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Widespread white matter tract aberrations in youth with familial risk for bipolar disorder

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Abstract

Few studies have examined multiple measures of white matter (WM) differences in youth with familial risk for bipolar disorder (FR-BD). To investigate WM in the FR-BD group, we used three measures of WM structure and two methods of analysis. We used fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) to analyze diffusion tensor imaging (DTI) findings in 25 youth with familial risk for bipolar disorder, defined as having both a parent with BD and mood dysregulation, and 16 sex-, age-, and IQ-matched healthy controls. We conducted a whole brain voxelwise analysis using tract based spatial statistics (TBSS). Subsequently, we conducted a complementary atlas-based, region-of-interest analysis using Diffeomap to confirm results seen in TBSS. When TBSS was used, significant widespread between-group differences were found showing increased FA, increased AD, and decreased RD in the FR-BD group in the bilateral uncinate fasciculus, cingulum, cingulate, superior fronto-occipital fasciculus (SFOF), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus, and corpus callosum. Atlas-based analysis confirmed significant between-group differences, with increased FA and decreased RD in the FR-BD group in the SLF, cingulum, and SFOF. We found significant widespread WM tract aberrations in youth with familial risk for BD using two complementary methods of DTI analysis.

Keywords

Diffusion tensor imaging; Pediatric; Tract-based spatial statistics; Diffeomap; Atlas-based analysis; Neuroimaging

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.psychresns.2015.02.007>.

1. Introduction

Children with bipolar disorder (BD) have a more severe course of illness (Geller et al., 2002; Togen and Angst, 2002; Carter et al., 2003; Geller and DelBello, 2003; Perlis et al., 2004; Birmaher et al., 2006, 2009) with higher relapse, psychosocial impairment, substance use, and twice the rate of attempted suicides (Axelson et al., 2006) when compared with children with unipolar depression. Childhood-onset BD is linked to genetic heritability, placing children of parents with BD at highest risk for the disorder (Craney and Geller, 2003; Faraone et al., 2003; Dilsaver and Akiskal, 2004; Lin et al., 2006; Rende et al., 2007). These children with familial risk for BD also may exhibit early mood symptoms or attention deficit/hyperactivity disorder (ADHD) (Carlson and Weintraub, 1993; Chang et al., 2000; Tillman and Geller, 2006) before the first manic episode. These early symptoms are often the catalyst for treatment initiation. Nearly half of those children with familial risk for BD will develop BD 4–5 years after their initial assessment (Axelson et al., 2011). Whether or not they develop the illness, these children have ongoing mood dysregulation and functional impairment (Birmaher et al., 2009; Carlson, 2009; Luby and Navsaria, 2010). Understanding their pathophysiology may have important implications for the course of BD, regardless of whether vulnerable children go on to develop full syndromal BD.

Converging evidence suggests white matter (WM) abnormalities in BD (Yendiki et al., 2011). Previous diffusion tensor imaging (DTI) studies of adults (Adler et al., 2004; Beyer et al., 2005; Haznedar et al., 2005; Wang et al., 2008a, 2008b; Sussmann et al., 2009) and adolescents (Adler et al., 2006; Frazier et al., 2007; Pavuluri et al., 2009; Gonenc et al., 2010) with BD using a region-of-interest (ROI) approach have shown WM tract abnormalities in the frontal cortex, corpus callosum (CC), inferior longitudinal fasciculus (ILF), thalamic pathways, uncinate fasciculus (UF), cingulate-paracingulate, cingulum, and superior longitudinal fasciculus (SLF). However, an ROI approach is limited in that it only allows for analyses of pre-defined *a priori* regions. Whole brain DTI analyses using standard voxel-based morphometry (VBM) in adults (Haznedar et al., 2005; Bruno et al., 2008; Wang et al., 2008a, 2008b; Chaddock et al., 2009; Mahon et al., 2009; Sussmann et al., 2009; Barysheva et al., 2013) and adolescents (Kafantaris et al., 2009; Chen et al., 2012; Barysheva et al., 2013; Emsell et al., 2013) have shown additional abnormalities in the inferior fronto-occipital fasciculus (IFOF), corona radiata, anterior thalamic radiation (ATR), orbitofrontal regions, subgenual, precuneus, postcentral gyrus, cortical and thalamic association fibers, ILF, CC, cingulum, and inferior and superior fronto-occipital fasciculi (SFOF). DTI whole brain studies using tract-based spatial statistics (TBSS) address some of the limitations of VBM, such as registration of images to a common template, smoothing kernel selection, and adjusting for partial volume effects, via a skeletonization process (Smith et al., 2006). Studies of adolescents with BD using TBSS have found WM aberrations in the CC, fornix, cingulate, and parietal/occipital corona radiata (Barnea-Goraly et al., 2009; James et al., 2011; Lu et al., 2012; Gao et al., 2013b). In summary, previous studies in adults and youth with BD suggest WM tract aberrations in limbic circuitry and major association and commissural tracts.

To date, few studies have examined individuals with familial risk for bipolar disorder (Frazier et al., 2007; Versace et al., 2008; Chaddock et al., 2009; Sprooten et al., 2011,

2013a, 2013b), and only two of these studies are in youth (Frazier et al., 2007, Versace et al., 2008). Healthy unaffected relatives of those with BD were found to have decreased fractional anisotropy (FA) in the CC, posterior thalamic radiation (PTR), internal capsule, temporal WM, and SLF (Sprooten et al., 2011, 2013a). FA reflects the degree of diffusion anisotropy (how diffusion varies along the 3 axes) within a voxel. One study also found no differences in WM tracts between adults with BD and their unaffected first degree relatives (Chaddock et al., 2009). In studies of youth with familial risk for BD, Versace et al. found that asymptomatic youth had a linear decrease between age and FA in the left CC, whereas healthy controls (HCs) showed a linear increase in the same region (Versace et al., 2010). Another study compared WM in symptomatic children with familial risk for BD with one affected first-degree relative, children with BD, and HCs. It showed decreased FA in the bilateral SLF between children with BD when compared with HC, and decreased FA between children with BD and those at risk in bilateral cingulate-paracingulate WM (Frazier et al., 2007).

Given the findings in previous studies of aberrant WM in youth with BD, it is not well known whether these WM differences are present in youth with familial risk for the disorder, perhaps representing vulnerability markers. We therefore examined WM structure in a group of youth with familial risk for BD. Underlying aberrant circuitry in BD is thought to involve disruption of limbic circuitry, including prefrontal–striatal–thalamic pathways, the cerebellum, and medial temporal limbic areas (Strakowski et al., 2005; Green et al., 2007). We therefore hypothesized that youth with familial risk for BD would have WM tract aberrations, specifically decreased FA, compared with HC youth, in pathways connecting prefrontal to limbic system structures. In this study, we used two complementary methods to analyze WM structure in youth with familial risk for BD. One method (TBSS) is a commonly used whole brain analysis which compared WM structure in voxels in a generated WM skeleton (Smith et al., 2006). The other method (Diffeomap) is an atlas-based analysis which measures WM structure in large fiber tracts (ROI) (Zhang et al., 2010). We chose to use two methods due to the limitations of each. TBSS uses a skeletonization process that reduces partial volume effects but also reduces the WM examined, whereas Diffeomap transforms the subject's brain into a pre-fibertracked atlas and, thus, is more prone to registration errors. Using two different methods strengthens the analysis and allows us to detect different types of WM involvement. Specifically, local alterations may be detected by TBSS and more diffuse alterations may be detected by Diffeomap. As the effects of having familial risk for BD on WM structure are not well established, we used TBSS initially for voxel-based whole brain analysis and added a post hoc analysis using Diffeomap, an atlas-based, ROI analysis, to confirm results that were relevant to this population. In addition to FA, we examined axial diffusivity (AD), a measure of diffusivity along the main axis of diffusion within a voxel, and radial diffusivity (RD), the mean of diffusivities perpendicular to the vector with the largest eigenvalue.

2. Methods

2.1. Participants

The Stanford University Administrative Panel of Medical Research in Human Subjects approved the protocol. We recruited 25 youth with familial risk for BD (FR-BD) between the ages of 10 and 18 from a pediatric bipolar disorders clinic and 16 sex-, age-, and IQ-matched HCs from the surrounding community (Table 1). We obtained both written informed consent and assent from the parents and youth, respectively. Youth were administered the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Children's Depression Rating Scale-Revised Version (CDRS-R) (Poznanski et al., 1984) by raters with established inter-rater reliability ($ICC > 0.9$). The FR-BD group was defined as having at least one biological parent with BD I or BD II and having mood dysregulation (a score of at least 11 or higher on the YMRS, or a score of at least 29 or higher on the CDRS-R). Parental BD I or BD II diagnoses were determined by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) (First et al., 1995).

The affective module of the Washington University in St. Louis Kiddie-Schedule for Affective Disorders and Schizophrenia (WASH-U KSADS) ($\kappa > 0.9$ for diagnostic reliability) (Geller et al., 1996, 2001) and the Kiddie-Schedule for Affective Disorders and Schizophrenia, Present and Lifetime ($\kappa 0.77-1.00$ for diagnostic reliability) (Kaufman et al., 1997) were administered to parents and youth in separate interviews by a trained masters-level clinician and/or board-certified psychiatrist to evaluate for the presence of current and lifetime psychiatric disorders. DSM-IV-TR criteria were used to determine current and lifetime psychiatric diagnoses. The FR-BD group was discontinued from any psychostimulant use 24 h before the scan due to a separate yet concurrent functional magnetic resonance imaging (fMRI) study. Any other psychotropic medications were allowed to be continued, including mood stabilizers, antipsychotics, and/or antidepressants.

Youth with familial risk for BD were excluded if they had BD I or II, pervasive development disorder, intellectual disability, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, a history of head trauma with loss of consciousness, or Tourette's syndrome. HCs were excluded if they were taking psychotropic medications or if they or any of their first degree relatives had a current or lifetime DSM-IV-TR diagnosis. Further excluded were any youth (FR-BD or HC) with a neurologic condition (e.g. seizure disorder), substance use disorder, the presence of metallic implants or braces, or IQ below 80 or greater than 140, as determined by the Wechsler Scale of Intelligence.

2.2. DTI acquisition

Magnetic resonance images were acquired using a GE-Signa 3-Tesla scanner (General Electric, Milwaukee, WI) running the following DTI sequence: single-shot spin-echo echo-planar imaging (EPI) with diffusion-sensitizing gradients on either side of the 180° refocusing pulse, field of view (FOV)=24 cm, matrix size 128×128 , echo time (TE)/repetition time (TR) = 106/6000ms, 64 axial oblique slices, slice thickness 2 mm, skip=0. The scan was prescribed from the top of the brain to the superior part of the cerebellum with a diffusion gradient duration of $\Delta = 32$ ms and diffusion weighting of $b=900$ s/mm². A T2-

weighted image was also obtained by removing the diffusion-sensitizing gradients. Two repetitions were performed to increase signal to noise ratio along 60 different directions. Linear image registration (automated image registration [AIR] algorithm) (Woods et al., 1998) was used to correct for head motion and eddy currents in the diffusion weighted images.

2.3. DTI preprocessing

We first inspected each individual image visually to discard any slices with artifacts, and we added any remaining images to each slice. We then used DTI Studio to create an FA, AD, and RD image based on the respective calculated FA, AD, and RD for each voxel (Basser and Pierpaoli, 1996).

2.4. DTI analysis

2.4.1. Tract based spatial Statistics (TBSS)—Whole brain voxelwise analyses were then performed using the FMRIB Software Library (FSL, www.fmrib.ox.ac.uk/fsl/) with tract based spatial statistics (TBSS) v 1.2 (Smith et al., 2006). General linear models (GLM) were created to investigate differences between youth with familial risk for BD and HC youth, and within-group associations (regression analyses) with measures of depression (CDRS-R) and mania severity (YMRS). FA, AD, and RD maps were averaged to create a group mean image for each. We applied a standard skeletonization algorithm to the group mean FA (Smith et al., 2006), which was then applied to the AD and RD maps. FA, AD, and RD skeletons were thresholded to FA = 0.3. Statistical analyses of the data were performed using threshold-free cluster enhancement (TFCE) and permutation analyses implemented in FSL (“randomize”) (Nichols et al., 2002). All significant statistical analyses are reported for $p < 0.05$ and were individually corrected using family-wise error (FWE). Analyses of between-group differences were covaried for age and full scale IQ, due to a significant between-group IQ difference, using GLM in randomize. We covaried for age based on several studies delineating increases in FA with age in children and adolescents (Barnea-Goraly et al., 2005; Faria et al., 2010; Tamnes et al., 2010).

2.4.2. Diffeomap—A whole brain, ROI, atlas-based analysis of diffusion-weighted data was performed using Diffeomap (Faria et al., 2010) (implemented in www.mristudio.org). First, affine (linear) normalization of the “JHU_MNI_single-subject” atlas (Mori et al., 2008) is warped to individual native space. This image is then registered non-linearly to a presegmented WM atlas using a highly elastic algorithm employing dual-contrast Large Deformation Diffeomorphic Metric Mapping (LDDMM) (Miller et al., 2005) and a single α/γ ratio at 0.002 (Ceritoglu et al., 2009). The transformation matrices produced from this non-linear registration are then applied in reverse to the pre-segmented WM parcellation map (WMPM) of the “JHU_MNI_SS” atlas (Oishi et al., 2009). The resulting WMPM is applied to each subject’s native space using an FA threshold of 0.25. This allows for an automated segmentation of each native-space FA map into 130 WM brain regions from which average FA values for each region were obtained. The matrix resulting from the FA was then applied to the native AD and RD maps to generate average AD and RD values for the 130 WM brain regions. An FA threshold of 0.25 was applied, further segmenting the brain into 176 WM regions, from which average FA values for each region were obtained.

See Fig. 1 for examples of this transformation and segmentation. The matrix resulting from the FA was then applied to the native AD and RD maps to generate average AD and RD values.

ROI's with significant between-group differences in TBSS and previously implicated in BD DTI studies were selected for a post hoc Diffeomap analysis. In previous WM studies of youth with and with familial risk for BD, these regions included the SLF, which is one of the most consistent findings, and the cingulum, which connects limbic system structures that are relevant to BD (Frazier et al., 2007; Pavuluri et al., 2009; Versace et al., 2010). The SFOF was also selected because of its close functional association to the SLF and also based on previous studies of WM in BD (Haznedar et al., 2005; Bruno et al., 2008). Group comparisons for mean FA, AD, and RD for the SLF, SFOF, and cingulum were examined using multivariate analysis of variance (MANCOVA) in SPSS v 20, covarying for age and IQ. ANCOVAs were performed for individual regions that made up a dependent variable set when overall models were significant or approached significance, correcting for multiple comparisons by the FDR procedure ($p < 0.05$). We also conducted exploratory analysis in SPSS v. 20 to correlate FA, AD, and RD values of each selected fiber with significant group differences with depression and mania severity as determined by the CDRS-R score and the YMRS score, respectively, adjusting for multiple comparisons by FDR ($p < 0.05$).

3. Results

3.1. Demographics

There were no significant group differences in mean age [$t=0.75$ (39), $p=0.46$], but there was a significant difference in mean IQ ($t=-2.12$ (39), $p=0.04$), with the HC group having a higher mean IQ (116 ± 10.73) than the FR-BD group (108 ± 10.56). The female to male ratio in the HC group was 10:6, and for the BD group, the female to male ratio was 13:12. As expected, the mean YMRS score was significantly different between the FR-BD and HC groups [$t= 6.16$ (38), $p < 0.001$]. The mean CDRS score was also significantly different between groups [$t= 7.37$ (38), $p < 0.001$]. Fourteen youth with familial risk had a history of a major depressive episode or dysthymia with a CDRS score > 40 . Sixty percent of the FR-BD group had at least one comorbid disorder. The most common comorbid disorder was generalized anxiety disorder, accounting for 50% of those with a comorbidity. Within the FR-BD group, 74% had been exposed to medication, with the most common exposure being to selective serotonin reuptake inhibitors (SSRIs). Table 1 shows demographic data in detail. One subject was excluded from Diffeomap analysis due to abnormal warping.

3.2. TBSS

Using TBSS, we found significant group differences with significantly increased FA, increased AD, and decreased RD bilaterally in the FR-BD group compared with the HC group in the SLF, SFOF, IFOF, ILF, ATR, internal capsule (IC), external capsule (EC), anterior and posterior corona radiata (PCR), CC (body, splenium, and genu), forceps minor, cingulum, cingulate, and UF (mostly FA and RD). The FR-BD group also had significantly increased FA, increased AD, and decreased RD in the right PTR. Increased FA was also

found in the left PTR, but there were no significant differences found in AD or RD in that region. Detailed results are shown in Fig. 2.

3.3. Diffeomap

Significant group differences were found with increased FA in the FR-BD group when compared with the HC group in the left SFOF ($F(1,36) = 11.14$, $p = 0.002$), bilateral cingulum (left: $F(1,36) = 9.33$, $p = 0.004$); (right: $F(1,36) = 9.69$, $p = 0.004$), and left SLF ($F(1,36) = 5.32$, $p = 0.027$). Significantly decreased RD was also found for the FR-BD group in the bilateral cingulum (left: $F(1,36) = 6.74$, $p = 0.014$; right: $F(1,36) = 5.92$, $p = 0.02$). Tables 2–4 present atlas-based results in detail.

3.4. Behavioral and medication analyses

No correlations with mood symptoms severity were found by TBSS. For Diffeomap, greater FA and lower RD were significantly correlated with greater mania severity in the right cingulum (FA: $\rho = 0.48$, $p = 0.012$; RD: $\rho = -0.45$, $p = 0.024$, FDR corrected). Lower AD and lower RD were significantly correlated with greater depression severity in the right cingulum (AD: $\rho = -0.44$, $p = 0.03$; RD: $\rho = -0.55$, $p < 0.001$, FDR corrected). Greater FA in the left cingulum was also significantly correlated with greater depression severity ($\rho = 0.49$, $p = 0.004$, FDR corrected). Lower depression severity was significantly correlated with greater RD in the right SLF ($\rho = -0.39$, $p = 0.045$, FDR corrected). No significant group differences were found between the medicated ($n = 16$) vs. unmedicated groups for FA, AD, and RD, although the unmedicated sample size was small ($n = 6$).

4. Discussion

Our findings using TBSS, a whole-brain, voxelwise method of analysis, showed significant group differences between youth with familial risk for BD and HC youth in the structure of major WM association pathways extending from frontal to occipital lobes in addition to the structure of WM tracts involved with emotion regulation. Significant between-group differences in the SLF, SFOF, and cingulum were further supported using Diffeomap, an ROI, atlas-based method of analysis. No correlations were found between manic or depressive symptom severity and FA, AD, or RD values in TBSS. In Diffeomap, greater mania severity was correlated with greater FA and lower RD in the right cingulum. Greater depression severity was correlated with lower AD and lower RD, also in the right cingulum, whereas lower depression severity was correlated to greater RD in the right SLF.

To our knowledge, these are the first reported findings of FA, AD, and RD in symptomatic youth with familial risk for BD. As no other published study has examined symptomatic youth in this age range examining FA, AD, and RD, it is difficult to compare results. Only one previous study examined group differences between symptomatic youth of a much younger age range (4–12 years old, mean 8.9 ± 3.0 years) with a first degree relative with BD and HCs. In that study, Frazier et al. found significantly decreased FA in bilateral SLF in symptomatic youth compared with HCs using a voxelwise method (Frazier et al., 2007). The BD group also had significantly greater reduction in FA when compared with the at-risk group in the cingulate-paracingulate WM. In contrast, the current study found much more

widespread increased FA, including the cingulate and SLF. Discrepancy between the two studies can be explained by the significant difference in mean age, method of DTI analyses used, and characteristics of the groups examined. The mean age of the current study was much higher than in the Frazier et al. study (14.5 ± 2.5 years vs. 8.9 ± 3.0 years). The two studies therefore examined youth at very different stages of brain maturation and disease progression. Patients in the previous study had no significant mood symptoms, with a mean CDRS-R score of 23.4 ± 6.1 and a mean YMRS score of 2.1 ± 3.7 . The sample also consisted of 57% with ADHD and one subject with Asperger's syndrome. In contrast, the current study participants' mean CDRS-R score was 40.0 ± 11.3 and the mean YMRS score was 12.0 ± 6.6 , indicating an FR-BD group with much greater mood dysregulation. The current study also had many medicated participants unlike the Frazier et al. study where participants were not regularly taking medications. The Frazier et al. study was also not a whole brain analysis and examined FA of significant clusters within a priori defined ROIs. The two studies are therefore difficult to compare but are suggestive of common WM pathways involved in youth with BD.

As there are no other published studies with which we could compare our WM findings in symptomatic youth at *familial risk* for BD, we also compared our results to studies on WM changes in youth *with* BD. Few studies examined FA in youth *with* BD, and these studies found *decreased* FA, whereas our study found *increased* FA in the FR-BD group. Possible explanations for increased FA in youth with familial risk for BD include WM tract development in symptomatic youth, mania effects on WM, and medication use. Previous studies have suggested that increased AD and decreased RD may indicate increased myelination and coherence in these WM tracts, perhaps reflective of overdeveloped pathways (Beaulieu, 2002; Houenou et al., 2007). Decreased fiber density is associated with increased FA and has been found in subjects with BD in the CC and ILF (Torgerson et al., 2013). These studies indicate that perhaps increased FA, increased AD, and decreased RD are indicative of overdeveloped pathways compensating for pathological processes. In a study of unmedicated adolescents in their first episode of mania, FA was decreased in superior frontal WM tracts when compared with findings in HCs (Adler et al., 2006). Similarly, FA in the right anterior cingulate was decreased in youth experiencing a manic episode (Gao et al., 2013a). These two studies are suggestive of increased WM disorganization and/or axonal integrity or myelin breakdown during mania. Thus, FA in brains of youth with familial risk for BD may not decrease until mania occurs. The effect of medications on FA measures also is not well understood. Prospective, longitudinal DTI studies are warranted to further examine WM changes as they relate to medication use over the course of BD in youth.

The magnitude of abnormalities in WM tracts found in our study is more consistent with the extensive WM aberrations found in BD (Roybal et al., 2012). BD neuropathophysiology is thought to partially involve prefrontal-striatal circuitry reflecting poor emotion regulation (Roybal et al., 2012). Our findings reflect this theoretical approach. For example, the UF connects the orbitofrontal cortex with limbic structures such as the amygdala (Schmahmann and Pandya, 2006), a crucial part of the limbic network for emotion regulation. Alterations in the UF would suggest aberrant frontal lobe connection to limbic structures that may contribute to mood dysregulation. Further, the ILF connects the ventrolateral prefrontal

cortex to the occipitotemporal cortices and, pertinent to BD, connects cortical areas involved with the recognition and social emotional processing of faces (Schmahmann and Pandya, 2006). Previous fMRI studies in youth with BD have shown temporal hyperactivation in the amygdala to particular facial expressions when compared to HCs (Kalmar et al., 2009; Kim et al., 2012). The IFOF connects visual and auditory association cortices with the prefrontal cortex and intermingles with the UF (Schmahmann and Pandya, 2006). Altered IFOF structure has been associated with auditory, visual, and tactile hallucinations in schizophrenia, which shares genetic heritability with BD, and suggests a pathway for hallucinations seen during psychotic mania or depression (Szeszko et al., 2008).

BD symptomatology also encompasses motor hyperactivity, attention difficulties, poor executive functioning, and neurocognitive deficits, including verbal memory, sustained attention, and visuospatial working memory deficits (Quraishi and Frangou, 2002). The SLF is a major association fiber connecting frontal to temporal, parietal, and occipital lobes and plays a role in working memory retrieval of visuospatial information, visuospatial attention, and regulating motor behavior (Schmahmann and Pandya, 2006). Similarly, the SFOF is a parietal-frontal pathway involved with visuospatial awareness and constitutes part of a bundle of axons involved with the control of speech, which in patients with BD can be either rapid or slowed depending on mood state (Thiebaut de Schotten et al., 2005; Duffau, 2008). The corticospinal tract runs through the IC and carries sensory and motor information to the frontal cortex for regulatory processing, and the EC carries striatal fibers and the IFOF (Schmahmann and Pandya, 2006). This suggests that both the IC and EC are therefore associated with motor symptomatology seen in BD. The cingulum connects the hippocampus to the frontal cortex, and disruptions in this pathway are implicated in cognitive impairment (Metzler-Baddeley et al., 2012). Finally, the CC is one of the most well studied tracts with many studies showing aberrant CC in youth with BD, indicating difficulties in the integration of sensory inputs and subsequent processing (Roybal et al., 2012). Taken together, these widespread aberrant WM tracts suggest differential connectivity development between major lobes of the brain and particularly between regulatory frontal cortex with limbic, memory, visual, and motor areas.

Lastly, the absence of significant behavioral correlations in TBSS suggests that no differences were found at the voxel level and that such differences may be better examined at the level of mean DTI measures for entire ROIs. Previous work by our laboratory also showed no behavioral correlations with FA in adolescents with BD using TBSS analysis (Barnea-Goraly et al., 2009). Single points in the brain may therefore not be sensitive enough to correlate with symptomatology, and entire pathways of connectivity may be more indicative of the changes in WM as they pertain to behavioral measures.

Methodological limitations with DTI warrant further discussion and add to cautious interpretation of these WM measures. As with any DTI study, this current study can determine the FR-BD group had aberrant WM tracts when compared with HC, but we cannot definitively attribute these aberrations to a particular pathological or histological process. Putative reasons for axonal changes contributing to increased FA include fiber diameter and density, myelination and intravoxel fibertract coherence (increases in which would increase FA), as well as extracellular diffusion and interaxonal spacing (increases in

which would decrease FA) (Beaulieu, 2002; Sen and Basser, 2005; Alba-Ferrara and de Erausquin, 2013). AD comprises fiber coherence, structure of axonal membranes (increases in which would increase AD), microtubules, neurofilaments, and axonal branching (increases in which would decrease AD) (Kinoshita et al., 1999; Sen and Basser, 2005). RD is affected by axonal “leakiness” (which would increase RD) and degree of myelination (more myelin decreases RD) (Song et al., 2002; Chen et al., 2011). However, the individual contribution of each of these WM characteristics can lead to opposing effects in the final observed FA/AD/RD value. DTI measures of WM should therefore not be interpreted universally as “good” or “bad” (Hoefl et al., 2007). These WM measures instead show between group differences and relationships between WM structure and clinical variables that are suggestive of underlying histology. Definitive conclusions regarding the exact constitution of such histology can only be made by microscopic examination of the WM tracts.

DTI unfortunately cannot untangle all these factors affecting FA/AD/RD. Of particular concern is the occurrence of crossing fibers, which may interfere with interpretations of RD and AD. Changes in RD can cause a change in AD and vice versa in the areas of crossing fibers (Wheeler-Kingshott and Cercignani, 2009). TBSS also has limitations stemming from image registration, partial volume effects and image noise level. WM in subcortical structures that are often contaminated by CSF and partial volume effects in voxel-based analysis are often cleaner in atlas-based analysis because peripheral WM is separated by FA threshold in each individual brain after the brain is parcellated (Faria et al., 2010). However, changes in WM that occur at the level of the voxel may be missed in atlas-based analysis. Future studies using high-angular-resolution diffusion imaging or diffusion spectrum imaging would be more sensitive to recognizing crossing fibers and provide a more accurate picture of fiber diffusion.

Other limitations to this study include incomplete capture of the lower cerebellum and lower temporal lobes in all subjects, which may have excluded findings in these areas. We also did not use an automated motion correction algorithm but instead, qualitatively inspected each slice for each repetition and removed slices that had movement. This study also is cross sectional in nature, and as such it is not clear whether these WM differences are a cause, risk factor, or a result of symptomatology. Additionally, compared with HC, this symptomatic FR-BD sample had increased FA values, but in most previous studies on youth with BD, FA was found to be decreased. Longitudinal studies could therefore address whether FA in youth with familial risk for BD gradually decreases with increasing manic symptoms. Furthermore, our behavioral measures may not have been sensitive enough and our sample size too small to capture correlations with FA in the TBSS analysis. Similarly, due to the small sample size of non-medicated subjects ($n = 6$), additional analyses of medicated vs. non-medicated subjects was not performed. However, previous studies have shown that medications had limited impact in DTI studies of BD (Phillips et al., 2008; Hafeman et al., 2012). In addition, future post-mortem studies would be helpful to provide information on the possible cellular and microstructural contributions to changes in FA, AD, and RD.

In summary, we observed significant widespread differences in major projection, association and commissural WM tracts in a symptomatic population of youth with familial risk for BD

using two different methods of DTI analysis and more sensitive scanning parameters than previous studies. To our knowledge, this is the first published study demonstrating such widespread WM differences in these youth. These WM findings not only occur in limbic circuitry but are also seen in areas associated with visuospatial attention, spatial awareness, and working memory. These findings may underlie multi-domain cognitive deficits. While previous studies examined cognitive deficits in patients with BD, possible deficits in children with familial risk for the disorder are not well studied. Therefore, obtaining neuropsychiatric correlates of working memory, visuospatial attention, and other cognitive domains reflected in these affected WM tracts might prove clinically useful to inform social and educational functioning, and potentially for ameliorating mood symptoms. Future studies should also examine these children at an earlier age, prior to any symptoms developing, to determine whether WM changes represent a vulnerability marker or are a consequence of symptomatology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

(a) Image of matrices generated for one healthy subject after Large Deformation Diffeomorphic Metric Mapping is employed. (b) The transformation matrices and white matter (WM) parcellation map are then combined to create one transformation matrix that segments the brain into 130 regions. (c) WM is then separated out by applying an threshold of $FA < 0.25$.

Fig. 2.

Axial views of significant between group differences showing fractional anisotropy (FA, in red), axial diffusivity (AD, in blue), and radial diffusivity (RD, in green) using Tract Based Spatial Statistics (TBSS). FA and AD overlap is shown in purple. FA and RD overlap is shown in yellow. An average T1 Montreal Neurological Institute (MNI) template was used to map between group differences. *Note: Because it is difficult to see the regions of overlap on the original TBSS skeleton, the white matter tracts were thickened in this representation of the results* (Smith et al., 2006). The group with familial risk for bipolar disorder shows increased FA, increased AD, and decreased RD compared with healthy controls. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1

Demographics.

	Familial risk (n=25)	Healthy-controls (n=16)	<i>p</i> -Value
Gender			
Males	12	6	
Females	13	10	
Mean age	15.1 yrs $\pm$ 2.9 yrs	14.5 yrs $\pm$ 2.4 yrs	0.46
Mean YMRS ^a	12.0 $\pm$ 6.6	1.37 $\pm$ 1.3	< 0.001
Mean CDRS-R ^b	40.0 $\pm$ 11.3	18.3 $\pm$ 1.0	< 0.001
IQ (WASI) ^c	108 $\pm$ 10.6	116 $\pm$ 10.7	0.04
Diagnoses (primary)			
Mood disorder	14		
Comorbid diagnoses			
ADHD ^d	5		
Dysthymia	1		
Generalized anxiety disorder	5		
ODD ^e	2		
Specific phobia	1		
Adjustment disorder	1		
Taking or tried meds (%)	74		
Medication exposure			
SSRI's ^f	30		
Stimulant (%)	22		
Lithium (%)	13		
Other Mood stabilizers (%)	26		
Antipsychotics (%)	17		
Anxiolytics (%)	9		

^aYMRS=Young Mania Rating Scale.

^bCDRS=Children's Depression Rating Scale-Revised Version (CDRS-R).

^cWASI=Wechsler Abbreviated Scale of Intelligence.

^dADHD=Attention Deficit Hyperactivity Disorder.

^eOppositional Defiant Disorder.

^fSelective Serotonin Reuptake Inhibitor.

Table 2

Diffeomap Results – FA.

Fiber	Mean HR group	Mean HC group	<i>F</i>	<i>p</i> -Value
SLF left	0.506	0.479	5.32	0.027
SLF right	0.422	0.421	0.00	0.968
SFOF left	0.464	0.435	11.14	0.002
SFOF right	0.419	0.432	0.26	0.611
Cingulum left	0.473	0.442	9.33	0.004
Cingulum right	0.583	0.554	9.69	0.004

Table 3

Diffeomap results – AD.

Fiber	Mean HR group	Mean HC group	<i>F</i>	<i>p</i> -Value
SLF left	0.00157	0.00153	2.97	0.094
SLF right	0.00131	0.00129	0.66	0.421
SFOF left	0.00119	0.00116	3.62	0.065
SFOF right	0.00120	0.00120	0.09	0.763
Cingulum left	0.00130	0.00132	3.73	0.061
Cingulum right	0.00138	0.00138	0.00	1.000

Table 4

Diffeomap results – RD.

Fiber	Mean HR group	Mean HC group	<i>F</i>	<i>p</i> -Value
SLF left	0.00067	0.00069	2.21	0.146
SLF right	0.00062	0.00063	0.10	0.759
SFOF left	0.00057	0.00059	3.61	0.066
SFOF right ^{<i>l</i>}	0.00059	0.00061	4.36	0.044
Cingulum left	0.00060	0.00063	6.74	0.014
Cingulum right	0.00049	0.00053	5.92	0.020

^{*l*} Was not significant after correcting overall model for multiple comparisons by FDR (threshold $p < 0.05$).