiata
Benedetti[49]	Corona radiata
Versace[42]	Optic radiation, anterior thalamic radiation
Oertel-Knöchel[31]	Right thalamic radiation
Other tracts	
Torgerson[52]	Corticospinal tract

effects of BD.[79] The cognitive decline that occurs over the course of the disease seems to be associated, at least in part, with vulnerability to the toxic effects of inflammation.[79] Additionally, immune disturbances have been linked to BD and symptom severity, mood episodes, staging, effect of medications, metabolic disturbances, neurotrophin alterations, and increased frequency of comorbid autoimmune and allergic disorders.[80] In this context, DTI findings could provide a better understanding of the neurobiological underpinnings of pathophysiology in BD.

Disclosure

The authors report no conflicts of interest.

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