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Research paper

White matter – emotion processing activity relationships in youth offspring of bipolar parents

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A B S T R A C T

Background: Early detection of Bipolar Disorder (BD) is critical for targeting interventions to delay or prevent illness onset. Yet, the absence of objective BD biomarkers makes accurately identifying at-risk youth difficult. In this study, we examined how relationships between white matter tract (WMT) structure and activity in emotion processing neural circuitry differentiate youth at risk for BD from youth at risk for other psychiatric disorders.
Methods: Offspring (ages 8–17) of parents with BD (OBP, n = 32), offspring of comparison parents with non-BD psychopathology (OCP, n = 30), and offspring of healthy parents (OHP, n = 24) underwent diffusion tensor and functional magnetic resonance imaging while performing an emotional face processing task. Penalized and multiple regression analyses included GROUP(OBP,OCP)xWMT interactions as main independent variables, and emotion processing activity as dependent variables, to determine significant group differences in WMT-activity relationships.
Results: 8 GROUPxWMT interaction variables contributed to 16.5% of the variance in amygdala and prefrontal cortical activity to happy faces. Of these, significant group differences in slopes (inverse for OBP, positive for OCP) existed for the relationship between forceps minor radial diffusivity and rostral anterior cingulate activity (p = 0.014). Slopes remained significantly different in unmedicated youth without psychiatric disorders (p = 0.017) and were moderated by affective lability symptoms ($F(1,29) = 5.566$, p = 0.036).
Limitations: Relatively small sample sizes were included.
Conclusions: Forceps minor radial diffusivity-rostral anterior cingulate activity relationships may reflect underlying neuropathological processes that contribute to affectively labile youth at risk for BD and may help differentiate them from youth at risk for other psychiatric disorders.

1. Introduction

Bipolar Disorder (BD) is a debilitating psychiatric disorder characterized by recurrent, episodic disturbances in mood, sleep, behavior, perception, and cognition, rendering it a leading cause of disability, morbidity, and mortality worldwide (Mahon et al., 2010). BD

Abbreviations: BD, Bipolar Disorder; WMT, White Matter Tract; OBP, Offspring of Bipolar Parents; OCP, Offspring of Comparison Parents; vlPFC, Ventrolateral Prefrontal Cortex; ACC, Anterior Cingulate Cortex; FA, Fractional Anisotropy; RD, Radial Diffusivity; BIOS, Bipolar Offspring Study; OHP, Offspring of Healthy Parents; LAMS, Longitudinal Assessment of Manic Symptoms; MRI, Magnetic Resonance Imaging; SES, Socioeconomic Status; K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children; SCARED, Screen for Child Anxiety Related Disorders; CALS, Children's Affective Lability Sale; MFQ, Mood and Feelings Questionnaire; KMRS, K-SADS Mania Rating Scale; SPM, Statistical Parametric Mapping; ROIs, Regions of Interest; AD, Axial Diffusivity; cACC, Caudal ACC; rACC, Rostral ACC; SGoF, Sequential Goodness of Fit

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affects 1–3% of the adult population and has a heritability of 59–87%, placing first-degree relatives of individuals with BD at a 10-fold increased risk of the disorder versus relatives of unaffected controls (Merikangas et al., 2007; Phillips and Swartz, 2014; Singh and Chang, 2013; Smoller and Finn, 2003). Yet, the absence of objective biomarkers of BD makes it difficult to identify young individuals who are likely to develop BD in the future.

Neuroimaging studies can identify such biomarkers by detecting abnormal structure and activity in neural circuitries important for processes aberrant in individuals with BD, such as emotion processing (Phillips and Swartz, 2014). Neural regions implicated in emotion processing include the amygdala, ventrolateral prefrontal cortex (vlPFC), and anterior cingulate cortex (ACC) (Dolcos et al., 2011; Phillips et al., 2003, 2008). Studies have reported elevated amygdala activity (Blumberg et al., 2005; Lawrence et al., 2004), lower vlPFC activity (Hafeman et al., 2014; Phillips et al., 2003, 2008), and lower ACC activity (Blumberg et al., 2005) during emotion processing tasks in youth and adults with BD versus healthy controls.

Given that structural integrity of white matter is key for ensuring intact functioning of a given neural circuitry, studying relationships between white matter tract (WMT) structure and activity may provide a more comprehensive understanding of BD. Abnormal WMT structure in youth and adults with BD is observed in several WMTs important for emotion processing, including the cingulum (Benedetti et al., 2011b; Linke et al., 2013; Versace et al., 2014), forceps minor (Benedetti et al., 2011b; Chaddock et al., 2009; Haller et al., 2011; Versace et al., 2014; Wang et al., 2008b), uncinate fasciculus (Benedetti et al., 2011a; Linke et al., 2013; Versace et al., 2008, 2014), and superior longitudinal fasciculus (Benedetti et al., 2014, 2011b; Chaddock et al., 2009; Raichle et al., 2001; van der Schot et al., 2010; Versace et al., 2008, 2010a). Specific abnormalities include the following in frontal WMTs (Emsell et al., 2013; Mahon et al., 2010; Versace et al., 2008, 2014; Wang et al., 2008a, 2008b) and WMTs connecting prefrontal cortical to anterior limbic (Benedetti et al., 2011a, 2011b) and temporal regions (Ashtari, 2012; Bruno et al., 2008; Mahon et al., 2013; Saricicek et al., 2016; Versace et al., 2014): lower fractional anisotropy (FA), likely reflecting lower collinearity of longitudinally-aligned fibers (Versace et al., 2008); greater radial diffusivity (RD), reflecting abnormal myelination, more obliquely oriented fibers, and/or local inflammation (Mahon et al., 2010; Song et al., 2005); and reduced tract length, likely reflecting altered axonal myelination or myelin loss (Atmaca et al., 2007; Barnea-Goraly et al., 2009; Brambilla et al., 2003; Hong et al., 2011; Torgerson et al., 2013; Wang et al., 2008b).

There are several gaps in the literature that hinder progress in understanding the underlying pathophysiology of BD. First, while most neuroimaging studies examined individuals diagnosed with BD, few examined youth at genetic risk for the disorder (Ladouceur et al., 2013; Olsavsky et al., 2012; Phillips et al., 2008; Singh and Chang, 2013; Singh et al., 2014; Tseng et al., 2015; Versace et al., 2010b). Focusing on BD at-risk youth unaffected by the disorder may identify biomarkers of BD before illness onset. The few studies of activity in BD at-risk youth reported abnormally elevated amygdala and lower ACC activity during facial emotion processing (Chan et al., 2016; Olsavsky et al., 2012; Phillips et al., 2008; Tseng et al., 2015) and abnormally elevated vlPFC activity during reward processing (Singh et al., 2014). Studies of WMTs in BD at-risk youth reported lower FA widespread, in tracts connecting prefrontal cortical and limbic regions, and in the anterior limb of the internal capsule (Ganzola et al., 2018, 2017; McIntosh et al., 2005; Versace et al., 2010b).

Second, while several WMT and activity abnormalities have been identified in youth with, and at risk for, BD, few studies have examined the relationships between them in this population. Combining diffusion imaging and functional magnetic resonance imaging (fMRI) techniques has become increasingly important in fields of cognitive and clinical neuroscience (Zhu et al., 2014). Such studies have examined relationships between WMT structure and either blood-oxygen-level dependent (BOLD) activity (Baird et al., 2005; Conturo et al., 1999; Madden et al., 2007; O'Donnell et al., 2012; Olesen et al., 2003; Toosy et al., 2004; Werring et al., 1999; Ystad et al., 2011) or functional connectivity (Calamante et al., 2013; Greicius et al., 2009; Guye et al., 2003; Koch et al., 2002; Supekar et al., 2010; van den Heuvel et al., 2008). Both types of structure-function relationships have the potential to contribute to our understanding of mechanisms underlying psychiatric disorders; however, such studies have yet to be performed in youth with, or at risk for, BD.

Third, relating WMT-activity measures and symptoms is very important in OBP, as youth at genetic risk for BD with greater symptom severity are likely to be more at risk for developing BD in the future. Specifically, symptoms of depression, mania, affective lability, and anxiety have been shown to be precursors of BD in OBP (Hafeman et al., 2016). Yet, no studies to date have combined structural and functional imaging to study WMT-activity relationships and their relationships with symptoms in BD at-risk youth.

Additionally, of the studies that examined BD at-risk youth, few compared youth at genetic risk for BD to those at risk for other disorders (Manelis et al., 2016, 2015; Soehner et al., 2016). It thus remains difficult to determine the extent to which neuroimaging findings represent biomarkers of specific risk for BD. The Bipolar Offspring Study (BIOS) examines emotion processing neural circuitries in offspring of bipolar parents (OBP) and offspring of comparison parents (OCP) who have non-BD disorders, including Major Depressive Disorder, Attention-Deficit/Hyperactivity Disorder, and/or an Anxiety Disorder (Birmaher et al., 2009). While OBP and OCP are heterogeneous on a risk continuum, putting the sample at risk for factors that may contribute to sample skew or group differences, studies have shown that OBP are more likely to develop a bipolar spectrum disorder by age 21 (23%) than OCP (3.2%) (Axelson et al., 2015), placing OBP at greater risk for developing BD than OCP. OCP thus serve as a control group both for genetic risk for non-BD disorders, since OBP are also at higher risk for these disorders than the general population (Birmaher et al., 2009), and for the presence of non-BD disorders in parents, since parents with BD have high rates of non-BD comorbidity (Merikangas et al., 2007). The few neuroimaging studies comparing OBP and OCP found patterns of activity and functional connectivity in the amygdala and vlPFC that distinguish OBP from OCP (Manelis et al., 2016. 2015; Soehner et al., 2016). No studies of OBP and OCP to date, however, employed multimodal neuroimaging techniques to identify biomarkers of specific risk for BD. Studies are needed to determine whether neuroimaging techniques can identify biomarkers that confer specific risk for BD in OBP.

Furthermore, while non-BD disorders may confound neuroimaging findings, these disorders are common in BD at-risk youth. Including at-risk youth with, and without, these disorders in neuroimaging studies can help determine the extent to which findings are confounded, or not, by present psychopathology. Indeed, we previously reported that neuroimaging findings distinguishing OBP from OCP remained even after excluding youth with non-BD disorders (Manelis et al., 2016, 2015). However, the effects of non-BD disorders on WMT-activity relationships have yet to be studied. Further examination of the effects of these disorders in at-risk youth may also enhance our understanding of how WMT-activity relationships confer risk for BD.

The goal of the present study was thus to explore relationships between WMT structure and activity in emotion processing neural circuitry that distinguish youth at genetic risk for BD from youth at risk for non-BD disorders. We examined the effects of GROUP(OBP,OCP)xWMT interactions on activity in emotion processing circuitry to identify whether WMT-activity relationships distinguished OBP from OCP, and how non-BD disorders impacted these relationships. We hypothesized that:

1. OBP would show relationships between lower prefrontal WMT (cingulum, forceps minor, uncinate fasciculus, superior longitudinal