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

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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 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; Phillips et al., 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; Phillips et al., 2008), and lower ACC activity(Blumberg et al., 2005) during emotion processing tasks in youth and adults with BD versus healthy controls.

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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; Versace et al., 2014), and superior longitudinal fasciculus(Benedetti et al., 2014; Benedetti et al., 2011b; Chaddock et al., 2009; Raichle et al., 2001; van der Schot et al., 2010; Versace et al., 2008; Versace et al., 2010a). Specific abnormalities include the following in frontal WMTs(Emsell et al., 2013; Mahon et al., 2010; Versace et al., 2008; Versace et al., 2014; Wang et al., 2008a; Wang et al., 2008b) and WMTs connecting prefrontal cortical to anterior limbic(Benedetti et al., 2011a; Benedetti et al., 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; Ganzola et al., 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; Manelis et al., 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; Manelis et al., 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; Manelis et al., 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 fasciculus) fiber collinearity and greater amygdala and/or lower prefrontal (vlPFC, ACC) cortical activity.
2. These WMT-activity relationships would distinguish OBP from OCP.
3. These relationships would remain when excluding youth with non-BD disorders.

Additional analyses examined: how these relationships compared to a reference group of healthy offspring of healthy parents (OHP); the relationships between WMT-activity and symptoms; correlations between WMT measures and FA; and whether or not main findings were affected by psychotropic medications or age.

Methods

Participants

OBP and OCP, ages 8–17 years, were recruited from BIOS. OBP had at least one parent with BD, while OCP had at least one parent with a non-BD disorder, including Major Depressive Disorder, Attention-Deficit/Hyperactivity Disorder, and/or an Anxiety Disorder. A third group of OHP, ages 8–17 years, were recruited from the healthy comparison youth group of the Longitudinal Assessment of Manic Symptoms (LAMS) study(Findling et al., 2010; Horwitz et al., 2010). OHP had parents with no psychiatric diagnoses.

Exclusion criteria included: history of serious medical illness, head injury, or neurological disorder; IQ <70, as assessed by the Wechsler Abbreviate Scale of Intelligence(Wechsler, 1999); diagnosis of BD, autism, or schizophrenia; MRI contraindication (e.g., pregnancy, metal in the body); and substance abuse on the day of the scan or substance abuse disorder in the last three months. For OHP, additional exclusion criteria included history of DSM-5 disorder.

Thirty-two OBP (mean age=13.81(2.45), 15 female), thirty OCP (mean age=13.98(2.30), 12 female), and twenty-four OHP (mean age=13.80(1.72), 10 female), matched for age, sex, IQ, and socioeconomic status (SES), were included in this study (Table 1). Fourteen OBP and fifteen OCP had non-BD disorders. Prior to study participation, parents and guardians provided written informed consent, and youth provided written informed assent. Participants received monetary compensation.

Psychiatric diagnoses were confirmed by a licensed psychiatrist or psychologist prior to scanning using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS)-Present and Lifetime Version(Kaufman et al., 1997) for offspring and the Structural Clinical Interview for DSM-IV(First, 1996) and Family History Screen(Weissman et al., 2000) for parents. Symptom assessments included the Screen for Child Anxiety Related Disorders (SCARED)(Birmaher et al., 1999; Birmaher et al., 1997), Children's Affective Lability Sale (CALS)(Gerson et al., 1996), Mood and Feelings

Questionnaire (MFQ)(Sund et al., 2001), and K-SADS Mania Rating Scale (KMRS) (Axelson et al., 2003). Parent- and child-reported SCARED, CALS, and MFQ were administered on the scan day; KMRS interviews, based on both parent and child information, were administered, on average, two months after the scan. Three OBP were taking psychotropic medications for non-BD diagnoses.

Neuroimaging Data Acquisition and Analyses

Participants completed an emotional face processing task during fMRI (Supplementary Figure 1)(Almeida et al., 2011; Perlman et al., 2012; Phillips et al., 2008; Tottenham et al., 2009). Functional images were preprocessed using Statistical Parametric Mapping (SPM8), including realignment and unwarping steps. Task stimulus contrasts of interest included positive (happy) and negative (sad, angry, and fearful, averaged together) emotional faces versus shapes. Regions of interest (ROIs) were anatomically defined using Center for Morphometric Analysis standard labels proposed in FreeSurfer. Individual-level averaged BOLD waveforms to the onset of each stimulus type were extracted in native space from anatomic ROIs to main stimulus contrasts per task. Global probabilistic tractography determined the distributions of 18 WMTs, and FA, RD, Axial Diffusivity (AD), volume, and length were extracted for each tract.

Statistical Analyses

Elastic net regression analysis was used for variable selection and reduction through GLMNET(Friedman, 2014; Zou and Hastie, 2005). We used a k=10-fold cross-validation approach. 6 outcome variables included activity in the bilateral amygdala, bilateral vlPFC, and caudal (cACC) and rostral (rACC) ACC to positive and negative emotional faces, in two separate models, in OBP and OCP. 163 predictor variables included: demographics (age, gender, IQ, SES (assessed by the Hollingshead Four Factor Index of Social Status(Hollingshead, 1975)), handedness, and highest parental education); diagnoses; WMT measures (RD, AD, volume, and length of the forceps major/minor and the left/right anterior thalamic radiation, cingulum-angular bundle and -cingulate gyrus, corticospinal tract, inferior longitudinal fasciculus, superior longitudinal fasciculus-parietal and -temporal, and uncinate fasciculus); and GROUP(OBP,OCP)xWMT measure interactions to examine between-group differences in WMT-activity relationships.

Elastic net is particularly useful when the number of predictor variables is much larger than the number of observations, or subjects(Zou and Hastie, 2005). Thus, to maximize the usefulness of our model, we increased the number of predictors by including all WMT measures for all tracts identifiable through TRActs Constrained by UnderLying Anatomy (TRACULA)(Yendiki et al., 2011). While FA is the most widely used invariant measure of anisotropy used in diffusion tensor imaging, it is calculated from the same eigenvectors (λ_1, λ_2, and λ_3) that are used to calculate AD (λ_1) and RD ((λ_2+ λ_3)/2)(Alexander et al., 2007). This strong correlation between FA and both AD and RD rendered us unable to put all three measures in a single model. In keeping with our aim to maximize our model's usefulness, we included twice as many variables (AD and RD) in the model, in lieu of FA, and instead examined FA in additional analyses.

This was followed with post-hoc analyses to examine the contribution of non-zero variables observed with elastic net to the dependent variables, as well as the proportion of variance in dependent variables explained by the models. A test statistic or p-value for elastic net that has a simple and exact asymptotic null distribution is still under development(Lockhart et al., 2014); however, significance was determined in all other analyses.

The goal of the present study was to identify WMT-activity relationships that differed between OBP and OCP. Thus, only GROUPxWMT interactions were examined further. For all non-zero predictors of GROUPxWMT interactions on activity measures, post-hoc analyses determined the nature of between-group differences in the slopes of WMT-activity relationships, using(Paternoster et al., 1998): $Z=(Slope_{OBP} - Slope_{OCP})/\sqrt{(SE^2_{OBP} + SE^2_{OCP})}$. To control for multiple parallel tests of between-group differences in slopes of the above relationships, sequential goodness of fit (SGoF) metatests were used(Carvajal-Rodriguez et al., 2009). This method was chosen because it is a multitest adjustment methodology that increases its statistical power when the number of tests increases(Carvajal-Rodríguez et al., 2009). Under favorable conditions, this test can show a statistical power up to two orders of magnitude higher than Benjamini and Hochberg and Bonferroni methods without appreciably increasing the false discovery rate(Carvajal-Rodríguez et al., 2009). Thus, it is an important tool for multitest adjustment when working with high-dimensional biological data(Carvajal-Rodríguez et al., 2009), rendering it well-suited for the large number of multiple comparison adjustments performed in this study.

Additional Analyses

Additional analyses focused on WMT-activity relationships that significantly differentiated OBP from OCP. We repeated the above analyses separating youth into those with and without non-BD disorders. We also conducted the above analyses in OHP as a comparison group for OBP and OCP. We determined how WMT measures correlated with FA and age. We examined between-group differences in WMT and activity measures and determined whether main findings remained after excluding youth taking psychotropic medications. Finally, we examined between-group differences in symptom severity (using SCARED, CALS, MFQ, and KMRS) and determined whether symptoms that differed between groups impacted significant between-group differences in WMT-activity relationships. Here, we examined how symptom severity measures moderated WMT-activity relationships by determining whether there were significant interactions between symptom severity and WMT measures on neural activity.

See Supplementary Material for more information regarding participant diagnoses and medications, power analyses, neuroimaging data acquisition and analyses, and elastic net.

Results

Analyses Testing Hypotheses 1–2

When examining responses to negative emotional faces in all ROIs, no predictors optimized model fit, indicating that there was no significant relationship between any of the predictors

and activity to negative emotions. Thus, we will focus on findings pertaining to positive (i.e. happy) emotional faces.

When examining responses to happy faces in all ROIs, 14 non-zero predictors together optimized model fit using the minimum λ (λ=1.436) identified by cross-validation (Figure 1A–G). Eight GROUPxWMT interactions showed relationships with activity in all ROIs (inverse for OBP, positive for OCP): forceps minor RD, right cingulum-cingulate gyrus volume and length, right inferior longitudinal fasciculus length, left cingulum-angular bundle volume, forceps major volume and RD, and left superior longitudinal fasciculus-parietal AD. Four variables showed positive relationships with activity in all ROIs for all youth: left cingulum-cingulate gyrus volume, left superior longitudinal fasciculus-temporal volume and length, and left handedness. Two variables showed inverse relationships with activity in all ROIs for all youth: right handedness and medium SES.

A pseudo r-squared of .165 was calculated containing 14 predictors from the model versus an intercept only model, indicating that 16.5% of the variance in activity to happy faces in all ROIs was explained by the 14 predictors. Eight of these predictors were GROUPxWMT interaction variables (Figure 1H). Of these interactions, the slopes of 2 WMT-activity relationships significantly differed between OBP and OCP after correcting for multiple comparisons (Table 2): right cingulum-cingulate gyrus length and cACC activity ($p=0.033$), and forceps minor RD and rACC activity ($p<0.001$) (Figures 2A, 2D). In OBP, longer right cingulum-cingulate gyrus length and greater forceps minor RD were associated with lower cACC and rACC activity to happy faces, respectively. Conversely, in OCP, longer right cingulum-cingulate gyrus length and greater forceps minor RD were associated with greater cACC and rACC activity, respectively.

Additional Analyses

These WMT-activity relationships remained significantly different between OBP and OCP only in youth without non-BD disorders (Figures 2B–C, 2E–F). The relationships for OHP were in between those of OBP and OCP, but differences in these relationships were not statistically significant (Figure 3, Supplementary Table 1). Removing youth taking psychotropic medications caused the significance of the right cingulum-cingulate gyrus length-cACC activity relationship to be substituted by trend-level significance ($p=0.069$), but not the significance of the forceps minor RD-rACC activity relationship ($p=0.017$) (Supplementary Figure 2). Additional analyses thus focused on the forceps minor RD-rACC activity relationship, which was not susceptible to medication effects.

Greater forceps minor RD was significantly associated with lower forceps minor FA ($p<0.001$). Age was not significantly associated with forceps minor RD or rACC activity (Supplementary Figure 3). When comparing individual WMT and activity measures in all OBP and OCP, no group differences were found.

OBP had significantly greater CALS-P and KMRS scores versus OCP ($p=0.044$ and $p=0.004$, respectively) (Figure 4A–B). Regression analyses showed a significant interaction between CALS-P score and forceps minor RD on rACC activity in OBP ($F(1,29)=5.566$, $p=.036$), but not in OCP. Separating OBP into those with higher and lower CALS-P scores,

based on a median split, revealed that those with higher CALS-P scores (M(SD)=15.33(10.52)) had greater inverse WMT-activity relationships (r=−.214, p=.443) than those with lower scores (M(SD)=2.13(2.00)) (r=−.181, p=.503) (Figure 4C).

Discussion

To our knowledge, this is the first study to use multimodal neuroimaging techniques to identify WMT-activity relationships that distinguish youth at genetic risk for BD from youth at risk for non-BD psychiatric disorders. Our goal was to explore WMT-activity relationships in emotion processing circuitry that distinguish OBP from OCP which may lead to the identification of potential biomarkers of BD that precede illness onset. An elastic net regression model indicated that 16.5% of the variance in activity to happy faces in the amygdala, vlPFC, and ACC was predicted by 14 GROUPxWMT interaction, WMT, and demographic variables. This admittedly small amount of variance may be partly explained by the fact that six outcome regions were included in a single elastic net regression model. In other words, the 14 predictor variables, together, explained 16.5% of the variance in all 6 outcome regions at the same time. This also points toward the complex nature of the interaction between WMT measures and activity in the amygdala and prefrontal cortical regions and suggests that many additional factors are likely contributing to activity in these regions.

The primary aim of the elastic net regression analysis was to determine which WMT variables had significant relationships with activity in the amygdala, vlPFC, and/or ACC that distinguished OBP from OCP. Of the 8 GROUPxWMT interaction variables that resulted from the model, only 2 relationships significantly differed between OBP and OCP: right cingulum-cingulate gyrus length-cACC activity, and forceps minor RD-rACC activity. However, neither relationship significantly differentiated either at-risk group from OHP. Removing youth taking psychotropic medications caused the significance of the right cingulum-cingulate gyrus length-cACC activity relationship to be substituted by trend-level significance; however, medications did not affect the forceps minor RD-rACC activity relationship. The latter finding was thus the main focus of our additional analyses.

Greater forceps minor RD was associated with lower rACC activity to happy faces in OBP but greater activity in OCP. Additional analyses revealed that greater forceps minor RD was associated with lower FA and, thus, lower fiber collinearity. This indicates that, in OBP alone, lower fiber collinearity in the forceps minor was significantly associated with lower activity in the rACC. When comparing this WMT-activity relationship in youth with and without non-BD disorders, the between-group differences in this relationship remained significant only in OBP and OCP without disorders. Together, these findings indicate that the key WMT-activity relationship differentiating OBP from OCP was the forceps minor RD-rACC activity relationship to happy faces, which remained evident when excluding youth with non-BD psychiatric disorders.

Previous neuroimaging studies of youth and adults with BD provide similar findings regarding WMT and activity abnormalities during emotion processing. Studies reported that individuals with, and at risk for, BD have abnormally low ACC activity(Blumberg et al.,

2005; Chan et al., 2016; Dolcos et al., 2011; Phillips et al., 2003; Phillips et al., 2008) and fiber collinearity in the forceps minor(Benedetti et al., 2011b; Chaddock et al., 2009; Emsell et al., 2013; Haller et al., 2011; Jenkins et al., 2016; Ji et al., 2017; Nortje et al., 2013; Versace et al., 2014; Versace et al., 2010b; Wang et al., 2008b). Our findings add to this literature by showing that, in OBP, lower fiber collinearity in the forceps minor was associated with lower activity to happy faces in the rACC. The forceps minor is the major interhemispheric WMT that anteriorly connects the cerebral hemispheres, integrates emotion, language, attention, arousal, memory, and sensory-motor functions, and is vulnerable to repeated stresses such as psychosis and impulsivity(Lavagnino et al., 2015; Sarrazin et al., 2015). The rACC has extensive connections to the amygdala and is involved in conditioned emotional learning, modulating internal emotional responses, and assigning emotional valence to internal and external stimuli(Devinsky et al., 1995; Zimmerman et al., 2006). Thus, the inverse relationship between forceps minor RD and rACC activity in OBP may indicate that, in this at-risk group, abnormal myelination and/or more obliquely oriented fibers in the forceps minor may contribute to lower activity in the rACC by reducing the integrity of connections between regions that are important to positive emotional processing(Morgan et al., 2009).

Conversely, the relationship between forceps minor RD and rACC activity was positive in OCP such that lower fiber collinearity in forceps minor contributed to greater rACC activity in this group. Additionally, while not statistically significant, the forceps minor RD-rACC relationship for OHP was intermediate between those of OBP and OCP. Thus, because the at-risk groups did not differ from the healthy controls, it is not possible at this point to determine whether this WMT-activity relationship is a biomarker preceding BD illness. Given the significantly greater genetic risk for BD in OBP versus OCP, however, we may speculate that the forceps minor RD-rACC relationship suggests diverging pathophysiological mechanisms in OBP versus OCP. Further study, including larger sample sizes and longitudinal analyses, is needed to understand the implications of this main finding to BD risk and development.

Despite the lack of differences with OHP, additional analyses showed that OBP had significantly greater affective lability and manic symptom severity than OCP. Furthermore, there was a significant interaction between parent-reported affective lability severity and forceps minor RD on rACC activity to happy faces in OBP: greater affective lability was associated with a greater inverse WMT-activity relationship. Given that affective lability is a precursor of BD in OBP(Hafeman et al., 2016), the forceps minor RD-rACC activity relationship to happy faces may represent a neural basis for this clinical risk marker in OBP.

Six other variables (right cingulum-cingulate gyrus volume, right inferior longitudinal fasciculus length, left cingulum-angular bundle volume, forceps major volume and RD, and left superior longitudinal fasciculus-parietal AD) showed GROUPxWMT interactions (inverse for OBP, positive for OCP). These measures, except left superior longitudinal fasciculus-parietal AD, were inversely associated with FA, indicating that lower right cingulum-cingulate gyrus, right inferior longitudinal fasciculus, left cingulum-angular bundle, and forceps major fiber collinearity were associated with lower activity in OBP, but greater activity in OCP; the opposite was true for the left superior longitudinal fasciculus-

parietal AD relationship. None of these relationships significantly differed between groups after SGoF corrections, however. Three WMT variables (left cingulum-cingulate gyrus volume and left superior longitudinal fasciculus-temporal volume and length) showed positive relationships with activity to happy faces in all ROIs for all youth. These measures were inversely associated with FA, indicating that lower left cingulum-cingulate gyrus and left superior longitudinal fasciculus-temporal fiber collinearity were associated with greater activity in all ROIs in OBP and OCP. Handedness also showed relationships with activity in all ROIs for all youth (inverse for right, positive for left); however, very few youth were left- (n=4) or mixed-handed (n=3), suggesting that handedness did not have a significant effect on the model. Similarly, youth with medium SES were relatively few (n=11), and neither very low, low, high, nor very high SES had any predictive value in the elastic net model, suggesting that SES also did not have a significant effect on the model. In summary, none of these relationships significantly differed between OBP and OCP. Thus, while these variables showed relationships with activity in emotion processing neural circuitry to happy faces, they are unlikely to be markers that either distinguish OBP from OCP or indicate specific risk for BD.

All findings were specific to happy faces, reflecting the importance of positive emotion processing abnormalities in the development of BD. A common theme that has emerged from neuroimaging studies of BD is that of abnormal activity in emotion processing circuity to positive emotional stimuli(Phillips and Swartz, 2014). Specifically, an emerging pattern is that of abnormally elevated amygdala, striatal, and medial prefrontal cortical activity in response to positive emotional stimuli in individuals affected with BD(Blumberg et al., 2005; Lawrence et al., 2004). Several studies have shown that adults with BD have abnormally increased amygdala and medial prefrontal cortex activity(Keener et al., 2012; Surguladze et al., 2010), as well as abnormally decreased positive bilateral orbitofrontal cortex-amygdala effective connectivity(Almeida et al., 2009), to emotional faces, particularly happy faces. These results suggest that individuals with BD have a dysregulated amygdala response to positive emotional stimuli(Phillips and Swartz, 2014). Overall, our findings suggest that abnormal perception of happy faces may reflect an underlying attentional bias to positive emotional stimuli, which may predispose to deficits in social processing, heightened perception of social reward, and, ultimately, hypo/mania.

There were limitations to this study. The primary limitations were the exploratory nature of our analyses and limited sample size, particularly when comparing subsamples of high-risk youth who had a non-BD disorder to those who did not have any disorders. Small sample size may have contributed to the reason why no significant differences were found between OHP and either OBP or OCP. Future studies should aim to replicate our findings with more targeted hypotheses and larger sample sizes. As this was the first study to examine structure-function relationships in BD at-risk youth, we chose to initially examine relationships between WMT structure and BOLD activity; future studies can examine relationships among functional connectivity, gray matter volume, and cortical thickness measures to additionally enhance our understanding of relationships between brain structure and function in BD at-risk youth. WMT length may, in part, be influenced by the tractography propagation mask and definition of end regions; future studies can employ different approaches to examine WMT length in OBP and OCP. We assumed a linear model between

WMT structure and activity; nonlinear models may be considered in future studies. While other clinical assessments could have been included, our primary aim was to determine measures of specific symptoms that, at subthreshold levels, may confer risk for BD(Hafeman et al., 2016). Additionally, while we showed that age did not significantly affect either structural or functional measure, pubertal development, as well as other environmental effects such as childhood adversity, cannot be entirely ruled out as contributing factors in our results. Furthermore, while most parents with non-BD psychiatric disorders were beyond the most common age of onset for BD, it is possible that some of these individuals may have been misdiagnosed or may still develop BD later in life. Every effort was made, however, to ensure the correct diagnoses for each offspring and parent involved in this study, including follow-up evaluations that were conducted at the time of the scan. Finally, recent studies have debated the possible inflation of predictions in neuroimaging studies in individuals with psychiatric disorders(Whelan and Garavan, 2014). We used a well-validated approach that penalizes complex models using regularization, cross-validation, and sparsity enforcement in model fit. Future studies can aim to replicate our findings and employ longitudinal follow-up designs to determine how the WMT-activity relationships identified in this study predict future BD in OBP.

In this study, we showed that the relationship between forceps minor RD and rACC activity significantly differentiated youth at genetic risk for BD from youth at risk for non-BD psychiatric disorders, was evident in youth unaffected by psychiatric disorders, and was moderated by symptoms of affective lability. Given these findings, it is possible that this WMT-activity relationship reflects 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. This is an important step toward identifying neurobiological measures in BD risk to improve accuracy in identifying youth most at risk for future BD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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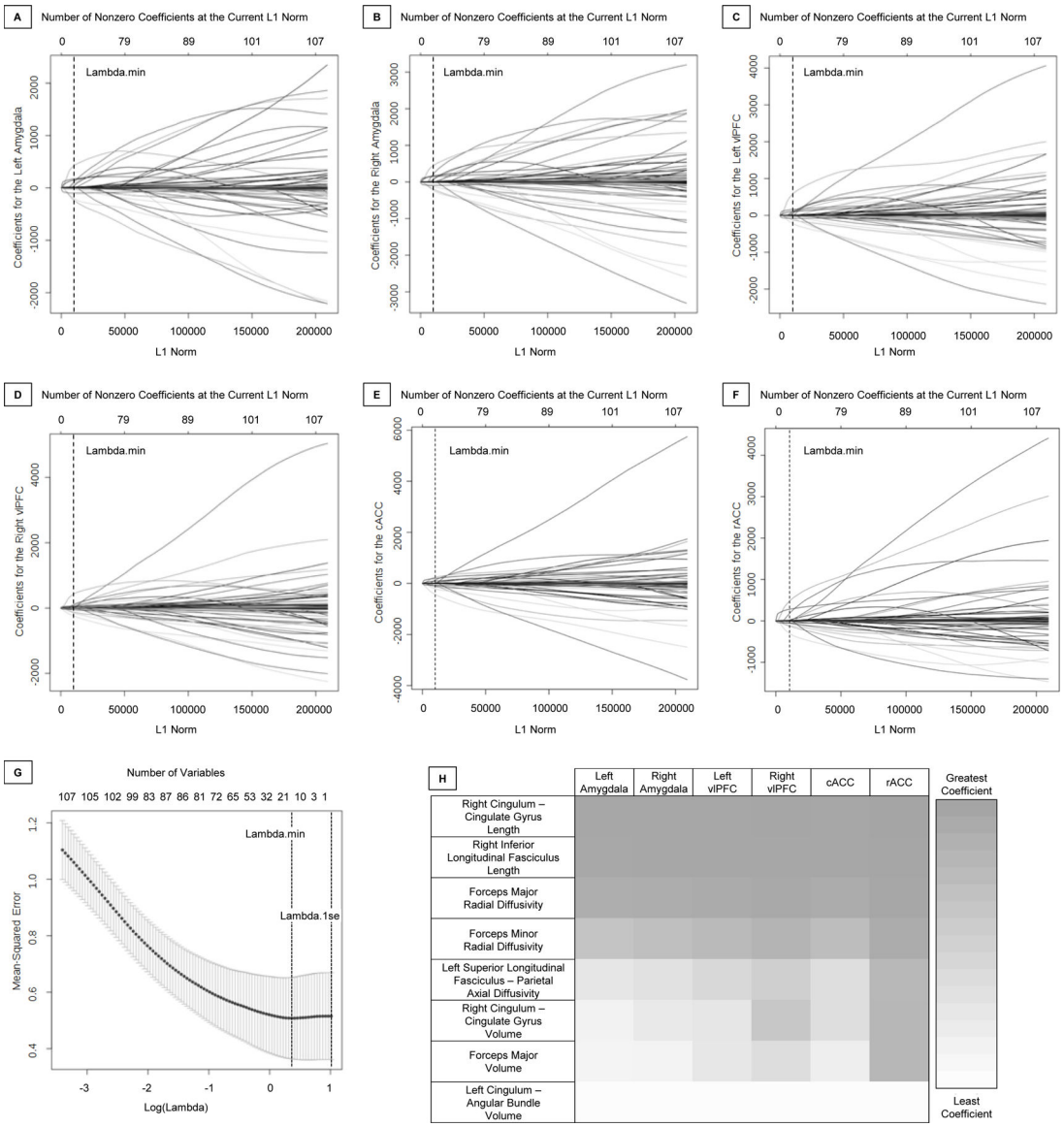

Figure 1. Elastic Net Plots Generated in GLMNET and Heat Map of Select Exponentiated Coefficients

A–F. Plots of variable fit for activity in response to happy faces in the left amygdala (A), right amygdala (B), left vlPFC (C), right vlPFC (D), cACC (E), and rACC (F). Each curve corresponds to an independent variable in the full model prior to optimization. Curves indicate the path of each variable coefficient as λ varies. Lambda.min (λ=1.436) corresponds to the λ which minimizes mean squared error in the model and was used for the selection of the 14 predictor variables. **G.** Plot of non-zero variable fit after cross validation. Representation of the 10-fold cross validation performed for the elastic net regression that chooses the optimal λ. Lambda.min corresponds to the λ which minimizes mean squared error and was used for variable selection. Lambda.1se (λ=2.754) corresponds to the λ that is one standard error from the lambda.min. **H.** Heat map representing color-coded exponentiated coefficients for group x white matter interaction variables in the elastic net model. Each row represents a variable with group interaction between OBP and OCP that

was found to be a significant predictor variable in the model. Each column represents one of the six regions for which the predictor variables predicted activity in response to happy faces. Exponentiated coefficients, representing the degree to which the predictor variables are associated with activity, are depicted with increased coefficients ranging from white to gray, representing the least and greatest coefficient observed of these variables in this model, respectively.

Abbreviations: Ventrolateral Prefrontal Cortex (vlPFC); Caudal Anterior Cingulate Cortex (cACC); Rostral Anterior Cingulate Cortex (rACC); Offspring of Bipolar Parents (OBP); Offspring of Comparison Parents (OCP).

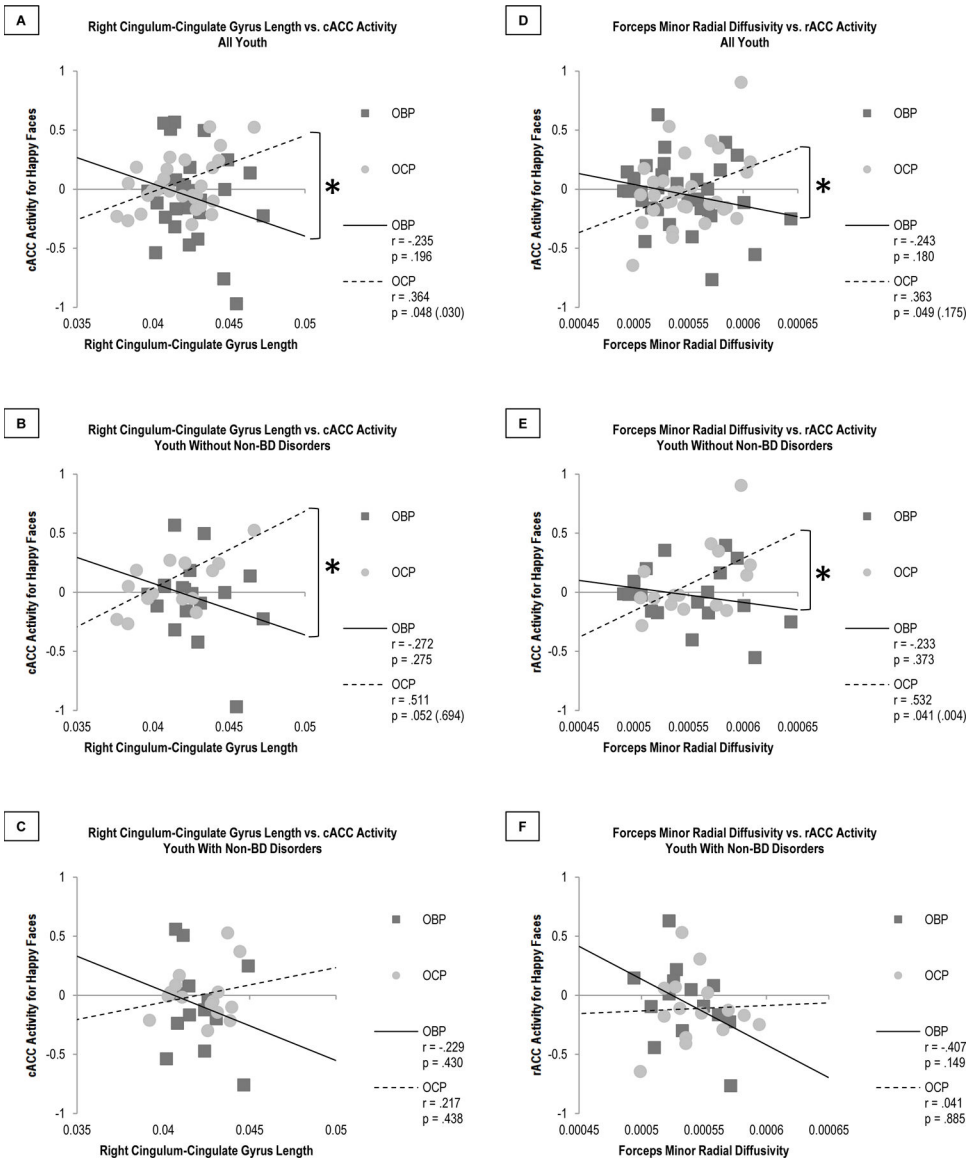

Figure 2. Comparison of Significant White Matter Tract-Activity Relationships in OBP and OCP

A–C. Comparison of relationships between right cingulum-cingulate gyrus length and cACC activity for happy faces. This relationship significantly differed in all youth (p = .024 (.033), **A**) and in those without non-BD disorders (p = 0.023 (0.002), **B**) but not in youth with non-BD disorders (p = 0.276, **C**). **D–F.** Comparison of relationships between forceps minor radial diffusivity and rACC activity for happy faces. This relationship significantly differed in all youth (p = 0.014 (<0.001), **D**) and in those without non-BD disorders (p = 0.017 (<0.001), **E**) but not in youth with non-BD disorders (p = 0.204, **F**).

p-values are uncorrected, with SGoF-corrected values in parentheses. Bolded p-values are those that are significant after SGoF correction.

Abbreviations: Offspring of Bipolar Parents (OBP); Offspring of Comparison Parents (OCP); Caudal Anterior Cingulate Cortex (cACC); Rostral Anterior Cingulate Cortex (rACC); Bipolar Disorder (BD); Sequential Goodness of Fit (SGoF).

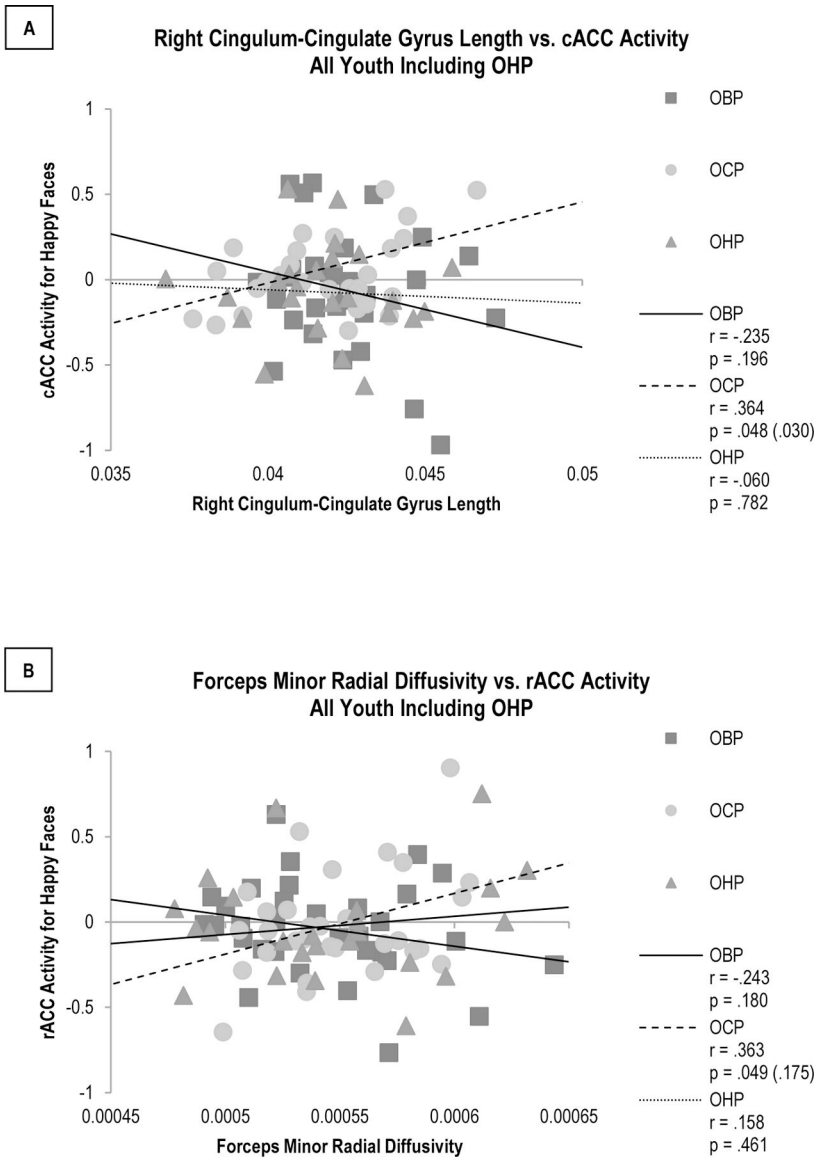

Figure 3. Comparison of Significant White Matter Tract-Activity Relationships in OHP Compared to OBP and OCP

A. Comparison of relationships between right cingulum-cingulate gyrus length and cACC activity for happy faces. This relationship did not significantly differ between OHP and either BOP (p = .401) or OCP (p = .126). **B.** Comparison of relationships between forceps minor radial diffusivity and rACC activity for happy faces. This relationship did not significantly differ between OHP and either OBP (p = .258) or OCP (p = .107).

p-values are uncorrected, with SGoF-corrected values in parentheses.

Abbreviations: Offspring of Bipolar Parents (OBP); Offspring of Comparison Parents (OCP); Offspring of Healthy Parents (OHP); Caudal Anterior Cingulate Cortex (cACC); Rostral Anterior Cingulate Cortex (rACC); Sequential Goodness of Fit (SGoF).

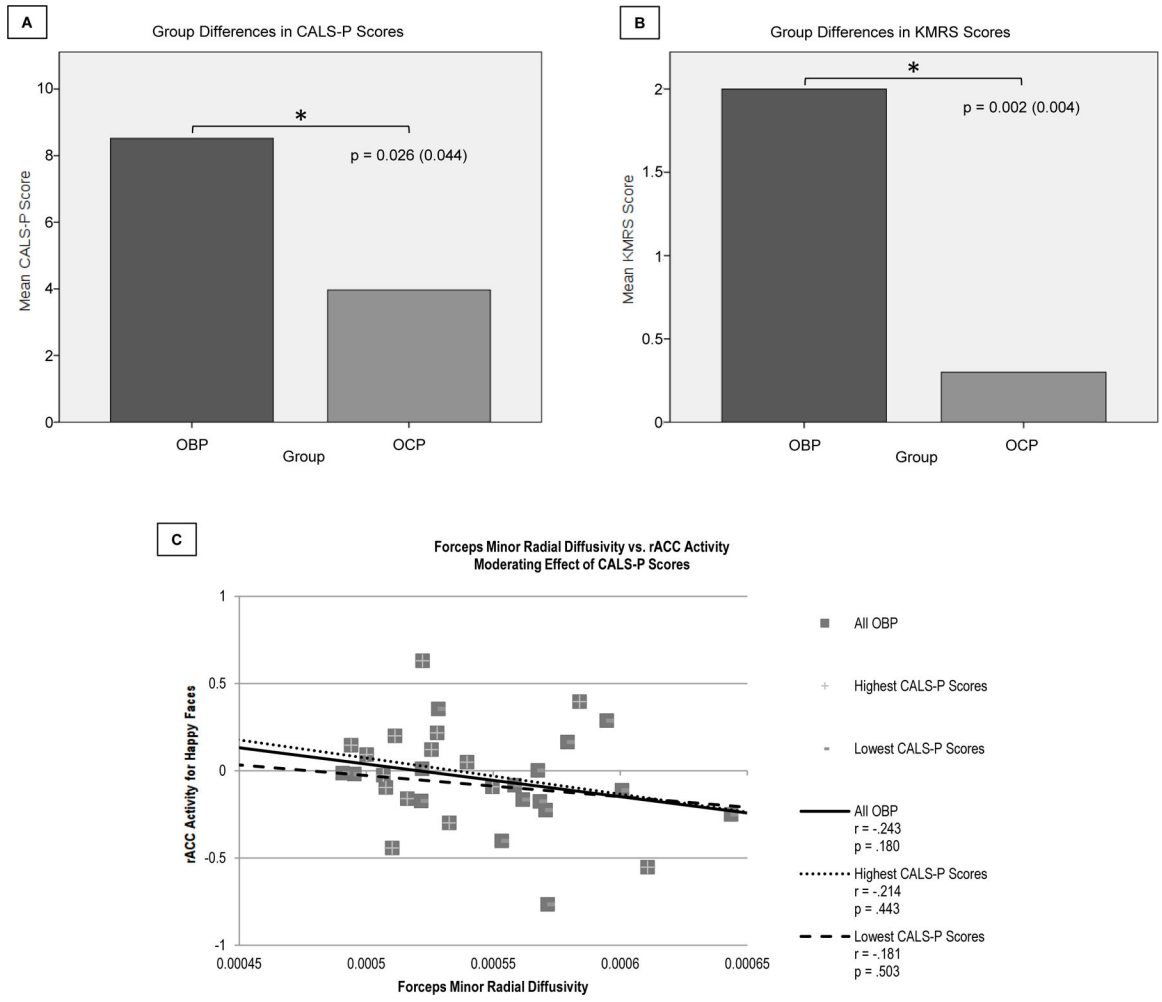

Figure 4. Group Comparisons in Clinical Scores, and Effects on White Matter Tract-Activity Relationships

A–B. Comparison of CALS-P and KMRS scores for OBP versus OCP. OBP had significantly greater CALS-P (p=0.026(0.044), **A**) and KMRS (p=0.002(0.004), **B**) scores versus OCP. **C.** Moderating effect of CALS-P scores on the relationship between forceps minor radial diffusivity and rACC activity for happy faces. CALS-P scores had a significant moderating effect on the relationship between forceps minor radial diffusivity and rACC activity in OBP (F(1,29)=5.566, p=.036). OBP with higher CALS-P scores (M=15.33; SD=10.52) had more negative white matter tract-activity relationships (r=−.214, p=.443) than OBP with lower CALS-P scores (M=2.13; SD=2.00) (r=−.181, p=.503).

p-values are uncorrected, with SGoF-corrected values in parentheses. Bolded p-values are those that are significant after SGoF correction.

Abbreviations: Children's Affective Lability Scale – Parent (CALS-P); Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale (KMRS); Offspring of Bipolar Parents (OBP); Offspring of Comparison Parents (OCP); Rostral Anterior Cingulate Cortex (rACC); Sequential Goodness of Fit (SGoF).

Table 1

Comparison of OBP (n=32), OCP (n=30), and OHP (n=24).

	OBP n=32	OCP n=30	OHP n=24	Statistic	p
Demographic Information					
Age	13.81(2.45)	13.98(2.30)	13.80(1.72)	F = 0.061	.941
Sex (females)	15	12	10	$\chi^2 = 0.324$	.851
IQ	99.97(15.80)	102.97(14.22)	104.00(13.60)	F = 0.591	.556
SES (primary caregiver education)				$\chi^2 = 7.037$	.134
No/some HS or HS Diploma	16	7	7		
Some post HS	6	5	3		
Associate's Degree or Higher	10	18	14		
Clinical Measures					
Diagnosis	14	15	N/A	t = −0.486	.629
Major Depressive Disorder	4	4	N/A	t = −0.096	.924
Anxiety Disorder	4	6	N/A	t = −0.793	.431
Attention Deficit/Hyperactivity Disorder	7	7	N/A	t = −0.135	.893
Oppositional Defiant or Conduct Disorder	2	3	N/A	t = −0.534	.595
Obsessive Compulsive Disorder	0	2	N/A	t = −1.439	.161
Eating Disorder	2	0	N/A	t = 1.438	.161
Psychotropic Medication Use	3	0	N/A	t = 1.791	.083
Scan day assessments					
SCARED-P	9.10(5.67)	10.27(11.61)	4.75(4.59)	F = 3.084	**.051**
SCARED-C	12.52(15.20)	8.62(13.40)	10.23(11.66)	F = 0.651	.524
CALS-P	7.93(9.57)	3.73(4.54)	1.67(2.55)	F = 7.494	**.001**
CALS-C	9.97(12.67)	6.42(10.57)	6.00(13.08)	F = 0.889	.415
MFQ-P	6.52(9.38)	3.81(3.56)	1.63(2.06)	F = 4.211	**.018**
MFQ-C	8.07(10.89)	8.62(11.20)	5.83(10.66)	F = 0.506	.605
Assessment closest to scan					
KMRS	1.86(2.80)	0.27(0.60)	0.08(0.28)	F = 10.524	**.000**

P indicates parent version and C indicates child version. Data are mean (SD) for age, IQ, and clinical assessments. For all other variables, data are total n.

Abbreviations: Offspring of Bipolar Parents (OBP); Offspring of Comparison Parents (OCP); Offspring of Healthy Parents (OHP); Screen for Child Anxiety Related Emotional Disorders (SCARED); Children's Affective Lability Sale (CALS); Mood and Feelings Questionnaire (MFQ); Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale (KMRS); Socioeconomic Status (SES); High School (HS).

Table 2

Slope comparisons between OBP (n=32) and OCP (n=30) for the eight white matter-activity relationships for which there were non-zero group x white matter interaction predictors of ipsilateral neural activity variables.

Predictor Variable	Outcome Variable	Z	p =
Right CCG Length	**Right Amygdala**	−2.17	.030 (.451)
	Right vlPFC	−1.38	.168
	cACC	−2.26	**.024 (.054)**
	rACC	−0.72	.472
Right ILF Length	**Right Amygdala**	−0.95	.342
	Right vlPFC	−0.71	.478
	cACC	−1.28	.201
	rACC	−1.01	.312
FMAJOR Radial Diffusivity	**Left Amygdala**	−1.68	.093
	Right Amygdala	−1.80	.072
	Left vlPFC	−0.29	.772
	Right vlPFC	−0.86	.390
	cACC	−0.45	.653
	rACC	−0.17	.865
FMAJOR Radial Diffusivity	**Left Amygdala**	−2.07	.038 (.941)
	Right Amygdala	−1.89	.059
	Left vlPFC	−1.56	.119
	Right vlPFC	−1.37	.171
	cACC	−1.80	.072
	rACC	−2.47	**.014 (.014)**
Left SLFP xial Diffusivity	**Left Amygdala**	−1.62	.105
	Left vlPFC	−1.59	.112
	cACC	−2.07	.038 (1.00)
	rACC	−2.20	.028 (.173)
Right CCG Volume	**Right Amygdala**	−0.27	.787
	Right vlPFC	0.65	.516
	cACC	−0.30	.764
	rACC	0.08	.936
FMAJOR Volume	**Left Amygdala**	−0.55	.582
	Right Amygdala	−1.08	.280
	Left vlPFC	0.41	.682
	Right vlPFC	−0.47	.638
	cACC	−0.73	.465
	rACC	0.00	1.00
Left CAB Volume	**Left Amygdala**	0.91	.363

Predictor Variable	Outcome Variable	Z	p =
	Left vlPFC	0.90	.368
	cACC	0.49	.624
	rACC	1.45	.147

p-values are uncorrected, with SGoF-corrected values in parentheses. Bolded p-values are those that are significant after SGoF correction.

Abbreviations: Offspring of Bipolar Parents (OBP); Offspring of Control Parents (OCP); Ventrolateral Prefrontal Cortex (vlPFC); Caudal Anterior Cingulate Cortex (cACC); Rostral Anterior Cingulate Cortex (rACC); Cingulum – Cingulate Gyrus (CCG); Inferior Longitudinal Fasciculus (ILF); Forceps Major (FMAJOR); Superior Longitudinal Fasciculus (SLFP); Cingulum – Angular Bundle (CAB).