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Review Article

White matter alterations in bipolar disorder: potential for drug discovery and development

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Objectives: Brain white matter (WM) alterations have recently emerged as potentially relevant in bipolar disorder. New techniques such as diffusion tensor imaging allow precise exploration of these WM microstructural alterations in bipolar disorder. Our objective was to critically review WM alterations in bipolar disorder, using neuroimaging and neuropathological studies, in the context of neural models and the potential for drug discovery and development.

Methods: We conducted a systematic PubMed and Google Scholar search of the WM and bipolar disorder literature up to and including January 2013.

Results: Findings relating to WM alterations are consistent in neuroimaging and neuropathology studies of bipolar disorder, especially in regions involved in emotional processing such as the anterior frontal lobe, corpus callosum, cingulate cortex, and in fronto-limbic connections. Some of the structural alterations are related to genetic risk factors for bipolar disorder and may underlie the dysfunctional emotional processing described in recent neurobiological models of bipolar disorder. Medication effects in bipolar disorder, from lithium and other mood stabilizers, might impact myelinating processes, particularly by inhibition of glycogen synthase kinase-3 beta.

Conclusions: Pathways leading to WM alterations in bipolar disorder represent potential targets for the development and discovery of new drugs. Myelin damage in bipolar disorder suggests that the effects of existing pro-myelinating drugs should also be evaluated to improve our understanding and treatment of this disease.

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Bipolar disorder (BD) is a severe mental illness that affects 1% of the population. In recent years, studies using neuroimaging methods have attempted to clarify the neurobiology underpinning this disorder. Earlier studies focused mainly on gray matter alterations. More recently, white matter (WM) abnormalities have been consistently reported in neuroimaging and neuropathological studies of BD. The development of advanced neuroimaging techniques such as diffusion tensor imaging (DTI) has allowed these WM changes to be explored in greater detail in BD. In this article, we critically review WM alterations in BD, explored both with neuroimaging and neuropathological studies, in the context of potential drug discovery and development. The potential role of these WM changes in BD neurobiology is integrated into existing neurobiological models. Finally, we discuss the molecular effects of drugs currently used on the WM, to illustrate how they may inform drug discovery and development.

In January 2013, we conducted a systematic PubMed and Google Scholar search of all English-language BD articles recently published. These were cross-referenced with the following terms: *white matter*, *oligodendrocytes*, *diffusion tensor imaging*, *MRI*, *lithium*, *valproate*, and *myelin*. We also checked the reference lists of the identified

studies and of relevant scholarly reviews. We present ten papers of special interest in Table 1.

Neuroimaging of WM alterations in BD

Magnetic resonance imaging (MRI) studies

In the 1990s, several MRI studies reported higher frequencies of WM hyperintensities (WMH) in T2-weighted images in patients with BD than in healthy subjects; these abnormalities were primarily located in the deep WM, subcortical WM, and periventricular WM (1–3).

Findings relating to WMH are among the most replicated in BD neuroimaging literature. Beyer et al. (4), found a strong association between BD and WMH located in the deep WM and subcortical WM, but not with periventricular WMH. Similarly, Kempton et al. (5, 6) found that patients with BD had higher frequencies of WMH in the deep WM of the left and right hemisphere and, specifically, in the frontal and parietal lobes. WMH seem to be present at early stages of the disease (7) and in children and teenage patients (8–10) but some results are conflicting (10). Definitive conclusions regarding the course of WMH in BD cannot be made at this time because of a lack of longitudinal studies.

The clinical significance of WMH on classical T2 structural MRI in BD remains unclear. WMH are not specific to BD, as they are also found in normal aging, in cardiovascular and cerebrovascular disease, and in various psychiatric conditions such as unipolar depression. It is thought that

Table 1. Ten papers of special interest concerning white matter alterations in bipolar disorder

Study	Title	Special interest
Sprooten et al. 2011 (53)	White matter integrity in individuals at high genetic risk of bipolar disorder	The largest diffusion tensor imaging study in healthy relatives of patients with bipolar disorder to date
Vederine et al. 2011 (34)	A meta-analysis of whole-brain diffusion tensor imaging studies in bipolar disorder	A meta-analysis of diffusion tensor imaging studies in bipolar disorder
van der Schot et al. 2009 (67)	Influence of genes and environment on brain volumes in twin pairs concordant and discordant for bipolar disorder	A magnetic resonance imaging study investigating gray and white matter volumes in twins (concordant and discordant for bipolar disorder); white matter measures are related to the genetic risk of developing bipolar disorder
Hasler et al. 2006 (41)	Toward constructing an endophenotype strategy for bipolar disorders	Describes the strategy for endophenotype discovery in bipolar disorder and suggests that white matter abnormalities are a potential endophenotype for bipolar disorder
Tkachev et al. 2003 (59)	Oligodendrocyte dysfunction in schizophrenia and bipolar disorder	A post-mortem study of oligodendrocyte-specific and myelination-associated gene expression in schizophrenia and bipolar affective disorder; lower gene expression is associated with disease
Roy et al. 2007 (79)	Loss of ErbB signaling in oligodendrocytes alters myelin and dopaminergic function, a potential mechanism for neuropsychiatric disorders	An animal model of white matter abnormalities in bipolar disorder: a study of transgenic mice in which ErbB signaling is blocked in oligodendrocytes *in vivo*, leading to changes in oligodendrocyte number and morphology, reduced myelin thickness, and dopaminergic and behavioral alterations
McIntosh et al. 2008 (77)	The effects of a neuregulin 1 variant on white matter density and integrity	An imaging genetics study in healthy controls, suggesting that neuregulin-1 genetic variation is associated with reduced white matter density and integrity
Linke et al. 2012 (83)	Genome-wide supported risk variant for bipolar disorder alters anatomical connectivity in the human brain	A prototypical imaging genetics study, showing that one of the most commonly identified bipolar disorder risk genes is associated with changes in white matter and behavioral phenotypes
Azim and Butt 2011 (120)	GSK3β negatively regulates oligodendrocyte differentiation and myelination *in vivo*	The injection of GSK3 inhibitors (including lithium) into mice was associated with an increased number of oligodendrocyte precursors and oligodendrocytes, and promotes myelination, suggesting a mechanism of action for lithium
Benedetti et al. 2011 (38)	Tract-specific white matter structural disruption in patients with bipolar disorder	A diffusion tensor imaging study in patients with bipolar disorder, suggesting that treating patients with lithium was associated with normal fractional anisotropy measurements in the uncinate fasciculus

GSK-3 = glycogen synthase kinase-3.

WMH reflect WM damage (such as degradation of myelin sheaths, axonal destruction, and glial cell alterations), which leads to disruption of the connectivity between different brain areas.

Significant reductions in total WM volume, without changes in brain and gray matter volumes, have been found at the onset of BD (11, 12). MRI studies have investigated local WM volumes using voxel-based morphometry techniques (VBM). These studies reported volumetric deficits and lower WM density in patients with BD than in healthy controls; these observations were found in the anterior limb of the internal capsule, the corona radiata, and the left temporal stem (13, 14), but global cerebral volume appears to be conserved (15). Reductions in the volume of the WM are more marked in first-episode BD than in first-episode schizophrenia; in schizophrenia, gray matter volume reductions are more evident (12).

DTI studies

In the last 15 years, there have been major advances in the structural brain imaging of the WM owing to the development of DTI MRI. DTI allows both WM microstructure (local organization) and macrostructure (brain anatomical connectivity based on tracts) to be imaged. DTI can detect abnormalities of the WM due to fiber orientation, even when macrostructural changes are absent. DTI has made it possible to study the WM connecting the parts of the brain network involved in emotion regulation, supposedly implicated in BD pathophysiology. This network includes WM tracts which connect frontal, prefrontal, and cingulate regions to subcortical limbic structures, as discussed later in this article.

DTI methodology. DTI MRI permits non-invasive *in vivo* mapping of water molecule diffusion in biological tissues (i.e., restricted Brownian movement). In liquid environments such as the cerebrospinal fluid, the diffusion of WM molecules is free and equivalent in all directions. Such diffusion is termed *isotropic*. In tissues, molecular diffusion is restricted by interactions with structures such as macromolecules, fibers, and membranes. Hydrophobic membranes, in particular, hinder the diffusion of water molecules in the direction which is transverse to them. In brain WM, parallel-organized axonal architecture and hydrophobic myelin sheaths facilitate water molecule diffusion in a direction parallel to axons but restrict diffusion in a transverse direction. Such diffusion is *anisotropic* (16, 17).

Diffusion is a three-dimensional process; DTI can characterize water diffusion in each voxel of the brain by mathematical representation using three vectors. Water molecule diffusion is schematized as an ellipsoid, with three main axes representing diffusion directions; the length of vectors represents directional diffusion mobility. Isotropic diffusion corresponds to a sphere, whereas anisotropic diffusion corresponds to a sectioned sphere. The diffusion process is described using several variables. Fractional anisotropy (FA) describes the degree of anisotropy. Diffusion can be isotropic (FA = 0; diffusion is unrestricted in all directions, as is the case in cerebrospinal fluid) or anisotropic (FA = 1; diffusion is strongly restricted by compactly organized WM fibers and is only possible along the axis parallel to their direction). High FA values denote highly organized and normally myelinated axons. Lower FA values reflect axonal loss and demyelination. Mean diffusivity (MD), also expressed as the apparent diffusion coefficient (ADC), has a high value when there is free diffusion of water (for example, in ventricles or demyelinated WM) but is low in intact myelinated axons. Axial diffusivity (AD) describes diffusivity along the principal axis, whereas radial diffusivity (RD) describes diffusivity along the two minor axes.

FA and MD can be used to characterize ultrastructural properties and the integrity of brain WM: high FA and low MD are assumed to be associated with intact WM. AR and RD reflect axonal and myelin integrity: low AD and high RD are associated with axonal and myelin alterations, respectively.

Regions of interest studies. The first DTI studies of BD used manually traced regions of interest within the mood regulation system. Diffusion abnormalities in the prefrontal-subcortical WM (18–22) and low FA in the deep WM of the frontal and occipital areas (23–25), the orbito-frontal cortex (18), and the anterior cingulum (21) were reported in patients with BD. Low FA was also reported in major WM tracts such as the genu, rostral body, and anterior midbody of the corpus callosum (20, 26), the anterior corona radiata (22), and the internal capsule and fronto-occipital fasciculus (19). A small number of studies observed higher FA in the frontal WM (19) and corpus callosum (20) of patients with BD.

These observations suggest a loss of bundle coherence and alignment of WM fibers in the regions reported above. However, a limitation of regions of interest studies is that they only provide information about selected brain regions, which can differ in nomenclature and precise location between studies.

Whole-brain DTI studies. Whole-brain approaches are not limited by the need to select a region of interest, and have been developed using specific algorithms that process DTI data [tract-based spatial statistics (27)]. These BD studies have generated heterogeneous results in FA and MD variation, and in the precise location of these changes. Decreased FA values have been found mainly in anterior frontal and limbic brain areas such as the uncinate and inferior longitudinal fasciculus (28, 29), the left anterior limb of the internal capsule, and the anterior and superior thalamic radiations. Such observations are also found in the corpus callosum (30) and in the bilateral temporal lobes, the left occipital lobe (31), and the left cerebellum (32). However, some studies report increased FA values in the left uncinate fasciculus, the left optic radiation and right anterothalamic radiation (29, 32), and the left frontal WM (32). One study found increased FA values in more diffuse brain regions (33) and others report increased MD values in frontal, cingulate, and temporal brain WM (28, 31).

Due to the heterogeneity of these results, we carried out a meta-analysis of whole-brain DTI studies to identify consistent clusters of FA and MD modifications in the WM of individuals with BD. This meta-analysis identified two significant clusters of decreased FA in the right hemisphere: the first was located close to the parahippocampal gyrus, and the second close to the anterior cingulate cortex and the subgenual cingulate cortex (34). The first cluster is an area of interest in BD as it is crossed by four important WM pathways: the superior longitudinal fasciculus, the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus, and the posterior thalamic radiations. These pathways are part of the brain network that regulates emotion; alterations to this network seem to be involved in the pathophysiology of BD (discussed later in this article). The second cluster is situated close to the right anterior and subgenual cingulate cortex, which plays a key role in emotional processing (namely, the emotional salience of stimuli, and the unconscious and automatic emotional experience).

DTI tractography studies. Using DTI data, it is possible to reconstruct representations of WM tracts in the whole brain and make comparisons between them (35). DTI-based tractography explores brain connectivity in terms of the characteristics of WM bundles. Tractography techniques have several limitations; for example, their use is constrained for modeling crossing-fiber regions or extracting metric parameters of fibers. However, new techniques like high angular resolution diffusion imaging (HARDI) and Q ball vector analysis attempt to overcome these using a mathematical alternative to the tensor model. Tractography studies may therefore provide new ways to determine how WM bundle tract alterations are involved in BD pathophysiology at a structural and anatomic level.

We used tractography to study euthymic patients with BD, and found a significantly increased number of reconstructed fibers between the left subgenual cingulate and the left amygdalo-hippocampal complex, corresponding to the uncinate fasciculus tract (36). Other tractography studies have confirmed the existence of alterations in the uncinate fasciculus, and reported decreased FA in this tract (37–39). Connectivity changes in the uncinate fasciculus are of particular interest as this structure connects critical limbic areas of the brain, such as the amygdala, the subgenual cingulate cortex, and the orbito-frontal cortex.

More generally, tractography studies indicate that WM abnormalities are present in the frontal and subcortical regions of patients with BD, and involve the WM tracts connecting the frontal cortex with the temporal and parietal cortices and the frontal-subcortical circuits (38, 39).

The interpretation of DTI changes in anterior limbic WM tracts is not straightforward. Increases or decreases in FA have often been interpreted as markers of changes in tract coherence due to alterations in the myelination, axonal organization, density, alignment, or diameter of WM fibers or exposure to medication (16). The presence of local edema and partial volume averaging from fibers oriented in different directions may also account for changes in FA. The changes observed in anterior limbic networks using DTI are generally considered to be indicators of abnormal structural connectivity. One study used magnetization transfer MRI in patients with BD (40). This technique measures macromolecular density and is assumed to be a more direct measurement of myelin integrity and axonal loss in the WM. In this report by Bruno et al. (40), macromolecular density was lower in the WM adjacent to the right subgenual anterior cingulate in patients with BD than in controls. This result supports the view that changes found with DTI are linked to myelin and axonal alterations.

Neuroimaging studies identifying WM alterations as biomarkers and endophenotypes of BD

WMH and MRI WM alterations have been proposed as trait biomarkers of BD (41, 42) and are

observed at the onset of the disorder or in adolescent patients (9, 31, 43). They are of pathophysiological significance in BD as they are associated with a poor clinical and functional outcome (44–46), and with cognitive decline (47). WM abnormalities seem to be associated with suicide attempts in BD; a meta-analysis reported that patients with BD who had attempted suicide had periventricular WMH 5.4 times greater than those who had not (48). WM abnormalities are also associated with treatment resistance; in one study, the volume of deep WMH on MRI in patients with BD correlated with treatment resistance (44) and, in another, subcortical WMH correlated with poor BD outcome (defined by less than eight weeks of remission in a two-year period and poor response to treatment) (45).

The presence of qualitatively similar deficits in non-affected co-twins, siblings, and offspring of patients with BD supports their role as endophenotypes. It suggests that at least some of these abnormalities are closely related to the genetic risk for the disorder, and are independent of environmental or illness effects.

Imaging studies have investigated WM alterations in the relatives of patients with BD; three addressed WMH in the relatives of patients with BD. Ahearn et al. (49) found WMH in 60% of high-risk subjects and 100% of patients with BD, suggesting that MRI hyperintensities cosegregate with BD. Gulseren et al. (50) showed that hyperintensities in patients with BD were higher than in their siblings and healthy controls. Lesions were detected in 67% of the patient group, 17% of their siblings, and 33% of the control group. However, a recent study with a large sample found comparable proportions of WMH in affected familial, unaffected high-risk, and control groups (10).

DTI has been used to assess the integrity of WM tracts in the brain of genetic high-risk subjects. Frazier et al. (51) showed lower fractional anisotropy in the superior longitudinal fasciculus of high-risk subjects than in controls. In a second study, genetic susceptibility to BD was correlated with lower fractional anisotropy in several major WM tracts of the brain. No significant differences in fractional anisotropy were observed between high-risk individuals and controls, but the high-risk group had an intermediate level of alterations to that observed in controls and patients with BD (52). Sprooten et al. (53) reported large clusters of WM integrity alterations in unaffected relatives of patients with BD; these were found in the corpus callosum, internal and external capsules, inferior and superior longitudinal fasciculi, inferior fronto-occipital fasciculi, uncinate fasciculi, parts of the corticospinal tract, and subcortical WM around the central sulci. Unaffected relatives with cyclothymic temperaments had low FA values in both the internal capsules and the WM of the left temporal lobe.

These findings support the notion of WM integrity as an endophenotype for BD and suggest that impaired WM integrity might be one of the underlying characteristics of genetic predisposition to BD.

WM alterations are common findings during neuroimaging studies of BD; standard structural MRI often identifies alterations in the deep and subcortical WM in the frontal and parietal lobes of patients with BD. Recently developed DTI and tractography methods have identified alterations in WM microstructure in regions involved in emotional processing [including the anterior frontal lobe, corpus callosum, cingulate cortex, and temporal lobe (54)], with clusters of particular interest considered as key points of association pathways. Most tractography studies show altered connectivity in fibers connecting limbic structures to fronto-cortical areas, particularly in the uncinate fasciculus. This is consistent with the neural models of BD described below. Although the exact significance of WM alterations is not fully understood, they seem to be present in the early stage of the disease, in healthy relatives, and in genetically high-risk individuals, thus constituting potential endophenotypes for BD.

Neuropathology of WM alterations in BD

Neuropathological studies of WM alterations in BD are much fewer in number than MRI studies. This is partly due to the difficulty in getting brain samples from patients with BD. Studies usually focus on gray matter (for example, analyzing neuron count) but existing work on WM is convergent and some alterations have a genetic correlation. In the context of drug development, we will focus on oligodendrocytes and myelination abnormalities in BD and their genetic correlates.

Oligodendrocytes and myelination in BD

Oligodendrocytes are cells of the glia. Their function is to insulate axons with myelin sheaths in order to form WM tracts in the central nervous system.

Several studies have reported a decrease in the number of oligodendrocytes in BD; most of these studies focus on the prefrontal cortex. Ongür et al. (55) carried out a histological exploration of the cellular composition of Brodmann area 24 (subgenual cingulate) in the brains of patients with

familial forms of major depressive disorder and BD. Glial cell count was lower in patients with major depressive disorders and BD. There were no cases in which the number or size of neurons was lower, and glial cell count was normal in patients with schizophrenia. A lower oligodendrocyte count in BD has also been reported by other groups and is associated with ultrastructural signs of apoptosis and necrosis (56, 57). The formation of concentric lamellar bodies, an indicator of damage to the myelin sheath, was detected in BD and schizophrenia. Low levels of oligodendrocytes in the prefrontal cortex have also been found to be more severe in BD than in schizophrenia and major depressive disorder (58).

In addition to structural changes, oligodendrocyte and oligodendrocyte-related gene expression is modified in BD. Tkachev et al. (59) explored oligodendrocyte and myelin gene expression profiles in brain samples from the Stanley Foundation brain collection using quantitative polymerase chain reaction and microarrays. They used brains from 15 patients with BD, 15 patients with schizophrenia, and 15 controls. The expression profiles of most oligodendrocyte-related and myelin-related genes were reduced in patients with disease, and this was more significant for genes [such as the genes encoding proteolipid protein 1 (PLP1), myelin-associated glycoprotein 1 (MAG1), claudin-11 (CLDN11), galactocerebrosidase (GALC), ErbB3, Transferrin, oligodendrocyte lineage transcription factor 2 (OLIG2), and SRY-related HMG box 10 (SOX-10)] in patients with BD than in those with schizophrenia.

Some studies have made direct observations of variation in myelin content. Regenold et al. (60) examined 60 transverse sections of fixed dorsolateral prefrontal cortex (15 from each group of controls, patients with BD, unipolar patients, and patients with schizophrenia). They observed less significant myelin staining in the deep dorsolateral prefrontal WM of BD and unipolar patients than in that of controls. This was not the case in superficial WM and the reduced staining was only observed as a trend in patients with schizophrenia. These results are consistent with neuroimaging studies suggesting that WM lesions are most prevalent in the deep WM. Decreased myelination has also been observed in the hippocampus of female patients with BD and schizophrenia (61).

WM consists mostly of neuronal axons and glial cells containing myelinated sheaths. Given that both axonal membranes and myelin sheaths are largely made up of lipids (80%), Versace et al. (62) suggested that WM alterations could be linked to lipid damage caused by oxidative stress. They measured early [lipid hydroperoxides (LPH)] and late [4-hydroxy-2-nonenal (4-HNE)] products of lipid peroxidation in peripheral serum samples from patients with BD type I. DTI and tractography analyses of prefrontal WM tracts were carried out to test for correlations between abnormalities in peripheral measures and in the WM; these showed WM damage in patients with BD. The patient group had a significant effect on FA and RD measures in the WM tracts. LPH levels, but not 4-HNE levels, significantly differed between groups. These findings suggest that serum LPH may be useful in the development of peripheral biomarkers of BD.

Some WM changes may also be linked to gray matter abnormalities in BD. For example, a reduction in the density of gray matter neuronal cell bodies could result in fewer efferent axonal fibers in the WM. The directionality of this association has not been fully assessed.

Few studies have investigated the neurons present in the WM of patients with BD. Connor et al. (63) reported higher WM neuronal density in the cingulate cortex of patients with BD and schizophrenia and made a similar observation for the prefrontal cortex. Beasley et al. (64) compared the density and spatial pattern distribution of WM neurons in the frontal lobe. They observed no differences between groups of patients with schizophrenia, BD, unipolar disorder, and controls.

Genetic evidence for the origin of WM abnormalities in BD

BD is a neuropsychiatric disorder resulting from interacting genetic and environmental factors. Genetic susceptibility may be explained by a polygenic model with small effects; the genes involved also interact with environmental factors (65). The genetic risk of BD may be partly mediated by WM alterations. Twin studies strongly suggest that low WM volume is related to the genetic risk of BD (66), while environmental factors seem to correlate more closely with low gray matter volume in patients with BD (67).

Genes related to oligodendrocytes and myelin have repeatedly been found to be involved in BD; the neuregulin-1/ErbB pathway is of particular interest. Neuregulin-1 is one of the four neuregulin family proteins that act on the epidermal growth factor family of receptors. The neuregulin-1/ErbB pathway is crucial for neuronal migration, synapse formation, oligodendrocyte growth and differentiation, and neuronal myelination, and, thus, brain connectivity (68). Some allelic variants of neuregu-

lin-1 have repeatedly been associated with BD (69–74). Several groups have reported that neuregulin-1 variants are associated with differences in FA (measured by DTI) in the frontal medial area (75), the anterior cingulate cortex (76), and the anterior limb of the internal capsule (77). The findings for healthy controls are similar to those in patients with BD. ErbB3 and ErbB4, the receptors for neuregulin-1, have also been found to be associated with BD. Expression of the ErbB3 gene has been reported to be downregulated in the brains of patients with BD (59). Similarly to neuregulin-1, variants of the ErbB4 gene have been found to be associated with differences in FA measured in the anterior limb of the internal capsule (78).

Animal models, in which ErbB signaling is blocked *in vivo*, have been developed to examine the neuregulin/ErbB pathway further. In one such model, the brains of mice display changes in oligodendrocyte number and morphology, and fewer branch points. Myelin thickness in the corpus callosum was lower, and axon conduction velocity slower. Higher levels of dopamine functional transporters and receptors were measured by positron emission topography scan. These mice also exhibit behavioral differences such as heightened anxiety-like behavior and increased amphetamine sensitization. The ultrastructural, neurophysiological, and behavioral changes observed are similar to those recorded in patients with BD (79). This model therefore suggested that the neuregulin/ErbB pathway regulates oligodendrocyte maturation and development, but also myelin structure and function, leading to behavioral changes which are consistent with some symptoms of BD.

Other BD susceptibility genes have a direct effect on WM structure. Meta-analyses, genome-wide association studies, and replication studies show the gene encoding ankyrin 3 *(ANK3)* to be one of the most widely identified risk genes for BD (80). ANK3 protein, also known as ANKG, is an ankyrin which is encoded in humans by *ANK3*. ANK3 is a key protein in the axonal initial segment (AIS) of neurons. The AIS defines neuronal polarity (between the somatodendritic and axonal domains) and is essential for axonal identity. Hedstrom et al. (81) silenced *ANK3* using adenovirus-mediated RNA and found that ANK3 protein is necessary for the initial recruitment and stability of the AIS protein, and for AIS maintenance. Loss of ANK3 causes the axon to develop spines and alters the distribution of somatodendritic membrane proteins. Silenced *ANK3* also led to excitatory synapse development by the formation of excitatory postsynaptic densities on the proximal region of the axon. Modulation of the action potential threshold may be regulated by ANK3. Ankyrins, acting with spectrin, seem to be important for the assembly, maintenance, and coordination of ion transporters and cell adhesion molecules in diverse cell–cell contact regions (for example, in the nodes of Ranvier, AISs of myelinated nerves, and neuromuscular junctions of skeletal muscle) (82). Disease or injuries that disrupt ANK3 protein expression may contribute to nervous system dysfunction through loss of neuronal polarity and cell adhesion.

The ANK3 variant suggested to relate to BD susceptibility has been associated with lower FA and longitudinal diffusivity in the anterior limb of the internal capsule (83). The risk allele was also associated with impaired set-shifting and increased risk-taking, phenotypes similar to those observed in BD.

Genetic variants of brain-derived neurotrophic factor (BDNF) are of interest in BD. BDNF is a neurotrophin, produced in the brain and spinal cord, which plays an important role in guiding brain development and connectivity. BDNF regulates the growth, differentiation, and maintenance of neural cells, and modulates the plasticity of neuronal synapses. BDNF seems to be involved in learning and memory by modulating hippocampal neurogenesis and synaptic transmission. Some studies have shown a reduction in serum BDNF levels during acute manic and depressive episodes, with recovery to normal levels after treatment and in euthymic states. They have also illustrated lower BDNF levels with age and length of illness (84, 85). A common BDNF variant, Val66Met [methionine (Met) for valine (Val) substitution at codon 66 in the 5′-proregion], seems to be related to poor episodic memory and hippocampal activation in cognitively intact adults (86). The BDNF Val66Met variant has repeatedly been related to BD (87) and found to impact brain morphology in patients; the anterior cingulate cortex, dorsolateral prefrontal cortex, and hippocampal volumes are modulated by this variant (88). In a large study of 455 healthy adult twins and their non-twin siblings, Chiang et al. (89) used DTI to assess the effect of the BDNF Val66Met polymorphism on WM structural integrity. The Val-BDNF genetic variant was associated with lower WM integrity in the splenium of the corpus callosum, left optic radiation, inferior fronto-occipital fasciculus, and superior corona radiata.

These two examples of susceptibility genes (coding for ANK3 and BDNF) suggest that WM alterations could represent a potential intermediate phenotype of BD which mediates the genes' effects.

Changes in WM oligodendrocyte number, structure, and myelination have repeatedly been

observed in BD. Recent studies suggest that some of these ultrastructural alterations are related to genes conveying susceptibility to BD, such as some of those responsible for the neuregulin-1/ErbB pathway, ANK 3, and BDNF. Changes in WM seem to be larger in patients with BD than in those with major depressive disorder or schizophrenia. However, there are not enough studies to fully conclude on the specificity of these findings, mainly due to the sample sizes required. Most of the studies have focused on prefrontal and cingulate regions. Neuropathological studies are also poorly integrated with MRI findings. Studies that correlate postmortem MRI brains scans with neuropathological findings in the same brains would be of particularly interest.

WM abnormalities and neural models of BD

Recent integration of the numerous BD neuroimaging studies has permitted neural models to be developed. These mainly focus on emotional processing and its deregulation in patients with BD. The most recent models suggest dysfunctional connectivity within the anterior limbic networks. The WM abnormalities previously described may ultimately result in altered connectivity, leading to dysfunctional emotional processing and mood swings in cases of BD.

Most of the proposed neural models put emphasis on the production of aberrant emotional responses and the parallel failing of emotional regulation. They describe cortico-limbic dysregulation with hyperactivity of the subcortical and ventrolimbic regions (amygdala, orbito-frontal cortex, prefrontal ventral cortex, and subgenual and anterior cingulate cortex). This hyperactivity could lead to a hyperreactivity to emotional stimuli and an aberrant increase in the production of affective states. Structures from a cortico-dorsal network (encompassing the dorso-lateral and dorso-medial prefrontal cortex, and the dorsal cingulate) could be hypoactive and of lower volume in patients with BD (90); the models also propose failure of connectivity between the two networks. The cortico-dorsal network would therefore fail to regulate the limbic ventral areas. This would result in an enhanced emotional response (poorly controlled by the cortical-cognitive areas) and would lead to emotional hyperreactivity, mood instability, and mood episodes.

Neural models of BD assume an abnormal prefrontal-subcortical connectivity. We described anatomical alterations in this prefrontal-subcortical connectivity earlier in this article. Very recently, neuroimaging studies of BD have focused on the functional connectivity between brain regions, with a special focus on prefrontal-limbic connectivity. Functional connectivity (FC) is the 'temporal correlation between spatially remote neurophysiological events' (91). In MRI, it is described by the correlation between the activity of different brain areas, observed in a patient during a task or when at rest. FC models allow brain areas communicating with each other during visual, emotional, motor, or language tasks to be identified (92, 93). When a patient is at rest, these models have led to the identification of the *default-mode network* (92).

Several studies have explored brain functional connectivity either at rest or during emotional tasks. Their results are concordant and point to an alteration of the functional connectivity between the prefrontal/perigenual cortex and the amygdalo-hippocampal complex (94), both during emotional processing (95) and when the brain is at rest (96–98). These results are consistent with those of the DTI studies (see above), all of which converge to illustrate an alteration in prefrontal-limbic anatomical connectivity.

Based on DTI, functional connectivity MRI, and neuropathological studies, we suggest that BD could be seen as a connectivity disorder. Variations in genes such as those encoding Neuregulin-1/erbB or ANK3 may cause alterations in oligodendrocyte structure and function. These oligodendrocyte changes could lead to impaired myelination (as observed in DTI) and defects in synaptic transmission. These local modifications could impair long-range anatomical and functional connectivity, particularly between the prefrontal and limbic regions. The resulting poor regulation of the limbic regions by the prefrontal regions could then lead to emotional hyperreactivity and trigger the affective instability and mood swings present in patients with BD.

Drugs for BD and WM

Different classes of medication, known as mood stabilizers, have been used for the treatment of BD. The choice of drugs and indications for their differential use depend on psychopathological and clinical features. For example, clinicians may need to consider acute-phase treatment of BD versus long-term prophylaxis, the predominance of depressive versus maniac phases, and the severity or frequency of episodes (99).

According to international guidelines, lithium and valproate are first-line treatment options and lamotrigine is indicated in long-term treatment of bipolar depression; carbamazepine lost its first-line place owing to evidence regarding its side-effect

profile. First-generation antipsychotic agents such as haloperidol are widely used in acute maniac episodes, whereas atypical anti-psychotic agents such as aripiprazole, risperidone, olanzapine, or quetiapine have only recently been investigated for their use in the treatment of acute episodes and long-term prophylaxis.

No new class of medication has been approved in over five years. There is an urgent need to develop new medications, with new mechanisms of action, because of the high degree of treatment resistance in patients with BD.

Understanding the effects of existing BD drugs on the WM may lead to new insights and avenues for research. Studying the origins of WM abnormalities in BD may also help to identify new targets for drug development.

Effects of existing mood stabilizers on WM

Lithium has been used to treat BD for more than 50 years but its precise mechanism of action is still unclear. Lithium has neurotrophic and neuroprotective properties. A study investigated its effects in ten BD type I patients using T1 MRI scans performed at baseline and after four weeks of lithium treatment; it was found to increase total gray matter by about 3% (100). This finding has been confirmed by other studies which have also reported increased volume or density of gray matter in patients taking lithium (101–103). Increased *N*-acetyl-aspartate concentrations (measured using magnetic resonance spectroscopy) support the notion of improvements in neuron number in patients receiving lithium therapy (104, 105). Animal models confirm that lithium has neurotrophic (106) and neuroprotective (107) properties.

There is less evidence for the impact of lithium on the WM. Benedetti et al. (38) used DTI to show normal FA values in the uncinate fasciculus of patients treated with lithium, but not in those who were lithium free (38). These authors suggest that lithium has a protective effect in the WM tracts connecting the amygdala with the subgenual cingulate cortex and that it is likely to counteract the neuropathological process associated with WM changes. An effect of lithium on FA values has also been observed in human immunodeficiency virus type 1 infection (108).

Valproate may be associated with macroscopic WM changes, although there is currently little evidence for this. One study compared unmedicated and valproate-medicated patients with BD by measuring cingulate volumes. Volumes were significantly higher in the valproate group than in the drug-free group (109). However, another study of 74 patients reported that valproate use was associated with a lower WM volume than when lithium, carbamazepine, or antipsychotic agents were used (110).

Several studies have used neuroimaging to explore the impact of antipsychotic agents on the WM, but mostly in patients with schizophrenia. These suggest that antipsychotic agent use is associated with a mitigated WM loss in patients with schizophrenia, and have led to speculation that there may be a better outcome when using second-generation and long-acting injectable antipsychotic agents (111–114). A preserved or increased WM volume in patients treated with long-acting risperidone was associated with faster reaction times in tests involving frontal lobe function (113). A novel method was used to reanalyze the MRI images of a previous study and assess whether the difference in WM volumes could be caused by a differential effect of medications on the intracortical myelination process. This method combined distinct tissue contrasts, provided by inversion recovery, and proton density images used to estimate intracortical myelin volume. Treatment with risperidone was associated with greater intracortical myelin volume than the use of typical antipsychotic agents. This suggests that second-generation antipsychotic agents may positively impact adult myelinization processes (115). A T1 study of 125 BD subjects and 87 controls showed that current treatment with antipsychotic agents was significantly associated with larger volumes of WM in the bilateral temporal lobes (116). However, the putative neuroprotective action of antipsychotic agents on the brain structure is still highly debatable and limited by poor evidence. High-power longitudinal studies in drug-naïve subjects, from the first episode of mania or schizophrenic psychosis, will help to assess the impact of cumulative antipsychotic agent exposure on the WM and gray matter.

In summary, neuroimaging studies using structural MRI suggest that medication influences global brain structure in term of the WM and gray matter. However, heterogeneous results are found in functional MRI and DTI studies. The main effect of mood stabilizers such as lithium could be to normalize neuroimaging alterations. As a result, medicated BD individuals can appear more similar to healthy subjects than to unmedicated BD controls (117).

Mood-stabilizer mechanisms of action on WM

Lithium is the leading drug for treating bipolar episodes and relapse prevention, but also affects other processes such as embryonic development,

glycogen synthesis, and hematopoiesis. A number of enzymes have been proposed as potential targets of lithium action, including inositol monophosphatase and glycogen synthase kinase-3 (GSK-3). GSK-3, a critical regulator of multiple signal transduction pathways, is directly inhibited by lithium. It is a protein kinase with broad enzymatic influence in neural systems (118). Inhibition of GSK-3 can have effects on early development and insulin signaling/glycogen synthesis, which are also known effects of lithium.

Data from animal models suggest that the inhibition of GSK-3 mediates some of the behavioral effects of lithium (119). Azim and Butt (120) found a high number of oligodendrocyte precursors and oligodendrocytes, and enhanced myelination, in mice which had been injected with GSK-3 inhibitors. This suggests that lithium may exert some of its therapeutic effects in BD via the regeneration of oligodendrocytes and the promotion of myelination. Lithium also suppresses experimental autoimmune encephalomyelitis, which has been used as a model of WM autoimmune disease (121).

Lithium also inhibits inositol monophosphatase, several structurally related phosphomonoesterases, phosphoglucomutase, and the scaffolding function of beta-arrestin-2. Through its action on beta-arrestin-2 and protein phosphatase 2A, lithium activates Akt (protein kinase B). Akt activation inhibits GSK-3 and has promyelinating effects (122, 123); Akt deficiency can impair prefrontal cortex function and is associated with expression of myelin genes (124). A recent mRNA array revealed that the factors involved in myelin damage or repair may be modulated by lithium (125).

Recent data suggest that valproate is also an inhibitor of GSK-3 (126) and that some if its behavioral effects in mice are mediated by this inhibition (127). Valproate therefore also promotes myelinization through its action on Akt/GSK-3b (described previously). In addition to this, valproate activates the Notch3/c-FLIP signaling cascade that attenuates WMH in BD, particularly in later life (128). It has been shown to activate histone deacetylase, which modulates FLIP gene expression, and the action on histones is likely to influence the expression of several other genes of interest. Valproate may induce the transcription/expression of BDNF and glial-derived neurotrophic factor genes in astrocytes and consequently provide a neuroprotective effect *in vitro* (129, 130). This suggests that astrocytes could be important targets for the therapeutic effect of valproate, and histone modification could be the underlying molecular mechanism.

Recent studies using rats have shown that the antidepressant effect of lamotrigine may be related to GSK-3 inhibition by Akt activation. Both acute and chronic administration of lamotrigine reduced GSK-3 levels in the prefrontal cortex, amygdale, and hippocampus as well as increasing pro-apoptotic B-cell lymphoma 2 protein (Bcl-2) expression in the same regions. Acute and chronic treatment increased BDNF expression in the prefrontal cortex but only chronic treatment increased nerve growth factor levels in the prefrontal cortex (131). Lamotrigine efficacy in the acute and long-term treatment of bipolar depression could be linked to promyelinating factors; for long-term prophylaxis, neurotrophic pathways are important.

The effects of antipsychotic agents may also be mediated by GSK-3 inhibition. Dopaminergic D2 transmission dephosphorylates Akt, which ultimately the GSK-3 pathway (132). Most antipsychotic agents block D2 transmission and this could thus explain their pro-myelinating effects, as observed in rodent models (133, 134). Second-generation antipsychotic agents block 5-hydroxytryptamine 2 (5-HT2) receptors. As 5-HT2 receptors also regulate GSK-3, this additional pro-myelinating effect could explain why second-generation antipsychotic agents have a greater impact than first-generation agents on the WM (115, 135). One study has used cuprizone, a copper chelator that can selectively damage mouse WM, to examine the effects of antipsychotic agents. In mice, cuprizone induces myelin breakdown and demyelination, and oligodendrocyte damage. Cuprizone-induced WM damage in the prefrontal cortex, and behavioral alterations, were completely or partly reversed by antipsychotic agents (haloperidol, clozapine, and quetiapine) (136). This provides evidence for the neuroprotective effects of antipsychotic agents in the WM and the subsequent behavioral alterations, in animal models.

The therapeutic effects of lithium and other mood stabilizers are heterogeneous in their mechanisms of action, but all promote myelination. One common key pathway of this pro-myelinating effect is the inhibition of GSK-3. Other mechanisms are more drug-specific: oligodendrocyte regeneration with lithium, astrocyte proliferation with valproate, nerve growth factor elevation with the chronic administration of lamotrigine, and potential GSK-3 inhibition by 5HT2 receptor blockage with second-generation antipsychotic agents. Further studies are needed to specifically understand how these various mechanisms are important in the treatment of acute phases, long-term prophylaxis, depressive phases, and maniac phases. This will enhance our ability to prescribe mood stabilizers for different phases of illness.

Perspectives and conclusions

We have reviewed the literature on WM abnormalities in patients with BD in the context of neural models. This avenue of research has long been neglected but is now proving to be very informative. WM alterations have been found using several modalities of research: neuroimaging, neuropathological studies, genetics, and also the study of the mechanisms of action of drugs used to treat BD. As an example, both WM neuroimaging and genetic data have identified the importance of the neuregulin-1/ErbB pathway and of animal models for researching the illness.

Our summary of research exploring WM alterations can be used to develop and discover new drugs for BD treatment in three ways, as follows (see Fig. 1).

The different molecular pathways leading to WM changes, described in this review, represent potential targets for new drugs. Some of these pathways are already targets of existing drugs for treating BD (for example, lithium, valproate, lamotrigine, and antipsychotic agents target GSK-3). The other pathways implicated in oligodendrocyte differentiation and development, myelination, and MRI WM abnormalities are therefore new potential targets. Translational research into the erbB/neuregulin-1 pathway has led to the development of an animal model showing some signs of BD. The ANK3 pathway is a potential target as genetics and neuroimaging data both illustrate a role for ANK3 in WM alterations linked with cognitive deficits. BDNF, although not specific for WM, may represent another target. Finally, other parts of the GSK-3 pathway could also be investigated further for additional new drug development.

The extent of WM and myelin alterations, and their link with clinical and functional outcome, suggests that the efficacy of known pro-myelinating agents should be evaluated in the context of BD. Pro-myelinating agents are currently researched in other therapeutic domains such as multiple sclerosis or inflammatory diseases (137). The promyelinating agent progesterone is one such example; it has been shown to be effective in a pilot study treating mania and hypomania (138).

Treatment to reduce WM abnormalities may be a key objective to focus on as these abnormalities are associated with poor outcome and treatment resistance. However, there is a lack of evidence from longitudinal studies that the diminution of

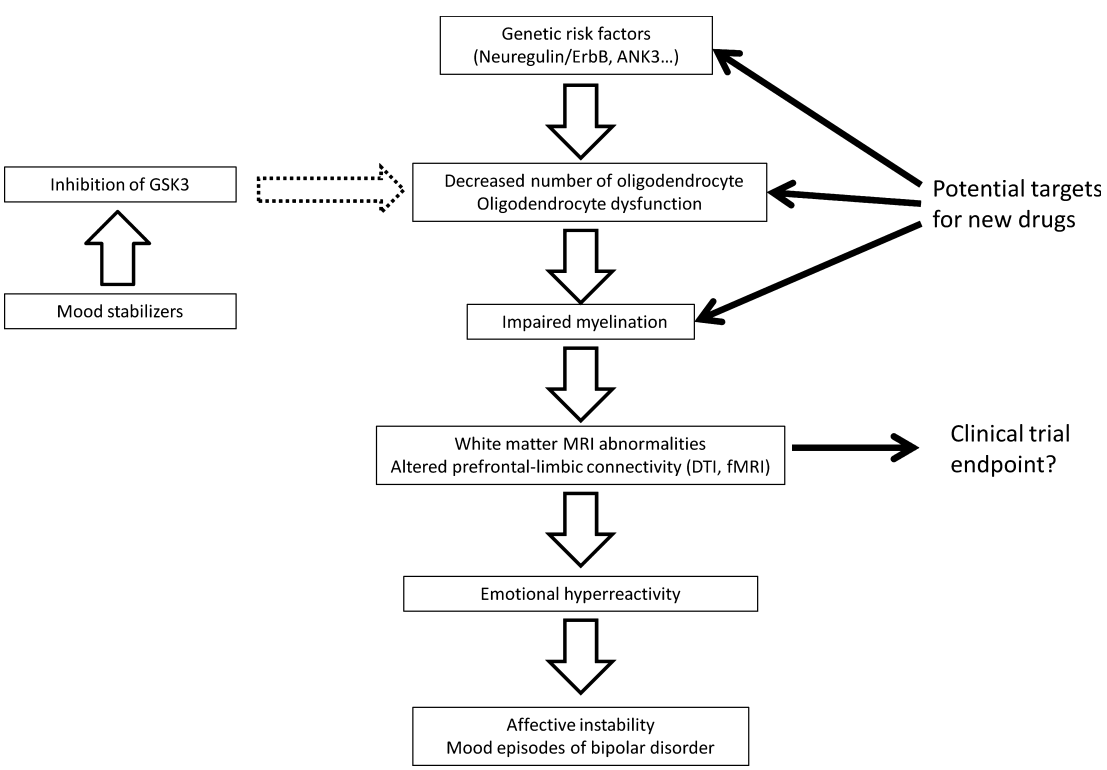

Fig. 1. White matter abnormalities in bipolar disorder: the putative mechanism and potential implications for drug development. Dotted arrow = negative action [i.e., the inhibition of glycogen synthase kinase-3 (GSK-3) enhances the number of oligodendrocytes]. ANK3 = ankyrin 3; DTI = diffusion tensor imaging; fMRI = functional magnetic resonance imaging; MRI = magnetic resonance imaging.

WM abnormalities predicts the clinical, cognitive, and functional outcome in patients with BD. Should such evidence arise, assessments of WM abnormalities may be used as endpoints in clinical trials of new drugs for the treatment of BD.

Whether changes in myelin gene expression or WM structure are a direct cause of BD or are secondary consequences of abnormal brain functioning needs to be understood further. Neuroimaging studies show that human brain structures are modified by experience (for example, by learning and information processing), using a mechanism called neural plasticity. The process of myelination can occur for decades in the human brain, and recent studies have shown that WM changes are associated with learning (139). For example, musicians have greater gray matter volume and cortical thickness in the auditory cortices; they also have differences in WM organization in the spinothalamic tract, similar to the WM changes in the visual area which were observed in subjects after a three-month 'learning to juggle task' (140, 141). Such effects on WM generally increase with practice time, supporting the evidence for WM plasticity in association with learning tasks. Regarding future treatments for BD, WM plasticity should be of interest both for the development of psychotherapy (in psychoeducation or cognitive rehabilitation) and at the pharmacological level. Our knowledge of the mechanisms underlying WM plasticity at the cellular and molecular level (for example, in glial cells or myelination) is still scarce and further neuroimaging studies could be greatly beneficial.

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