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A Role for White Matter Abnormalities in the Pathophysiology of Bipolar Disorder

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Abstract

Bipolar disorder is a chronically disabling psychiatric disorder characterized by manic states that is often interspersed with periods of depression whose neurobiology remains largely unknown. There is, however, increasing evidence that white matter (WM) abnormalities may play an important role in the neurobiology of the disorder. In this review we critically evaluate evidence for WM abnormalities in bipolar disorder obtained from neuroimaging, neuropathological, and genetic research. Increased rates of white matter hyperintensities, regional volumetric abnormalities, abnormal water diffusion along prefrontal-subcortical tracts, fewer oligodendrocytes in prefrontal WM, and alterations in the expression of myelin and oligodendrocyte-related genes are among the most consistent findings. Abnormalities converge in the prefrontal WM and, in particular, tracts that connect prefrontal regions and subcortical gray matter structures known to be involved in emotion. Taken together, the evidence supports and clarifies a model of bipolar disorder that involves disconnectivity in regions implicated in emotion generation and regulation.

Keywords

bipolar disorder; white matter; diffusion tensor imaging

1. Introduction

Bipolar disorder (BD) is a serious affective illness that affects approximately 1.5% of the population (Angst, 1998; Narrow et al., 2002) and remains a leading worldwide cause of disability, morbidity, and mortality from suicide (Goodwin et al., 2007; Murray and Lopez, 1996). The disease is characterized by a recurrent and episodic course involving disturbances of mood, sleep, behavior, perception, and cognition (Goodwin and Jamison, 2007). BD has a spectrum presentation, with major subtypes of bipolar I and bipolar II, seemingly falling along a continuum of severity. According to current diagnostic categorization, patients with bipolar

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I disorder experience full mania, marked by symptoms of elated or irritable mood, reduced need for sleep, increased goal-directed activity, rapid speech, flight of ideas, and increased energy (DSM-IV, 1994). Additionally, in approximately 50% of bipolar I cases (DSM-IV, 1994), acute episodes are characterized by concurrent symptoms of psychosis, including auditory/visual hallucinations, and delusions that are typically focused around mood-congruent themes (i.e. religious preoccupations or manic beliefs in one's own supernatural powers). Bipolar II patients have milder symptoms of mania which, by definition, do not involve psychosis, are typically shorter in duration, and do not significantly interfere with daily functioning. Both bipolar I and bipolar II subtypes experience intermittent major depressive episodes with sad mood, suicidal ideation, and changes in appetite, sleep, and energy, often interfering significantly with psychosocial functioning (DSM-IV, 1994). The notable heterogeneity in the clinical phenotype, including multiple subtypes (bipolar I, bipolar II) and several characteristics that are present only in a subgroup of patients (i.e. psychosis, cognitive impairment), complicate the attempts to elucidate the underlying pathophysiology of the illness.

Although the exact etiologies of bipolar disorder remain unknown, data from post-mortem, genetic, computed tomography (CT), positron emission tomography (PET), and magnetic resonance (MR) imaging studies provide evidence that brain abnormalities contribute to the disorder. The cause and significance of these abnormalities remain somewhat speculative, and findings are often contradictory. Recent models of BD (Adler et al., 2006b; Green et al., 2007; Lyoo et al., 2006; Phillips et al., 2003b; Phillips et al., 2008; Soares & Mann, 1997; Strakowski et al., 2005), however, suggest that the sometimes inconsistent and even contradictory findings involving abnormal brain anatomy, structure, and function may be understood within a framework of emotional dysregulation in circuits involving frontal cortical and limbic structures (Mayberg, 1997). Several influential accounts of BD have suggested that the interplay between phylogenetically new cortical and phylogenetically old limbic regions is compromised in patients with BD and may be responsible for the core symptoms of the disease (Drevets et al., 1997; Mayberg et al., 1999; Strakowski et al., 2005). Dysregulation of various nodes in the limbic system may produce affective symptoms, including depression and mania. Limbic system structures include the amygdala, hippocampus and parahippocampal gyrus, ventral striatum, insula, anterior cingulate (ACC), and orbitofrontal cortex (OFC) (Mesulam and Gueula, 1988; Öngür and Price, 2000). The system is thought to reflect an evolutionary advance critical in the development of a distinctly mammalian CNS (MacLean, 1990). The structures are involved in response to or appraisal of threat (amygdala), the integration of autonomic, affectively valenced information and behavioral "scripts," especially as they relate to anticipated social outcome (ventral prefrontal cortex), autonomic processing, and affective and conflict monitoring (subgenual and dorsal cingulate). Because of reciprocal connectivity between these areas it is likely that both "top-down" and "bottom-up" dysfunction exists and brings about both the emotional dysregulation that characterizes the illness as well as the concomitant neurocognitive impairment that is common in BD.

The majority of brain research in bipolar disorder has focused on the gray matter (GM). This is likely due to the fact that the white matter (WM), comprised of fiber tracts interconnecting cortical and subcortical GM, has been much more difficult to visualize and quantify than GM (see Figure 1). Alterations in WM tissue would likely have significant implications for the functioning of the brain as a whole, as it is the WM which serves as the circuitry and connective wiring of the brain. With the advent of techniques such as diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS) that allow for better quantification and characterization of the WM, it has become possible to move toward a connectivity-based model of brain abnormality that both supports and clarifies cortico-limbic models of emotional dysregulation.

2. Models of BD

An abnormal relationship between the cortex and limbic structures as a basis for mood dysregulation was proposed by Mayberg (1997) as a general, adaptable framework for unipolar depression. Many recent reviews of neuroanatomical findings in BD suggest that this framework is useful for conceptualizing BD as well (Adler et al., 2006b; Bearden et al., 2001; Green et al., 2007; Haldane and Frangou, 2004; Lyoo et al., 2006; Phillips et al., 2003b; Phillips et al., 2008; Savitz and Drevets, 2009; Soares & Mann, 1997; Strakowski et al., 2005; Vawter et al., 2000). GM volumetric and metabolic abnormalities in regions such as the orbital frontal cortex, the subgenual anterior cingulate cortex, amygdala, hippocampus, striatum, and cerebellar vermis have been widely reported (see Savitz & Drevets, 2009 for a review) and suggest a pathophysiological mechanism that affects a wide network of structures.

Several researchers have proposed models that seek to define the specific networks that may be disrupted in BD (see Figure 2). The central feature of these models is deficient prefrontal modulation of subcortical and limbic structures. A disrupted anterior limbic network comprised of prefrontal-striatal-thalamic pathways as well as cerebellum and medial temporal limbic structures was proposed by Strakowski and colleagues (2005) as a model of BD. These authors proposed that abnormal modulation of the anterior limbic network by the prefrontal cortex may result in the mood dysregulation that characterizes the disorder. This model is consistent with findings of decreased modulatory control of the frontal cortex over the subcortical and temporal structures purported to be involved in mood regulation (e.g., Altshuler et al., 2005; Foland et al., 2008; Pavuluri et al., 2007). Subsequent models have generally built upon the notion of anterior limbic network disruption (Adler et al., 2006b; Green et al., 2007; Lyoo et al., 2006; Savitz and Drevets, 2009) and have incorporated additional altered networks.

Phillips et al. (2008) have recently proposed a comprehensive neural model of BD that extends their previous work on both normal (Phillips et al., 2003a) and abnormal (Phillips et al., 2003b) emotion perception and regulation. This model focuses in particular on evidence that the OFC may serve as a mediator within the anterior limbic network between subcortical limbic regions involved in emotion perception and generation, and dorsal and lateral prefrontal regions involved in higher order processing of emotional information. In addition, the model proposes that the basis of mood dysfunction in BD may lie within circuits subserving automatic, as opposed to voluntary, emotional processes.

Subregions involved in automatic emotion regulation processes include the orbitofrontal cortex (OFC), subgenual anterior cingulate gyrus (sgACG), dorsal ACG and left rostral ACG, medial-dorsal PFC (MdPFC), and the hippocampus and parahippocampus. These GM regions have been extensively studied in BD, yet the WM connecting these regions has only recently become a focus of study. This is largely due to technological advances, such as diffusion tensor imaging (DTI), that allow for the quantification and visualization of WM fiber tracts. Recent evidence indicates that WM tracts connecting OFC and subcortical regions involved in emotion perception and generation are abnormal in BD (Figure 1). In this review we evaluate the evidence for WM abnormalities in the pathogenesis of BD from recently developed techniques, including DTI, and from other long-established methodologies to incorporate these findings into existing models.

3. Evidence from Neuroimaging Studies

3.1 White Matter Hyperintensities

An increased number and/or severity of white matter hyperintensities (WMH), which are hyper-intense bright spots that may be detected in T2-weighted and fluid-attenuated inversion recovery (FLAIR) MR images, is one of the most consistently reported abnormalities in bipolar

disorder (Ahn et al., 2004; Altshuler et al., 1995; Aylward et al., 1994; de Asis et al., 2006; Dupont et al., 1990; Dupont et al., 1995; Figiel et al., 1991; Gulseren et al., 2006; Kempton et al., 2008; Lloyd et al., 2009; Lyoo et al., 2002; McDonald et al., 1991; McDonald et al., 1999; Moore et al., 2001a; Moore et al., 2001b; Pillai et al., 2002; Regenold et al., 2008; Silverstone et al., 2003; Swayze et al., 1990; Tamashiro et al., 2008; Woods et al., 1995), although several negative reports have appeared (Botteron et al., 1995; Breeze et al., 2003; Brown et al., 1992; Chang et al., 2005; Dolan et al., 1990; Krabbendam et al., 2000; Lewine et al., 1995; López-Larson et al., 2002; Persuad et al., 1997; Sassi et al., 2003; Strakowski et al., 1993b; Zanetti et al., 2008). Regarding these negative findings, however, Ahn et al. (2004) have pointed out that studies using thinner MR imaging slices, a larger sample size, and that have rated the severity of WMH, in addition to their presence or absence according to an established rating scale, tend to produce more consistent, positive results. In adults with BD, there is evidence for an association between more severe WMH and a greater number of hospitalizations and poorer response to treatment (Moore et al., 2001b; but see Breeze et al., 2003).

Traditionally, WMH have been classified by location into those that occur in the periventricular space (known as periventricular WMH) or in the deep WM (deep WMH). In unipolar depression (UD) and BD, increased deep WMH, but not necessarily periventricular WMH, have been frequently noted (Ahn et al., 2004; de Asis et al., 2006; Figiel et al., 1991; McDonald et al., 1999; Moore et al., 2001b; Regenold et al., 2008; Thomas et al., 2002a; Thomas et al., 2002b), although the opposite has also been reported (Altshuler et al., 1995). An association between increased rates of periventricular WMH and previous suicide attempts among patients with affective disorders has been reported (Pompili et al., 2008), suggesting that periventricular WMH may be potential neurological markers of suicidal behavior. Increased deep WMH in UD and BD are generally localized in the deep prefrontal and frontal white matter, suggesting disruption in the tracts connecting fronto-cortical and subcortical regions (Aylward et al., 1994; de Asis et al., 2006; Lyoo et al., 2002) and provide support for a model of BD featuring disruption along these tracts.

There are several possible causes of WMH, including ischemia, demyelination, edema, and gliosis, and it has been difficult to determine which cause or combination of causes might underlie particular incidences of WMH in both healthy groups and in patients with BD. In healthy adults, the presence of WMH is generally associated with advanced age and increased cardiovascular risk factors such as hypertension (e.g. Kirkpatrick and Hayman, 1987; O'Brien et al., 2006). Given that there is an association between increased cardiovascular risk factors and BD, it is possible that a common process confers vulnerability to both vascular sequelae and some subtypes of BD. Dos Santos et al. (2008) have suggested that perhaps elevated serum homocysteine levels, which were correlated with functional decline in BD (Osher et al., 2004) are one aspect of this common process. Complicating this picture are findings of increased WMH in BD samples relative to control samples after controlling for cardiovascular risk factors (e.g. McDonald et al., 1991; McDonald et al., 1999), as well as in pediatric BD samples (Lyoo et al., 2002; Pillai et al., 2002) although negative results have also been reported (Botteron et al., 1995; Breeze et al., 2003; Chang et al., 2005). In elderly depressed subjects, deep WMH are thought to be primarily ischemic in origin (Thomas et al., 2002a; Thomas et al., 2002b), whereas in healthy elderly controls, this is not necessarily the case. Thomas and colleagues (2002a, 2002b) have proposed that a small degree of loss in perfusion with increased age is normal, but that in depressed elderly patients, this loss in perfusion may be more severe, leading to ischemia.

More recently, late-onset BD has been associated with increased rates and severity of deep frontal WMH, suggesting that BD as well as UD may be a consequence of the interaction between advanced age and ischemia (Takahashi et al., 2008; Tamashiro et al., 2008; Zanetti

et al, 2007). Tamashiro et al. (2008) have recently demonstrated that late-onset BD is associated with an increased number and severity of deep WMH relative to both healthy controls and, interestingly, age-matched early-onset BD patients, suggesting that late-onset BD is particularly associated with deep WMH and is likely to be a distinct subtype of the disorder. Some groups (e.g., Zanetti et al., 2007) have proposed that late-onset BD characterized by deep frontal WMH indicates that vascular mania may be a distinct clinical entity analogous to vascular depression (Alexopoulos et al., 1997). It may be that vascular depression and vascular mania are the result of similar ischemic processes that disrupt white matter tracts.

Inconsistent reports of laterality effects have been reported, with some studies reporting an excess of left-sided deep frontal WMH occurring in BD subjects relative to controls (Lloyd et al., 2009) and others reporting an excess of right-sided deep WMH (Gulseren et al., 2006). The WMH of unaffected siblings of patients with BD were investigated in one small study; results indicated that BD patients had increased WMH relative to their siblings and to controls, but that both the patient group and the sibling group had predominantly right-sided lesions relative to the control group, who tended to have more left-sided lesions (Gulseren et al., 2006). The investigation of unaffected siblings is a crucial but as yet relatively understudied line of research in characterizing the endophenotypic character of WMH in BD.

The presence and severity of WMH in healthy, elderly samples has been found to be correlated with decreased performance on a range of cognitive tasks (Gunning-Dixon & Raz, 2000), and this correlation has been reported in younger BD adults with WMH as well (Dupont et al., 1990; Dupont et al., 1995 but see Krabbendam et al., 2000). Although the etiology of WMH is not yet understood, research has provided evidence that the presence of WMH indicates disruption in the WM fiber (Leuchter et al., 1994; Soares and Mann, 1997; Taylor et al., 2001). More specifically, some types of WMH may be indicative of early localized demyelination (Hajek et al., 2005).

An inverse correlation between WMH and intracellular pH, as well as a positive correlation between WMH and an elevated phosphodiester peak, has been reported in a sample of euthymic, drug-free BD patients (Kato et al., 1998). The authors noted that these metabolic abnormalities arose not from the WMH themselves, which were generally mild, but from the surrounding, normal-appearing tissue. This finding provides empirical support for the hypothesis that WMH are markers of a generalized neuropathophysiologic process in at least a subsample of BD patients. Although the significance of decreased intracellular pH is not clear, the authors proposed that it may signify an ischemia-induced excess of lactate in the tissue surrounding WMH; alternatively, they suggested that it may indicate an alteration in the Na⁺/H⁺ exchanger (Kato et al., 1998).

Increased deep WMH have been found to distinguish patients with BD from patients with schizophrenia (SCZ) as well as from healthy controls (Regenold et al., 2008). This same study found significant correlations between deep WMH volume and cerebrospinal fluid (CSF) concentrations of both sorbitol and fructose in the BD group, but not in the SCZ or control groups. Taken together with evidence that diabetes mellitus is associated with BD, this study indicates that abnormalities in glucose metabolism are associated with BD, or at least the subset of BD patients who exhibit WMH. Abnormal glucose metabolism was also found to be associated with a measure of treatment resistance in this sample. In a subsequent study, this group demonstrated that a sample of BD and SCZ patients exhibited increased CSF lactate concentrations relative to a control group (Regenold et al., 2009). The authors suggest that this finding provides further evidence for abnormal glucose metabolism in at least a subset of patients with BD and SCZ and points specifically to mitochondrial dysfunction, a mechanism of psychiatric disease, and BD in particular, that has been receiving much attention in recent years (Kato & Kato, 2000; Quiroz et al., 2008; Shao et al., 2008; Stork & Renshaw, 2005).

Further investigation is required to evaluate the possible connections between WMH, BD, and mitochondrial dysfunction, a line of research that appears to be promising in identifying subtypes of BD that may respond to metabolic therapy as well as elucidating the pathophysiology of this disorder.

Recent evidence suggests that valproate therapy may attenuate the formation of WMH by activating the Notch signaling pathway, a cascade which plays an important role in cell fate determination and vasculogenesis (Yuan et al., 2009). This research grew out of the realization that WMH are quite similar in appearance to the lesions associated with the cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) syndrome, a hereditary stroke disorder marked by changes in mood, progressive dementia, migraine, and stroke (e.g., Chabriat et al., 1995; Joutel et al., 1996; Yuan et al., 2009). CADASIL is now known to be caused by mutations in Notch3 that ultimately lead to the progressive deterioration of vascular smooth muscle cells in the brain. It may be that the WMH seen in a subset of BD patients are a result of a less severe alteration in the Notch pathway. Given this speculation, it is interesting to note that valproate, commonly used to treat BD, has been shown to be related to the attenuation of Notch signaling abnormalities (Yuan et al., 2009).

It is important to note that WMH are nonspecific factors that do not appear to be present in all BD patients, and that any consistent and unique characteristics of the subsample of BD patients with WMH remain to be elucidated. Increased WMH have been demonstrated in BD I relative to BD II (Altshuler et al., 1995) and in poor outcome relative to good outcome BD (Moore et al., 2001b; Regenold et al., 2008), although the majority of studies have not assessed these characteristics or have not found such correlations. Although the exact cause and significance of WMH in general and in BD specifically are not currently known, the reported preponderance of WMH in BD is a strong indication that WM abnormalities are present in the disorder, and that they appear most robust in WM comprising frontocortico-limbic pathways.

3.2 Structural MR Imaging Studies

Studies that have assessed WM through structural volumetric imaging have provided evidence of subtle abnormalities in patients with BD compared to healthy volunteers. Some investigators reported a non-significant trend toward reduced cerebral WM in patients with bipolar disorder compared to controls (Strakowski et al., 1993a; Rosso et al., 2007), and, interestingly, reported an association between gross WM volume and amygdala volume in first-episode patients, but not in controls (Rosso et al., 2007). The majority of traditional volumetric studies that have sought to measure total cerebral WM volume in BD have reported no differences between BD samples and controls (Atmaca et al., 2007; Beyer et al., 2009; Brambilla et al., 2001; Lim et al. 1999; Sassi et al., 2002; Zipursky et al., 1997), although there have been some findings to the contrary (Davis et al., 2004). Studies that have used methods that are sensitive to regional differences in WM volume, such as voxel-based morphometry (VBM) and region-of-interest (ROI) analyses have produced mixed results, however (see Table 1).

Voxel-based morphometry allows for the examination of differences in tissue volume and/or density throughout the brain without restricting analyses to pre-defined regions (Ashburner and Friston, 2000). Using this methodology, several groups have reported regional WM deficits in BD samples relative to controls (Bruno et al., 2004; Farrow et al., 2005; McDonald et al., 2005; McIntosh et al., 2005; Stanfield et al., 2009) whereas others have not found any differences (Lyoo et al., 2004; Sarnicola et al., 2009). Volumetric deficits have been found in frontal and parietal WM in first-episode patients relative to controls (Farrow et al., 2005), and in distributed regions throughout the brain in chronic BD samples (McDonald et al., 2005). Several studies have reported reductions in WM density in patients compared to controls in prefrontal WM (Bruno et al., 2004; McIntosh et al., 2005; Stanfield et al., 2009) although there

have been negative reports as well (Lyoo et al., 2004). Some groups have found that WM volume reductions are restricted to familial BD (McIntosh et al., 2005).

Subregional investigations of WM volume have reported deficits in bilateral superior temporal gyrus in pediatric BD (Chen et al., 2004) and in prefrontal WM in an adult BD sample (Haznedar et al., 2005). These latter findings are in contrast to those of López-Larson and colleagues (2002), in which no volumetric differences were found in prefrontal or paracingulate WM between patients and controls.

The most-studied WM subregion in BD is the corpus callosum (CC), the largest WM tract that connects the two hemispheres of the brain. Among studies that have measured the volume of the CC in BD samples relative to controls, most have found that the CC is smaller in BD (Arnone et al., 2008; Atmaca et al., 2007; Brambilla et al., 2003; Coffman et al., 1990 but see Hauser et al., 1989; Walterfang et al., 2009b). A recent study found that lithium-naïve BD patients had significantly less CC area than lithium-treated BD patients as well as controls, suggesting that CC deficits may be ameliorated by lithium treatment (Walterfang et al., 2009a). This study also found that length of illness was negatively correlated with CC midbody area among the entire BD group. Several groups have found decreased CC signal intensity in adult (Brambilla et al., 2004) and pediatric (Caetano et al., 2008) BD samples. A decrease in CC signal intensity may reflect an increase in water content in these regions, which in turn may result from decreased myelination. Yasar and colleagues (2006) found a decrease in the circularity of the splenium of the CC in a sample of pediatric patients with BD relative to controls, suggesting that CC abnormalities begin early in the course of the disorder and, given the preponderance of evidence for adult CC abnormalities, are likely to progress.

Recent work has been directed at identifying neuroanatomic correlates of genetic risk for BD, and WM abnormalities have consistently emerged as endophenotypes. In a study that investigated patients with bipolar disorder and their unaffected twins, both members of the twin pair were found to have a decrease in left hemisphere WM volume relative to controls (Kieseppä et al., 2003). McDonald and colleagues (2004) found that genetic risk for developing BD was significantly associated with WM volume deficits throughout the brain, including in bilateral prefrontal regions. Negative reports have also appeared (McIntosh et al., 2006). Recently, van der Schot et al. (2009) demonstrated that a lobar WM decrease in BD is genetically mediated, thus supporting the hypothesis that WM abnormalities are involved in the pathophysiology of BD.

Taken together, the evidence suggests that WM abnormalities appear to exist in BD, but are more likely to reflect subtle alterations in contrast to gross volumetric abnormalities. These subtle alterations may require more sensitive imaging techniques to better understand their role in the neurobiology of BD.

3.3 Magnetic Resonance Spectroscopy Studies

Magnetic resonance spectroscopy (MRS) is a specialized form of MRI in which the chemical properties of the tissue are analyzed, in addition to the structural properties. Specifically, MRS provides measures of concentrations of various metabolites in brain tissue. The large variation in techniques and approaches in MRS imaging makes it difficult to compare the results of individual studies; at the same time, the variation in techniques allows for a wide range of positive and negative findings that are potentially reconciled by the fact that experimental designs differ so greatly. To date, relatively few MRS studies have been carried out in bipolar disorder, and those that have been conducted have tended to focus on GM structures.

Of the few studies that have used MRS to investigate WM directly, many have reported negative results for WM abnormalities in patients with bipolar disorder (Blasi et al., 2004;

Friedman et al., 2004; Frye et al., 2007), although GM abnormalities are frequently found (Stoll et al., 2000) (see Table 2). Dager and colleagues (2004) found that choline, creatine, N-acetyl aspartate, myoinositol, and lactate concentrations were unchanged in the frontal and parietal WM of unmedicated BD patients. Unmedicated BD II patients demonstrated an elevation in glutamate, glutamine, and GABA (measured aggregately as Glx) in frontal WM relative to controls, although unmedicated BD I patients did not show this elevation (Dager et al., 2004). This group also found that, across participants, depression scores on the Hamilton Depression Rating Scale (Hamilton, 1960) were inversely correlated with WM concentrations of creatine and phosphocreatine.

A higher concentration of glutamate/glutamine has been reported in orbital-lateral WM in patients with BD I experiencing either a manic or a mixed episode relative to controls (Cecil et al., 2002). Although the clinical significance of this finding is not yet understood, the authors point out that the concentration of these amino acids was significantly negatively correlated with duration of valproate therapy. This finding is consistent with reports that both lithium and valproate increase the reuptake of glutamate (Dixon et al., 1997;1998). It is not clear how this result may relate to that of Dager et al. (2004), in which unmedicated patients with BD II but not BD I demonstrated elevated Glx in frontal WM. It may be that an increased concentration of amino acids in the prefrontal WM is an underlying substrate of some types of BD. Consistent with this idea, Öngür et al. (2008) recently reported evidence for an elevated glutamine/glutamate ratio in the anterior cingulate cortex and in the parieto-occipital cortex in acutely manic BD patients, relative to both acutely psychotic SCZ patients and matched controls. These results did not covary with medication status, although it is not possible to rule out such effects. The authors suggested that this result could be indicative of glutamatergic overactivity as well as abnormal neuronal-glial interactions, and that both mechanisms could be operating in combination. Further evidence for amino acid concentration abnormalities in frontal WM comes from a recent p-MRS study by Port and colleagues (2008), in which decreased glutamine/glutamate concentrations were found in the WM of the dorsolateral PFC. This pattern of increased orbital and decreased dorsal concentrations of amino acids in prefrontal WM needs to be replicated and may indicate a system of abnormal glutamatergic functioning in prefrontal WM pathways. Further MRS investigation of WM is required to fully examine neuronal-glial interactions in BD. Few MRS studies have examined WM in BD, though information regarding the molecular profile of this tissue is critically important in furthering our understanding of this disorder.

3.4 Magnetization Transfer Imaging Studies

Magnetization transfer (MT) imaging is another specialized form of MRI that permits the detection of myelin and axonal abnormalities, even in the absence of volume loss (Bruno et al., 2006, van Buchem and Tofts, 2000). This technique is therefore sensitive to changes in the myelin sheath that are not detectable by traditional MRI. MT imaging quantifies tissue abnormalities through the magnetization transfer ratio (MTR), an index of macrostructural integrity. In white matter, the degree to which MTR is reduced has been found to correlate with neuronal integrity (Pendlebury et al., 1999), as well as with the degree of myelin and/or axonal loss in the WM (van Buchem and Tofts, 2000). To date, only two studies have applied MT imaging to the study of bipolar disorder, both by the same group. Bruno et al. (2004) conducted the first study to assess WM integrity using MT imaging in BD. This study provided evidence that the MTR is significantly reduced in the right subgenual portion of the anterior cingulate and in the subgyral WM surrounding this area in patients with bipolar disorder relative to controls (Bruno et al., 2004). Given that the anterior cingulate is believed to be involved in a wide range of executive and emotional functions, and damage to this area has been shown to result in dysregulated emotional responses (Damasio, 1997), the finding that the WM subserving this region is abnormal lends support to a model of bipolar disorder featuring WM

disconnectivity in regions involved in emotion generation and regulation. As noted above, this study also found a reduction in WM density in prefrontal areas bilaterally. On the right side, this area of reduced WM density overlapped with, but was not identical to, the area of reduced MTR observed through the analyses of the MT images. The authors speculated that, while the areas of abnormality identified through the two different procedures (MTI and VBM) and analyses were not identical, the fact that both areas overlapped and are part of a larger frontostriatal connectivity pathway that is involved in emotional functioning may be noteworthy.

In terms of the functional correlates, Bruno et al. (2006) correlated MTR reduction with an index of decreased cognitive functioning. The authors administered a battery of cognitive tests designed to assess premorbid and current IQ to a subsample of patients from their original MT imaging study (Bruno et al., 2004) as a means of examining the relationship between MTR and IQ decline. Several brain areas were found in which MTR reduction was significantly correlated with IQ decline, but these areas were only significant for patients with BD II; this is perhaps related to the finding that IQ decline was greater among this subset of patients than it was among patients with BD I. The areas in which IQ decline correlated with MTR reduction in BD II patients included those areas found to have significant MTR reduction relative to controls in the previous study (Bruno et al., 2004): the right subgenual anterior cingulate cortex and the adjacent white matter. However, additional locations of correlation between IQ reduction and MTR reduction were observed in these patients: the right superior and middle temporal gyri and the adjacent subgyral white matter, the right cingulate gyrus and the adjacent white matter, and regions within the frontal and parietal WM (Bruno et al., 2006). Thus, the regions that showed a significant correlation between myelin and axonal abnormalities and IQ reduction were all areas that have previously been implicated in cognitive functioning. Ideally, longitudinal studies would best address the issue of cognitive decline and its neuropathological correlates in bipolar disorder.

3.5 Diffusion Tensor Imaging Studies

Diffusion tensor imaging (DTI) provides a measure of WM integrity and microstructure that is potentially more sensitive than traditional T1-weighted imaging. DTI measures the movement of water molecules within the brain as a means of assessing the coherence of brain tissue. DTI also allows for the potential to investigate WM macrostructure through the visualization of fiber tracts. Three indices of WM integrity are commonly reported in DTI studies: the apparent diffusion coefficient (ADC), mean diffusivity (MD) and fractional anisotropy (FA). ADC is an index of the degree to which water freely diffuses within a brain region. Within the neuronal white matter, a greater degree of axonal myelination and/or axonal density is thought to be associated with lower ADC; that is, an increase in myelinated axonal fibers results in restricted water diffusion. Likewise, local brain regions with known axonal demyelination and/or axonal loss have been shown to have higher ADC (Beaulieu, 2002). MD is related to ADC and is simply the mean diffusion occurring within a given voxel or brain region. FA is an index of the preferential diffusion of water parallel to the main fiber orientation relative to other directions. That is, the micro- and macrostructure of the axons and axonal bundles of the WM influence water diffusion; FA quantifies the preferential diffusion of water in one direction (i.e. parallel to the main fiber orientation) relative to the restricted diffusion in all other directions. Thus, FA values can range from 1 (indicating completely anisotropic diffusion) to 0 (indicating completely isotropic diffusion).

To date, several DTI studies have been used to investigate the pathophysiology of BD (see Table 3). During the relatively short time that DTI has been used in research studies, several methodological innovations have already been implemented (for reviews, see Assaf & Pasternak, 2008; Mori et al., 2009). The analysis of the diffusion tensor allows for the

visualization of fractional anisotropy color maps, in which the directionality of each tract is color-coded (e.g., anterior-posterior tracts are colored green, inferior-posterior tracts are blue, left-right tracts are red, etc). Visualization of the color map allows for more precise localization of clusters of significant voxels, as well as the ability to isolate specific tracts for post-hoc analyses. Voxelwise analysis of DTI data allows for brain-wide exploration of diffusion without constraining the analysis to pre-determined ROIs. An additional development in DTI has been the ability to estimate tractography using either probabilistic or deterministic algorithms. Tractography is used in several general ways: one is for the estimation of tracts passing through a specified ROI or significant cluster of voxels, which allows for the visualization and quantification of estimated tracts along which an abnormality is suspected or identified; another application of tractography is to specify two or more seed regions within the brain and to allow a tractography algorithm to propagate between the two regions. This allows for an estimation of fiber pathways that may exist between these regions and the ability to analyze the microstructural properties (i.e., FA, ADC) of these estimated pathways. A third major innovation in DTI which has been applied to the investigation of BD is tract-based spatial statistics (TBSS; Smith et al., 2006). TBSS overcomes some of the problems in registration and spatial smoothing of DTI data associated with voxelwise analyses of such data and enables local cross-subject comparisons (Smith et al., 2006). We now review the findings that have been reported in studies of BD using each of these approaches (Table 3). We then discuss some of the limitations of and future directions in DTI studies in BD.

3.5.1. Region of interest-based approaches—The first report of diffusion abnormalities in BD using DTI found lower FA in regions of prefrontal WM in BD compared to healthy controls (Adler et al., 2004), providing evidence that WM tracts connecting the prefrontal cortex with subcortical areas and other cortical structures are abnormal in patients with BD. More recently, the same group examined ADC and FA in similarly placed regions of interest among a sample of medication-naïve adolescents with BD experiencing their first episode of mania and found similar results (Adler et al., 2006a). This evidence suggests that prefrontal-subcortical WM abnormality is not a result of medication, and that it is present early in the course of the disorder. A sample of pediatric BD patients was found to have lower FA in the anterior corona radiata as well as greater ADC in the splenium of the corpus callosum (Pavuluri et al., 2009), supporting the existence of WM abnormalities in early-onset BD.

Several other groups employing ROI-based methodology reported diffusion abnormalities in prefrontal-subcortical WM (Beyer et al., 2005; Haznedar et al., 2005; Pavuluri et al., 2009; Wang et al., 2008a; Wang et al., 2008b; Yurgelun-Todd et al., 2007). Altered FA has been reported in distributed regions of prefrontal-thalamic-subcortical WM (Haznedar et al., 2005) in a sample of BD spectrum (subtypes I, II, and cyclothymia) patients. Lower FA has been found in the orbitofrontal cortex (Beyer et al., 2005), anterior cingulum (Wang et al., 2008a), and the genu (Yurgelun-Todd et al., 2007; Wang et al., 2008b), rostral body, and anterior midbody of the CC (Wang et al., 2008b) in adult BD samples. These latter results are consistent with previous reports of volumetric deficits and lower signal intensity in the CC in BD (Arnone et al., 2008; Atmaca et al., 2007; Brambilla et al., 2003; Brambilla et al., 2004; Caetano et al., 2008; Coffman et al., 1990). Decreased FA in the anterior, but not posterior cingulum in BD (Wang et al., 2008a) is consistent with findings that suggest the anterior, but not necessarily the posterior, cingulate is directly involved in emotional functioning and perception (Phillips et al., 2003a, 2003b, 2008).

3.5.2. Voxelwise approaches—Whole-brain voxelwise analyses allow for the assessment of DTI data across the entire brain without necessarily restricting analyses to hypothesis-driven regions of interest. Despite the removal of regional constraints in whole-brain voxel-wise analyses, each study that has used this approach to investigate diffusion in BD has found evidence for diffusivity abnormalities in prefrontal-subcortical WM in children (Fraizer et al.,

2007), adolescents (Barnea-Goraly et al., 2009; Kafantaris et al., 2009) and adults with BD (Bruno et al., 2008; Chaddock et al., 2009; Mahon et al., 2009; Sussman et al., 2009; Versace et al., 2008; Wessa et al., 2009; Zanetti et al., 2009). With the use of colormaps and/or tractography, diffusion abnormalities identified through whole-brain studies have been localized to specific white matter tracts (Table 3 and Figure 1). The majority of tracts along which diffusion abnormalities have been reported are those that connect regions within the anterior limbic network, suggesting that WM connections between these regions are an important component of the pathophysiology of BD.

Recent evidence suggests that mood state may have an effect on WM microstructural abnormalities in BD (Zanetti et al., 2009). A sample of currently-depressed BD I patients was found to have extensive diffusion abnormalities compared to currently-remitted BD I patients, particularly in ventromedial PFC WM and distributed association and projection tracts within the right hemisphere. This result suggests that mood episodes are marked by subtle yet detectable anatomical changes. The authors speculate that these changes may be related to an aberrant inflammatory process occurring in acute mood states in BD, a mechanism that has been proposed by several other groups (see Brietzke and Kapczinski, 2008 for a review).

Consistent with evidence suggesting that WM volume is both abnormal and highly heritable in BD, evidence that genetic liability to BD is associated with abnormal FA has been reported (Chaddock et al., 2009; Frazier et al., 2007). In a sample of adults with BD, their unaffected relatives, and healthy controls, genetic liability to develop BD was associated with decreased FA within extensive regions of the brain including bilateral uncinate fasciculus, deep prefrontal WM, cerebellum, superior longitudinal fasciculus, and corpus callosum (Chaddock et al., 2009). Frazier et al. (2007) reported that children at-risk for developing BD had lower FA in bilateral superior longitudinal fasciculus compared to a sample of control children. Abnormal WM microcircuitry, in addition to WMH, appears to be a potentially valid endophenotypic marker for at least a subset of BD cases. Further evaluation of WM diffusion as an endophenotype is likely to yield useful information regarding the pathophysiology of BD.

3.5.2.1 Tract-based spatial statistics: One of the major limitations of voxelwise analysis of DTI data is that of potential misregistration leading to partial volume effects and/or misinterpretation of crossing fibers. In the context of traditional voxelwise analysis, it is not possible to know if a result of lower FA is due to a genuinely greater level of isotropic diffusion along a uniformly directed tract, the result of misregistration or an area of crossing fibers thus lowering the anisotropic diffusion of water more generally. In the first case, an interpretation of diffusion abnormality is supported whereas in the latter two, abnormality cannot be assumed. Tract-based spatial statistics (TBSS; Smith et al., 2006) partially overcomes these problems by registering each image to the same mean FA tract skeleton comprised of the center of each tract. Analyses are then conducted within the tract skeleton so that the likelihood of partial volume effects is much lower than in traditional voxelwise analysis.

To date, three studies have used TBSS to examine WM in BD. Lower FA in prefrontal-thalamic tracts was reported in a sample of adolescents with familial BD I using TBSS (Barnea-Goraly et al., 2009). Additional areas of lower FA in patients included distributed regions of the corpus callosum as well as in the fornix, the corona radiata, and a left mid-posterior portion of the cingulate. Two separate studies reported higher FA in left frontal tracts in patients compared to controls (Versace et al., 2008; Wessa et al., 2009). In a sample of euthymic patients, Wessa and colleagues reported higher FA in left frontal WM, as well as in bilateral occipital and parietal WM. These findings were replicated using traditional voxel-based methods as well. Versace et al. (2008) reported higher FA in regions in the orbito-medial PFC along the left uncinate fasciculus and decreased FA along the right uncinate fasciculus in patients compared to controls. Furthermore, increased FA along the left uncinate fasciculus was driven by an

increase in longitudinal diffusivity (i.e., increased diffusivity along the main fiber direction), along with reductions in radial diffusivity (i.e., decreased diffusivity in directions other than along the main fiber direction). The authors noted that this finding is consistent with an increase in longitudinally aligned fibers of the uncinate fasciculus, along with a decrease in obliquely oriented fibers of this tract. Decreased FA in the right UF was driven by an increase in radial diffusivity in the absence of any significant change in axial diffusivity. The authors suggested that such increased radial diffusivity may indicate an increase in the number of obliquely oriented fibers, although they noted the possibility that local inflammation could also account for decreased FA driven by increased radial diffusivity. The same study reported higher FA in the left optic radiation and the right anterior thalamic radiation. Subgroup analyses revealed lower FA in the left uncinate fasciculus among BD subjects with a history of lifetime alcohol and/or substance abuse compared to BD subjects without such a history, as well as lower FA in the left optic radiation and right anterior thalamic radiation in BD patients receiving mood stabilizers versus those who were not. Acute mood state also contributed to diffusion abnormalities in that depressed BD patients had lower FA in the left optic radiation relative to remitted BD patients. These data thus highlight the importance of investigating the effects of clinical state and medications on diffusion measures.

3.5.3 Tractography—Given the theoretical importance and empirical evidence of abnormalities along WM tracts that connect prefrontal and subcortical regions, several groups have used tractography to estimate the number and microstructural properties of such tracts. Using fiber tractography, Houenou et al. (2007) investigated the uncinate fasciculus, the WM tract connecting the subgenual cingulate and the amygdala-hippocampal complex, in a sample of BD patients and matched controls. The tractography algorithm produced significantly more estimated fibers along the left uncinate fasciculus in patients relative to controls; there were no differences in the number of estimated fibers on the right side, nor were there any differences between the groups in the FA or ADC along the reconstructed fibers on either side. It may be that the usual right greater than left asymmetry of the uncinate fasciculus found in healthy individuals (Highley et al., 2002) is altered or reversed in BD. This result is notable not only for the implications it may have for abnormal frontal-limbic connectivity in BD, but also for providing evidence that WM tract alterations may still be present even in the absence of significant findings in traditional diffusion indices such as FA and ADC. McIntosh et al. (2008) used probabilistic tractography to investigate diffusivity along the uncinate fasciculus and portions of the anterior thalamic radiation in a sample of patients with familial SCZ or BD, as well as matched controls. In contrast to Houenou et al. (2007), FA was found to be significantly lower along both the uncinate fasciculus and the anterior thalamic radiations bilaterally and in both patient groups relative to controls. Despite the differences in the particular findings in these two studies, the consistency of altered uncinate fasciculus diffusivity in BD relative to controls reported in both indicates that this region should be a focus of future investigation in BD. The lack of specificity to BD in the latter study suggests that uncinate fasciculus abnormalities may be a common feature of both BD and SCZ with larger neurobiological implications.

3.5.4 Limitations of DTI and Future Directions—A limitation of many studies reported to date is the potentially insufficient number of directions that are sampled in the acquisition. Jones (2004) has provided evidence that at least 20 orientations are required to achieve robust estimations of anisotropy and that at least 30 orientations are required to estimate MD as well as the directionality of the tensor. Eight of the 21 DTI studies in BD conducted to date have acquired 6 orientations to estimate FA, and only 7 studies have acquired 30 or more orientations (Table 3). Future studies that wish to estimate FA or tractography should include an adequate number of directions to permit proper assessments. Another important consideration in DTI

analyses is that of using age as a covariate, especially when examining patient populations (e.g., Jones et al., 2006).

It is important to acknowledge that DTI results provide evidence for abnormalities without concomitant information about what may be driving such an effect. For example, lower FA and higher ADC values have been identified in patients with demyelinating diseases such as multiple sclerosis relative to healthy controls (Ge et al., 2005). Axonal demyelination, however, is just one of several possible causes that can result in decreased FA (Beaulieu, 2002); damage to and/or disruption of the axonal tract, neuronal loss, or a less rigidly oriented or less coherent alignment of axonal organization within the fiber bundles of the WM may also yield decreased FA (Moeller et al., 2007; Song et al., 2003). Thus, findings of abnormal FA in either direction that are not followed up by definitive post-mortem investigations should be interpreted with caution.

An additional limitation of DTI is that one cannot infer whether a particular WM fiber bundle functions as a feedforward or feedback pathway. Multimodal studies that employ fMRI and DTI may assist in this regard. Recently, de Almeida and colleagues (2009) reported altered effective connectivity between the orbital-medial PFC (OMPFC) and the amygdala in BD patients relative to controls. Using dynamic causal modeling (Friston et al., 2003) of fMRI data, this group showed that left-sided top-down effective connectivity between OMPFC and amygdala was reduced in BD and UD patients compared to controls and that right-sided bottom-up effective connectivity was abnormal in BD subjects compared to UD and control subjects when performing an emotion-labeling task. It may be that WM abnormalities between these regions (e.g., via the uncinate fasciculus) may mediate altered patterns of connectivity.

An empirical study linking functional and diffusion data in BD by Wang and colleagues (2009) measured event-related BOLD in response to emotional stimuli and FA in the same sample of BD and control subjects. These authors reported decreased functional connectivity between the perigenual anterior cingulate cortex and the amygdala in the BD group that was significantly correlated with decreased FA along tracts that connect these two regions (i.e., the uncinate fasciculus and surrounding WM). Emotional stimuli are likely to elicit greater and more theory-driven functional abnormalities in BD samples and should thus be used in multimodal structure-function paradigms. Future studies that assess both structural and functional connectivity are likely to provide the most compelling evidence for circuit dysfunction in BD, and will help to elucidate the nature of both the circuitry and the abnormalities within it.

Findings from DTI studies in BD conducted to date appear to converge on diffusion abnormalities along the uncinate fasciculus and other WM tracts subserving the OFC, particularly on the left side, as well as on the WM adjacent to the anterior cingulate. The OFC is directly connected with the limbic cortex and structures, and as proposed by Phillips et al. (2008) it may serve as a moderator between subcortical limbic structures and the more lateral and dorsal regions of the PFC. Results of DTI studies conducted thus far, using a variety of different methodologies and patient samples (children, adolescents, adults, and unmedicated patients), suggest that the WM fibers connecting the OFC and the limbic cortex are abnormal in BD. In addition, there is evidence for diffusion abnormalities in large projection and association tracts such as the thalamic radiation fibers and the superior longitudinal fasciculus, respectively. Although the implications for these more diffuse findings are not currently clear, such abnormalities may become incorporated into existing models and help to clarify the neurobiology of BD.

4. Neuropathological Evidence

Relatively few neuropathological studies have been conducted in BD, yet the results indicate that cytoarchitectural and neurochemical abnormalities are present in this disorder (Connor et

al., 2009; Harrison, 2002; Rajkowska, 2002). As is the case for neuroimaging studies, neuropathological studies have tended to focus on GM and have not investigated the WM to the same extent. Of particular relevance for WM investigation is the study of oligodendrocytes and myelin, although few studies have directly assessed these in BD. Oligodendrocytes are found in the GM as well as the WM, although it is generally the WM oligodendrocytes that produce the myelin sheath that surrounds axon fibers. The majority of studies that have assessed oligodendrocytes in BD have focused on the perineuronal oligodendrocytes that exist in the GM. Although alterations in GM neuronal and glial organization are related to WM changes, the impact of these alterations and the directionality of the relationship between the two remain unclear.

Guided by evidence from neuroimaging studies and by models of BD pathophysiology, researchers have repeatedly targeted the ACC and the DLPFC as regions of investigation. The evidence accumulated thus far appears to suggest fewer glial cells in the GM of the subgenual ACC (Öngür et al., 1998) and a lower neuronal density in the sub- and pre-genual ACC (Benes et al., 2001; Bouras et al., 2001). A reduction in neuronal cell bodies in subregions of the ACC could potentially result in a reduction in efferent axonal fibers, although this possibility has not been examined. Further studies are needed to investigate the ODC populations in the afferent and efferent projections of the ACC that are strongly implicated in BD pathophysiology (eg Phillips et al., 2008). Recently, Connor et al., (2009) reported a significantly increased population of neurons in the WM beneath the ACC in BD. Analysis of post-mortem samples from patients with SCZ, patients with BD, and controls indicated that approximately 25% of each patient group demonstrated an increased density of neuron-specific nuclear protein (NeuN) positive cells in the WM subserving BA 33. The authors concurrently demonstrated that in normal development, the density of NeuN+ neurons in this region decreases within the first year of life but then remains stable throughout the lifespan. Taken together, the evidence suggests that at least a subset of cases of SCZ or BD may be characterized by abnormal WM neurodevelopment.

Thomas et al. (2004) examined the level of intracellular adhesion molecule-1 (ICAM-1), a marker of cerebral inflammation, in the supragenual portion of the ACC as well as in the DLPFC and the surrounding WM in samples from patients with BD, UD, and SCZ, as well as from controls. ICAM-1 was found to be increased in the ACC GM and WM in BD samples and to a lesser extent in UD samples relative to both SCZ and control samples; there were no differences between the groups in the DLPFC. This is consistent with reported evidence that abnormal inflammatory processes are an important pathophysiological mechanism in BD (Brietzke and Kapczinski, 2008; Kim et al., 2007; O'Brien et al., 2006). The authors noted that this result may be consistent with reduced GM glial populations reported in the ACC (Öngür et al., 1998; Todtenkopf et al., 2005), in that fewer glial cells in this region in BD could lead to ischemia-induced inflammation in this area (Cotter et al., 2001). One of the many functions of glial cells is to regulate the amount of blood flow to neurons; thus, a loss of such cells might lead to a decrease in perfusion. It is therefore conceivable that WMH may reflect ischemia induced by glial reduction.

Several studies have investigated the cytoarchitecture of the DLPFC (BA 9 and BA 46) in BD and have found evidence for abnormalities in cellular organization in this region as well. In particular, neuronal and glial density (Rajkowska et al., 2001; Vostrikov et al., 2007), smaller glial size (Cotter et al., 2002), and signs of apoptosis (Uranova et al., 2001) have been reported. Uranova et al. (2004) examined oligodendrocytes in the GM as well as in the surrounding WM of BA 9 and found that the numerical density of GM oligodendrocytes was decreased in layer VI in BD, UD, and SCZ samples relative to control samples. Investigation of the myelin-producing oligodendrocytes located in the superficial WM adjacent to BA 9 suggested that numerical density of these cells is unchanged in SCZ, BD and UD samples. Regenold et al.

(2007) reported evidence for myelin pallor in the deep but not superficial WM underlying BA 9 and BA 46 in samples from BD, UD, and SCZ samples relative to control samples, providing neuropathological evidence that WM is abnormal in these illnesses in the deep WM, but may be uncompromised in the superficial WM. Beasley et al., (2002) examined interstitial neurons in the superficial WM underlying the DLPFC (BA 9 and BA 46) and found no differences in the density or distribution of such neurons in SCZ, UD, BD, and control samples. Abnormalities in the distribution and organization of interstitial neurons are believed to be the result of abnormal neuronal migration during development. Molnar et al. (2003) examined the distribution of WM interstitial cells in the DLPFC (BA 9) of the left hemisphere in 7 control samples and 7 samples from a combined depressed group made up of UD and BD samples. Although this study investigated a deeper level of WM than that examined by Beasley et al. (2002), the results suggested that there were no differences in interstitial cell distribution in any of the layers studied. The available evidence thus indicates that neuronal migration may not be disrupted in BD, although further examination is required to fully evaluate this possibility.

Although relatively few studies have examined the neuropathology of BD, and even fewer have directly investigated WM oligodendrocytes and myelin, it appears that there are important cytoarchitectural differences in brain regions involved in emotion regulation in BD. Glial reduction in the subgenual ACC (Öngür et al 1998; Todtenkopf et al., 2005) accompanied by increased inflammation in this region and the surrounding WM (Thomas et al., 2004) may imply a loss in perfusion. Given the consistent evidence for subgenual ACC involvement in emotion regulation (eg Mayberg et al., 2005; Phillips et al., 2008) abnormalities in this region are intriguing and require further investigation. Neuronal (Cotter et al., 2002; Rajkowska et al., 2001), glial (Rajkowska et al., 2001), and GM oligodendrocyte (Uranova et al., 2001; Uranova et al 2004; Vostrikov et al., 2007) abnormalities in DLPFC indicate that the cytoarchitecture of this region, also critically involved in emotion regulation, is disturbed. Rajkowska (2002) has demonstrated that these abnormalities, taken together, suggest that a fundamental alteration in cell resiliency and plasticity in regions involved in emotion generation and regulation may underlie BD. This suggestion is supported by neuroimaging findings that demonstrate altered connectivity rather than gross volumetric differences in WM and is consistent with circuit-based models of BD (Adler et al., 2006b; Green et al., 2007; Lyoo et al., 2006; Phillips et al., 2003b; Phillips et al., 2008; Soares and Mann, 1997; Strakowski et al., 2005).

5. Genetic Evidence

There is no doubt that the genetic underpinnings of BD are likely to be immensely complex. Twin studies have estimated the concordance rate for monozygotic twin pairs to be approximately 43%, whereas the rate for dizygotic twins appears to be approximately 6% (Kiessepä et al., 2003). Van der Schot et al. (2009) found that WM deficits in BD appear to be genetically mediated, whereas this was not found to be the case for GM deficits. Data from microarray and genetic linkage studies suggest that genes and proteins involved in connectivity, synaptic plasticity, and myelination are abnormal in BD. Evidence from various groups indicates that genes related to oligodendrocytes and myelin appear to be abnormally expressed in SCZ (Hakak et al 2001; Pongrac et al 2002; Tkachev et al 2003; Aston et al 2004; Dracheva et al 2006; Carter et al 2007a), and the evidence is accumulating to suggest that this is also the case in BD (Tkachev et al 2003; Carter et al 2007a). A potential limitation, however, is that the influence of antipsychotics on gene expression is not well understood, and that findings may be related to medication rather than to pathophysiology.

Tkachev and colleagues (2003) analyzed the expression of a wide range of myelin-and oligodendrocyte-related proteins in BD, SCZ, and control post-mortem tissue samples. mRNA

expression of proteolipid protein 1, the most abundant myelin-related protein in the brain, was reduced in BA 9 in both SCZ and BD samples relative to control samples, with a greater reduction reported in BD (Tkachev et al., 2003). Proteolipid protein 1 is believed to play a role in neuronal-glial interactions, so this finding may be consistent with early indications of abnormal neuronal-glial interactions in mania (Öngür et al., 2008). In fact, recent evidence suggests that transgenic mice with extra copies of the proteolipid protein 1 gene have abnormal neuronal-glial interactions, as well as reduced prepulse inhibition, abnormal anxiety-related behaviors, and deficits in working memory (Tanaka et al., 2009). Other myelin- and oligodendrocyte-related proteins that were found to be altered in BD and SCZ include oligodendrocyte-specific protein, myelin-associated glycoprotein, and myelin oligodendrocyte glycoprotein (Tkachev et al., 2003).

Transferrin, a gene associated with the initiation of myelination, was downregulated in both patient groups in the same study (Tkachev et al., 2003), as was SOX10, a transcription factor that is believed to regulate the expression of several myelin-related genes (Stolt et al., 2002). The authors noted that downregulation of key myelin- and oligodendrocyte-related genes could certainly have implications for micro- and macrostructural impairment of WM, and are consistent with findings suggesting such impairments from neuroimaging and neuropathological studies.

Another important finding from the study by Tkachev et al. (2003) is that of downregulation of ERB3, a receptor for neuregulin1 that is known to be involved in ODC growth and differentiation. This downregulation was apparent in both patient groups, although the effect was more pronounced in BD. An intriguing study on ERB signaling pathways and their effect on oligodendrocytes in mice found that when ERB signaling in oligodendrocytes is blocked, the mice exhibited subtle but functionally significant changes (Roy et al., 2007). Although the number of myelinated axons was unchanged, the thickness of the myelin sheath was lower in the transgenic mice. Furthermore, the population of smaller oligodendrocytes was greater in these mice; this morphometric change may contribute to the overall decrease in myelin thickness that was observed along with the preservation of the number of myelinated axons. A decrease in the myelin sheath may have led to the reduction in conduction velocity that was observed in the experimental mice. Unexpectedly, mice in which ERB signaling was blocked also exhibited an increase in dopamine receptors and transporters in regions known to be involved in emotion regulation (cortex, striatum, and nucleus accumbens) and that have been implicated in BD and SCZ. Behavioral abnormalities observed in the experimental animals, such as reduced social activity and locomotion, emphasize the link between seemingly subtle neurochemical alterations and gross behavioral effects. Given these results in mice, it is noteworthy that ERB signaling appears to be abnormal in BD and SCZ.

ERB3 and ERB4 are receptors for neuregulin1, a growth factor that is crucial in myelination and which has also been linked to both SCZ and BD (Georgieva et al., 2008; Green et al., 2005; Thomson et al., 2007; Walss-Bass et al 2006). McIntosh et al. (2007) demonstrated that healthy volunteers with the risk-associated genotype at the single-nucleotide polymorphism SNP8NRG243177 demonstrated reduced WM density and integrity in the anterior limb of the internal capsule as assessed by both T1-weighted and DTI. These findings converge with those of neuroimaging studies that have demonstrated similar alterations in the brains of BD patients (Strakowski et al., 2005). Neuregulin1 was not found to have altered expression in the study by Tkachev et al. (2003), although more recent studies have confirmed that the neuregulin1 SNP appears to be a susceptibility locus for BD and SCZ (Georgieva et al., 2008; Green et al., 2005; Thomson et al., 2007; Walss-Bass et al., 2006). Genetic expression work in BD is in the very early stages, but as is the case for neuropathological studies of BD, the evidence accumulated thus far suggests the existence of alterations in oligodendrocytes and myelination that may have particular relevance for connectivity in BD.

6. Summary and Integration with Existing Models

Evidence for altered WM metabolism and compromised WM coherence and organization, in addition to a wealth of evidence suggesting functional disconnection in BD, indicates that WM connectivity is likely to be an important component in the pathophysiology of this disorder. In general, models of BD and SCZ have moved beyond discrete lesion-based proposals to models based on circuit-wide dysfunction, and WM investigation is an essential facet of this more recent focus. The lack of consistent gross WM volumetric abnormalities, coupled with the evidence for an increased prevalence of WMH in BD, suggests that the WM pathology present in BD may be characterized by subtle but potentially crucial disruptions in the WM connections of the brain.

Theoretical and empirical research suggests a model of BD in which structures involved in emotion perception, generation and regulation are abnormal. Evidence from fMRI investigations using emotional stimuli suggests a complicated pattern of abnormal activity in VLPFC (Altshuler et al., 2005; Elliott et al., 2004; Lawrence et al., 2004; Malhi et al., 2005; Robinson et al., 2008), DLPFC (Chang et al., 2004), MdPFC (Elliott et al., 2004; Malhi et al., 2007), OFC (Wessa et al., 2007), anterior cingulate cortex (Lennox et al., 2004; Malhi et al., 2007), and subcortical structures (Caligiuri et al., 2003; Chang et al., 2004; Lagopoulos and Malhi, 2007; Lawrence et al., 2004; Malhi et al., 2004a; Malhi et al., 2004b; Wessa et al., 2007), especially the amygdala (Altshuler et al., 2005; Foland et al., 2008; Lennox et al., 2004; Malhi et al., 2004b; Yurgelun-Todd et al., 2000). Findings across studies appear to be moderated by mood state and medication status, although differences in samples and study designs preclude direct comparison. Taken together with evidence from genetic and neuropathological studies of BD, as well as studies of healthy emotional regulation, several groups have proposed models of BD that may account for this complicated pattern of findings. A common feature of such models is that of hypothesized alterations in circuits comprised of subcortical limbic structures and prefrontal regions involved in executive functioning and cognitive appraisal, and in particular, deficient prefrontal modulation of subcortical regions involved in emotion perception and generation (Phillips et al 2003b, 2008; Strakowski et al 2005; Green et al 2007). Despite the circuit-based nature of such models, the WM that forms the structural connections between GM structures has been relatively under-emphasized.

Evidence for alterations along several of the tracts that connect prefrontal and subcortical structures implicated in emotional regulation has been reported (Table 3 and Figure 1). Given that emotional regulation is hypothesized to consist of both top-down and bottom-up processing of emotional stimuli via reciprocal connections between sensory cortex, subcortical limbic structures, and PFC subregions, alterations along these tracts is likely to play a role in the deficient emotional regulation that characterizes BD. Deficits in prefrontal modulation of subcortical hyper- or hypoactivation could be mediated through abnormal WM connectivity, in particular along the uncinate fasciculus and the anterior cingulum. Persistence of abnormal subcortical emotional activation as a result of deficient inhibitory inputs from prefrontal regions may play a role in exaggerated mood states. Foland et al. (2008) have recently reported evidence for deficient prefrontal modulation of amygdala activity in manic BD subjects relative to controls in an emotional labeling task. The effective connectivity between OMPFC and amygdala in BD patients performing an emotional labeling task has recently been investigated (de Almeida et al., 2009). Effective connectivity, when analyzed using dynamic causal modeling (Friston et al., 2003), allows for inferences to be made regarding causal relationships between activation in two or more brain regions. In this regard, de Almeida and colleagues (2009) reported that WM alterations may mediate an altered functional relationship between OMPFC and amygdala.

Phillips et al. (2003a, 2003b, 2008) suggest a distinction between automatic emotional processes, such as involuntary attention to emotional stimuli, inhibition of the stress response, and implicit cognitive appraisal and reappraisal, and voluntary emotional processes, such as selective attention, attentional inhibition, and behavioral suppression. Evidence suggests that automatic emotional processes are associated most consistently with the OFC, ventral PFC including subgenual ACC, and subcortical limbic structures such as the amygdala; voluntary processes, in contrast, are associated most consistently with DLPFC and VLPFC (see Phillips et al., 2008). A further distinction has been made between more ventral and medial emotionally-generative regions and more dorsal and lateral emotionally-appraising regions. Numerous studies suggest that the OFC serves as a kind of way station between dorsal and lateral regions of the PFC and limbic regions, in that these PFC regions are indirectly connected to limbic structures through direct connections with the OFC (Beauregard, 2007; Cavada et al., 2000) via tracts such as the uncinate fasciculus, anterior cingulum, the anterior fronto-occipital fasciculus, and others. Notably, these tracts are among those that appear to be abnormal in BD.

The complicated pattern of altered activation reported in fMRI studies across mood states suggests that the occurrence of mood episodes may be a result of subtle pathway disruption rather than fixed GM structural or functional abnormalities. A lack of normal anatomical connectivity among regions involved in emotional functioning suggests that errors occurring in any region along a circuit may be perpetuated, maintained, and even compounded by a lack of regulatory feedback. Thus, the same pathophysiologic process could allow different stimuli (e.g. lack of sleep, social rejection) to trigger an abnormal feedback loop that generates and maintains a manic or depressed episode. For example, the lateral nucleus of the amygdala is known to receive sensory information from the cortex that is then “tagged” with an emotional valence that is transmitted to other subcortical and cortical brain regions, including the PFC (eg Cardinal et al., 2002; Davis and Whalen, 2001; Gallagher and Chiba, 1996; LeDoux, 2003; LeDoux et al., 1990; Quirk et al., 1995). Given the evidence for significant (over 40%) neuronal deficits in the lateral nucleus in BD (Berretta et al., 2007), as well as the evidence for altered amygdalar activation in BD mania and depression (Altshuler et al., 2005; Blumberg et al., 2005; Lawrence et al., 2004; Yurgelun-Todd et al 2000), it is possible that altered processing of emotional valence by the amygdala is a factor in BD. The dense reciprocal connections between the amygdala and the OFC, and the anterior cingulate in particular, have been found to be altered in BD (see Figure 1). Given that the OFC is hypothesized to play a role as a moderator between subcortical and more dorsal and lateral prefrontal regions, it is notable that findings in BD appear to converge on tracts that subserve this region. It may be that an abnormal relationship between the OFC and subcortical limbic structures results in a larger disconnection between lateral PFC and the limbic system. Potential errors in emotionally valenced coding in the amygdala could then be perpetuated in higher order brain regions such as the lateral PFC through deficiencies in normal feedback circuits. Much research is required to begin to identify disruptions along these circuits; the investigation of both the structural and functional relationships between GM and WM is a promising step in this direction (Wang et al., 2009). As imaging, neuropathological, and genetic methodology improves, it will likely be possible to assess more specific subdivisions of larger tracts, as well as examine smaller, but theoretically important tracts such as the stria terminalis.

Models featuring circuit disruption are inherently more complex than discrete lesion models, and allow for the integration of critical interactions between genes, environment, affect, and behavior. It may be that the subtle WM pathology observed in BD is the result of abnormal signaling between groups of neurons that are genetically vulnerable to environmental stresses. Carter (2007b) reviewed the genes demonstrated to be associated with BD and outlined the interactions between the environment and such genes and the implications for signaling pathways and ultimately ODC vulnerability that appears to be a critical mechanism of BD pathophysiology. Similarly, Hains and Arnsten (2008) have recently elaborated upon the

molecular signaling pathways that are commonly found to be disrupted in BD and SCZ, and have related these disruptions to molecular mechanisms of stress. Evidence for molecular dysfunction also appears to be supported by recent evidence suggesting abnormal glucose metabolism in SCZ and BD and may be crucial to understanding at least some subtypes of these disorders (Kato & Kato, 2000; Quiroz et al., 2008; Shao et al., 2008; Stork & Renshaw, 2005). Abnormal glucose metabolism is likely related to WM abnormalities documented in both disorders, and to WMH in BD in particular (Regenold et al., 2008).

7. Conclusions and Future Directions

Long neglected due to the limited feasibility of examining such tissue *in vivo*, researchers are increasingly turning to WM examination as a means of more fully understanding the neurological underpinnings of bipolar disorder. Imaging, genetic, and neuropathological evidence suggest that abnormalities in WM tissue play an important role in BD pathophysiology and phenomenology. In particular, theoretical and empirical research suggests a model of BD in which the connections within and between structures involved in emotion generation and regulation are altered. Broadly, this model proposes alterations along WM tracts interconnecting the amygdala, hypothalamus, striatum, and the subdivisions of the frontal cortex.

Evidence for alterations along several of these implicated tracts has been reported (Table 3). Evidence from genetics and post-mortem research appears to support the imaging findings of WM pathology. In particular, altered expression of oligodendrocyte and myelin genes (Tkachev et al., 2003) and a lower density of oligodendroglial (Uranova et al., 2004) and glial (Rajkowska et al., 2001) cells have been reported in the prefrontal cortex of patients compared to healthy volunteers. The large discrepancies among results in all areas of research in BD are likely influenced by heterogeneity of patient samples and methodological differences. Patient heterogeneity in BD research is a notorious problem, and comprises many attributes among which patients regularly differ. In addition to the traditional problem of medication effects, varying mood states, multiple subtypes (bipolar I and II), and subgroups of patients that experience psychosis as part of their illness add significantly to the complexity of the phenotype. As BD I is viewed as a more severe form of the illness, patients with this form of BD could be a primary focus of research at the descriptive level. Within BD I patients, there is enormous variation, however, in characteristics such as age, substance abuse and/or dependence, length and severity of illness, medication history and status, pre-morbid and current cognitive functioning, and family history of illness. Although the vast majority of studies in BD seek to control for these variables, it is rare that samples are large enough to allow for their systematic investigation. Additional variables that may be important to consider are the absolute and relative lengths of time that an individual remains in manic, euthymic, and depressed states. Although there is a decrement to generalizability when focusing on such a specific subset of individuals, it is possible that heterogeneous patient groups obscure the subtle alterations that underlie BD. Until these alterations are understood, more homogeneous patient groups may be needed to speed the pace of discovery.

Studies that combine imaging and other assessment techniques in a multi-modal fashion are likely to increase our ability to place findings in a meaningful context and to empirically connect structure and function. For example, resting and/or task-related brain activation as assessed through fMRI may inform results from concurrent microcircuitry analyses and ultimately, the functional consequences of abnormal circuitry may become apparent. The first study to attempt such an investigation in BD yielded compelling evidence that functional disconnectivity between the pregenual anterior cingulate cortex and the amygdala is associated with structural abnormalities within the anatomical WM connections between these regions (Wang et al., 2009). WM investigations in bipolar disorder are largely conducted at the level

of preliminary description, and replication and refinement are very much needed. As knowledge of WM structure advances, studies that link WM pathology with clinical, genetic, metabolic, and functional correlates, as well as with GM pathology, may further elucidate the ways in which these neural abnormalities contribute to BD and advance progress toward a unifying theory of underlying pathophysiological mechanisms in BD.

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Figure 1. Major white matter tracts

The approximate location of major white matter tracts, represented by the center of each tract (the “mean FA skeleton” [Jones et al., 2006]). A mean FA skeleton has been colored and labeled and is shown overlaid on the FA-weighted average brain template, both available in Tract Based Spatial Statistics (TBSS; Jones et al., 2006). Labeled/colored tracts have been found to be altered in BD, although not necessarily at the location represented in this figure (individual studies are provided in the figure key).

(A) red = corpus callosum: Frazier et al., 2007; Yurgelun-Todd et al., 2007; Wang et al., 2008b; Barnea-Goraly et al., 2009; Sussman et al., 2009; (B) magenta = frontal occipital fasciculus: Bruno et al., 2008; Chaddock et al., 2009; Zanetti et al., (in press); (C) yellow = uncinate fasciculus: Houenou et al., 2007; McIntosh et al., 2008; Versace et al., 2008; Sussmann et al., 2009; Wang et al., 2009; Zanetti et al. (in press); (D) orange = pontine crossing tract: Mahon et al., 2009; (E) green = cingulum bundle: Barnea-Goraly et al., 2009; Frazier et al., 2007; Wang et al., 2008a; (F) brown = inferior longitudinal fasciculus: Barnea-Goraly et al., 2009; Bruno et al., 2008; Chaddock et al., 2009; Zanetti et al., (in press); (G) blue = thalamic radiations/corticospinal/corticopontine tracts: Frazier et al., 2007; Mahon et al., 2009; Wessa et al., 2009; Zanetti et al., (in press); (H) cyan = superior longitudinal fasciculus: Chaddock et al., 2009; Mahon et al., 2009; Zanetti et al., (in press); (I) black = fornix: Barnea-Goraly et al., 2009; white = miscellaneous tracts/ unspecified.

Figure 2. Schematic representation of networks proposed to be disrupted in BD1

Proposed model of disrupted white matter tracts in the neurobiology of bipolar disorder. Disruption along frontocortical-striatal-thalamic-frontocortical circuits may lead to abnormal processing of emotional information and deficient emotion regulation. Disruption along tracts (e.g., the uncinate fasciculus) that connect regions involved in automatic emotion regulation, such as the medial orbital frontal cortex and the amygdala/hippocampus, may result in extreme mood states. Errors in processing anywhere along a circuit may be propagated through disruptions within both top-down (emotion regulation) and bottom-up (emotion generation/perception) systems. Evidence for disruption along major tracts within these circuits has been reported (see text and Table 3); however, future research is required to define these abnormal tracts more specifically and to determine which sub-circuits are affected. In particular, research conducted to date in BD does not allow for a reliable distinction between cortico-striatal tract disruption and thalamic-frontal tract disruption, although this distinction is likely to be important in our understanding of BD pathophysiology. Note that not all connections between regions are shown in the figure.

Abbreviations: DLPFC = dorsolateral prefrontal cortex; sgACC = subgenual anterior cingulate cortex; OFC = orbital frontal cortex; GP= globus pallidus; VP = ventral pallidum

¹ Adapted from Haldane & Frangou, 2004; Phillips et al., 2008; Soares & Mann, 1997; Strakowski et al., 2005; Vawter et al., 2000.

Table 1**Volumetric Studies of White Matter in Bipolar Disorder**

Study	BD Sample, age at scan (SD)	Comparison Sample, age at scan (SD)	WM Regions Measured	Results
Hauser et al., 1989	-22 BD, 40.4 (11.6)	-25 matched controls, 37.0 (8.6)	-CC width and area	-No differences in CC width or area between groups -Males had larger CC area than females in control but not BD group
Coffman et al., 1990	-25 BD with psychotic features, 32.0 (6.2)	-29 matched controls, 28.8 (7.2)	-CC width and area	-BD group had significantly smaller corpus callosum size compared to controls
Strakowski et al., 1993b	-17 first episode BD, 31.3 (11.8)	-16 matched controls, 32.4 (8.8)	-total cerebral WM	-total cerebral WM was smaller in BD group relative to controls
Zipursky et al., 1997	-14 BD, 35.9 (7.2)	-17 matched controls, 29.9 (6.6)	-total cerebral WM	-no differences in total cerebral WM between BD group and controls
Lim et al., 1999	-9 BD (4 manic, 3 depressed, 2 mixed), 44.4 (9.2)	-16 matched controls, 44.3 (6.8)	-total cerebral WM	-no differences in total cerebral WM between BD group and controls
Brambilla et al., 2001	-22 BD, 36 (10)	-22 matched controls, 38 (10)	-total cerebral WM	-no differences in total cerebral WM between BD group and controls
López-Larson et al., 2002	-17 manic BD, 29 (8)	-12 matched controls, 31 (8)	-WM within the superior, middle, inferior, and orbital prefrontal region, as well as WM surrounding the cingulate -did not measure the deep prefrontal WM	-no differences between BD group and controls in WM volume within any prefrontal subregion
Sassi et al., 2002	-11 untreated BD (4 euthymic, 7 depressed, 1 hypomanic), 37.7 (10.6) -17 lithium-treated BD (14 euthymic, 3 depressed), 31.1 (8.6)	-46 matched controls, 35.5 (10.3)	-total cerebral WM	-no differences in total cerebral WM between BD group and controls. Medication status had no effect on the results.
Brambilla et al., 2003	-16 BD I, 34 (9)	-27 matched controls, 38 (10)	-CC subregions: genu, anterior body, posterior body, isthmus, and splenium	-BD group had smaller volumes in the genu, posterior body, and isthmus, as well as smaller total volume of the CC relative to controls
Kieseppä et al., 2003	-24 BD I (1 manic, 1 hypomanic, 22 euthymic) probands, 44.4	-15 unaffected MZ and DZ co-twins, 44.5 -27 control twins, 46.7	-measured WM volume across right and left hemispheres, as well as in frontal and temporal lobes	-BD group and unaffected co-twins had significantly smaller WM volume in the left hemisphere relative to control twins -BD group had smaller WM volumes in the right hemisphere and bilateral frontal regions relative to co-twin group and to matched control twins.
Brambilla et al., 2004	-29 BD (17 euthymic, 11 depressed), 1	-36 matched controls, 37 (10)	-measured the signal intensity of CC subregions	-BD group had less signal intensity in all subregions of the CC relative to controls

Study	BD Sample, age at scan (SD)	Comparison Sample, age at scan (SD)	WM Regions Measured	Results
	hypomanic), 35 (11)			
Bruno et al., 2004	-39 BD (28 BD I, 11 BD II), 39.1	-35 matched controls, 34.8	-voxel-based morphometry of whole brain WM volume and density	-no WM volumetric differences between BD group and controls -WM density was significantly less in bilateral prefrontal regions in BD group relative to controls
Chen et al., 2004	-16 pediatric/adolescent BD (12 BD I, 3 BD II, 1 BD NOS), 15.5 (3.4)	-21 matched controls, 16.9 (3.8)	-measured the WM volume of the superior temporal gyrus bilaterally	-BD group has significantly smaller WM volume in bilateral superior temporal gyrus relative to controls
Davis et al., 2004	-22 male euthymic familial BD I, 43.1 (11.4)	-32 matched controls, 37.8 (10.8)	-measured cerebral WM volume	-BD group had significantly smaller cerebral WM compared to controls
Lyoo et al., 2004	-39 BD (22 depressed, 17 manic/hypomanic/mixed), 38.3 (11.6)	-43 matched controls, 35.7 (10.1)	-voxel-based morphometry of whole brain WM volume density	-no differences in WM density between BD group and controls in any region of the brain
McDonald et al., 2004	-37 BD I with psychotic features, 40.7 (11.6)	-50 unaffected relatives of the BD group, 44.1 (15.7)	-voxel-based morphometry of whole brain WM volume density	-genetic risk for BD was significantly associated with smaller volume in anterior CC, L temporoparietal, R parietal, and bilateral frontal WM
Farrow et al., 2005	-8 BD adolescents with psychotic features, 17.5 (2)	-22 matched controls, 20.5 (4)	-voxel-based morphometry of whole brain WM volume at first episode of psychosis -two year follow up scan in BD group	-at first episode, BD group had significantly less WM volume in L frontal cortex and bilateral posterior parietal-temporal junction relative to controls -at 2 year follow up, BD group had increased WM volume in R posterior frontal-parietal cortex, L temporal-parietal junction, R parietal-occipital junction, L posterior lobe, R cerebellum relative to the first episode scans -increases may have been due to normal maturational processes
Haznedar et al., 2005	-40 BD (17 BD I, 7 BD II, 16 cyclothymia), 42.2 (10.8)	-36 matched controls, 40.7 (11.6)	-measured WM volume in 11 prefrontal subregions: BAs 25 and 32 (ventral PFC); BAs 11 and 12 (OFC); BAs 8, 9, 44, 45, 46, and 47 (DLPFC); and BA 10 (frontal pole)	-Combined BD group had smaller total prefrontal WM volume relative to controls, as well as smaller WM volume in BAs 25, 32, 12, 8, 9, 45, 46 -BD I group had smaller WM volume in R BA 32 compared to controls -BD II group had smaller WM volume in L BA 32 compared to controls -cyclothymia group had smaller WM volume in bilateral BA 32 compared to controls
McDonald et al., 2005	-37 BD I with psychotic symptoms, 40.7 (11.6)	-52 matched controls, 39.3 (14.8)	-voxel-based morphometry of the whole brain WM	-BD group had 4 clusters of smaller WM volume relative to controls in the brain stem, prefrontal, temporal, and parietal lobes approximating bilateral superior longitudinal fasciculus and occipital frontal fasciculus
McIntosh et al., 2005	-26 familial BD I (no SCZ in	-22 unaffected relatives from families with BD	-voxel-based morphometry of frontal subgyral WM	-BD group had lower WM density in L anterior limb of the

Study	BD Sample, age at scan (SD)	Comparison Sample, age at scan (SD)	WM Regions Measured	Results
	family), 40.5 (12.1) -19 familial BD I (SCZ in family), 39.74 (9.2)	I only, 34.73 (12.6) -26 unaffected relatives from families with both BD I and schizophrenia, 34.12 (13.0) -49 control participants, 35.27 (11.1)	density and the WM density of the anterior limb of the internal capsule	internal capsule relative to controls and unaffected relatives -unaffected relatives from families with both BD I and schizophrenia had lower WM density in R superior frontal subgyral tissue and in R medial frontal gyral WM relative to controls
McIntosh et al., 2006	-26 familial BD I (no SCZ in family), 40.5 (12.1) -19 familial BD I (SCZ in family), 39.74 (9.2)	-22 unaffected relatives from families with BD I only, 34.73 (12.6) -26 unaffected relatives from families with both BD I and schizophrenia, 34.12 (13.0)	-voxel-based morphometry of the whole brain and the prefrontal cortex	-No association between genetic liability for BD and WM volume
Yasar et al., 2006	-16 pediatric/adolescent BD (12 BD I, 3 BD II, 1 BD NOS), 15.5 (3.4)	-21 matched controls, 16.9 (3.8)	-length, area, and circularity of the entire CC measured	-no differences between the groups in CC length or area -BD group had less circularity of the splenium of the CC compared to controls
Atmaca et al., 2007	-12 medication-naïve first manic/mixed episode BD, 28.2 (6.5)	-12 matched controls, 26.8 (7.6)	-total cerebral WM volume -total and subregional volumes of the CC (subregions: genu, anterior body, posterior body, isthmus, splenium)	-no differences in total cerebral WM volume -BD group had smaller total CC area and smaller anterior body, posterior body, and isthmus areas compared to controls
Rosso et al., 2007	-20 first-episode BD (14 manic, 4 mixed, 2 depressed), 23 (3)	-23 matched controls, 25 (3)	-total cerebral WM volume	-BD group had a trend toward lower total cerebral WM volume relative to controls -In BD group but not control group, there was a significant positive correlation between amygdala volume and total cerebral WM volume
Caetano et al., 2008	-16 pediatric/adolescent BD (12 BD I, 3 BD II, 1 BD NOS), 15.5 (3.4)	-21 matched controls, 16.9 (3.8)	-Signal intensity of the CC	-BD group had lower signal intensity for all CC subregions (genu, anterior body, posterior body, isthmus, and splenium) relative to controls
Beyer et al., 2009	-56 older adults with BD, 60.5 (9.1)	-49 matched controls, 58.1 (6.3)	-Whole brain parcellation of WM	-BD group had WM deficits relative to controls in frontal regions that did not reach statistical significance
Sarnicola et al., 2009	-71 BD I, 43.8 (11.4)	-82 matched controls, 40.5 (11.6)	-voxel-based morphometry of whole brain WM volume	-no differences between the groups on WM volume -no association between WM volume and neuropsychological data
Stanfield et al., 2009	-66 familial BD I, 36.4 (11.1)	-66 matched controls, 39.0 (10.9)	-voxel-based morphometry of whole brain, ventral prefrontal, and temporal lobe WM density	-BD group had reductions in WM density in L temporal stem and L corona radiata, extending into the middle and posterior CC, relative to controls

Study	BD Sample, age at scan (SD)	Comparison Sample, age at scan (SD)	WM Regions Measured	Results
van der Schot et al., 2009	-24 MZ twin pairs (9 concordant for BD, 15 discordant for BD), 37.4 (10.6) -26 DZ twin pairs (4 concordant for BD, 22 discordant for BD), 43.8 (8.5)	-39 MZ control twin pairs, 39.0 (9.9) -28 DZ control twin pairs, 39.0 (7.5)	-WM volume of the cerebrum, cerebellum, and frontal, temporal, parietal, and occipital lobes	-BD group had smaller WM volume in temporal, frontal, and parietal lobes relative to unaffected twins -structural equation modeling revealed that lobar WM volume is genetically mediated -approximately 99% of WM lobar volume deficits in BD were explained by additive genetic factors; gray matter volume was not associated with genetic factors in BD
Walterfang et al., 2009b	-22 BD with first episode psychosis, 21.73 (2.35)	-36 matched controls, 20.70 (3.19)	-length, area, and curvature of the entire CC measured	-no differences between BD group and control group in any parameter measured
Walterfang et al., 2009a	-70 BD I (23 treated with lithium, 47 not treated with lithium), 43.64 (11.81)	-45 unaffected relatives, 34.80 (12.49) -75 matched controls, 36.10 (13.51)	-length, area, bending angle, regional and mean thickness of the entire CC measured	-BD subgroup not treated with lithium had smaller mean CC area relative to BD subgroup treated with lithium, controls and unaffected relatives -no differences in CC length or bending angle between any of the groups -BD subgroup not treated with lithium had regional thinning in the body of the CC relative to lithium-treated subgroup, controls, and unaffected relatives -In BD but not unaffected relatives or controls, increasing age was associated with reductions in the midbody of the CC -Length of illness was associated with reductions in the midbody of the CC in the BD group as a whole

Abbreviations: BD, bipolar disorder; CC, corpus callosum; HC, healthy control; L, left; R, right; UD, unipolar depression; WM, white matter

Table 2**Magnetic Resonance Spectroscopy Studies of White Matter in Bipolar Disorder**

Study	BD Sample, age at scan (SD)	Comparison Sample, age at scan (SD)	Methods	Findings related to white matter
Kato et al., 1998	-7 drug-free euthymic BD (4 BD I, 3 BD II), 44.1 (16.9) -13 lithium-treated BD plus 1 drug-free BD (examined for WMH; age of this sample not given)	-60 matched controls, 39.6 (13.9)	-phosphorus-31 MRS -T2-weighted MRI, Coffey scale to rate WMH	-drug-free BD group had significantly lower intracellular pH than controls -9 of 14 T2 BD scans had WMH (control scans not rated for WMH) -subjects with WMH had significantly lower intracellular pH than controls; subjects without WMH did not differ from controls in intracellular pH -subjects with WMH had increased phosphodiester peak relative to those without WMH and to controls
Cecil et al., 2002	-17 manic/mixed BD I, 22.3 (7.3)	-21 matched controls, 21.7 (5.2)	-proton MRS -one voxel placed in the orbital-lateral WM	-The amino acid composite (comprised of glutamate, glutamine, GABA, and aspartate) was significantly elevated in BD group relative to controls
Blasi et al., 2004	-7 first episode manic BD I with psychotic features-10 first episode major depression with psychotic features (age of combined patient group = 26.8 (7.6))	-17 matched controls, 25.5 (6.8)	-proton MRS -one ROI placed in the prefrontal WM (size not specified)	-the combined patient group had reductions in NAA and CHO compared to controls in the prefrontal WM -this finding did not survive correction for multiple comparisons
Dager et al., 2004	-32 drug-free mixed or depressed BD (11 BD I, 17 BD II), 30.3 (10.8)	-26 matched controls, 31.9 (7.7)	-proton MRS -WM voxels placed axially through the cingulate	-No differences in metabolite distribution or concentration within the WM between the groups
Friedman et al., 2004	-12 lithium-treated BD (3 BD I, 9 BD II), 31.3 (9.6) -9 valproate-treated BD (5 BD I, 4 BD II), 28.4 (8.5)	-12 matched controls, 30.6 (5.5)	-proton MRS -WM ROIs placed in bilateral frontal and parietal WM -patient sample was a subset of the drug-free sample in Dager et al., 2004; comparisons were made from drug-free baseline to post-treatment	-No differences in metabolite concentration in the WM among groups or timepoints
Frye et al., 2007	-16 manic BD I, 37.5 (11.5)	-17 matched controls, 32.9 (11.5)	-proton MRS -WM ROI placed in the left occipital-parietal WM	-no differences between the groups in metabolite concentration within the WM ROI
Port et al., 2008	-21 BD, 30.8 (range = 18.9 - 54.7)	-21 matched controls, 31.1 (range = 18.4 - 52.9)	-proton MRS -WM ROIs placed in bilateral dorsolateral prefrontal WM, parietal WM, and occipital WM	-in the dorsolateral prefrontal WM, the concentration of glutamate/glutamine was significantly decreased in BD group compared to controls

Abbreviations: BD, bipolar disorder; CHO, choline; HC, healthy control; MRS, magnetic resonance spectroscopy; NAA, N-acetyl aspartate; ROI, region of interest; WMH, white matter hyperintensity

Table 3**Diffusion Tensor Imaging Studies in Bipolar Disorder**

Study	BD Sample, age at scan (SD)	Comparison Sample, age at scan (SD)	Methods	Results (BD group compared to controls unless otherwise specified)
Adler et al., 2004	-9 BD I, 32 (8)	-9 matched controls, 31 (7)	-ROIs placed 15, 20, 25, and 30 mm above the AC -analysis of FA and ADC -mean FA and ADC in each ROI were combined bilaterally -5 mm contiguous coronal slices, 25 directions	-lower FA in the ROIs 25 and 20 mm above the AC -no differences in ADC
Beyer et al., 2005	-14 male BD, 44.0 (17.6)	-21 matched controls, 44.6 (13.5)	-ROIs placed in bilateral OFC, SFG, MFG -FA and ADC measured -5 mm axial slices, 2.5 mm gap, 6 directions	-higher ADC in bilateral OFC -no differences in FA
Haznedar et al., 2005	-40 BD (17 BD I, 7 BD II, 16 cyclothymia), 42.2 (10.8)	-36 matched controls, 40.7 (11.6)	-manual ROIs placed in caudate, putamen, thalamus -relative anisotropy (RA) measured -5 mm contiguous axial slices, 6 directions	BD spectrum group compared to controls: -lower RA in internal capsule WM -higher anisotropy in right anterior frontal WM, most pronounced in BD I subgroup
Adler et al., 2006a	-11 adolescent first episode manic BD (total sample age = 14 (2))	-17 matched controls	-12 ROIs placed from 2 mm below the AC-PC to 28 mm above it anteriorly and posteriorly. -FA and ADC measured -5 mm contiguous axial slices, 25 directions	-Lower FA in superior frontal ROIs, especially in L hemisphere
Regenold et al., 2006	-8 BD, 58.4 (12.9)	-8 neurologic controls, 54.5 (12.8)	-40 ROIs placed on 8–10 consecutive slices rostral to the midbrain in each lobe -ADC measured -5 mm axial slices, 1 mm gap, 3 directions	-higher combined average ADC over all ROIs -trend toward higher ADC in frontal ROIs
Frazier et al., 2007	-10 pediatric BD, 9.2 (3.0) -7 children at risk for BD, 8.9 (3.0)	-8 matched controls, 9.2 (2.4)	-ROIs placed along SLF I and in CG-PAC WM -voxelwise analysis -FA measured -5 mm contiguous axial slices, 6 directions	-lower FA in SLF I and CG-PAC WM -lower FA in L orbital frontal WM and right CC body in BD At risk group compared to controls: -lower FA in bilateral SLF I BD group compared to at risk group: -lower FA in bilateral CG-PAC
Houenou et al., 2007	-16 euthymic BD, 41.88 (12.82)	-16 matched controls, 40.50 (12.82)	-Probabilistic tractography used to reconstruct fibers between SC and AH bilaterally -FA and ADC measured along reconstructed fibers	-increased number of reconstructed fibers between the L SC and L AH -no changes in ADC or FA

Study	BD Sample, age at scan (SD)	Comparison Sample, age at scan (SD)	Methods	Results (BD group compared to controls unless otherwise specified)
			-2 mm contiguous axial slices, 41 directions	
Yurgelun-Todd, et al 2007	-11 BD I, 32.9 (10.5)	-10 matched controls, 32.4 (9.1)	-ROIs placed in the genu of CC, R and L projecting arms of the genu, and the splenium -FA and ADC measured -5 mm contiguous axial slices, 6 directions	-higher FA in the midline of the genu -no differences in ADC
Bruno et al., 2008	-36 BD (25 BD I, 11 BD II), 39 (range: 21–63)	-28 matched controls (age not provided)	-Voxelwise analysis -FA and MD measured -5 mm contiguous axial slices, 7 directions	-higher MD in R posterior frontal and bilateral prefrontal WM corresponding to the anterior portion of FOF -Lower FA in inferior and middle temporal and middle occipital regions corresponding to portion of the L ILF
McIntosh et al., 2008	-40 familial BD, 39.9 (10.1) -25 familial SCZ, 37.2(9.2)	-49 matched controls, 35.3 (11.0)	-Probabilistic tractography used to reconstruct fibers along the UF and ATR -mean FA measured along reconstructed tracts -2.8 mm contiguous axial slices, 51 directions	BD and SCZ groups compared to controls: -lower FA along the UF and ATR BD group compared to SCZ group: -no differences
Versace et al., 2008	-31 BD I, 35.9 (8.9)	-25 matched controls, 29.48 (9.43)	-Tract-based spatial statistics used to analyze FA along the UF -3 mm contiguous coronal slices, 6 directions	BD group compared to controls: -higher FA along the L UF, L optic radiation, R ATR -lower FA along R UF -significant negative correlation between age and FA in bilateral UF and R ATR BD group on mood stabilizers compared to BD group not on mood stabilizers: -lower FA in L optic radiation and R ATR BD group with lifetime history of alcohol and/or substance abuse compared to BD without: -lower FA in L UF Currently depressed BD compared to remitted BD: -lower FA in left optic radiation
Wang et al 2008a	-42 BD, 32.6 (10.1)	-42 matched controls, 28.7 (9.10)	-ROIs placed along the cingulum -FA measured -3 mm contiguous coronal slices, 32 directions	-lower FA in anterior, but not posterior, cingulum
Wang et al 2008b	- 33 BD (7 manic/mixed or hypomanic, 7 depressed, 19 euthymic), 32.0 (10.1)	-40 matched controls, 29.2, (9.2)	-ROI and voxelwise analyses of the corpus callosum -FA measured -3 mm contiguous coronal slices, 32 directions	Combined BD group compared to controls: -lower FA in genu, rostral body, and anterior midbody of corpus callosum -no effect of mood status on results

Study	BD Sample, age at scan (SD)	Comparison Sample, age at scan (SD)	Methods	Results (BD group compared to controls unless otherwise specified)
Barnea-Goraly et al., 2009	-21 familial BD adolescents, 16.1 (2.7)	-18 matched controls, 14.5 (2.7)	-Whole-brain (excluding cerebellum) tract-based spatial statistics analysis with ROI confirmation -FA, ADC, trace measured -5 mm contiguous axial oblique slices, 6 directions	-lower FA in fornix, CC, parietal corona radiata, L posterior cingulate, and in tracts extending from the fornix to the thalamus -no differences in ADC or trace
Chaddock et al., 2009	-19 remitted BD I with personal and family hx of psychotic symptoms, 43.3 (10.2)	-21 unaffected 1st degree relatives, 42.5 (13.6) - 18 matched controls, 41.7 (12.2)	-Voxelwise analysis -FA measured -2.5 mm contiguous slices (orientation not specified), 64 directions	-lower FA in BD relative to controls in bilateral frontal deep WM corresponding to the genu of the CC, anterior portions of FOF and SLF, superior frontal WM corresponding to L SLF and L ACR, and right temporal WM corresponding to R ILF and R IFO. -no FA differences between relatives and controls, but relatives had FA values intermediate between BD and controls. -significant negative correlation between genetic liability and FA.
Kafantaris et al., 2009	-26 adolescent BD I, 16.0 (1.5)	-26 matched controls, 15.3 (1.5)	-Voxelwise analysis -FA and ADC measured -5 mm contiguous axial slices, 6 directions	-lower FA in R orbito-frontal WM, bilateral temporal lobe, L occipital lobe -higher ADC in bilateral subgenual WM, precuneus, R occipital lobe, L temporal lobe -lower FA correlated positively with a measure of visuo-motor speed
Mahon et al., 2009	-30 BD, 33.4 (8.7)	-38 matched controls, 31.9 (8.6)	-Voxelwise analysis with ROI confirmation -FA measured -5 mm contiguous axial slices, 25 directions	-higher FA in 3 clusters of deep prefrontal WM corresponding to bilateral CPT/CST, STR, and R SLF -lower FA in cerebellar WM corresponding to PCT
Pavuluri et al., 2009	-13 pediatric BD, 14.8 (2.5) -13 pediatric ADHD, 13.4 (2.7)	-15 matched controls, 13.7 (2.7)	-Tract of interest analysis -FA, ADC, and regional fiber coherence index measured -5 mm axial slices, 1 mm gap, 27 directions	Combined patient group compared to controls: -lower FA in the ACR -ADHD group had greater diffusion abnormalities than both the BD and control groups
Sussmann et al., 2009	-42 familial BD, 39.6 (10.1) -28 familial SCZ, 38.0 (9.9)	-38 matched controls, 37.2 (11.9)	-Voxelwise analysis with ROI confirmation -FA measured -2.8 mm contiguous axial slices, 51 directions	Combined patient group compared to controls: -lower FA along UF, ATR, and L ALIC -no FA differences between BD and SCZ groups
Wang et al., 2009	-33 BD (10 manic/mixed or hypomanic), 7 depressed, 16 euthymic), 31.8 (9.6)	-31 matched controls, 30.4 (10.8)	-fMRI/DTI analysis that correlated functional connectivity in the pACC with WM structural alterations -FA and BOLD activation measured	-decreased functional pACC-amygdala connectivity significantly correlated with decreased FA along tracts connecting these two regions (i.e. UF and neighboring WM).

Study	BD Sample, age at scan (SD)	Comparison Sample, age at scan (SD)	Methods	Results (BD group compared to controls unless otherwise specified)
			-3mm contiguous coronal slices, 32 directions	
Wessa et al., 2009	-22 euthymic BD (14 BD I, 8 BD II), 45.41 (12.60)	-21 matched controls, 42.95 (13.17)	-Whole-brain voxelwise analysis using two parallel methods (statistical parametric mapping [SPM] and tract-based spatial statistics) -FA and MD measured -2mm contiguous axial slices, 41 directions	-increased FA in L medial frontal gyrus, L precentral gyrus, bilateral precuneus, inferior parietal WM, and superior occipital WM using both voxelwise approaches. -No differences in MD
Zanetti et al., (in press)	-37 BD I (16 depressed, 21 remitted), 34.1 (19.0)	-26 matched controls, 28.8 (9.5)	-Whole-brain voxelwise analysis -FA and MD measured -3 mm contiguous axial slices, 6 directions	-Combined BD I group compared to controls: -lower FA in bilateral external capsule -higher MD in R ILF and SLF -Depressed BD relative to both remitted BD and controls: -higher FA in ventromedial PFC WM including bilateral UF and IFO -lower FA in L paracingulate WM -higher MD in R UF, R IFO, R ATR, R CPT, R SLF, R ILF -Depressed BD relative to controls only: -higher MD in L UF, L STR -Depressed BD relative to remitted BD only: -higher MD in bilateral fronto-limbic-parietal regions -no differences between remitted BD and control group in FA or MD -FA and MD were significantly associated with longer illness duration and earlier age at illness onset

Abbreviations: AC, anterior commissure; AC-PC, anterior-posterior commissure; ACR, anterior corona radiata; ADC, apparent diffusion coefficient; ADHD, attention-deficit/ hyperactivity disorder; AH, amygdala-hippocampal complex; ALIC, anterior limb of the internal capsule; ATR, anterior thalamic radiations; BD, bipolar disorder; CC, corpus callosum; CG-PAC, cingulate-paracingulate; FA, fractional anisotropy; MFG, medial frontal gyrus; L, left; OFC, orbital frontal cortex; PCT, pontine crossing tract; R, right; ROI, region of interest; SC, subgenual cingulate; SCZ, schizophrenia; SFG, superior frontal gyrus; SLF I, superior longitudinal fasciculus I; STR, superior thalamic radiation; UF, uncinate fasciculus