White matter abnormalities in bipolar disorder: insights from diffusion tensor imaging studies

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Abstract Diffusion tensor imaging (DTI) is a neuroimaging technique with the potential to elucidate white matter abnormalities. Recently, it has been applied to help in better understanding of the pathophysiology of bipolar disorder (BD). This review sought to synthesise existing literature on DTI studies in BD, summarise current findings and highlight brain regions that have consistently been implicated in BD, as well as posit possible future directions for DTI research in BD. The extant findings from this review suggest loss of white matter network connectivity as a possible phenomenon associated with bipolar disorder, involving prefrontal and frontal regions, projection, associative and commissural fibres, with sparse and less consistent evidence implicating the subcortical and non-frontal lobes of the brain. There are some differences in the direction of changes observed in white matter indices, and these may be attributed to factors including sample heterogeneity and limitations of DTI techniques. The possible roles of the parietal, temporal and occipital lobes and subcortical regions in BD await further investigation. Studies of bipolar disorder using DTI lag behind other neuropsychiatric diseases such as schizophrenia, but DTI research in BD is fast gaining pace. The emerging trends from these DTI findings underscore the importance of further research to unravel the underlying neural
mechanisms and clinico-anatomical correlations involving white matter in BD.

Introduction

Bipolar disorder or manic depressive psychosis is a potentially debilitating psychiatric illness that typically has its onset during adolescence or early adulthood. It can manifest clinically as depression or mania, followed by affective alternations between the two poles of mood with intervening periods of euthymia. Episodes of depression are characterised by feelings of low mood, loss of interest in activities, fatigue, poor sleep and appetite, sense of hopelessness, poor concentration and even thoughts of suicide. Episodes of mania on the other hand are typified by elevated or irritable mood, flight of ideas and pressure of speech, inflated self esteem, increased goal-directed activities at home, work or study and engagement in activities with potentially painful consequences such as fast driving, excessive spending, sexual promiscuity and drug abuse. Psychotic symptoms such as hallucinations and delusions may also be present in some cases (American Psychiatric Association 2000).

An accurate diagnosis of bipolar disorder may be delayed due to the fact that its symptoms may be mild and not obvious early in the course of the illness and that the symptoms may overlap with that of other illnesses such as unipolar depression and schizophrenia. As such, delays in diagnosis can occur and hamper the timely initiation of appropriate treatment. Conversely, the prompt delivery of suitable treatment can help to reduce the frequency and

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severity of episodes in most patients. It is hoped that better prognosis of patients can be procured with earlier intervention of bipolar disorder. This can be facilitated with a better understanding of the underlying neurobiological changes which can also serve as potential biomarkers of the illness.

In this regard, findings from neuroimaging studies can inform and reform thinking about the underlying neural changes in bipolar disorder. Neuroimaging technologies have advanced at a rate which is faster than their application in bipolar disorder (Stoll et al. 2000). Existing neuroimaging technologies can be classified into structural and functional neuroimaging techniques. Structural neuroimaging techniques include computerised tomography (CT), magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI), whilst functional neuroimaging techniques encompass positron emission tomography (PET), single photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI). In particular, MRI relies on a magnetic field to align protons in water molecules in order to create anatomical brain images. An extension of the MRI technology is diffusion MRI which measures the anisotropic diffusion of water molecules in biological tissues like the brain. The myelin membranes of axons in the brain act as natural barriers to diffusion of water. Hence, water molecules diffuse along the longitudinal axes of these myelinated fibres, instead of random directions as predicted by Brownian motion. Diffusion MRI (and later DTI) relies on this principal to elucidate the directionality of axon fibres in the brain (Kubicki et al. 2002). Thus, DTI is able to detect abnormalities of white matter tissue in the brain in terms of fibre orientation even when macrostructural changes are absent (Yurgelun-Todd et al. 2007; Bruno et al. 2008). Unlike conventional structural MRI which gives intensity images reflecting the density and relaxation characteristics of the white matter, DTI measures the anisotropy and diffusivity which can highlight microstructural abnormalities, thereby better reflecting the nature of white matter integrity within neural tissues. Furthermore, DTI tractography has enabled the virtual visualization of white matter fibre tracts (Pavuluri et al. 2009) and axon fibres (Adler et al. 2004), with the potential to confer greater insight into the cerebral changes in bipolar disorder (Houenou et al. 2007).

White matter abnormalities in bipolar disorder have been investigated using a variety of strategies, including postmortem examination (Regenold et al. 2007), microarray expression analysis of oligodendrocyte related genes (Sokolov 2007), magnetic imaging studies of white matter volumes and hyperintensities (Aylward et al. 1994; Kieseppä et al. 2003), magnetization transfer studies of macromolecular density (Bruno et al. 2004) and magnetic resonance spectroscopy studies of neurochemical changes (Cecil et al. 2002). In terms of focus, this paper sought to systematically review and synthesise all the available data from published DTI studies on white matter integrity in bipolar disorder. First, we summarise the main DTI findings involving the different brain regions (cortical, subcortical white matter and white matter tracts) in bipolar disorder. Second, we discuss clinical implications of these white matter disruptions and the limitations of current studies. Third, we suggest potential future research directions using DTI in bipolar disorder.

Materials and methods

A literature search of published DTI studies in bipolar disorder up till July 2009 was conducted using two major databases: National Centre for Biotechnology Information (NCBI) PubMed (MEDLINE) and ScienceDirect Online. The focus of the search was defined by the key words 'bipolar disorder' and 'diffusion tensor imaging'. Studies were included if they satisfied the following criteria: (1) the patient population had a diagnosis of bipolar disorder, (2) diffusion tensor imaging was an imaging technique used and (3) the article was published in English. Additionally, references from the selected papers were evaluated and included if they were found to be relevant to the focus of this systematic review.

Useful DTI parameters

Diffusion tensor

The water diffusion process in the human brain can be analysed mathematically by a tensor model. It can be conceptually treated as an ellipsoid, with its three principal axes representing the three cardinal diffusion directions and their respective lengths proportionally indicating the directional mobility. Specifically, the diffusion tensor can be represented by a 3×3 symmetric matrix that describes the molecular mobility along the three principal diffusion directions and also the correlation between these directions (Le Bihan et al. 2001). Given these six unknowns, a minimum of six non-collinear diffusion gradient directions are required to determine the diffusion tensor. Three-dimensional diffusion ellipsoids can then be constructed on a voxel by voxel basis. The length and orientation of the longest, middle and shortest axes of the ellipsoid are known as the eigenvalues (λ_1, λ_2 and λ_3) and the directions of the eigenvectors (V_1, V_2 and V_3), respectively (Mori and Zhang 2006). The eigenvector V_1 of the tensor's longest axis (i.e. longitudinal axis) can be used to identify the orientation of the fibre (Mori and Zhang 2006). Although

six gradient directions are sufficient to determine a tensor, in recent years, there is a growing trend of using more gradient encoding directions in order to reduce bias in sampling direction and map fibre orientations more accurately (Le Bihan et al. 2001).

Fractional anisotropy

Fractional anisotropy (FA) is a rotationally invariant and scalar measure of the anisotropy of water diffusion. It is derived from DTI tensor and ranges from 0 to 1 (FA is the highest in major white matter tracts, lower in grey matter and approaches 0 in the cerebrospinal fluid) as determined in Eq. 1 (calculation of fractional anisotropy; Mori and Zhang 2006). An FA value of 0 indicates isotropic diffusion, where water diffuses equally in the x-, y-, and z-directions, with no directional preference. This unrestricted diffusion of water is also known as total isotropy. On the other hand, an FA value approaching 1 indicates high anisotropy where there are structural limitations to the diffusion of water, such as in axons where there is limited diffusivity across the axons. The degree of FA will vary according to the presence or absence of structural restrictions. Differences in FA indicate variations in diffusion anisotropy, thus providing exclusive information on the directionality of axons in the brain

$$\mathrm{FA} = \sqrt{\frac{1}{2}} \frac{\sqrt{\left((\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2\right)}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \qquad (1)$$

Axial and radial diffusivities

Axial and radial diffusivities are specific measures of diffusivity in the longitudinal and transverse diffusion directions, respectively. They may provide information about possible alterations in the axonal and myelin integrity, respectively, thus potentially allowing a more accurate interpretation white matter abnormality in bipolar patients. A reduction in the axial diffusivity and increase in radial diffusivity could indicate a loss of axonal and myelin integrity, and the reverse may also be true (Versace et al. 2008).

Mean diffusivity

Mean diffusivity (MD) is the average of the principal diffusivities in three diffusion directions, and is an expression of the average magnitude of water diffusion for any given diffusion tensor. It is measured in units of area per unit time, or square millimetre per second. It can be a sensitive indicator of the overall developmental changes in the brain tissue (Pierpaoli et al. 1996).

Apparent diffusion coefficient

At a macroscopic level (e.g. across an inhomogeneous voxel or region), researchers often use the term apparent diffusion coefficient (ADC) as a scalar index of the rate of water diffusion in cerebral tissues. Similar to MD, it is measured in units of area per unit time. A high value of ADC indicates less restricted diffusion and implies the presence of fewer organised structures in the white matter, or the presence of intra-axonal structures like microtubules or microfilaments that enhance diffusion via facilitated transport along the axoplasm (Le Bihan 1990). Conversely, a low value of ADC indicates the presence of organised tracts and fibres that impede diffusion, or the presence of thick myelin layers that decrease water mobility across fibres (Le Bihan 1990). ADC is unique for each voxel (measurement volume), but in the presence of multiple compartments can be dependent on b values which characterise the timing, amplitude and shape of gradient pulses (Le Bihan et al. 2001). A brain map can be constructed using ADC values, where brighter regions on the map indicate a higher rate of diffusion than darker regions, as the pixel intensities are proportional to the rates of diffusion (Mori and Zhang 2006).

Regional fibre coherence index (r-FCI)

The regional fibre coherence index (r-FCI) is a relatively new DTI measure that evaluates the coherence of a fibre tract (Zhou and Leeds 2005). Individual fibre orientations are determined by the fibre orientation vector (λ_j) at voxel j, which is in turn, estimated from the main diffusion direction determined by DTI. The r-FCI for voxel j can then be calculated with an equation [Eq. 2; calculation of regional fibre coherence index (Zhou and Leeds 2005)], where i is the index of voxels that are adjacent to voxel j, $g(i,j)$ is a weighting function defining the regions where summation is performed and N is the total voxel pairs involved in the calculation of the inner vector product (Zhou and Leeds 2005)

$$\mathrm{FCI}_j = \frac{1}{N}\left| \sum_{i=1}^{N} (\lambda_j \cdot \lambda_i) g(i,j) \right| \qquad (2)$$

DTI study approaches

There are various different approaches to the analyses of DTI data, including the region-of-interest (ROI) approach, voxel-based morphometry (VBM) approach, tract-based spatial statistics (TBSS) and DTI tractography. In ROI analyses, brain regions are preselected for investigation. The ROI approach can focus on specific brain regions which have been previously linked to bipolar disorder.

Unlike the VBM method which performs whole brain analyses, the ROI approach is more directed and can be hypothesis driven, based on extant understanding of neural substrates in the condition. However, the ROI method has also been criticised to be presumptuous in the selection of specific brain regions, as this may leave out novel regions which may be involved in the neurobiology of any condition (Kanaan et al. 2006).

Tract-based spatial statistics is a more recent technique that seeks to eliminate existing problems using the VBM approach. In the VBM approach, it can be challenging to ensure that each voxel contains only data from the same part of the white matter tract in all subjects due to alignment inaccuracies (Smith et al. 2006). TBSS reduces this alignment problem by first projecting FA images onto a common space using a nonlinear registration before creating a mean of the aligned FA images from all subjects to form an alignment invariant FA skeleton (Smith et al. 2007). This invariant skeleton represents the centre of all major tracts common to the subject group, where the aligned FA of every individual is then projected to resolve any residual alignment problems (Smith et al. 2007).

The localised statistical testing of FA eliminates the need for spatial smoothing that is usually required, prior to conducting voxelwise statistics. This prevents distortion of results due to smoothing, and abolishes the problem of deciding on an appropriate extent of smoothing (Smith et al. 2006). TBSS hence enables a comparison of DTI data between groups of individuals in an automated and reliable fashion (Houenou et al. 2007).

DTI tractography is a qualitative method which allows visualization of white matter tracts, thus facilitating the study of the connectivity and continuity of neural pathways. Like the ROI method, it works on an a priori hypothesis. It identifies a seed (pixel of interest) on the structural map, from which a line is propagated along the fibre orientation as determined by V_1 (Basser et al. 2000; Mori and Zhang 2006), enabling the virtual reconstruction of white matter fibre bundles and their microstructural properties (Basser et al. 1994). However, DTI tractography only graphically illustrates the directionality of fibre pathways; it cannot be assumed to be completely anatomically realistic because it is often an estimation based on a tractography algorithm (Houenou et al. 2007).

Results

There have been, to date, 18 published DTI studies of bipolar patients in the literature, and the main findings are shown in Table 1.

White matter abnormalities in cortical regions

Frontal and prefrontal lobes

White matter hyperintensities have been detected in the prefrontal regions of adolescents experiencing their first episode of mania. A significantly lower FA was observed in the left superior frontal region of the brain, and was attributed to axonal disorganization and loss of neural network connectivity (Adler et al. 2006). In a more recent study, adolescents with bipolar I disorder also exhibited decreased FA values but in the right orbital frontal regions (Kafantaris et al. 2009). This was accompanied with a significantly increased ADC in the right and left subgenual regions. Such prefrontal and frontal white matter abnormalities present early in the disease may be the first anatomical signs of bipolar disorder, and can potentially act as biomarkers of the disease.

In adult subjects, DTI studies also revealed increased ADC or MD in frontal areas of the brain. Adults with bipolar disorder showed bilaterally increased MD in the prefrontal and right posterior frontal white matter, where the prefrontal areas coincided with regions previously found to have decreased white matter density (Bruno et al. 2008). This bilateral prefrontal increase in MD is consistent with an earlier study, where increases in ADC were found in the orbital frontal gyri, suggestive of cortical white matter abnormalities in BD (Beyer et al. 2005). In a study which compared group mean ADC average (ADC_{av}) values for combined white matter ROIs, bipolar patients had significantly higher ADC_{av} than controls in the frontal lobe (Regenold et al. 2006).

Contrary to most studies that report reduced FA in the frontal and prefrontal lobes of bipolar patients, some studies reported elevated FA in patients with bipolar disorder. A voxel-based analysis of white matter in patients revealed bilateral increases of FA in the frontal white matter (Mahon et al. 2009), whilst a TBSS study demonstrated increased FA in the orbito-medial frontal cortex of bipolar patients (Versace et al. 2008). Small increases in FA have also been found in the fronto-polar prefrontal cortex of bipolar patients, particularly in the upper portion of Brodmann area 10 and the lower portion of Brodmann area 9 (Adler et al. 2004).

In summary, most of the studies to date reported white matter abnormalities characterised by reduced FA and elevated ADC in the frontal and prefrontal lobes of bipolar patients, with the exception of a few that report elevated FA in bipolar disorder.

Parietal, temporal and occipital lobes

In a study which compared ADC_{av} values in combined white matter ROIs between patients and healthy controls,

Table 1 Main DTI studies and findings

Authors (year)	Subjects	Age (years) (mean ± SD), gender (M/F)	Duration of illness (years) (mean ± SD)	Imaging parameters	Analysis technique	Findings
Adler et al. (2004)	9 BD 9 HC	32 ± 8, 4/5 31 ± 7, 6/3	–	3.0 T 25 gradient directions 5 mm	ROI	Decrease in FA in ROIs 25–30 mm above the anterior commissure Decreased FA in peripheral white matter tracts linking the prefrontal cortex to the subcortical and other cortical regions
Adler et al. (2006)	11 BD (FE and MIX) 17 HC	14 ± 2, 5/6 14 ± 2, 7/10	–	3.0 T 25 gradient directions 5 mm	ROI	Decreased FA in the left superior frontal region.
Barnea-Goraly et al. (2009)	21 BD 18 HC	16.1 ± 2.7, 15/6 14.5 ± 2.7, 14/4	3.1 ± 2.3	3 T 6 gradient directions 5 mm	TBSS	Decrease in FA in fornix, posterior cingulate, corpus callosum and parietal and temporal corona radiata
Beyer et al. (2005)	14 BD 21 HC	44.0 ± 17.6, 4/10 44.6 ± 13.5, 4/17	13.6 ± 12.1	1.5 T 6 gradient directions 5 mm	ROI	Increases in ADC in the orbital frontal gyri
Bruno et al. (2008)	25 BDI 11 BDII 28 HC	37.4, 10/15 42.8, 3/8	13.8	1.5 T 7 gradient directions 5 mm	VBM	Increased MD in the prefrontal and right posterior frontal white matter, anterior and posterior fronto-occipital fasciculus and part of the corpus callosum Decreased FA in the inferior longitudinal fasciculus
Chaddock et al. (2009)	19 BD 21 Unaffected first degree relatives 18 HC	43.3 ± 10.2, 9/10 42.5 ± 13.6, 12/9 41.7 ± 12.2, 10/8	–	1.5 T 64 gradient directions	VBM	Decrease FA in genu of corpus callosum, right inferior and left superior longitudinal fasciculus
Frazier et al. (2007)	10 BD 8 HC	9.2 ± 3.0, 4/6 9.2 ± 2.4, 5/3	–	1.5 T 6 gradient directions 5 mm	ROI	Decreased FA in bilateral frontal tracts, left orbitofrontal white matter and right corpus callosum
Haznedar et al. (2005)	17 BDI 7 BDII 16 Cyc 36 HC	39.8 ± 13.4 43.8 ± 6.7 43.9 ± 9.2 40.7 ± 11.6	–	1.5 T 7 gradient directions 5 mm	ROI	Increased FA in the superior longitudinal fasciculus Decreased FA in the posterior limb of the internal capsule in bipolar patients
Houenou et al. (2007)	16 BD (EU) 16 HC	41.88, 8/8 40.50, 9/7	–	1.5 T 41 gradient directions 2 mm	TG	Significant increase in the virtual reconstructed fibres between the left subgenual cingulate and the left amygdala-hippocampal region No difference in FA or ADC of all reconstructed fibre tracts in the amygdala-hippocampal complex, pons and cerebellum

Table 1 continued

Authors (year)	Subjects	Age (years) (mean ± SD), gender (M/F)	Duration of illness (years) (mean ± SD)	Imaging parameters	Analysis technique	Findings
Kafantaris et al. (2009)	26 BD 26 HC	16 ± 1.5, 12/14 15.3 ± 1.5, 14/12	–	1.5 T 6 gradient directions 5 mm	VBM	Increased ADC in the right and left subgenual regions, precuneus, postcentral gyrus, temporal and occipital lobes Decreased FA in the right orbital frontal regions, precuneus, postcentral gyrus, temporal and occipital lobes
Mahon et al. (2009)	30 BD 38 HC	33.4 ± 8.7, 15/15 31.9 ± 8.6, 22/16	–	1.5 T 25 gradient directions 5 mm	VBM, TG	Increased FA in the frontal white matter, corticopontine and corticospinal tracts and superior thalamic radiation fibres Decreased FA in the left cerebellum and pontine crossing tracts No difference in FA along the superior longitudinal fasciculus
McIntosh et al. (2008a)	40 BD 25 SCZ 49 HC	39.9 ± 10.1, 21/19 37.2 ± 9.2, 14/11 35.3 ± 11.0, 28/21	18.8 16.4	1.5 T 51 gradient directions 2.8 mm	–	Decreased mean FA in the uncinate fasciculus and anterior thalamic radiation
Pavuluri et al. (2009)	13 PBD (EU) 13 ADHD 15 HC	14.8 13.4 13.7	–	3.0 T 27 gradient directions 5 mm	ROI	Increased mean ADC across seven white matter tracts. Decreased FA in anterior corona radiate and white matter tracts Reduced regional fibre coherence index (r-FCI) in the splenium
Sussmann et al. (2009)	42 BD 28 SCZ 38 HC	39.6 ± 10.1, 22/20 38.0 ± 9.9, 15/13 37.2 ± 11.9, 19/19	18.3 ± 11.1 16.8 ± 9.6	1.5 T 51 gradient directions 2.8 mm	ROI, VBM	Decreased FA in left part of the anterior limb of the internal capsule, the superior thalamic radiation fibres, anterior thalamic radiation and uncinate fasciculus
Versace et al. (2008)	31 BD 25 HC	35.9 ± 8.9, 11/20 29.48 ± 9.43, 11/14	11.8 ± 6.3	3.0 T 6 gradient directions 3 mm	TBSS	Increased FA in the left orbito-medial frontal cortex, cuneus, temporal cortex and left uncinate fasciculus Decreased FA in the right uncinate fasciculus
Wang et al. (2008a)	33 BD 40 HC	32 ± 10.1, 24.73% F 29.2 ± 9.2, 27.68% F	–	3.0 T 32 gradient directions 3 mm, 5 mm	ROI, VBM	Decreased FA in the genu, rostrum and anterior and middle portions of the corpus callosum

Table 1 continued

Authors (year)	Subjects	Age (years) (mean ± SD), gender (M/F)	Duration of illness (years) (mean ± SD)	Imaging parameters	Analysis technique	Findings
Wang et al. (2008b)	42 BD 42 HC	32.6 ± 10.1, 69% F 28.7.2 ± 9.1, 65% F	–	3.0 T 32 gradient directions 3 mm	ROI	Reduced FA in the anterior cingulum
Yurgelun-Todd et al. (2007)	11 BD (EU) 10 HC	32.9 ± 10.5, 6/5 32.4 ± 9.1, 4/6	12.0 ± 9.8	1.5 T 6 gradient directions 5 mm	ROI	Increased FA in the genu of corpus callosum
Zanetti et al. (2009)	37 BD 26 HC	34.1 ± 9.0, 13/24 28.8 ± 9.5, 12/14	11.6 ± 7.5	3 T 6 gradient directions 3 mm	VBM	Decreased FA, MD in inferior fronto-occipital, superior and inferior longitudinal fasciculus

BD bipolar disorder; *PBD* paediatric bipolar disorder; *Cyc* cyclothymia; *ADHD* attention-deficit hyperactivity disorder; *SCZ* schizophrenia; *HC* healthy controls; *EU* euthymic; *FE* first episode; *MIX* mixed episode; *DTI* diffusion tensor imaging; *T* Tesla; *ROI* region of interest analysis; *VBM* voxel-based morphometry; *TG* tractography; *TBSS* tract-based spatial statistics

patients with bipolar disorder were found to have significantly higher ADC_{av} than controls in the parietal, temporal and occipital lobes (Regenold et al. 2006). This indicates the presence of microstructural white matter abnormalities in extensive parts of the brain. However, a recent TBSS study showed the opposite results, in that there was increased FA in the cuneus (occipital lobe, Brodmann area 17) and temporal cortex of bipolar patients, both of which were associated with trend level increases in longitudinal diffusivity (Versace et al. 2008).

At present, the findings implicating involvement of brain regions other than the frontal lobes were inconsistent and needed further replication.

White matter abnormalities in subcortical regions

Subcortical regions implicated include the thalamus and amygdala-hippocampal complex. A diffusion tensor tractography study of bipolar patients found that the mean FA and ADC of all reconstructed fibre tracts in the amygdala-hippocampal complex and pons were comparable between patients and controls (Houenou et al. 2007). This was in contrast with the findings of another study which revealed that the pontine fibres of bipolar patients had lower FA when compared to healthy controls (Mahon et al. 2009). There is a still a paucity of findings involving specific subcortical regions which warrants better examination.

White matter tract abnormalities in bipolar disorder

Abnormalities in the white matter tracts have been observed in bipolar patients across the age spectrum. Adults with bipolar disorder have exhibited abnormalities in their peripheral white matter tracts that form a network with the subcortical and cortical regions of the brain. These white matter tracts have decreased FA as compared to controls, suggesting a loss in bundle coherence (Adler et al. 2004). Similarly, young bipolar patients have decreased FA in the white matter tracts and also a significantly higher mean ADC value across several white matter tracts—namely the anterior corona radiata, anterior limb of the internal capsule, posterior limb of the internal capsule, superior region of the internal capsule, superior longitudinal fasciculus, cingulum and splenium (Pavuluri et al. 2009)—suggesting possible time- and illness-specific white matter changes.

Projection fibres

The internal capsule is a bundle of myelinated fibres that can be sub-classified into the anterior and the posterior limb. The anterior limb which is located between the lentiform nucleus and the caudate nucleus contains the

thalamocortical and corticothalamic fibres, whilst the posterior limb found between the lentiform nucleus and the thalamus encompasses the corticobulbar and corticospinal tracts (Waxman 2003).

Decreased FA have been found in the posterior limb (Haznedar et al. 2005) and the left part of the anterior limb (Sussmann et al. 2009) of the internal capsule in bipolar patients. Decreased FA have also been found in the anterior corona radiata of paediatric bipolar patients (Pavuluri et al. 2009) and the pontine crossing tracts of bipolar patients receiving psychotropic medication including mood stabilisers (Mahon et al. 2009).

In a cohort study, subjects homozygous for the T allele of the neuregulin 1 gene were found to have reduced FA in the anterior limb of the internal capsule and a lower white matter density in the right tip of the ALIC, as compared to patients homozygous for the C allele (McIntosh et al. 2008b). The TT genotype has been associated with increased risk for psychosis, and these results suggest that reduced structural connectivity could be a reason for the heightened susceptibility to psychosis.

Of interest, the corticopontine and corticospinal tract of bipolar patients were found to have higher FA than in healthy controls (Mahon et al. 2009). This may reflect greater fibre coherence and directionality in the interconnecting regions, suggesting non-uniform changes across brain regions in bipolar patients.

Apart from the internal capsule, thalamic radiations which originate from the lateral surface of the thalamus and terminate in the cerebral cortex have also been implicated in bipolar disorder. Higher FA was revealed in the superior thalamic radiation fibres of bipolar patients in a VBM study (Mahon et al. 2009), which seems to be in line with the findings of increased FA in the anterior thalamic radiation when using the TBSS approach (Versace et al. 2008). However, another study which complemented the VBM approach with an ROI analysis found reduced FA in the superior thalamic radiation fibres of patients (Sussmann et al. 2009).

The same study found decreased FA in the anterior thalamic radiation after small volumetric corrections were made to the frontal lobe (Sussmann et al. 2009). Patients on mood stabilisers in the TBSS study by Versace et al. (2008) found significantly decreased FA in the right anterior thalamic radiation and left optic radiation cluster, thus suggesting white matter changes related to treatment. Of note, the impact of medications on the integrity of cerebral white matter is less understood and requires further elucidation.

Overall, the extant DTI studies have found both elevated and reduced FA in the projection fibres of bipolar patients when compared to controls, although with a predominance towards decrease in FA. A reduced FA may be attributed to a loss in structural network connectivity, whilst an elevated FA could reflect an increase in the coherence and directionality of white matter fibres. It is possible that less studied factors such as treatment differences may have contributed to these findings.

Association fibres

Quantitative tractography has revealed a significant increase in the number of virtual reconstructed fibres between the left subgenual cingulate and the left amygdala-hippocampal region, suggesting that the uncinate fasciculus, which connects the frontal lobe to the temporal lobe, may have a role in the neurobiology of bipolar disorder (Houenou et al. 2007). As fibre density increases, these microstructural changes in the fibre may result in an increase in FA.

A recent TBSS study reported increased and decreased FA in the left and right uncinate fasciculus, respectively, in bipolar patients (Versace et al. 2008), consistent with another study in which decreased FA was found in the uncinate fasciculus in bipolar patients after small volume corrections to the frontal lobe (Sussmann et al. 2009). Amongst the patients within the study by Versace et al. (2008), those without a lifetime history of alcohol or drug abuse had significantly decreased FA in the left uncinate fasciculus. There was also a significant negative correlation between age at the point of imaging and FA in the left and right uncinate fasciculus (Versace et al. 2008), highlighting possible interactions between external chemical agents (such as drugs and alcohol), age and white matter changes in patients.

In another study involving bipolar and schizophrenic subjects, both groups had decreased mean FA in the uncinate fasciculus (McIntosh et al. 2008a), suggesting that there may be a similar neural basis underlying psychotic spectrum disorders.

Apart from the uncinate fasciculus, the superior longitudinal fasciculus (which connects the frontal lobe with the other lobes of the brain) has also been implicated in bipolar disorder. Bipolar I patients were found to have higher FA (Haznedar et al. 2005) or lower FA (Zanetti et al. 2009; Chaddock et al. 2009) in the superior longitudinal fasciculus than controls. However, a separate study revealed that white matter FA along the superior longitudinal fasciculus did not differ significantly between patients and controls (Mahon et al. 2009).

Other significant findings in bipolar patients included increased mean diffusivities in the anterior and posterior fronto-occipital fasciculus as well as decreased FA in the inferior longitudinal fasciculus (Bruno et al. 2008; Zanetti et al. 2009; Chaddock et al. 2009); in the peripheral white matter tracts linking the prefrontal cortex to the other cortical regions (Adler et al. 2004); and in the anterior

cingulum which connects the cingulate gyrus to the entorhinal cortex (Wang et al. 2008b).

In sum, studies that implicate association fibres in the pathophysiology of bipolar disorder mostly reported decreased FA, thus lending evidence to the idea of white matter disconnectivity in bipolar disorder. The involvement of these association fibres, which serve to connect the frontal and prefrontal cortex with various lobes of the cerebral hemisphere, point to the fact that disruptions in these vital white matter connections may contribute to the neural basis underlying bipolar disorder.

Commissural fibres

The corpus callosum is the largest commissural fibre bundle, which consists of the rostrum, genu, body and splenium (Bhatnagar 2002). Yurgelun-Todd et al. (2007) found higher FA in the genu of the corpus callosum using a region-of-interest analysis, whilst Wang et al. (2008a) found that FA was significantly reduced in the genu, rostrum and the anterior middle body of the corpus callosum in their voxel-wise analysis. Wang et al. (2008a) further confirmed their findings with an ROI analysis in the same study, where they found reduced FA in the same subregions within the corpus callosum.

The findings of white matter abnormalities in the corpus callosum were consistent with other observations of decreased FA in the corpus callosum of adolescents with BD (Barnea-Goraly et al. 2009), increased MD in part of the corpus callosum (Bruno et al. 2008), and that of reduced r-FCI in the splenium of bipolar patients (Pavuluri et al. 2009).

In short, there is data implicating the corpus callosum in bipolar disorder, which was first contemplated as early as 1903 (Wang et al. 2008a). The corpus callosum is important in transmission of information between the right and left cerebral hemispheres, and this may suggest serious disruptions in interhemispheric connectivity underlying bipolar disorder.

Discussion

The extant findings from this review suggest loss of white matter network connectivity as a possible phenomena associated with bipolar disorder, involving prefrontal and frontal regions, projection, associative and commissural fibres (Fig. 1), with sparse and less consistent evidence implicating the subcortical and non-frontal lobes of the brain (Table 2) (Adler et al. 2004; Beyer et al. 2005; Mahon et al. 2009; McIntosh et al. 2008a).

The majority of DTI studies in bipolar disorder report reduced FA and elevated ADC involving specific brain regions such as the frontal lobes, internal capsule, uncinate fasciculus and corpus callosum. There are several explanations that can account for an increased FA noted in regions such as the superior longitudinal fasciculus and non-frontal lobes of the brain. First, a decrease in the number of crossing fibres can account for a paradoxical increase in FA. Second, a lower signal to noise ratio contributes to an increase in FA (Anderson 2001), although it has also been argued that this may have limited impact because FA values have also been found to be less sensitive to noise (Skare et al. 2000). Third, there may be differential expression and progression of white matter disturbances over time and with course of illness. There are some data to point to the fact that the process of myelination is ongoing at least in the temporal lobes into the second decade of life (Benes et al. 1994) and there may be inherent anisotropy differences between adolescents and adults in different cerebral regions (Schneiderman et al. 2007). Fourth, concurrent volume reduction with myelin loss may also result
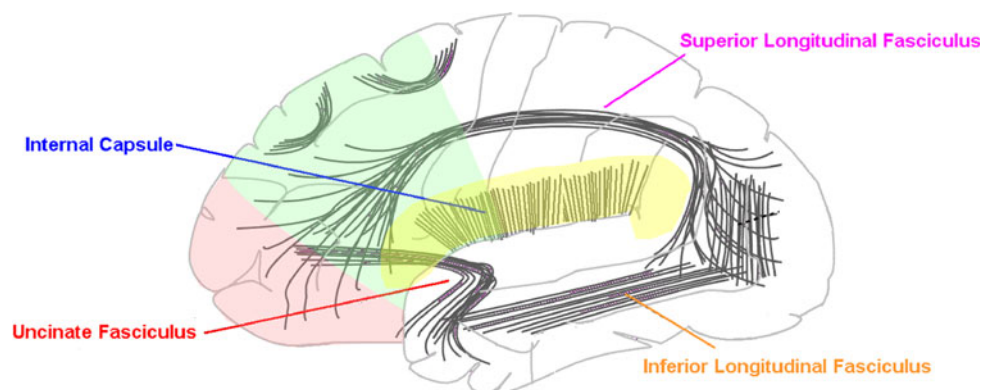
Fig. 1 Major brain regions implicated in bipolar disorder. A parasagittal section of the cerebrum shows the major brain regions and white matter tracts, i.e. prefrontal lobe (*highlighted pink*), frontal lobe (*highlighted green*), corpus callosum (*highlighted yellow*), internal capsule, uncinate fasciculus and superior and inferior longitudinal fasciculi that have been shown to exhibit white matter abnormalities in bipolar disorder

Table 2 Summary of DTI findings in bipolar disorder

Area of study[a]	Specific region	Studies of BD/HC	White matter index	Comments
Cortical regions	Prefrontal, Frontal	9/9 (Adler et al. 2004)	FA ↓	Increase in diffusion index associated with a decrease in white matter integrity.
		30/38 (Mahon et al. 2009)	FA ↑	
		11/17 (Adler et al. 2006)	FA ↓	
		26/26 (Kafantaris et al. 2009)	FA ↓/ADC ↑	
		14/21(Beyer et al. 2005)	ADC ↑	
		36/28 (Bruno et al. 2008)	MD ↑	
	Parietal, Temporal, Occipital	31/25 (Versace et al. 2008)	FA ↑	Data sparse but some abnormalities found.
		26/26 (Kafantaris et al. 2009)	FA ↓/ADC ↑	
Subcortical regions	Amgydala-hippocampal complex	16/16 (Houenou et al. 2007)	FA ↔	Data sparse
		16/16 (Houenou et al. 2007)	ADC ↔	
White matter tracts	Projection fibres (e.g. IC)	30/38 (Mahon et al. 2009)	FA ↑	Decrease in white matter integrity.
		40/36 (Haznedar et al. 2005)	FA ↓	
		13/13[b]/15 (Pavuluri et al. 2008)	FA ↓	
		40/25[c]/49 (McIntosh et al. 2008a)	FA ↓	
		42/28[c]/38 (Sussmann et al. 2009)	FA ↓	
		21/18 (Barnea-Goraly et al. 2009)	FA ↓	
	Association fibres (e.g. SLF, UF)	31/25 (Versace et al. 2008)	FA ↓ (right)	Predominant decrease in FA pointing to white matter disconnectivity
		36/28 (Bruno et al. 2008)	FA ↓	
		40/25[c]/49 (McIntosh et al. 2008a)	FA ↓	
		42/28[c]/38 (Sussmann et al. 2009)	FA ↓	
		30/38 (Mahon et al. 2009)	FA ↔	
		36/28 (Bruno et al. 2008)	MD ↑	
		16/16 (Houenou et al. 2007)	VRF ↑	
		10/8 (Frazier et al. 2007)	FA ↓	
		19/21[d]/18 (Chaddock et al. 2009)	FA ↓	
		37/26 (Zanetti et al. 2009)	FA ↓	
White matter tracts	Commissural fibres (i.e. CC)	33/40 (Wang et al. 2008a)	FA ↓	Findings implicate FA changes at the
		11/10 (Yurgelun-Todd et al. 2007)	FA ↑	Corpus callosum, suggesting disruptions in the interhemispheric
		10/8 (Frazier et al. 2007)	FA ↓	Connectivity
		13/13[b]/15 (Pavuluri et al. 2008)	r-FCI ↓	
		36/28 (Bruno et al. 2008)	MD ↑	
		19/21[d]/18 (Chaddock et al. 2009)	FA ↓	
		21/18 (Barnea-Goraly et al. 2009)	FA ↓	

IC internal capsule; *SLF* superior longitudinal fasciculus; *UF* uncinate fasciculus; *CC* corpus callosum; *BD* bipolar disorder subjects; *HC* healthy controls; *FA* fractional anisotropy; *ADC* apparent diffusion coefficient; *MD* mean diffusivity; *r-FCI* regional-fibre coherence index; *VRF* virtual reconstructed fibres; ↑ *or* ↓ increased or decreased FA/ADC/MD/r-FCI/VRF in BD subjects relative to normal controls; ↔ no statistically significant changes in FA/ADC/MD/r-FCI/VRF

[a] Studies may include one or more than one of the following areas of study

[b] Patients with attention-deficit hyperactivity disorder (ADHD)

[c] Patients with schizophrenia

[d] Unaffected first degree relatives

in an increase in the density of the underlying white matter fibres, and can possibly result in a rise in FA.

The frontal and prefrontal lobes have consistently been implicated in bipolar disorder, and most DTI studies describe white matter abnormalities characterised by reduced FA and elevated ADC, with the exception of a few that reported elevated FA in patients with BD. A reduced FA and elevated ADC indicate increased diffusion within

the brain white matter, which may be due to a reduction in its overall integrity. The prefrontal lobes are responsible for planning, organising and evaluating voluntary behaviour that is goal-oriented. In particular, the dorsolateral prefrontal area is intricately involved in working memory (Edin et al. 2009), and has connectivity with different cortical and subcortical brain regions. Working memory includes the cognitive ability to retain information whilst performing a task, to verify the relevance of information and to keep the task objectively in mind. Structural abnormalities, including white matter abnormalities in the prefrontal cortex, could thus provide a better understanding of the neural basis for some of the clinical manifestations of bipolar disorder such as poor judgement and impaired decision-making capacity during the illness episodes.

The frontal lobes are also important in the control of our emotions (Kawasaki et al. 2001) and personality and are also involved in language, initiation, judgement, impulse control and social and sexual behaviour. During an episode of mania, bipolar patients have reported racing thoughts and poor judgement, and they can manifest pressure of speech or flight of ideas with little coherence, indulge in spending sprees and have increased sexual drives, whilst patients in the depressive phase are known to be constantly fatigued, lacking in interest in activities they used to enjoy, have poor attention span and lower sexual drives. Structural abnormalities, including white matter disruptions in the frontal lobes, may form the neural basis of some of these symptoms.

Specifically, the right orbital frontal cortex has been implicated in bipolar disorder with decreased FA (Kafantaris et al. 2009), and is responsible for modulating social behaviours in patients. Previous lesion studies involving the frontal cortex revealed that patients exhibit highly volatile emotions, alternating between euphoria and indifference, thus lending evidence that mood changes observed in bipolar disorder may be attributed to anomalies in this region, including white matter disruptions. Additionally, the medial frontal cortex which is responsible for arousal and motivation was also found to show FA changes in a TBSS study (Versace et al. 2008).

Findings that implicate non-frontal cortical brain regions have been inconsistent and require further replication. Regenold et al. (2006) reported increased ADC in the parietal, temporal and occipital lobes of patients, whilst Versace et al. (2008) found increased FA in the temporal lobes of bipolar patients. Consistent with the functions of temporal lobes in the formation of working, emotional, visual and declarative memories, patients with bipolar disorder have been found to exhibit impaired verbal and visual recognition memories (Glahn et al. 2007; Murphy and Sahakian 2001), pointing to the possibility that white matter abnormalities may underlie the neuropsychology of

bipolar disorder. It is thus worthwhile to conduct further studies on these non-frontal cortical brain regions, so as to better elucidate their roles in bipolar disorder.

To date, there are only two DTI studies that point to an involvement of subcortical regions in bipolar disorder. One study did not find any difference in the white matter indices within the amgydala-hippocampal complex and pons between patients and controls (Houenou et al. 2007), which was in contrast to the finding of another study which found lower FA in the pontine fibres of patients (Mahon et al. 2009). The amygdala and hippocampal complexes are located in the medial temporal lobes, and are linked to separate memory systems. The amygdala modulates the encoding and storing of memories that depend on and is influenced by the hippocampal complex, whilst the hippocampal complex forms episodic representations of the emotional significance and interpretations of events (Phelps 2004). Whilst these studies may hint at the possibility of an involvement of white matter in particular subcortical structures, further examination of these specific subcortical regions are warranted.

Overall, extant DTI studies have shown an extensive involvement of white matter tracts in bipolar disorder within the projection, associative and commissural fibres. In general, both elevated and reduced FA values have been detected in the projection fibres of bipolar patients when compared to controls. The fibres involved include the anterior corona radiata, which converges to form the internal capsule; thalamic radiations, which are found in the internal capsule; and the pontine crossing tract, corticopontine and corticospinal tracts, which bypass the internal capsule. The superior thalamic radiation consists of thalamocortical fibres passing through the posterior limb of the internal capsule. These fibres send general sensory impulses from the ventral thalamic nuclei to the postcentral gyrus. White matter abnormalities in the superior thalamic radiation may disrupt the transmission of these sensory signals and affect how they are translated to accurate motor responses. This may be the cause of impaired sequential motor responses observed in paediatric bipolar patients (Dickstein et al. 2005). The anterior thalamic radiation serves to connect the anterior thalamic and dorsomedial nuclei with the prefrontal cortex and medial temporal cortex; variants of the neuregulin-1 gene that increase the risk of psychosis are thought to be related to a disruption of this connection (Sprooten et al. 2009).

The pontine crossing tract originates in the pontine reticular formation and terminates in the ventral grey matter. The corticopontine tract originates from the primary motor, premotor and primary somatosensory cortices and runs through the internal capsule to terminate in the pons, whilst the corticospinal tract originates from the primary motor cortex and terminates in the ventral horn of

the spinal cord, thus bypassing the internal capsule along the way. The corticopontine and the corticospinal tracts run parallel to each other, and together with the pontine crossing tract, are responsible for initiating and controlling movements. White matter abnormalities in these tracts can thus perpetuate deficits in motor inhibition, which can contribute to behavioural features observed in bipolar patients as they struggle with inhibition of their exaggerated physical and emotional responses to external stimuli (Soares and Young 2007).

The association fibres that have been implicated in the pathophysiology of bipolar disorder mostly reported decreased FA, thus lending evidence to white matter disconnectivity in bipolar disorder. These fibres include the uncinate fasciculus, superior and inferior longitudinal fasciculi, fronto-occipital fasciculi and anterior cingulum. The uncinate fasciculus is involved in memory integration, and a disruption in this fibre pathway can lead to memory deficits, which may be seen in depressed bipolar patients. The superior and inferior longitudinal fasciculi are involved in the integration of the auditory and speech areas of the brain (Hutchins et al. 2009). Disruptions of these pathways can potentially cause speech-related or hallucinatory symptoms which are seen in bipolar disorder. The fronto-occipital fasciculi can be subclassified into the superior and inferior fronto-occipital fasciculi. The former is important for spatial awareness and symmetrical processing, and white matter hyperintensities in this region have been associated with late life depression (Hutchins et al. 2009), suggesting its possible role in the aetiology of depressive episodes in bipolar disorder. The latter links the prefrontal cortex to the auditory and visual cortices; thus, abnormalities in this region can result in hallucinatory experiences which may be seen in patients with BD. The anterior cingulum is intimately linked with executive function; thus, white matter abnormalities in the cingulum may contribute to difficulties in planning and organization as observed in some patients (Glahn et al. 2007; Murphy and Sahakian 2001).

There are also some data which implicate the corpus callosum in bipolar disorder. As the corpus callosum is important for neurotransmission between the right and left cerebral hemispheres, white matter anomalies may disrupt interhemispheric communication and connectivity. It has been suggested that a genetic predisposition to delayed interhemispheric switches may underlie bipolar disorder. Pettigrew and Miller (1998) discovered that bipolar patients had a slower rate of switching between hemispheres as compared to controls, and they describe these switches as having twice the possibility of being 'stuck' in either hemisphere. Therefore, further investigation into the role of the corpus callosum and its interhemispheric communication will improve the understanding of mood fluctuations in bipolar disorder.

DTI has revealed a negative correlation between FA and age at the point of imaging (Versace et al. 2008). Additionally, an early age of onset of bipolar disorder has been associated with a poorer prognosis and a higher rate of comorbidities such as psychiatric comorbidities, substance use disorders and anxiety disorders, with males more inclined than females towards developing comorbidities (Cate Carter et al. 2003). Cate Carter et al. (2003) found that patients with early onset have a greater tendency to abuse drug and alcohol, and have twice the risk of developing rapid cycling, an indicator of bipolar severity progression. In addition, a study on euthymic bipolar patients found that FA was lower in the right orbital frontal, right temporal, left temporal and left occipital lobes of patients, and this was associated with a poorer overall score on neuropsychological functioning and a slower speed of performance on a visual-motor task (Houenou et al. 2007).

The pathophysiology of bipolar disorder is exacerbated by substance abuse, and bipolar patients with a lifetime history of substance abuse were found to have lower FA compared to those without a history of substance abuse (Versace et al. 2008). Patients who developed bipolar disorder at an earlier age have a higher propensity to develop a comorbid substance use disorder (SUD) at a later stage of life (Cate Carter et al. 2003). It is also known that personality disorders are more frequently seen in bipolar patients with SUD (Mazza et al. 2009). These patients also have a greater degree of impairment in social functioning, a heightened risk of relapse in substance abuse during the course of treatment and a reduced compliance and response to treatment (Mazza et al. 2009), which may be related to neurobiological changes including that occurring within white matter.

Pharmacotherapy in bipolar disorder includes the administration of mood stabilisers (such as lithium and sodium valproate) which are recommended in the management within all phases of treatment. Mood stabilisers can be used in concert with atypical (second generation) antipsychotics such as olanzapine, risperidone, quetiapine and aripiprazole (Bruno et al. 2008; Kafantaris et al. 2009; Yurgelun-Todd et al. 2007). Monotherapy is the first treatment choice, and patients are given a combination of medications only when monotherapy fails to work. The impact of medications on white matter changes is relatively understudied. In this regard, there is some evidence of a negative correlation between medication load and FA in the left optic radiation and right anterothalamic radiation, where mood stabilisers were associated with lower FA in bipolar subjects (Versace et al. 2008). Future DTI studies need to examine the impact of different psychotropic medications on white matter indices and their correlates, as well as study the relationship

between medication, white matter indices, clinical progress and symptomatic improvement.

Limitations of current studies

In general, the reviewed DTI studies on bipolar disorder suggest a loss of white matter network connectivity with reduced FA and elevated ADC in implicated brain regions. Some inconsistencies in findings such as those involving the subcortical and non-frontal brain regions may be related to limitations contributed by methodological variations, sample size, and differences in clinical and demographic profiles.

First, methodological variations include analytical methodologies such as ROI, VBM and TBSS approaches, use of tractography, procedures of data acquisition, number of directions used during image acquisition, slice thickness and differences in techniques of image processing. Second, the sample sizes of DTI studies in bipolar disorder range between 16 and 84, which can limit the statistical power of the studies to detect more subtle changes. Third, heterogeneity of the samples must also be borne in mind when comparisons are made across studies due to demographic differences such as age, gender and years of education. Age-related changes in DTI measures may confound any white matter changes as well as less understood impact of other clinical variables such as illness subtypes, phase of illness, medication effects, history of substance abuse and presence of other comorbidities.

Although DTI may be a promising new technique that can aid in better understanding of underlying white matter changes in bipolar disorder, it is not without its limitations. First, it does not reveal the specific underlying pathophysiological mechanism in the presence of changes in white matter indices (McIntosh et al. 2008a). Second, Type I error can be introduced when voxel-wise analysis is used in DTI (Kafantaris et al. 2009; Mahon et al. 2009). Third, the lack of standardisation in analytic techniques such as that used for tractography may preclude valid comparisons between studies. The virtually reconstructed fibres cannot be assumed to be anatomically realistic because different macro- and microstructural characteristics of fibres may affect the tractography algorithms and hence their results (Houenou et al. 2007). Fourth, there is no strong consensus on the use of particular white matter indices, thus accounting for the plethora of indices that may be found and reported. Fifth, the use of DTI in bipolar disorder is still a relatively recent development, and the imaging technology with its image processing methods and analytic tools are still evolving and undergoing constant improvements over time.

Future directions for DTI studies in bipolar disorder

Clinical considerations

First, future DTI investigations in bipolar disorder should endeavour to increase their sample size with better matched controls. This would increase the power to detect subtle changes in the white matter and in specific brain regions such as the thalamus and hippocampus, which are thought to be involved in the neurobiology of bipolar disorder. Second, it is important to improve our understanding of the impact of clinical factors such as substance use, alcohol, comorbidities and medication on white matter indices, in order to control for these confounders during the analyses (Adler et al. 2006; Strakowski et al. 2000; Versace et al. 2008). Third, a better appreciation of the normal developmental trajectories of white matter changes over one's lifetime, which will also allow better comparison and more accurate documentation of actual white matter changes in disease states.

Fourth, the relationship between white matter change and symptom severity (Mahon et al. 2009; Yurgelun-Todd et al. 2007), phase of illness and frequency of relapse are less studied at present, and a better understanding may allow prognostication and improved management of the condition. Fifth, longitudinal studies allow the tracking of white matter changes over time and can enhance the understanding of age-related changes in white matter. Potential challenges to longitudinal studies in bipolar disorder include high operational costs, attrition of subjects and upgrading of equipment and protocols over time that lead to incomparability of data.

Technical considerations

First, DTI image acquisition methods should be enhanced, so as to increase the contrast to noise ratio. Augmenting the contrast to noise ratio will allow better delineation of white matter changes within different brain regions. Second, there are a variety of DTI analysis techniques and software in use, each with their strengths and weaknesses (Bruno et al. 2008), and improvements can be made to probe into different indices of white matter aberrations. At present, there is neither a consensus on which specific white matter indices to use nor a definitive understanding of what the changes in various white matter indices reflect. This can make it difficult to make comparisons across studies when different indices are used. To enable valid and reliable comparisons across studies, the strengths of different DTI acquisition and analytic techniques should be harnessed, integrated and standardised to better delineate the diffusion tensor, and subsequently, to develop a set of preferred white matter indices which would be the most ideal. These

suggested improvements will greatly expand the utility of DTI in correlating with clinical parameters, comparisons across studies and in testing specific hypotheses pertaining to the neural basis of bipolar disorder.

Third, DTI can be used in tandem with other neuroimaging techniques in multimodality assessments (such as functional imaging, structural imaging and magnetic resonance spectroscopy), so as to allow a more extensive and deeper appreciation of white matter changes and other related volumetric, functional and chemical changes in bipolar disorder. A recent study of bipolar disorder by Wang et al. (2009) found that reduced functional connectivity between anterior cingulate cortex and amygdale was positively correlated with the FA changes in ventrofrontal white matter changes highlighting the fact that more studies of this nature can shed light on brain structural–functional relationships and their possible aberrations underlying BD. Additionally, intelligent and efficient combinatorial approaches of DTI with genomics, metabolomics, proteomics and other probe techniques may lead to exciting advances in the future of bipolar research.

Management considerations

A clinical challenge in the diagnosis of bipolar disorder is that on average, it can take up to several years before bipolar patients are accurately diagnosed and properly treated (Lish et al. 1994). Furthermore, in paediatric bipolar patients, each year of delay in treatment translates to a 10% decreased likelihood of recovery (Lish et al. 1994). It is thus imperative to detect the illness early so as to minimise sequelae of untreated illness (Adler et al. 2006; Berk et al. 2009). In this aspect, DTI may play an important role in the early detection of bipolar disorder because neuroimaging studies have turned up structural brain changes that precede the manifestation of flagrant clinical signs and symptoms (Berk et al. 2009; Frazier et al. 2007). Although there are many challenges (such as overlapping cognitive changes with schizophrenia and depression, non-specific clinical presentations at early stages and false positive diagnoses) in attaining the goal of early bipolar disorder intervention, it is worthwhile to pursue this course. This is because medication dose can be minimal in first episode, adherence can be enhanced, sequelae of illnesses prevented and the quality of life of bipolar disorder patients significantly improved, if the findings from DTI research can be translated appropriately and in a timely fashion into clinical practice.

Conclusion

This systematic review has attempted to synthesise existing literature on DTI studies in BD, and highlight white matter brain abnormalities that have consistently been implicated in BD. Available DTI studies suggest a predominance of white matter abnormalities involving the frontal lobe, prefrontal lobe and certain white matter tracts, including specific projection, associative and commissural fibres in the neurobiology of BD. There are some contradictions in the direction of changes observed in white matter indices, and these can be attributed to factors like sample heterogeneity and limitations of DTI techniques. The possible roles of the parietal, temporal and occipital lobes and subcortical regions in BD await further investigation. Bipolar research remains relatively unexplored as compared to other psychiatric diseases, but DTI research on BD is fast gaining pace. The emerging trends from these DTI findings underscore the importance of further research in this field to unravel the underlying neural mechanisms and clinical correlations with white matter changes in BD.

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