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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.

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;

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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

Table 1
Demographics.

	Familial risk (n=25)	Healthy-controls (n=16)	*p*-Value
Gender			
Males	12	6	
Females	13	10	
Mean age	15.1 yrs ± 2.9 yrs	14.5 yrs ± 2.4 yrs	0.46
Mean YMRS[a]	12.0 ± 6.6	1.3 ± 1.3	< 0.001
Mean CDRS-R[b]	40.0 ± 11.3	18.3 ± 1.0	< 0.001
IQ (WASI)[c]	108 ± 10.6	116 ± 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		

[a] YMRS=Young Mania Rating Scale.
[b] CDRS=Children's Depression Rating Scale-Revised Version (CDRS-R).
[c] WASI=Wechsler Abbreviated Scale of Intelligence.
[d] ADHD=Attention Deficit Hyperactivity Disorder.
[e] Oppositional Defiant Disorder.
[f] Selective Serotonin Reuptake Inhibitor.