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This Section of *Epidemiology and Psychiatric Sciences* regularly appears in each issue of the Journal to describe relevant studies investigating the relationship between neurobiology and psychosocial psychiatry in major psychoses. The aim of these Editorials is to provide a better understanding of the neural basis of psychopathology and clinical features of these disorders, in order to raise new perspectives in every-day clinical practice.

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Diffusion imaging studies of white matter integrity in bipolar disorder

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Diffusion tensor imaging (DTI) is a neuroimaging technique with a potential to elucidate white matter integrity. Recently, it has been used in the field of psychiatry to further understand the pathophysiology of major diseases, including bipolar disorder (BD). This review sought to focus on existing DTI findings on white matter organization in BD.

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In the last decade, several efforts have been made in order to detect possible biomarkers of bipolar disorder (BD) and recent advances in neuroimaging research have pointed out the putative role of white matter (Arnone *et al.* 2008; Doron & Gazzaniga 2008). In this regard, structural magnetic resonance imaging (MRI) studies described diffuse cortical and callosal white matter pathology in BD patients (Adler *et al.* 2006; Kempton *et al.* 2008; Vita *et al.* 2009), suggesting the presence of altered intra- and inter-hemispheric connectivity (Atmaca *et al.* 2007; Bellani *et al.* 2009*a*, *b*). A relatively recent application of MRI is the diffusion tensor imaging (DTI), a non-invasive imaging technique that measures the motion of water molecules in brain tissue and provides information about the microstructural coherence of white matter (Basser & Jones 2002). Water diffusion within the neural tissue is impeded by a myelin sheath, axonal density and thickness, and cellular structures. The degree of water molecule diffusion can be quantified by the apparent diffusion coefficient (ADC), and the fibre tract directionality can be evaluated indirectly by fractional anisotropy (FA; Beaulieu, 2002). ADC and FA may be considered as good markers of white matter microstructure organization. In particular, low FA values indicate probable damage to axonal membrane, de-/dys-myelination or reduced amount of intra-axonal structures, whereas high ADC measures are found when water diffusion is unimpeded, e.g. in ventricles or demyelinated white matter (Beaulieu & Allen, 1994). Several DTI data on BD have been published so far, showing some white matter abnormalities (Brambilla *et al.* 2009*a*). Most studies (see Table 1) reported reduced FA and/or elevated ADC values compared to healthy controls involving specific brain regions such as prefrontal, parietal, temporal and occipital lobes, internal capsule, uncinate fasciculus, superior longitudinal fasciculus and corpus callosum (for extensive review see Bellani *et al.* 2009*a*, *b*; Heng *et al.* 2010). However, the effect of mood states on

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Table 1. *DTI studies in bipolar disorder*

Study	Subjects	Age (years)	Findings in BD
Adler *et al.* (2004)	9 BD	32 ± 8	↓FA in superior prefrontal cortex, but not in the fronto-polar regions
	9 HC	31 ± 7	
Beyer *et al.* (2005)	14 BD	44.0 ± 17.6	↑ADC in orbital frontal white matter bilaterally, with normal FA
	21 HC	44.6 ± 13.5	
Haznedar *et al.*, (2005)	34 BD	43.9 ± 10.0	↓FA in posterior limb of the internal capsule
	33 HC	40.8 ± 11.7	
Regenold *et al.*, (2006)	8 BD	58.4 ± 12.9	↑ADC in combined white matter ROIs, but not in the four lobes separately
	8 HC	54.5 ± 12.8	
Yurgelun-Todd *et al.* (2007)	11 BD	32.9 ± 10.5	↑FA in the genu of corpus callosum
	10 HC	32.4 ± 9.1	
Wang *et al.* (2008*a*)	33 BD	32 ± 10.1	↓FA in anterior cingulum white matter
	40 HC	29.2 ± 9.2	
Wang *et al.* (2008*b*)	42 BD	32.6 ± 10.1	↓FA in genu, rostral body, and anterior midbody of corpus callosum
	42 HC	28.7.2 ± 9.1	
Versace *et al.* (2008)	31 BD	35.9 ± 8.9	↑FA in left uncinate fasciculus, left optic radiation, and right anterothalamic radiation
	25 HC	29.48 ± 9.43	↓ FA in right uncinate fasciculus
Bruno *et al.* (2008)	36 BD	37.4	↓FA in inferior longitudinal fasciculus
	28 HC	42.8	
Barnea-Goraly *et al.* (2009)	21 BD	16.1 ± 2.7	↓FA in fornix, posterior cingulate, corpus callosum and parietal and temporal corona radiate
	18 HC	14.5 ± 2.7	
Chaddock *et al.* (2009)	19BD	43.3 ± 10.2	↓FA in genu of corpus callosum, right inferior and left superior longitudinal fasciculus
	21 first degree Relatives	42.5 ± 13.6	
	18 HC	41.7 ± 12.2	
Mahon *et al.* (2009)	30 BD	33.4 ± 8.7	↓FA in the left cerebellum
	38 HC	31.9 ± 8.6	↑ FA in left frontal white matter and thalamic radiation
Sussmann *et al.* (2009)	42 BD	39.6 ± 10.1	↓FA in the left anterior limb of the internal capsule, bilateral uncinate fasciculus, anterior/superior thalamic radiation, and corpus callosum
	28 SCZ	38.0 ± 9.9	
	38 HC	37.2 ± 11.9	
Wessa *et al.* (2009)	22 BD	45.41 ± 12.60	↑FA in medial frontal, precentral, inferior parietal, and occipital white matter
	21 HC	42.95 ± 13.17	
Zanetti *et al.* (2009)	37 BD	34.1 ± 9.0	↓FA in inferior fronto-occipital, superior and inferior longitudinal fasciculus
	26 HC	28.8 ± 9.5	
Benedetti *et al.* (2011)	40 BD	45.11 ± 9.82	↓FA in the genu of corpus callosum and in anterior and right superior-posterior corona radiate
	21 HC	39.86 ± 11.05	

ADC, apparent diffusion coefficient; FA, fractional anisotropy; BD, bipolar disorder; HC, healthy controls.

white matter integrity is often not taken into account (Adler *et al.* 2004; Bruno *et al.* 2008; Mahon *et al.* 2009) or patients with different clinical states are just studied together (Beyer *et al.* 2005; Versace *et al.* 2008; Wang *et al.* 2008*a*, *b*; Barnea-Goraly *et al.* 2009). In this regard, patients suffering from different bipolar episode may be characterized by specific DTI 'signature'. Anyway, till date, few studies have been conducted on patients with homogeneous mood state. In euthymia, FA is usually increased in the genu of corpus callosum, internal capsule, anterior thalamic radiation and uncinate fasciculus (Haznedar *et al.* 2005; Yurgelun-Todd *et al.* 2007; Sussmann *et al.* 2009; Wessa *et al.* 2009; Zanetti *et al.* 2009), whereas in bipolar depression lower FA has been shown in the genu of the corpus callosum and in corona radiata (Regenold *et al.* 2006; Chaddock *et al.* 2009; Benedetti *et al.* 2011). Not surprisingly, in mixed samples higher and lower FA values were found in different brain regions (Beyer *et al.* 2005; Wang *et al.* 2008*a*, *b*; Barnea-Goraly *et al.* 2009).

The impact of mood stabilizers on white matter connectivity in BD should also be considered, particularly lithium and quetiapine, which have been suggested to potentially induce myelination processes (Bearden *et al.* 2008; Zhang *et al.* 2008; Brambilla *et al.* 2009*b*; Tondo & Baldessarini, 2009). However, a recent DTI study did not find any lithium effect on DTI measures in patients suffering from BD (Benedetti *et al.* 2011).

In summary, the DTI literature on BD suggests loss of white matter network connectivity as a possible

phenomenon of the disease, particularly including altered fronto-occipital, superior longitudinal fasciculus and callosal connections (Wang *et al.* 2008*a*; Barnea-Goraly *et al.* 2009; Chaddock *et al.* 2009). However, diffusion-imaging studies in BD are mostly limited by heterogeneity and relatively small size of the samples. Moreover, the impact of some clinical variables on white matter coherence such as mood states and mood stabilizer administration still needs to be fully elucidated. In this perspective, future DTI studies are expected to further investigate whether abnormal white matter may represent a trait or a mood state biomarker of BD, potentially being preserved by psychotropic drugs such as lithium.

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