

Review

Frontotemporal White Matter in Adolescents with, and at-Risk for, Bipolar Disorder

Sonja M. C. de Zwart¹, Jennifer A. Y. Johnston¹, Elizabeth T. Cox Lippard¹
and Hilary P. Blumberg^{1,2,3,*}

¹ Department of Psychiatry, Yale School of Medicine, 300 George Street, Suite 901, New Haven, CT 06511, USA; E-Mails: sonja.dezwarte@yale.edu (S.M.C.Z.); jennifer.johnston@yale.edu (J.A.Y.J.); elizabeth.cox@yale.edu (E.T.C.L.)

² Department of Diagnostic Radiology, Yale School of Medicine, New Haven, CT 06511, USA

³ Child Study Center, Yale School of Medicine, New Haven, CT 06511, USA

* Author to whom correspondence should be addressed; E-Mail: hilary.blumberg@yale.edu; Tel.: +1-203-785-6180; Fax: +1-203-737-2513.

Received: 20 December 2013; in revised form: 13 February 2014 / Accepted: 17 February 2014 / Published: 10 March 2014

Abstract: Frontotemporal neural systems are highly implicated in the emotional dysregulation characteristic of bipolar disorder (BD). Convergent genetic, postmortem, behavioral and neuroimaging evidence suggests abnormalities in the development of frontotemporal white matter (WM) in the pathophysiology of BD. This review discusses evidence for the involvement of abnormal WM development in BD during adolescence, with a focus on frontotemporal WM. Findings from diffusion tensor imaging (DTI) studies in adults and adolescents are reviewed to explore possible progressive WM abnormalities in the disorder. Intra- and interhemispheric frontotemporal abnormalities were reported in adults with BD. Although evidence in children and adolescents with BD to date has been limited, similar intrahemispheric and interhemispheric findings have also been reported. The findings in youths suggest that these abnormalities may represent a trait marker present early in the course of BD. Functional connectivity studies, demonstrating a relationship between WM abnormalities and frontotemporal dysfunction in BD, and DTI studies of vulnerability in first-degree relatives of individuals with BD, are discussed. Together, findings suggest the involvement of abnormal frontotemporal WM development in the pathophysiology of BD and that these abnormalities may be early trait markers of vulnerability; however, more studies are critically needed.

Keywords: bipolar disorder; frontal lobe; white matter; development; adolescents; diffusion tensor imaging

1. Introduction

Bipolar disorder (BD) can be a severe and disabling mood disorder, associated with detrimental outcomes, such as high rates of hospitalizations, substance abuse and suicide [1–3]. It is a recurrent illness that is characterized by manic or hypomanic episodes, which may alternate with depressive episodes and periods of normal mood, or euthymia. Dysregulated affective states are central to the acute episodes: euphoric or highly irritable states during mania or sad states during depression. The affective changes are accompanied by shifts in motivation, impulse regulation, energy, and activity levels, in addition to changes in sleep and appetite, implicating the brain regions that subserve emotional regulation and these associated functions.

BD shows a peak in emergence during adolescence and early adulthood [4,5], implicating this epoch as highly important in the development of the disorder. Early onset of BD has been of particular concern because it is associated with a more severe course of the disorder than later presentations, which may have alternate etiologies [6,7]. Therefore, early detection of the illness is of great importance and adolescence has been a major focus within BD-research. Understanding of the development of BD during this epoch could provide insights into the pathophysiology of the disorder. In youth diagnosed with BD, there is a strong overlap in clinical symptoms with other disorders, including attention deficit hyperactivity disorder and major depressive disorder. Misdiagnosis can lead to interventions that have the potential to worsen the outcome of BD [8–10]. Therefore, the detection of trait markers early in the disease course might be of importance in adolescents to ensure they receive needed treatments and avoid treatments that could be detrimental.

Convergent evidence supports a central role for altered development of frontotemporal neural systems in BD. Early studies of patients with lesions and seizure foci in anterior cortical and mesial temporal regions, and with lesions in white matter (WM) tracts connecting these regions, reported behavioral symptoms similar to those seen in BD [11–18]. Findings from neuroimaging studies support abnormalities in frontotemporal systems, including abundant findings of abnormal structure and functioning in the amygdala and ventral prefrontal cortex (vPFC) [19]. Recently, studies have suggested that a progression in regional brain abnormalities is present in BD. For gray matter (GM) structures, there is initial evidence that subcortical abnormalities, including the amygdala, may be present by adolescence, while PFC abnormalities, including in the vPFC and more rostral PFC regions, may progress during adolescence and into early adulthood [20–24].

Structural magnetic resonance imaging (MRI) studies and postmortem studies support the involvement of abnormal WM in adults with BD. There is little data available on whether abnormalities in WM appear early and whether they show a progression during adolescence in BD. WM connections continue to develop into adolescence and well into adulthood [25–30], suggesting that WM abnormalities in BD might be influenced by developmental changes. In the last decade, the advent of diffusion tensor imaging (DTI) techniques has provided the opportunity to investigate the

structural integrity of WM tracts *in vivo* more specifically. Studies have emerged in which this method is applied not only to adults with BD, but also to the study of youths with BD.

This article will review studies that implicate abnormal WM development in frontotemporal neural systems in BD, with a focus on what can be learned about WM in adolescents with BD. DTI findings in adolescents will be discussed in the context of findings in adults to explore the involvement of WM development in the disorder. Although DTI studies will be the focus of the review, studies using other structural imaging techniques will also be included to allow comparisons of DTI findings within the context of other work in the field. Furthermore, functional connectivity studies will be reviewed to explore the relationship between DTI findings and frontotemporal dysfunction in individuals with BD. Finally, this article will examine genetic studies related to WM and neuroimaging studies of first-degree relatives of BD individuals, considered at-risk for the disorder, as BD is a highly heritable illness [31,32] and these studies may help identify possible markers for early detection or even prevention of BD. Together, the studies reviewed support neurodevelopmental mechanisms underlying frontotemporal WM pathology in BD.

2. Frontotemporal Neural Circuitry Implicated in BD

Emotional dysregulation is the characteristic feature of BD, suggesting the involvement of abnormalities in frontotemporal brain regions, especially the amygdala and vPFC, which are central to emotional regulation. The amygdala plays an early and important role in emotional processing [33–37], while the vPFC integrates information from the amygdala and other brain regions that provide information about emotional and motivational relevance of stimuli, and synthesizes an adaptive executive feedback to regulate amygdala and other subcortical responses [38,39]. The involvement of frontotemporal abnormalities has been further implicated in BD by behavioral neuroanatomical and neuroimaging studies. Early reports of lesions within the PFC, particularly in the vPFC, provided descriptions of symptoms similar to those seen in BD, including depressive symptoms and manic-like symptoms such as inappropriate euphoria [11–13,17,18]. BD-type symptoms were also observed in patients with seizures with foci in the mesial temporal lobe, including in the amygdala [13,15,16]. As the vPFC and the amygdala are highly interconnected brain regions [40], these findings suggest that abnormalities within both the vPFC and amygdala and/or their connections might contribute to BD. Indeed, subsequent findings from structural and functional MRI studies in adults with BD have converged in demonstrating abnormalities in each of these frontotemporal neural system components in individuals with BD [19].

Recent evidence suggests a developmental progression in frontotemporal abnormalities in BD. Subcortical brain structures mature earlier than PFC structures and PFC structures continue to show dynamic maturational changes over adolescence. Therefore, it was theorized that, consistent with the pattern of maturation of brain structures, frontotemporal system abnormalities in BD might emerge earlier in subcortical structures and PFC abnormalities might progress during adolescence [21]. Preliminary structural and functional neuroimaging studies support this progression, with amygdala abnormalities demonstrated in adolescents with BD and PFC abnormalities appearing to progress during adolescence and early adulthood [20–22,24]. However, these studies are cross-sectional and must be considered as models of longitudinal outcomes with caution. There is a previous longitudinal

study that also supports this model; however, the sample size was small and the significance threshold modest, so findings should be considered preliminary and in need of replication in a larger cohort [23].

In addition to GM developmental changes during adolescence, evidence supports dynamic maturational changes in WM connections between the amygdala and vPFC [27]. Human postmortem and neuroimaging studies have shown that myelination of these connections continues through adolescence and well into adulthood in the normal developing brain [25,26,28–30]. The substantial developmental changes in these connections over adolescence and young adulthood suggest that if WM connections are involved in the developmental pathophysiology of BD, they may particularly show changes in their expression during these epochs in the disorder [22,27,29,41,42].

3. Frontotemporal WM Connections Implicated in BD

For more than a century, lesions in frontal WM and frontal-subcortical connections have been described in association with both depressive symptoms and manic-like states, including disinhibition and inappropriate excitement and laughter [14]. WM connections within frontotemporal neural systems have since been implicated in the pathophysiology of BD, as the frontotemporal GM structures in which abnormalities have been shown in BD are highly interconnected within these systems. Furthermore, postmortem studies have demonstrated reductions in glia cells, especially oligodendrocytes, and downregulation of genes related to oligodendrocytes and myelination, particularly in frontal brain regions, in individuals with BD [43–47]. These findings suggest abnormalities in myelin synthesis and axonal survival in individuals with BD and implicate the involvement of abnormal WM in the pathology of the disorder.

Frontotemporal WM tracts can be divided into intra- and interhemispheric, *i.e.*, connecting brain structures within one hemisphere or providing connection between the two hemispheres, respectively. Important intrahemispheric WM bundles in the frontotemporal neural circuitry include the uncinate fasciculus (UF) and the cingulum bundle (CB); both carry major connections between the amygdala and vPFC and thus are WM structures especially implicated in BD. Frontotemporal interhemispheric WM abnormalities are also highly implicated in the pathophysiology of the disorder, as the anterior corpus callosum (CC) provides major right-left vPFC connections [48]. Furthermore, studies have identified more widely distributed connections from the amygdala and vPFC, such as to more dorsal PFC, hippocampus, striatum, thalamus, cerebellum and hypothalamus, areas associated with motivational behaviors, biological rhythm and neurovegetative processes [40,49–52]. Thus, this may explain why impaired amygdala-vPFC connectivity could lead not only to emotional dysregulation, but also to a broader range of symptoms seen in BD.

Studies of structural abnormalities in WM in adults with BD have shown both decreases in volume of WM within ventral frontal regions [22], as well as decreases in CC area and signal intensity, *i.e.*, mean signal intensity thought to reflect myelination [53–55]. These implicate both intra- and interhemispheric frontotemporal WM abnormalities in the pathology of BD in adults. Additionally, decreased signal intensity in the CC in BD children and adolescents has been reported [56], suggesting that altered myelination may occur during neurodevelopment in BD and that these WM abnormalities may be an early feature of the disorder.

Other WM abnormalities reported in MRI studies of BD are WM hyperintensities (WMH). These are hyper-intense bright spots that may reflect brain regions of increased water density, possibly because of local altered vascular permeability or other processes [57,58]. However, the etiology of WMH remains unclear. WMH have been associated with aging [58,59], and an increase in their occurrence has also been reported in several studies in adults with BD [60–70]. These findings might suggest that the accumulation of WMH might be associated with aging processes in the disorder [71]. Furthermore, an association between increased WMH and previous suicide attempts has been reported [62], suggesting the involvement of WMH in risk for suicide attempts in BD individuals. Some of these studies reported WMH in the deep frontal WM, further suggesting that tracts connecting fronto-cortical and subcortical regions are affected in the disorder [61,68]. Evidence related to WMH in youths with BD is contradictory. In some studies of children and adolescents with BD, significant increases in WMH number were not detected [72,73]. There have also been reports of increases in WMH in children and adolescents with BD [74,75]. This suggests that WMH may involve pathophysiological processes other than aging or may be associated with particular subtypes of BD, such as early onset. However, the involvement of WMH early in the disorder remains unclear.

4. DTI Studies Implicating Frontotemporal WM Abnormalities in Adolescents with BD

DTI studies have started to focus on structural integrity differences between WM in adolescents with BD, compared to healthy comparison (HC) adolescents (Table 1). DTI studies provide noninvasive measures of the organization of WM [76]. Fractional anisotropy (FA) is a common DTI measure that provides information on the structural integrity and coherence of fibers within WM regions [77]. Some studies report additional measures to provide more insight on diffusivity in WM, such as apparent diffusion coefficient (ADC) or mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD); however, FA is the most consistently reported measure and therefore the main focus of this review.

Frontotemporal WM abnormalities implicated in BD, both intra- and interhemispheric, have been reported in many adult DTI studies. Reduced UF and neighboring orbitofrontal WM integrity [78–88] and reduced anterior CB integrity [86,89–92] have been among the most consistent WM integrity findings in adults with BD. Studies of adults with BD have also shown intrahemispheric WM abnormalities in connections between dorsal frontal regions, to regions such as the striatum or thalamus via connections within structures, including the anterior limb of the internal capsule (ALIC) [82,87,93,94]. More abundant interhemispheric findings include reduced structural integrity in the anterior CC in adults with BD, and supports abnormal interhemispheric frontotemporal circuitry in the disorder [70,87,88,94–99]. In addition to tensor-based diffusion MRI studies, recent research in adults with BD has also utilized alternative methodologies, such as high-angular resolution diffusion imaging (HARDI) and diffusion spectrum imaging (DSI), which are able to further parse heterogeneous diffusion directions and crossing fiber tracts [99,100]. These techniques are promising and may potentially provide additional insight into WM abnormalities in BD.

Table 1. Diffusion tensor imaging (DTI) studies of children and adolescents with bipolar disorder and/or at-risk for bipolar disorder.

Authors and Year	Subjects	Mean Age (year $\pm$ SD)	Age Range (years)	DTI Measures	Analysis Type	Regions of Interest	Findings and Overall Significance Levels
Studies of children and adolescents at-risk for BD							
Versace et al. 2010 [101]	20 AR-BD 25 HC	13.2 $\pm$ 2.5 13.9 $\pm$ 2.6	8–17	FA, RD, L1	TBSS	Whole brain	AR-BD > HC: FA in left CC body, L1 in right ILF AR-BD < HC: RD in left CC body, right ILF Significant group-by-age interaction: HC: FA increases/RD decreases with age in left CC body; RD decreases with age in right ILF; L1 increases with age in right ILF AR-BD: FA decreases/RD increases with age in left CC body; RD no relation with age in right ILF; L1 decreases with age in right ILF AlphaSim corrected $p < 0.05$
Studies of children and adolescents both with BD and at-risk for BD							
Frazier et al. 2007 [102]	7 AR-BD 10 BD 8 HC	8.9 $\pm$ 3.0 9.2 $\pm$ 3.0 9.2 $\pm$ 2.4	4–12	FA	Voxel-based	<i>A priori</i> CPC and SLF, and whole brain	BD < HC: FA in bilateral CPC and SLF, right CC body, left OF WM AR-BD < HC: FA in bilateral SLF BD < AR-BD: FA in bilateral CPC $p < 0.05$ Bonferroni corrected
Studies of children and adolescents with BD							
Adler et al. 2006 [103]	11 BD 17 HC	14 $\pm$ 2	10–18	FA, trace ADC	ROI	Frontal and posterior regions	BD < HC: FA in bilateral superior frontal WM tracts $p < 0.01$ uncorrected
Kafantaris et al. 2009 [104]	26 BD 26 HC	16.0 $\pm$ 1.5 15.3 $\pm$ 1.5		FA, ADC	Voxel-based	Whole brain	BD < HC: FA in right OF WM, bilateral temporal lobes, left occipital lobe BD > HC: ADC in bilateral subgenual region, bilateral precuneus, left postcentral gyrus, left temporal and right occipital lobes $p < 0.005$ uncorrected, cluster size ≥ 100
Pavuluri et al. 2009 [105]	13 BD 13 ADHD 15 HC	14.8 $\pm$ 2.5 13.4 $\pm$ 3.0 13.7 $\pm$ 2.7		FA, ADC, r-FCI	ROI and voxel-based	ACR, ALIC, CB, CC (splenium), ILF, PLIC, SLF, SRI	BD and ADHD < HC: FA in ACR, r-FCI in CC splenium BD and ADHD > HC: ADC in CC splenium $p < 0.05$ uncorrected

Table 1. Cont.

Studies of children and adolescents with BD (continued)							
Barnea-Goraly <i>et al.</i> 2009 [106]	21 BD 18 HC	16.1 ± 2.7 14.5 ± 2.7	9–18	FA, trace values (average diffusivity), ADC	TBSS	Whole brain	BD < HC: FA in CC, PCR, left mid-posterior CB, fornix, fibers from fornix to thalamus $p < 0.05$ corrected
Gönenç <i>et al.</i> 2010 [107]	10 BD (8 in study) 10 HC (8 in study)	3M: 16.6 ± 4.8 7F: 11.8 ± 4.5 6M: 10.6 ± 4.0 4F: 14.3 ± 1.9	6–18	FA, trace diffusivity, RD, AD	ROI	Bilateral CPC	BD < HC: FA left CPC BD > HC: left and right trace and left RD in CPC $p < 0.05$ uncorrected
Saxena <i>et al.</i> 2012 [108]	10 BD 10 HC	13.9 ± 3.6 13.6 ± 3.6	7–17	FA	TBSS	5 CC subdivisions, AC	BD < HC: FA genu CC and AC $p < 0.001$ uncorrected, $p < 0.05$ small-volume FDR correction
Gao <i>et al.</i> 2013 [109]	18 BD 18 HC	15.1 ± 1.8 14.1 ± 1.6	10–18	FA	TBSS	Whole brain	BD < HC: FA right anterior CB $p < 0.05$ FDR correction
Abbreviations							
AC	Anterior commissure			CPC	Cingulate-paracingulate		
ACR	Anterior corona radiate			DTI	Diffusion tensor imaging		
AD	Axial diffusivity			F	Female		
ADC	Apparent diffusion coefficient			FA	Fractional anisotropy		
ADHD	Attention deficit hyperactivity disorder			FDR	False discovery rate		
ALIC	Anterior limb of the internal capsule			HC	Healthy comparison		
AR-BD	At-risk for BD, <i>i.e.</i> , having a first-degree relative with BD			ILF	Inferior longitudinal fasciculus		
BD	Bipolar disorder			L1	Longitudinal diffusivity		
CB	Cingulum bundle region			M	Male		
CC	Corpus callosum			PCR	Posterior corona radiate		
				PLIC	Posterior limb of the internal capsule		
				OF	Orbitofrontal		
				r-FCI	Regional fiber coherence index		
				RD	Radial diffusivity		
				ROI	Region of interest		
				SD	Standard deviation		
				SLF	Superior longitudinal fasciculus		
				SRI	Superior region of the internal capsule		
				TBSS	Tract-based spatial statistics		
				WM	White matter		

Studies of children and adolescents with BD have also shown findings of reduced intrahemispheric structural integrity in ventral frontal WM regions, compared to HC children and adolescents [102,104] (Table 1). Decreased FA values have been reported in pericingulate regions, including the CB, in children and adolescents with BD [102,107,109]. These decreases in WM structural integrity include findings in prepubertal children [102,107]. This might be an indication that intrahemispheric frontotemporal WM abnormalities are already present in childhood, representing some of the earliest markers of the disorder.

Abnormalities in additional tracts have also been demonstrated in children and adolescents with BD, including tracts to other connection sites of frontotemporal circuitry, such as to more dorsal frontal regions, basal ganglia, thalamus and posterior association cortices [102,105,106]. Reduced structural integrity in superior frontal regions has been reported in BD adolescents [103]. Reductions of FA values have also been reported in frontal projections through the anterior corona radiata in children and adolescents [105,106], and in a group that included both adolescents and young adults [98], with BD. In contrast to findings in adults, abnormalities in the ALIC have not been a consistent finding in children and adolescents with BD. Studies have reported both no differences [105] and reduced structural integrity of the ALIC in children and adolescents with BD compared to HC youths [110]. The latter study included both adults and youths with BD and compared early- and late-onset of BD and reported lower FA values in the early-onset group, suggesting that early- and late-onset BD might represent different subtypes within the bipolar spectrum with different pathophysiologies, potentially accounting for some conflicting results in the literature.

Findings of frontotemporal interhemispheric WM abnormalities in adolescents with BD have also started to emerge. Lower FA values of interhemispheric connections in a group with both children and adolescents with BD have been found in the anterior commissure (AC) [108]. Decreases in structural integrity in the anterior CC have been reported in prepubertal children and adolescents [106,108]. The AC and the anterior CC link the right and left temporal lobes and prefrontal lobes respectively, and therefore could play a role in the frontotemporal neural circuitry suggested in BD. Findings suggest that reduced integrity of frontotemporal interhemispheric WM bundles might be present early in the disease course.

5. Functional Connectivity Studies and the Relationship between DTI Results and Dysfunction in BD

Functional connectivity neuroimaging studies further implicate the involvement of abnormal frontotemporal WM connections in BD. Functional connectivity MRI measures can be derived from the degree that activity is coordinated in time between different brain regions. Functional neuroimaging studies have provided support for trait abnormalities in functional connectivity between the amygdala and vPFC regions in both adults [81,111–116] and children and adolescents [117–119] with BD across mood states.

Several studies have aimed to examine the relationship between DTI results and dysfunction in BD. An investigation combining DTI and functional connectivity data showed an association between reduced structural integrity in the UF with decreases in the functional connectivity between the vPFC and the amygdala during processing of emotional stimuli by adults with BD [81]. This multimodal

neuroimaging study suggests that the WM aberrations may contribute to disruptions in the ability of the frontotemporal brain structures to work together in the regulation of responses to emotional stimuli.

Hemispheric lateralization of processing of positive and negative emotions is evident in normal affective processing, and the balance between the hemispheres has been proposed to be important in healthy emotional regulation [120]. A low frequency resting state functional connectivity study showed increased interhemispheric correlations between left and right vPFC in adults with BD, relative to healthy individuals [111]. This finding suggests that interhemispheric abnormalities might contribute to impaired hemispheric integration and the hemispherically-lateralized dysfunction in acute mood states of the disorder [48,111].

A functional connectivity study investigating children and adolescents with BD showed less functional connectivity between the amygdala and posterior association cortices during an emotional face identification task [121]. This finding suggests that youth with BD may have impaired communication in neural systems critical to processing faces and emotional stimuli and that WM connections to posterior regions may be early abnormalities in BD. As connections from posterior associations structures to amygdala may carry information used to associate stimuli with emotional information [122], abnormalities in these connections could contribute to abnormalities in the development of emotional associations to environmental stimuli. More multimodal studies are needed to further delineate the relationship between WM abnormalities and dysfunction in BD.

6. Association of WM Abnormalities with Genetic Risk for BD

Increasing evidence that genes related to WM and frontotemporal connectivity are associated with BD further implicate frontotemporal neural circuitry in the disorder. BD has strong genetic contributions with heritability estimates varying from 40% to 70% [123]. Studies have suggested that genes involved in cytoarchitecture of frontotemporal WM structures might be associated with an increased risk of BD [124]. For example, the neuregulin 1 (NRG1) gene plays a key role in neurodevelopmental processes in WM brain connections, such as in axonal guidance and myelination [125–127]. NRG1 is suggested to influence the susceptibility to BD and seems especially associated with psychotic features [128]. Abnormal frontotemporal WM volume, including in the CB and regions in the CC, has been found to be associated with a single nucleotide polymorphism (SNP) in the NRG1 gene (rs35753505) in adults with BD [129]. DTI evidence showed that another NRG1 SNP (rs6994992) is associated with reduced WM density and integrity in the ALIC [130], suggesting that NRG1 may increase susceptibility to psychopathology by altering connections between PFC and other brain regions. Another gene of particular interest in BD is the CACNA1C gene, which has been reported in genome-wide association studies to be related to BD [131,132]. The CACNA1C gene is implicated in the development and plasticity of the frontotemporal neural circuitry [133]. CACNA1C rs1006737 SNP variation has been associated with altered frontotemporal functional connectivity between the amygdala and vPFC [134]. This finding implicates variations in gene expression in the neural circuitry associated with BD, and that altered gene expression associated with BD may lead to abnormalities in WM connections, including in their development and plasticity, as well as in associated frontotemporal functional connectivity.

The high heritability rates in BD are supported by several longitudinal studies, showing offspring of individuals with BD to be at greater risk to develop BD [135,136]. First-degree relatives of affected BD individuals are considered to have more than a ten-fold higher risk of developing BD than the general population [137]. Thus, youths at-risk for BD (AR-BD), as they have a first-degree relative with BD but they themselves have not yet developed BD, are of particular interest to investigate. The presence of neurodevelopmental abnormalities in AR-BD youth, prior to the onset of acute episodes of the disorder, was suggested by a prospective study of a large cohort [138]. AR-BD youths might show brain differences that are apparent even before onset of mood episodes, revealing abnormalities associated with vulnerability to the disorder and minimizing confounds, such as the possibility that abnormalities are a result of having experienced an acute episode or medication exposure.

Structural MRI studies in AR-BD adults have shown reduced WM volume in the left hemisphere [139] and WMH abnormalities [140,141], suggesting that WM disconnectivity might also be present in AR-BD individuals. However, only limited DTI studies have to date explored structural integrity in AR-BD individuals with BD.

In DTI studies, frontotemporal structural integrity abnormalities have been reported in both adults with BD and their AR-BD adult relatives, both showing decreased FA values in the right UF [87]. Reductions of structural integrity in the ALIC and in frontal connections to posterior association cortices have also been reported in adult AR-BD individuals [87,94,142,143]. Decreased structural integrity found in the CC in BD individuals has not been detected in their relatives [87]; however, increased genetic liability for BD was reported to be associated with a trend towards reduced FA in the anterior CC, with intermediate values for AR-BD adults [94]. This suggests the possibility that intrahemispheric frontotemporal connections are more associated with genetic heritability than interhemispheric WM connections. The frontal system WM findings in AR-BD are consistent with reports of cognitive dysfunction in AR-BD adults [144]. Future research to combine tests of cognitive and behavioral functions with neuroimaging may help to identify relationships between cognitive dysfunction and underlying WM abnormalities.

To date, only limited numbers of studies have been reported that explore WM in AR-BD youths (Table 1). One study reported altered WM in the left CC during early adolescence in AR-BD youths, compared to youths with no family history of BD, with the AR-BD youths showing decreases in FA with age, while the low-risk youths showed an increase of FA with age [101], suggesting altered WM developmental trajectories in the AR-BD adolescents. Another study reported decreased structural integrity in bundles connecting frontal cortices with posterior association cortices in both prepubertal children with BD and AR-BD prepubertal children [102]. These results raise the intriguing possibility that abnormalities in WM connections may provide an early marker for vulnerability to BD. However, due to the limited DTI research conducted in AR-BD subjects, it remains unclear whether WM abnormalities are involved in the vulnerability for developing BD and whether they could potentially be a biomarker for the disorder.

7. Conclusions

While GM volumetric and functional changes have been a focus of neuroimaging research in BD, recent neuroimaging data have been converging to suggest WM abnormalities may be important in the

developmental pathophysiology of BD and have potential as early biomarkers. Intrahemispheric WM abnormalities in UF and CB are especially implicated in the disorder, and additional abnormalities in connections to dorsal frontal regions, striatum and thalamus, as well as to posterior association cortices, have also been shown in adults and adolescents. Interhemispheric anterior CC abnormalities have also been repeatedly shown in adults with the disorder, although less evidence is available in adolescents. WM abnormalities are associated with frontotemporal system dysfunction, as well as associated behaviors. Genetic variations associated with both the development of WM connections and with BD susceptibility have also shown association with frontotemporal structural and functional connection abnormalities, suggesting potential genetic mechanisms that may underlie connection abnormalities. The intrahemispheric abnormalities show promise as possible early markers of vulnerability to BD. There is less data to support interhemispheric abnormalities in vulnerability.

More research is critically needed. Longitudinal studies of adolescents with BD could help to identify the processes involved in the neurodevelopment of BD, contributing to understanding of the progression of abnormalities and the factors that contribute to them. Longitudinal studies of AR-BD children are especially needed. These could help to identify neurodevelopmental processes involved in the transition from risk to developing the disorder for children who go on to develop BD, as well as protective processes for those who do not. Increased sample sizes, as well as consideration of various heterogeneous demographic and clinic features, are needed. It will be important to investigate associations between specific regional findings with symptom and behavioral domains to provide a dimensional understanding of neuropathological mechanisms of BD.

Measures assessed in imaging studies have been limited, such as a focus primarily on FA in DTI studies. As additional measures may help to clarify the types of pathophysiological processes involved have been informative in studies of adults, and have shown some differences in studies of youths, they will be important to include in future studies. Previous studies have varied in other aspect of the imaging acquisition and analyses methods, including variation in the statistical thresholds used. The field will benefit from increasingly sensitive and specific measures of white matter features, and of studies with larger samples with more stringent statistical thresholds.

In summary, research on WM in BD supports an important role for frontotemporal WM. Neurodevelopmental abnormalities that affect trajectories of WM development during adolescence are implicated in the emergence of BD during this epoch. Future studies might reveal important insights into the pathophysiology of BD and identify brain differences and mechanisms to target for early identification, intervention and prevention strategies.

Acknowledgments

This work was supported by research grants from the National Institute of Health R01MH69747 (HPB), R01MH070902 (HPB), RC1MH088366 (HPB), RL1DA024856 (HPB), T32MH014276 (ETCL) and CTSA UL1RR0249139 from the NIH National Center for Research Resources (HPB) and the National Alliance for Research in Schizophrenia and Depression (HPB), American Foundation for Suicide Prevention (HPB), International Bipolar Foundation (HPB), Attias Family Foundation (HPB) and Women's Health Research at Yale (HPB).

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Chen, Y.W.; Dilsaver, S.C. Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other axis I disorders. *Biol. Psychiatry* **1996**, *39*, 896–899.
2. Dunner, D.L. Clinical consequences of under-recognized bipolar spectrum disorder. *Bipolar Disord.* **2003**, *5*, 456–463.
3. Kessler, R.C.; Chiu, W.T.; Demler, O.; Merikangas, K.R.; Walters, E.E. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. *Arch. Gen. Psychiatry* **2005**, *62*, 617–627.
4. Carlson, G.A.; Fennig, S.; Bromet, E.J. The confusion between bipolar disorder and schizophrenia in youth: Where does it stand in the 1990s? *J. Am. Acad. Child Adolesc. Psychiatry* **1994**, *33*, 453–460.
5. Lish, J.D.; Dime-Meenan, S.; Whybrow, P.C.; Price, R.A.; Hirschfeld, R.M. The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. *J. Affect. Disord.* **1994**, *31*, 281–294.
6. Perlis, R.H.; Miyahara, S.; Marangell, L.B.; Wisniewski, S.R.; Ostacher, M.; DelBello, M.P.; Bowden, C.L.; Sachs, G.S.; Nierenberg, A.A. Long-term implications of early onset in bipolar disorder: Data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol. Psychiatry* **2004**, *55*, 875–881.
7. Birmaher, B.; Axelson, D.; Strober, M.; Gill, M.K.; Valeri, S.; Chiappetta, L.; Ryan, N.; Leonard, H.; Hunt, J.; Iyengar, S.; *et al.* Clinical course of children and adolescents with bipolar spectrum disorders. *Arch. Gen. Psychiatry* **2006**, *63*, 175–183.
8. Thase, M.E. Bipolar depression: Issues in diagnosis and treatment. *Harv. Rev. Psychiatry* **2005**, *13*, 257–271.
9. Baumer, F.M.; Howe, M.; Gallelli, K.; Simeonova, D.I.; Hallmayer, J.; Chang, K.D. A pilot study of antidepressant-induced mania in pediatric bipolar disorder: Characteristics, risk factors, and the serotonin transporter gene. *Biol. Psychiatry* **2006**, *60*, 1005–1012.
10. Jenkins, M.M.; Youngstrom, E.A.; Washburn, J.J.; Youngstrom, J.K. Evidence-based strategies improve assessment of pediatric bipolar disorder by community practitioners. *Prof. Psychol. Res. Pract.* **2011**, *42*, 121–129.
11. Jastrowitz, M. Beiträge zur localisation im grosshirn und über deren praktische verwerthung. *Dtsch. Med. Wochenschr.* **1888**, *14*, 81–83.
12. Oppenheim, H. Zur pathologie der grosshirngeschwulste. *Arch. Psychiatry* **1889**, *21*, 560–578.
13. Cummings, J.L.; Mendez, M.F. Secondary mania with focal cerebrovascular lesions. *Am. J. Psychiatry* **1984**, *141*, 1084–1087.
14. Starr, M.A. *Organic Nervous Diseases*; Lea Brothers & Co.: New York, NY, USA, 1903.

15. Flor-Henry, P. Schizophrenic-like reactions and affective psychoses associated with temporal lobe epilepsy: Etiological factors. *Am. J. Psychiatry* **1969**, *126*, 400–404.
16. Bear, D.M.; Fedio, P. Quantitative analysis of interictal behavior in temporal lobe epilepsy. *Arch. Neurol.* **1977**, *34*, 454–467.
17. Damasio, A.R.; Anderson, S.W. The Frontal Lobes. In *Clinical Neuropsychology*, 3rd ed.; Heilman, K.M., Valenstein, E., Eds.; Oxford University Press: New York, NY, USA, 1993; pp. 409–460.
18. Rolls, E.T.; Hornak, J.; Wade, D.; McGrath, J. Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. *J. Neurol. Neurosurg. Psychiatry* **1994**, *57*, 1518–1524.
19. Strakowski, S.M.; Adler, C.M.; Almeida, J.; Altshuler, L.L.; Blumberg, H.P.; Chang, K.D.; DelBello, M.P.; Frangou, S.; McIntosh, A.; Phillips, M.L.; *et al.* The functional neuroanatomy of bipolar disorder: A consensus model. *Bipolar Disord.* **2012**, *14*, 313–325.
20. Blumberg, H.P.; Martin, A.; Kaufman, J.; Leung, H.C.; Skudlarski, P.; Lacadie, C.; Fulbright, R.K.; Gore, J.C.; Charney, D.S.; Krystal, J.H.; *et al.* Frontostriatal abnormalities in adolescents with bipolar disorder: Preliminary observations from functional MRI. *Am. J. Psychiatry* **2003**, *160*, 1345–1347.
21. Blumberg, H.P.; Kaufman, J.; Martin, A.; Charney, D.S.; Krystal, J.H.; Peterson, B.S. Significance of adolescent neurodevelopment for the neural circuitry of bipolar disorder. *Ann. N. Y. Acad. Sci.* **2004**, *1021*, 376–383.
22. Blumberg, H.P.; Krystal, J.H.; Bansal, R.; Martin, A.; Dziura, J.; Durkin, K.; Martin, L.; Gerard, E.; Charney, D.S.; Peterson, B.S. Age, rapid-cycling, and pharmacotherapy effects on ventral prefrontal cortex in bipolar disorder: A cross-sectional study. *Biol. Psychiatry* **2006**, *59*, 611–618.
23. Kalmar, J.H.; Wang, F.; Spencer, L.; Edmiston, E.; Lacadie, C.M.; Martin, A.; Constable, R.T.; Duncan, J.S.; Staib, L.H.; Papademetris, X.; *et al.* Preliminary evidence for progressive prefrontal abnormalities in adolescents and young adults with bipolar disorder. *J. Int. Neuropsychol. Soc.* **2009**, *15*, 476–481.
24. Wang, F.; Kalmar, J.H.; Womer, F.Y.; Edmiston, E.E.; Chepenik, L.G.; Chen, R.; Spencer, L.; Blumberg, H.P. Olfactocentric paralimbic cortex morphology in adolescents with bipolar disorder. *Brain* **2011**, *134*, 2005–2012.
25. Yakovlev, P.I.; Lecours, A.R. The Myelogenetic Cycles of Regional Maturation of the Brain. In *Regional Development of the Brain in Early Life*; Minkowski, A., Ed.; Blackwell Scientific: Oxford, UK, 1967; pp. 3–70.
26. Courchesne, E.; Chisum, H.J.; Townsend, J.; Cowles, A.; Covington, J.; Egaas, B.; Harwood, M.; Hinds, S.; Press, G.A. Normal brain development and aging: Quantitative analysis at *in vivo* MR imaging in healthy volunteers. *Radiology* **2000**, *216*, 672–682.
27. Cunningham, M.G.; Bhattacharyya, S.; Benes, F.M. Amygdalo-cortical sprouting continues into early adulthood: Implications for the development of normal and abnormal function during adolescence. *J. Comp. Neurol.* **2002**, *453*, 116–130.

28. Keshavan, M.S.; Diwadkar, V.A.; DeBellis, M.; Dick, E.; Kotwal, R.; Rosenberg, D.R.; Sweeney, J.A.; Minshew, N.; Pettegrew, J.W. Development of the corpus callosum in childhood, adolescence and early adulthood. *Life Sci.* **2002**, *70*, 1909–1922.
29. Sowell, E.R.; Peterson, B.S.; Thompson, P.M.; Welcome, S.E.; Henkenius, A.L.; Toga, A.W. Mapping cortical change across the human life span. *Nat. Neurosci.* **2003**, *6*, 309–315.
30. Lenroot, R.K.; Gogtay, N.; Greenstein, D.K.; Wells, E.M.; Wallace, G.L.; Clasen, L.S.; Blumenthal, J.D.; Lerch, J.; Zijdenbos, A.P.; Evans, A.C. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. *NeuroImage* **2007**, *36*, 1065–1073.
31. McGuffin, P.; Rijdsdijk, F.; Andrew, M.; Sham, P.; Katz, R.; Cardno, A. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Arch. Gen. Psychiatry* **2003**, *60*, 497–502.
32. Birmaher, B.; Axelson, D.; Monk, K.; Kalas, C.; Goldstein, B.; Hickey, M.B.; Obreja, M.; Ehmman, M.; Iyengar, S.; Shamseddeen, W.; *et al.* Lifetime psychiatric disorders in school-aged offspring of parents with bipolar disorder: The Pittsburgh Bipolar Offspring study. *Arch. Gen. Psychiatry* **2009**, *66*, 287–296.
33. Fried, I.; Cameron, K.A.; Yashar, S.; Fong, R.; Morrow, J.W. Inhibitory and excitatory responses of single neurons in the human medial temporal lobe during recognition of faces and objects. *Cereb. Cortex* **2002**, *12*, 575–584.
34. Baxter, M.G.; Murray, E.A. The amygdala and reward. *Nat. Rev. Neurosci.* **2002**, *3*, 563–573.
35. Bauman, M.D.; Lavenex, P.; Mason, W.A.; Capitanio, J.P.; Amaral, D.G. The development of social behavior following neonatal amygdala lesions in rhesus monkeys. *J. Cogn. Neurosci.* **2004**, *16*, 1388–1411.
36. Phelps, E.A.; LeDoux, J.E. Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron* **2005**, *48*, 175–187.
37. Bachevalier, J.; Loveland, K.A. The orbitofrontal-amygdala circuit and self-regulation of social-emotional behavior in autism. *Neurosci. Biobehav. Rev.* **2006**, *30*, 97–117.
38. Nauta, W.J. The problem of the frontal lobe: A reinterpretation. *J. Psychiatr. Res.* **1971**, *8*, 167–187.
39. Rolls, E.T. The Orbitofrontal Cortex. In *the Prefrontal Cortex: Executive and Cognitive Functions*; Roberts, A.C., Robbins, T.W., Weiskrantz, L., Eds.; Oxford University Press: New York, NY, USA, 1998; pp. 67–86.
40. Amaral, D.G.; Price, J.L. Amygdalo-cortical projections in the monkey (*Macaca fascicularis*). *J. Comp. Neurol.* **1984**, *230*, 465–496.
41. Giedd, J.N.; Blumenthal, J.; Jeffries, N.O.; Castellanos, F.X.; Liu, H.; Zijdenbos, A.; Paus, T.; Evans, A.C.; Rapoport, J.L. Brain development during childhood and adolescence: A longitudinal MRI study. *Nat. Neurosci.* **1999**, *2*, 861–863.
42. Sowell, E.R.; Thompson, P.M.; Holmes, C.J.; Jernigan, T.L.; Toga, A.W. *In vivo* evidence for post-adolescent brain maturation in frontal and striatal regions. *Nat. Neurosci.* **1999**, *2*, 859–861.
43. Öngür, D.; Drevets, W.C.; Price, J.L. Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proc. Nat. Acad. Sci. USA* **1998**, *95*, 13290–13295.
44. Rajkowska, G. Cell pathology in mood disorders. *Semin. Clin. Neuropsychiatry* **2002**, *7*, 281–292.

45. Tkachev, D.; Mimmack, M.L.; Ryan, M.M.; Wayland, M.; Freeman, T.; Jones, P.B.; Starkey, M.; Webster, M.J.; Yolken, R.H.; Bahn, S. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *Lancet* **2003**, *362*, 798–805.
46. Uranova, N.A.; Vostrikov, V.M.; Orlovskaya, D.D.; Rachmanova, V.I. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: A study from the Stanley Neuropathology Consortium. *Schizophr. Res.* **2004**, *67*, 269–275.
47. Roy, K.; Murtie, J.C.; El-Khodori, B.F.; Edgar, N.; Sardi, S.P.; Hooks, B.M.; Benoit-Marand, M.; Chen, C.; Moore, H.; O'Donnell, P.; *et al.* Loss of ErbB signaling in oligodendrocytes alters myelin and dopaminergic function, a potential mechanism for neuropsychiatric disorders. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 8131–8136.
48. Blumberg, H.P.; Leung, H.C.; Skudlarski, P.; Lacadie, C.M.; Fredericks, C.A.; Harris, B.C.; Charney, D.S.; Gore, J.C.; Krystal, J.H.; Peterson, B.S. A functional magnetic resonance imaging study of bipolar disorder: State- and trait-related dysfunction in ventral prefrontal cortices. *Arch. Gen. Psychiatry* **2003**, *60*, 601–609.
49. Mesulam, M.M.; Mufson, E.J. Insula of the old world monkey. Architectonics in the insulo-orbito-temporal component of the paralimbic brain. *J. Comp. Neurol.* **1982**, *212*, 1–22.
50. Morecraft, R.J.; Geula, C.; Mesulam, M.M. Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. *J. Comp. Neurol.* **1992**, *323*, 341–358.
51. Devinsky, O.; Morrell, M.J.; Vogt, B.A. Contributions of anterior cingulate cortex to behaviour. *Brain* **1995**, *118*, 279–306.
52. Vogt, B.A.; Nimchinsky, E.A.; Vogt, L.J.; Hof, P.R. Human cingulate cortex: Surface features, flat maps, and cytoarchitecture. *J. Comp. Neurol.* **1995**, *359*, 490–506.
53. Brambilla, P.; Nicoletti, M.A.; Sassi, R.B.; Mallinger, A.G.; Frank, E.; Kupfer, D.J.; Keshavan, M.S.; Soares, J.C. Magnetic resonance imaging study of corpus callosum abnormalities in patients with bipolar disorder. *Biol. Psychiatry* **2003**, *54*, 1294–1297.
54. Brambilla, P.; Nicoletti, M.; Sassi, R.B.; Mallinger, A.G.; Frank, E.; Keshavan, M.S.; Soares, J.C. Corpus callosum signal intensity in patients with bipolar and unipolar disorder. *J. Neurol. Neurosurg. Psychiatry* **2004**, *75*, 221–225.
55. Matsuo, K.; Nielsen, N.; Nicoletti, M.A.; Hatch, J.P.; Monkul, E.S.; Watanabe, Y.; Zunta-Soares, G.B.; Nery, F.G.; Soares, J.C. Anterior genu corpus callosum and impulsivity in suicidal patients with bipolar disorder. *Neurosci. Lett.* **2010**, *469*, 75–80.
56. Caetano, S.C.; Silveira, C.M.; Kaur, S.; Nicoletti, M.; Hatch, J.P.; Brambilla, P.; Sassi, R.; Axelson, D.; Keshavan, M.S.; Ryan, N.D.; *et al.* Abnormal corpus callosum myelination in pediatric bipolar patients. *J. Affect. Disord.* **2008**, *108*, 297–301.
57. Awad, I.A.; Johnson, P.C.; Spetzler, R.F.; Hodak, J.A. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. II. Postmortem pathological correlations. *Stroke* **1986**, *17*, 1090–1097.
58. Kirkpatrick, J.B.; Hayman, L.A. White-matter lesions in MR imaging of clinically healthy brains of elderly subjects: Possible pathologic basis. *Radiology* **1987**, *162*, 509–511.

59. O'Brien, J.T.; Firbank, M.J.; Krishnan, M.S.; van Straaten, E.C.; van der Flier, W.M.; Petrovic, K.; Pantoni, L.; Simoni, M.; Erkinjuntti, T.; Wallin, A.; *et al.* White matter hyperintensities rather than lacunar infarcts are associated with depressive symptoms in older people: The LADIS study. *Am. J. Geriatr. Psychiatry* **2006**, *14*, 834–841.
60. Figiel, G.S.; Krishnan, K.R.; Rao, V.P.; Doraiswamy, M.; Ellinwood, E.H., Jr.; Nemeroff, C.B.; Evans, D.; Boyko, O. Subcortical hyperintensities on brain magnetic resonance imaging: A comparison of normal and bipolar subjects. *J. Neuropsychiatry Clin. Neurosci.* **1991**, *3*, 18–22.
61. Aylward, E.H.; Roberts-Twillie, J.V.; Barta, P.E.; Kumar, A.J.; Harris, G.J.; Geer, M.; Peyser, C.E.; Pearlson, G.D. Basal ganglia volumes and white matter hyperintensities in patients with bipolar disorder. *Am. J. Psychiatry* **1994**, *151*, 687–693.
62. Pompili, M.; Innamorati, M.; Mann, J.J.; Oquendo, M.A.; Lester, D.; del Casale, A.; Serafini, G.; Rigucci, S.; Romano, A.; Tamburello, A.; *et al.* Periventricular white matter hyperintensities as predictors of suicide attempts in bipolar disorders and unipolar depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2008**, *32*, 1501–1507.
63. Altshuler, L.L.; Curran, J.G.; Hauser, P.; Mintz, J.; Denicoff, K.; Post, R. T2 hyperintensities in bipolar disorder: Magnetic resonance imaging comparison and literature meta-analysis. *Am. J. Psychiatry* **1995**, *152*, 1139–1144.
64. Dupont, R.M.; Butters, N.; Schafer, K.; Wilson, T.; Hesselink, J.; Gillin, J.C. Diagnostic specificity of focal white matter abnormalities in bipolar and unipolar mood disorder. *Biol. Psychiatry* **1995**, *38*, 482–486.
65. Moore, P.B.; Shepherd, D.J.; Eccleston, D.; Macmillan, I.C.; Goswami, U.; McAllister, V.L.; Ferrier, I.N. Cerebral white matter lesions in bipolar affective disorder: Relationship to outcome. *Br. J. Psychiatry* **2001**, *178*, 172–176.
66. Silverstone, T.; McPherson, H.; Li, Q.; Doyle, T. Deep white matter hyperintensities in patients with bipolar depression, unipolar depression and age-matched control subjects. *Bipolar Disord.* **2003**, *5*, 53–57.
67. Ahn, K.H.; Lyoo, I.K.; Lee, H.K.; Song, I.C.; Oh, J.S.; Hwang, J.; Kwon, J.; Kim, M.J.; Kim, M.; Renshaw, P.F. White matter hyperintensities in subjects with bipolar disorder. *Psychiatry Clin. Neurosci.* **2004**, *58*, 516–521.
68. De Asis, J.M.; Greenwald, B.S.; Alexopoulos, G.S.; Kiosses, D.N.; Ashtari, M.; Heo, M.; Young, R.C. Frontal signal hyperintensities in mania in old age. *Am. J. Geriatr. Psychiatry* **2006**, *14*, 598–604.
69. Tamashiro, J.H.; Zung, S.; Zanetti, M.V.; de Castro, C.C.; Vallada, H.; Busatto, G.F.; de Toledo Ferraz Alves, T.C. Increased rates of white matter hyperintensities in late-onset bipolar disorder. *Bipolar Disord.* **2008**, *10*, 765–775.
70. Macritchie, K.A.; Lloyd, A.J.; Bastin, M.E.; Vasudev, K.; Gallagher, P.; Eyre, R.; Marshall, I.; Wardlaw, J.M.; Ferrier, I.N.; Moore, P.B.; *et al.* White matter microstructural abnormalities in euthymic bipolar disorder. *Br. J. Psychiatry* **2010**, *196*, 52–58.
71. Zanetti, M.V.; Cordeiro, Q.; Busatto, G.F. Late onset bipolar disorder associated with white matter hyperintensities: A pathophysiological hypothesis. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2007**, *31*, 551–556.

72. Botteron, K.N.; Vannier, M.W.; Geller, B.; Todd, R.D.; Lee, B.C. Preliminary study of magnetic resonance imaging characteristics in 8- to 16-year-olds with mania. *J. Am. Acad. Child Adolesc. Psychiatry* **1995**, *34*, 742–749.
73. Chang, K.; Barnea-Goraly, N.; Karchemskiy, A.; Simeonova, D.I.; Barnes, P.; Ketter, T.; Reiss, A.L. Cortical magnetic resonance imaging findings in familial pediatric bipolar disorder. *Biol. Psychiatry* **2005**, *58*, 197–203.
74. Lyoo, I.K.; Lee, H.K.; Jung, J.H.; Noam, G.G.; Renshaw, P.F. White matter hyperintensities on magnetic resonance imaging of the brain in children with psychiatric disorders. *Compr. Psychiatry* **2002**, *43*, 361–368.
75. Pillai, J.J.; Friedman, L.; Stuve, T.A.; Trinidad, S.; Jesberger, J.A.; Lewin, J.S.; Findling, R.L.; Swales, T.P.; Schulz, S.C. Increased presence of white matter hyperintensities in adolescent patients with bipolar disorder. *Psychiatry Res.* **2002**, *114*, 51–56.
76. Basser, P.J.; Mattiello, J.; LeBihan, D. Estimation of the effective self-diffusion tensor from the NMR spin echo. *J. Magn. Reson.* **1994**, *103*, 247–254.
77. Beaulieu, C. The basis of anisotropic water diffusion in the nervous system—A technical review. *NMR Biomed.* **2002**, *15*, 435–455.
78. Beyer, J.L.; Taylor, W.D.; MacFall, J.R.; Kuchibhatla, M.; Payne, M.E.; Provenzale, J.M.; Cassidy, F.; Krishnan, K.R. Cortical white matter microstructural abnormalities in bipolar disorder. *Neuropsychopharmacology* **2005**, *30*, 2225–2229.
79. Versace, A.; Almeida, J.R.; Hassel, S.; Walsh, N.D.; Novelli, M.; Klein, C.R.; Kupfer, D.J.; Phillips, M.L. Elevated left and reduced right orbitomedial prefrontal fractional anisotropy in adults with bipolar disorder revealed by tract-based spatial statistics. *Arch. Gen. Psychiatry* **2008**, *65*, 1041–1052.
80. McIntosh, A.M.; Munoz Maniega, S.; Lymer, G.K.; McKirdy, J.; Hall, J.; Sussmann, J.E.; Bastin, M.E.; Clayden, J.D.; Johnstone, E.C.; Lawrie, S.M. White matter tractography in bipolar disorder and schizophrenia. *Biol. Psychiatry* **2008**, *64*, 1088–1092.
81. Wang, F.; Kalmar, J.H.; He, Y.; Jackowski, M.; Chepenik, L.G.; Edmiston, E.E.; Tie, K.; Gong, G.; Shah, M.P.; Jones, M.; *et al.* Functional and structural connectivity between the perigenual anterior cingulate and amygdala in bipolar disorder. *Biol. Psychiatry* **2009**, *66*, 516–521.
82. Sussmann, J.E.; Lymer, G.K.; McKirdy, J.; Moorhead, T.W.; Munoz Maniega, S.; Job, D.; Hall, J.; Bastin, M.E.; Johnstone, E.C.; Lawrie, S.M.; *et al.* White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging. *Bipolar Disord.* **2009**, *11*, 11–18.
83. Versace, A.; Almeida, J.R.; Quevedo, K.; Thompson, W.K.; Terwilliger, R.A.; Hassel, S.; Kupfer, D.J.; Phillips, M.L. Right orbitofrontal corticolimbic and left corticocortical white matter connectivity differentiate bipolar and unipolar depression. *Biol. Psychiatry* **2010**, *68*, 560–567.
84. Lin, F.; Weng, S.; Xie, B.; Wu, G.; Lei, H. Abnormal frontal cortex white matter connections in bipolar disorder: A DTI tractography study. *J. Affect. Disord.* **2011**, *131*, 299–306.
85. Sui, J.; Pearlson, G.; Caprihan, A.; Adali, T.; Kiehl, K.A.; Liu, J.; Yamamoto, J.; Calhoun, V.D. Discriminating schizophrenia and bipolar disorder by fusing fMRI and DTI in a multimodal CCA+ joint ICA model. *NeuroImage* **2011**, *57*, 839–855.

86. Benedetti, F.; Absinta, M.; Rocca, M.A.; Radaelli, D.; Poletti, S.; Bernasconi, A.; Dallspezia, S.; Pagani, E.; Falini, A.; Copetti, M.; *et al.* Tract-specific white matter structural disruption in patients with bipolar disorder. *Bipolar Disord.* **2011**, *13*, 414–424.
87. Linke, J.; King, A.V.; Poupon, C.; Hennerici, M.G.; Gass, A.; Wessa, M. Impaired anatomical connectivity and related executive functions: Differentiating vulnerability and disease marker in bipolar disorder. *Biol. Psychiatry* **2013**, *74*, 908–916.
88. Versace, A.; Andreazza, A.C.; Young, L.T.; Fournier, J.C.; Almeida, J.R.; Stiffler, R.S.; Lockovich, J.C.; Aslam, H.A.; Pollock, M.H.; Park, H.; *et al.* Elevated serum measures of lipid peroxidation and abnormal prefrontal white matter in euthymic bipolar adults: Toward peripheral biomarkers of bipolar disorder. *Mol. Psychiatry* **2013**, *19*, 200–208.
89. Wang, F.; Jackowski, M.; Kalmar, J.H.; Chepenik, L.G.; Tie, K.; Qiu, M.; Gong, G.; Pittman, B.P.; Jones, M.M.; Shah, M.P.; *et al.* Abnormal anterior cingulum integrity in bipolar disorder determined through diffusion tensor imaging. *Br. J. Psychiatry* **2008**, *193*, 126–129.
90. Chan, W.Y.; Yang, G.L.; Chia, M.Y.; Woon, P.S.; Lee, J.; Keefe, R.; Sitoh, Y.Y.; Nowinski, W.L.; Sim, K. Cortical and subcortical white matter abnormalities in adults with remitted first-episode mania revealed by tract-based spatial statistics. *Bipolar Disord.* **2010**, *12*, 383–389.
91. Barysheva, M.; Jahanshad, N.; Foland-Ross, L.; Altshuler, L.L.; Thompson, P.M. White matter microstructural abnormalities in bipolar disorder: A whole brain diffusion tensor imaging study. *NeuroImage* **2013**, *2*, 558–568.
92. Emsell, L.; Chaddock, C.; Forde, N.; van Hecke, W.; Barker, G.J.; Leemans, A.; Sunaert, S.; Walshe, M.; Bramon, E.; Cannon, D.; *et al.* White matter microstructural abnormalities in families multiply affected with bipolar I disorder: A diffusion tensor tractography study. *Psychol. Med.* **2013**, doi:10.1017/S0033291713002845.
93. Haznedar, M.M.; Roversi, F.; Pallanti, S.; Baldini-Rossi, N.; Schnur, D.B.; Licalzi, E.M.; Tang, C.; Hof, P.R.; Hollander, E.; Buchsbaum, M.S. Fronto-thalamo-striatal gray and white matter volumes and anisotropy of their connections in bipolar spectrum illnesses. *Biol. Psychiatry* **2005**, *57*, 733–742.
94. Chaddock, C.A.; Barker, G.J.; Marshall, N.; Schulze, K.; Hall, M.H.; Fern, A.; Walshe, M.; Bramon, E.; Chitnis, X.A.; Murray, R.; *et al.* White matter microstructural impairments and genetic liability to familial bipolar I disorder. *Br. J. Psychiatry* **2009**, *194*, 527–534.
95. Wang, F.; Kalmar, J.H.; Edmiston, E.; Chepenik, L.G.; Bhagwagar, Z.; Spencer, L.; Pittman, B.; Jackowski, M.; Papademetris, X.; Constable, R.T.; *et al.* Abnormal corpus callosum integrity in bipolar disorder: A diffusion tensor imaging study. *Biol. Psychiatry* **2008**, *64*, 730–733.
96. Benedetti, F.; Yeh, P.H.; Bellani, M.; Radaelli, D.; Nicoletti, M.A.; Poletti, S.; Falini, A.; Dallspezia, S.; Colombo, C.; Scotti, G.; *et al.* Disruption of white matter integrity in bipolar depression as a possible structural marker of illness. *Biol. Psychiatry* **2011**, *69*, 309–317.
97. Haller, S.; Xekardaki, A.; Delaloye, C.; Canuto, A.; Lovblad, K.O.; Gold, G.; Giannakopoulos, P. Combined analysis of grey matter voxel-based morphometry and white matter tract-based spatial statistics in late-life bipolar disorder. *J. Psychiatry Neurosci.* **2011**, *36*, 391–401.
98. Lagopoulos, J.; Hermens, D.F.; Hatton, S.N.; Tobias-Webb, J.; Griffiths, K.; Naismith, S.L.; Scott, E.M.; Hickie, I.B. Microstructural white matter changes in the corpus callosum of young people with bipolar disorder: A diffusion tensor imaging study. *PLoS One* **2013**, *8*, e59108.

99. Leow, A.; Ajilore, O.; Zhan, L.; Arienzo, D.; GadElkarim, J.; Zhang, A.; Moody, T.; van Horn, J.; Feusner, J.; Kumar, A.; *et al.* Impaired inter-hemispheric integration in bipolar disorder revealed with brain network analyses. *Biol. Psychiatry* **2013**, *73*, 183–193.
100. Canales-Rodríguez, E.J.; Pomarol-Clotet, E.; Radua, J.; Sarró, S.; Alonso-Lana, S.; del Mar Bonnín, C.; Goikolea, J.M.; Maristany, T.; García-Álvarez, R.; Vieta, E. Structural abnormalities in bipolar euthymia: A multicontrast molecular diffusion imaging study. *Biol. Psychiatry* **2013**, doi:10.1016/j.biopsych.2013.09.027.
101. Versace, A.; Ladouceur, C.D.; Romero, S.; Birmaher, B.; Axelson, D.A.; Kupfer, D.J.; Phillips, M.L. Altered development of white matter in youth at high familial risk for bipolar disorder: A diffusion tensor imaging study. *J. Am. Acad. Child Adolesc. Psychiatry* **2010**, *49*, 1249–1259.
102. Frazier, J.A.; Breeze, J.L.; Papadimitriou, G.; Kennedy, D.N.; Hodge, S.M.; Moore, C.M.; Howard, J.D.; Rohan, M.P.; Caviness, V.S.; Makris, N. White matter abnormalities in children with and at risk for bipolar disorder. *Bipolar Disord.* **2007**, *9*, 799–809.
103. Adler, C.M.; Adams, J.; DelBello, M.P.; Holland, S.K.; Schmithorst, V.; Levine, A.; Jarvis, K.; Strakowski, S.M. Evidence of white matter pathology in bipolar disorder adolescents experiencing their first episode of mania: A diffusion tensor imaging study. *Am. J. Psychiatry* **2006**, *163*, 322–324.
104. Kafantaris, V.; Kingsley, P.; Ardekani, B.; Saito, E.; Lencz, T.; Lim, K.; Szeszko, P. Lower orbital frontal white matter integrity in adolescents with bipolar I disorder. *J. Am. Acad. Child Adolesc. Psychiatry* **2009**, *48*, 79–86.
105. Pavuluri, M.N.; Yang, S.; Kamineni, K.; Passarotti, A.M.; Srinivasan, G.; Harral, E.M.; Sweeney, J.A.; Zhou, X.J. Diffusion tensor imaging study of white matter fiber tracts in pediatric bipolar disorder and attention-deficit/hyperactivity disorder. *Biol. Psychiatry* **2009**, *65*, 586–593.
106. Barnea-Goraly, N.; Chang, K.D.; Karchemskiy, A.; Howe, M.E.; Reiss, A.L. Limbic and corpus callosum aberrations in adolescents with bipolar disorder: A tract-based spatial statistics analysis. *Biol. Psychiatry* **2009**, *66*, 238–244.
107. Gönenç, A.; Frazier, J.A.; Crowley, D.J.; Moore, C.M. Combined diffusion tensor imaging and transverse relaxometry in early-onset bipolar disorder. *J. Am. Acad. Child Adolesc. Psychiatry* **2010**, *49*, 1260–1268.
108. Saxena, K.; Tamm, L.; Walley, A.; Simmons, A.; Rollins, N.; Chia, J.; Soares, J.C.; Emslie, G.J.; Fan, X.; Huang, H. A preliminary investigation of corpus callosum and anterior commissure aberrations in aggressive youth with bipolar disorders. *J. Child Adolesc. Psychopharmacol.* **2012**, *22*, 112–119.
109. Gao, W.; Jiao, Q.; Qi, R.; Zhong, Y.; Lu, D.; Xiao, Q.; Lu, S.; Xu, C.; Zhang, Y.; Liu, X.; *et al.* Combined analyses of gray matter voxel-based morphometry and white matter tract-based spatial statistics in pediatric bipolar mania. *J. Affect. Disord.* **2013**, *150*, 70–76.
110. Lu, L.H.; Zhou, X.J.; Fitzgerald, J.; Keedy, S.K.; Reilly, J.L.; Passarotti, A.M.; Sweeney, J.A.; Pavuluri, M. Microstructural abnormalities of white matter differentiate pediatric and adult-onset bipolar disorder. *Bipolar Disord.* **2012**, *14*, 597–606.

111. Chepenik, L.G.; Raffo, M.; Hampson, M.; Lacadie, C.; Wang, F.; Jones, M.M.; Pittman, B.; Skudlarski, P.; Blumberg, H.P. Functional connectivity between ventral prefrontal cortex and amygdala at low frequency in the resting state in bipolar disorder. *Psychiatry Res.* **2010**, *182*, 207–210.
112. Versace, A.; Thompson, W.K.; Zhou, D.; Almeida, J.R.; Hassel, S.; Klein, C.R.; Kupfer, D.J.; Phillips, M.L. Abnormal left and right amygdala-orbitofrontal cortical functional connectivity to emotional faces: State *versus* trait vulnerability markers of depression in bipolar disorder. *Biol. Psychiatry* **2010**, *67*, 422–431.
113. Vizueta, N.; Rudie, J.D.; Townsend, J.D.; Torrisi, S.; Moody, T.D.; Bookheimer, S.Y.; Altshuler, L.L. Regional fMRI hypoactivation and altered functional connectivity during emotion processing in nonmedicated depressed patients with bipolar II disorder. *Am. J. Psychiatry* **2012**, *169*, 831–840.
114. Townsend, J.D.; Torrisi, S.J.; Lieberman, M.D.; Sugar, C.A.; Bookheimer, S.Y.; Altshuler, L.L. Frontal-amygdala connectivity alterations during emotion downregulation in bipolar I disorder. *Biol. Psychiatry* **2013**, *73*, 127–135.
115. Torrisi, S.; Moody, T.D.; Vizueta, N.; Thomason, M.E.; Monti, M.M.; Townsend, J.D.; Bookheimer, S.Y.; Altshuler, L.L. Differences in resting corticolimbic functional connectivity in bipolar I euthymia. *Bipolar Disord.* **2013**, *15*, 156–166.
116. Liu, H.; Tang, Y.; Womer, F.; Fan, G.; Lu, T.; Driesen, N.; Ren, L.; Wang, Y.; He, Y.; Blumberg, H.P.; *et al.* Differentiating patterns of amygdala-frontal functional connectivity in schizophrenia and bipolar disorder. *Schizophr. Bull.* **2013**, *40*, 469–477.
117. Ladouceur, C.D.; Farchione, T.; Diwadkar, V.; Pruitt, P.; Radwan, J.; Axelson, D.A.; Birmaher, B.; Phillips, M.L. Differential patterns of abnormal activity and connectivity in the amygdala-prefrontal circuitry in bipolar-I and bipolar-NOS youth. *J. Am. Acad. Child Adolesc. Psychiatry* **2011**, *50*, 1275–1289.
118. Wang, F.; Bobrow, L.; Liu, J.; Spencer, L.; Blumberg, H.P. Corticolimbic functional connectivity in adolescents with bipolar disorder. *PLoS One* **2012**, *7*, e50177.
119. Passarotti, A.M.; Ellis, J.; Wegbreit, E.; Stevens, M.C.; Pavuluri, M.N. Reduced functional connectivity of prefrontal regions and amygdala within affect and working memory networks in pediatric bipolar disorder. *Brain Connect.* **2012**, *2*, 320–334.
120. Davidson, R.J. Anxiety and affective style: Role of prefrontal cortex and amygdala. *Biol. Psychiatry* **2002**, *51*, 68–80.
121. Rich, B.A.; Fromm, S.J.; Berghorst, L.H.; Dickstein, D.P.; Brotman, M.A.; Pine, D.S.; Leibenluft, E. Neural connectivity in children with bipolar disorder: Impairment in the face emotion processing circuit. *J. Child Psychol. Psychiatry* **2008**, *49*, 88–96.
122. Haxby, J.V.; Hoffman, E.A.; Gobbini, M.I. Human neural systems for face recognition and social communication. *Biol. Psychiatry* **2002**, *51*, 59–67.
123. Craddock, N.; Jones, I. Genetics of bipolar disorder. *J. Med. Genet.* **1999**, *36*, 585–594.
124. Kim, S.; Webster, M.J. Correlation analysis between genome-wide expression profiles and cytoarchitectural abnormalities in the prefrontal cortex of psychiatric disorders. *Mol. Psychiatry* **2010**, *15*, 326–336.

125. Moises, H.W.; Zoega, T.; Gottesman, I.I. The glial growth factors deficiency and synaptic destabilization hypothesis of schizophrenia. *BMC Psychiatry* **2002**, *2*, doi:10.1186/1471-244X-2-8.
126. Corfas, G.; Roy, K.; Buxbaum, J.D. Neuregulin 1-erbB signaling and the molecular/cellular basis of schizophrenia. *Nat. Neurosci.* **2004**, *7*, 575–580.
127. Lopez-Bendito, G.; Cautinat, A.; Sanchez, J.A.; Bielle, F.; Flames, N.; Garratt, A.N.; Talmage, D.A.; Role, L.W.; Charnay, P.; Marin, O.; *et al.* Tangential neuronal migration controls axon guidance: A role for neuregulin-1 in thalamocortical axon navigation. *Cell* **2006**, *125*, 127–142.
128. Green, E.K.; Raybould, R.; Macgregor, S.; Gordon-Smith, K.; Heron, J.; Hyde, S.; Grozeva, D.; Hamshere, M.; Williams, N.; Owen, M.J.; *et al.* Operation of the schizophrenia susceptibility gene, neuregulin 1, across traditional diagnostic boundaries to increase risk for bipolar disorder. *Arch. Gen. Psychiatry* **2005**, *62*, 642–648.
129. Cannon, D.M.; Walshe, M.; Dempster, E.; Collier, D.A.; Marshall, N.; Bramon, E.; Murray, R.M.; McDonald, C. The association of white matter volume in psychotic disorders with genotypic variation in NRG1, MOG and CNP: A voxel-based analysis in affected individuals and their unaffected relatives. *Transl. Psychiatry* **2012**, *2*, e167.
130. McIntosh, A.M.; Moorhead, T.W.; Job, D.; Lymer, G.K.; Munoz Maniega, S.; McKirdy, J.; Sussmann, J.E.; Baig, B.J.; Bastin, M.E.; Porteous, D.; *et al.* The effects of a neuregulin 1 variant on white matter density and integrity. *Mol. Psychiatry* **2008**, *13*, 1054–1059.
131. Ferreira, M.A.; O'Donovan, M.C.; Meng, Y.A.; Jones, I.R.; Ruderfer, D.M.; Jones, L.; Fan, J.; Kirov, G.; Perlis, R.H.; Green, E.K.; *et al.* Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. *Nat. Genet.* **2008**, *40*, 1056–1058.
132. Sklar, P.; Smoller, J.W.; Fan, J.; Ferreira, M.A.; Perlis, R.H.; Chambert, K.; Nimgaonkar, V.L.; McQueen, M.B.; Faraone, S.V.; Kirby, A.; *et al.* Whole-genome association study of bipolar disorder. *Mol. Psychiatry* **2008**, *13*, 558–569.
133. West, A.E.; Chen, W.G.; Dalva, M.B.; Dolmetsch, R.E.; Kornhauser, J.M.; Shaywitz, A.J.; Takasu, M.A.; Tao, X.; Greenberg, M.E. Calcium regulation of neuronal gene expression. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 11024–11031.
134. Wang, F.; McIntosh, A.M.; He, Y.; Gelernter, J.; Blumberg, H.P. The association of genetic variation in CACNA1C with structure and function of a frontotemporal system. *Bipolar Disord.* **2011**, *13*, 696–700.
135. Hillegers, M.H.; Reichart, C.G.; Wals, M.; Verhulst, F.C.; Ormel, J.; Nolen, W.A. Five-year prospective outcome of psychopathology in the adolescent offspring of bipolar parents. *Bipolar Disord.* **2005**, *7*, 344–350.
136. Duffy, A.; Alda, M.; Crawford, L.; Milin, R.; Grof, P. The early manifestations of bipolar disorder: A longitudinal prospective study of the offspring of bipolar parents. *Bipolar Disord.* **2007**, *9*, 828–838.
137. Goodwin, F.K.; Jamison, K.R. *Manic-Depressive Illness. Bipolar Disorders and Recurrent Depression*, 2nd ed.; Oxford University Press: New York, NY, USA, 2007.
138. Van Os, J.; Jones, P.; Lewis, G.; Wadsworth, M.; Murray, R. Developmental precursors of affective illness in a general population birth cohort. *Arch. Gen. Psychiatry* **1997**, *54*, 625–631.

139. Kieseppä, T.; van Erp, T.G.; Haukka, J.; Partonen, T.; Cannon, T.D.; Poutanen, V.P.; Kaprio, J.; Lönqvist, J. Reduced left hemispheric white matter volume in twins with bipolar I disorder. *Biol. Psychiatry* **2003**, *54*, 896–905.
140. Ahearn, E.P.; Steffens, D.C.; Cassidy, F.; van Meter, S.A.; Provenzale, J.M.; Seldin, M.F.; Weisler, R.H.; Krishnan, K.R. Familial leukoencephalopathy in bipolar disorder. *Am. J. Psychiatry* **1998**, *155*, 1605–1607.
141. Ahearn, E.P.; Speer, M.C.; Chen, Y.T.; Steffens, D.C.; Cassidy, F.; van Meter, S.; Provenzale, J.M.; Weisler, R.H.; Krishnan, K.R. Investigation of Notch3 as a candidate gene for bipolar disorder using brain hyperintensities as an endophenotype. *Am. J. Med. Genet.* **2002**, *114*, 652–658.
142. Sprooten, E.; Sussmann, J.E.; Clugston, A.; Peel, A.; McKirdy, J.; Moorhead, T.W.; Anderson, S.; Shand, A.J.; Giles, S.; Bastin, M.E.; *et al.* White matter integrity in individuals at high genetic risk of bipolar disorder. *Biol. Psychiatry* **2011**, *70*, 350–356.
143. Mahon, K.; Burdick, K.E.; Ikuta, T.; Braga, R.J.; Gruner, P.; Malhotra, A.K.; Szeszko, P.R. Abnormal temporal lobe white matter as a biomarker for genetic risk of bipolar disorder. *Biol. Psychiatry* **2013**, *73*, 177–182.
144. Arts, B.; Jabben, N.; Krabbendam, L.; van Os, J. Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. *Psychol. Med.* **2008**, *38*, 771–786.

© 2014 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (<http://creativecommons.org/licenses/by/3.0/>).