BRAIN STRUCTURE AND FUNCTION IN EMOTION PROCESSING, EMOTION REGULATION, AND REWARD PROCESSING NEURAL CIRCUITRIES IN OFFSPRING AT RISK FOR BIPOLAR DISORDER

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Bipolar Disorder (BD) is a serious psychiatric illness with demonstrated structural and functional abnormalities in emotion processing, emotion regulation, and reward processing neural circuitries. BD is also a highly heritable disorder, placing first-degree relatives of patients with BD at great risk for developing the disorder, themselves. There are many similarities, however, between BD and other psychiatric illnesses, such as Major Depressive Disorder, Attention Deficit/Hyperactive Disorder, and Anxiety Disorders, which often makes it difficult to diagnose BD. By detecting abnormalities in neural measures and symptomatology that uniquely distinguish youth at risk for BD, we have the potential to identify objective biological markers of BD risk that may aid in the development of improved diagnostic and therapeutic strategies for BD. In this dissertation, we use elastic net regression analyses to examine structural, functional, and symptomatic measures in offspring of bipolar parents (OBP) compared with offspring of comparison parents with non-BD psychiatric disorders (OCP) and offspring of healthy parents (OHP). In chapter 3, we present findings demonstrating greater rostral anterior cingulate cortex (ACC) activity when regulating attention away from positive (i.e. happy) emotions, as well as

greater bilateral amygdala-left caudal ACC functional connectivity (FC) when regulating attention away from all (i.e. fearful, happy, and neutral) emotions in OBP compared with OCP. In chapter 4, we demonstrate lower right ventral striatum-left caudal ACC FC when processing loss and greater right pars orbitalis-orbitofrontal cortex FC when processing reward in OBP compared with both OCP and OHP. In chapter 5, we demonstrate inverse relationships between right cingulum-cingulate gyrus length and bilateral caudal ACC activity, as well as between forceps minor radial diffusivity and bilateral rostral ACC activity, when processing positive emotions in OBP compared with OCP. Throughout these analyses, significant relationships were observed between the ACC and affective lability severity. Together, these studies identify the ACC as a key neural region that may help distinguish youth at risk for BD from youth at risk for other psychiatric disorders. These findings provide specific neural and symptomatic targets which may improve the diagnosis and treatment of BD, leading to overall better outcomes for youth at risk for BD.

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LIST OF ABBREVIATIONS

ACC: Anterior Cingulate Cortex

AD: Axial Diffusivity

ADHD: Attention Deficit/Hyperactivity Disorder

ANOVA: Analysis of Variance

BA: Brodmann's Area

BD: Bipolar Disorder

BIOS: Bipolar Offspring Study

BOLD: Blood-Oxygen-Level Dependent

cACC: Caudal ACC

CALS: Children's Affective Lability Scale

CALS-C: Child-Reported CALS

CALS-P: Parent-Reported CALS

DFT: Dynamic Faces Task

dlPFC: Dorsolateral Prefrontal Cortex

DSM: Diagnostic and Statistical Manual of Mental Disorders

DTI: Diffusion Tensor Imaging

ECT: Electroconvulsive Therapy

EF-0-BACK: Emotional Face 0-Back Task

EF-2-BACK: Emotional Face 2-Back Task

EPI: Echo Planar Imaging

FA: Fractional Anisotropy

FC: Functional Connectivity

fMRI: Functional Magnetic Resonance Imaging

gPPI: Generalized PPI

KDRS: K-SADS Depression Rating Scale

KMRS: K-SADS Mania Rating Scale

K-SADS: Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children

LAMS: Longitudinal Assessment of Manic Symptoms

MDD: Major Depressive Disorder

MFQ: Mood and Feelings Questionnaire

MFQ-C: Child-Reported MFQ

MFQ-P: Parent-Reported MFQ

MRI: Magnetic Resonance Imaging

OBP: Offspring of Bipolar Parents

OCP: Offspring of Comparison Parents

OFC: Orbitofrontal Cortex

OHP: Offspring of Healthy Parents

PFC: Prefrontal Cortical/Cortex

PPI: Psychophysiological Interactions

rACC: Rostral ACC

RD: Radial Diffusivity

ROI: Region of Interest

SCARED: Screen for Child Anxiety Related Disorders

SCARED-C: Child-Reported SCARED

SCARED-P: Parent-Reported SCARED

SES: Socioeconomic Status

SGoF: Sequential Goodness of Fit

tDCS: Transcranial Direct Current Stimulation

TMS: Transcranial Magnetic Stimulation

TRACULA: TRActs Constrained by UnderLying Anatomy

vlPFC: Ventrolateral Prefrontal Cortex

VS: Ventral Striatum

WMT: White Matter Tract

PREFACE

There are many people to whom I owe much gratitude for their support and guidance in the years leading up to this point. Without the help of those mentioned below, this work would not have been possible.

I would first like to thank Mary Phillips for welcoming me into her laboratory. From our very first meeting, it was clear to me that she would be an ideal mentor who would help me grow scientifically, intellectually, and personally. I have learned so much from her over these past few years and attribute much of my success to her mentorship. It has truly been an honor and a privilege working with and learning from such a wonderful physician-scientist.

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1.0 GENERAL INTRODUCTION

This chapter provides a general introduction regarding Bipolar Disorder (BD), youth at familial risk for BD, and several neural circuitries and symptoms that are important to the study of BD risk.

1.1 OVERVIEW OF BIPOLAR DISORDER

1.1.1 Bipolar Disorder (BD)

BD is a debilitating psychiatric disorder characterized by recurrent and episodic disturbances in mood, sleep, behavior, perception, and cognition, rendering it a leading cause of disability, morbidity, and mortality worldwide (Mahon, Burdick et al. 2010). BD is classified as a group of affective disorders that are characterized by episodes of depression and either mania or hypomania (Phillips and Kupfer 2013). The four main subtypes of BD, according to the DSM-V, are: BD type I, characterized by episodes of depression and mania; BD type II, characterized by episodes of depression and hypomania; Cyclothymic Disorder, characterized by depressive and hypomanic symptoms that do not meet full criteria for episodes; and Other Specified Bipolar and Related Disorder, characterized by symptoms that are related to BD but do not meet full criteria

for any other disorders that are related to BD (American Psychiatric Association 2013, Phillips and Kupfer 2013).

Criteria for major depressive episodes include at least five of the following symptoms: depressed mood, anhedonia, significant changes in weight or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or decreased energy, feelings of worthlessness or guilt, diminished ability to concentrate, and suicidal ideation (American Psychiatric Association 2013). Additionally, at least one of these symptoms must be either depressed mood or anhedonia (American Psychiatric Association 2013). Criteria for manic episodes include elevated, expansive, or irritable mood with at least three or four of the following symptoms: inflated self-esteem or grandiosity, decreased need for sleep, more talkative or pressured speech, flight of ideas or racing thoughts, distractibility, increased goal-directed activity or psychomotor agitation, and excessive involvement in activities with a high risk for painful consequences (American Psychiatric Association 2013). Manic episodes may additionally cause impaired social or occupational functioning, require hospitalization, and/or have psychotic features (American Psychiatric Association 2013). The criteria for hypomanic episodes are the same as for manic episodes with the following differences: hypomanic episodes require fewer days of symptoms and do not additionally cause impaired functioning, require hospitalization, or have psychotic features (American Psychiatric Association 2013).

BD affects 1-3% of the adult population and has a high heritability of 59-87% (Smoller and Finn 2003, Merikangas, Akiskal et al. 2007, Singh and Chang 2013, Phillips and Swartz 2014). BD often emerges during adolescence (Kowatch, Fristad et al. 2005, Kowatch, Youngstrom et al. 2005, Pavuluri, Birmaher et al. 2005) with 15-28% of adults having experienced illness onset before age 13 years and 50-66% having experienced illness onset

before age 19 years (Leverich, McElroy et al. 2002, Leverich, Altshuler et al. 2003, Perlis, Miyahara et al. 2004). Recent estimates place the mean prevalence of BD in children and adolescents at approximately 2% (Van, Moreira et al. 2011). Approximately 5.6% of adolescents have subthreshold manic, hypomanic, or depressive symptoms, and some symptoms of BD overlap with other disorders, such as Major Depressive Disorder (MDD), Attention Deficit/Hyperactive Disorder (ADHD), or Anxiety Disorders, which often makes it difficult to diagnose BD (Lewinsohn, Klein et al. 1995, Birmaher and Axelson 2006). Additionally, BD is one of the most frequent and costly primary mental health diagnoses in children and adolescents, with recent studies estimating that it makes up 18.1% of all mental health admissions and costs $702 million, nationally, in the United States (Bardach, Coker et al. 2014). It is thus important to detect objective biological markers to help differentiate BD from other disorders and identify young individuals who are likely to develop BD in the future.

1.1.2 Offspring at Risk for BD

The high heritability of BD places first-degree relatives of individuals with BD at a 10-fold increased risk of the disorder compared with relatives of healthy individuals (Smoller and Finn 2003, Merikangas, Akiskal et al. 2007, Singh and Chang 2013, Phillips and Swartz 2014). Compared with children of parents without psychiatric illness, offspring of bipolar parents (OBP) are at increased risk of BD and other mood and anxiety disorders (Chang, Steiner et al. 2000). Studying OBP and comparing them with offspring of healthy parents (OHP) can identify early phenotypes associated with BD risk. However, such comparisons are limited in their ability to distinguish risk for BD, specifically, from risk for psychiatric illness, in general. This is because OBP are also at risk for non-BD psychopathology (Chang, Steiner et al. 2000).

Because OBP are at an increased risk for not only BD but also other mood and anxiety disorders, an additional comparison group is necessary to determine whether risk markers are specific to BD or to general psychopathology. Comparing OBP to offspring of comparison parents (OCP) who have non-BD diagnoses, such as MDD, ADHD, or an Anxiety Disorder, can help distinguish specific BD risk. This is because, while both OBP and OCP are at higher risk for psychiatric disorders than the general population (Birmaher, Axelson et al. 2009), OBP have an additionally increased risk for developing BD, specifically. While both OBP and OCP are at increased risk for BD compared with healthy controls, OBP are at an approximate seven-fold increased risk for developing BD compared with OCP with a recent study finding that 23% of OBP developed a bipolar spectrum disorder by age 21 compared with 3.2% in OCP and OHP (Axelson, Goldstein et al. 2015). OCP thus serve as a control group for familial risk for non-BD psychiatric disorders. Additionally, OCP control for the presence of non-BD psychiatric disorders in parents, since parents with BD have high rates of non-BD comorbidity (Merikangas, Akiskal et al. 2007), as well as for the environmental effects of living with a parent with a psychiatric illness (Goldstein, Birmaher et al. 2005). Together, comparing OBP to both OHP and OCP can provide further insight into the underlying mechanisms of BD development and may lead to enhanced early identification and preventative treatment for youth who are likely to develop BD in the future.

1.2 CURRENT MODEL OF BD RISK

There are several predisposing factors, neurobiological processes, behaviors, and outcomes that comprise the current model of BD risk (Figure 3).

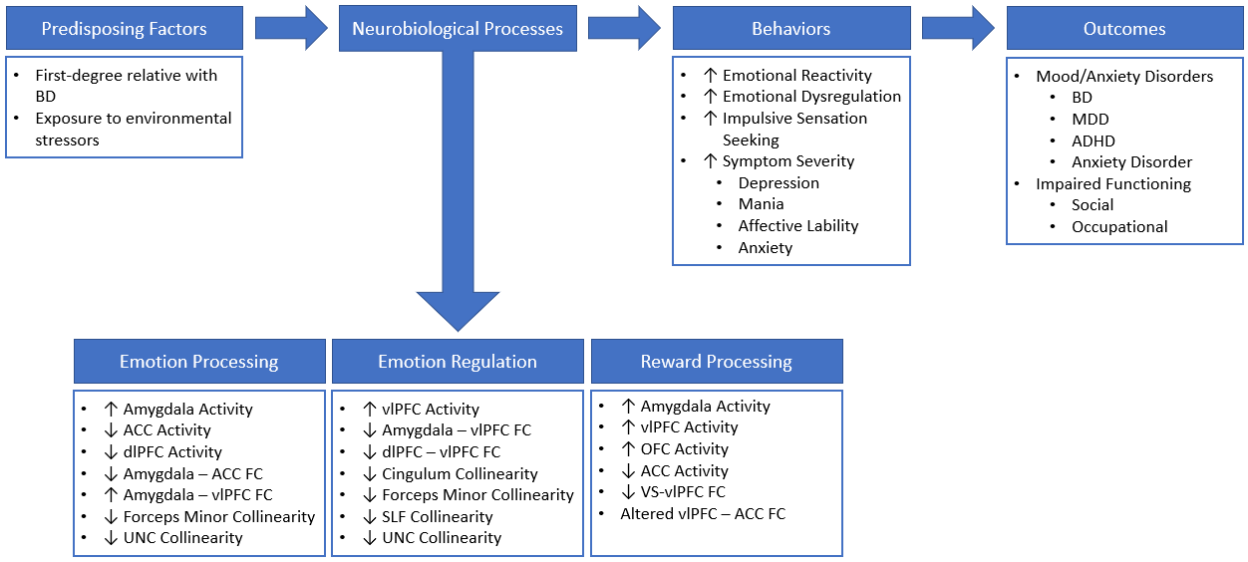

Figure 1: Current Model of BD Risk

Predisposing factors include a familial risk for BD and exposure to environmental stressors. Familial risk for BD is characterized by a family history of BD, particularly a first-degree relative (Smoller and Finn 2003, Merikangas, Akiskal et al. 2007, Singh and Chang 2013, Phillips and Swartz 2014). Abnormalities in gene expression likely underlie the neurobiology of BD at the molecular level and predispose at-risk individuals to the development of the disorder (Manji, Quiroz et al. 2003). Examples of environmental stressors include: *infections*, such as intrauterine infections predisposing to fetal and postnatal neurodevelopment and maternal exposure to influenza; *maternal smoking during pregnancy*, which has been shown to increase the risk of not only BD but many other mental illnesses; *birth complications*, including preterm birth; *climate*, such as weakened circadian rhythms and seasonal effects and variation; *childhood trauma*, which has been shown to increase the likelihood and occurrences of rapid cycling courses, psychotic features, lifetime mood episodes, suicidal ideation and attempts, and substance misuse; *life events*, described as substantial changes in personal surroundings that

result in personal and social consequences, including interpersonal problems; and *poor social support*, affecting ones perception of being loved, cared for, esteemed, valued, and/or a part of a network involving communication and mutual obligation (Aldinger and Schulze 2017). Together, these familial and environmental factors predispose to the development and worsening of BD.

Next in the model of BD risk are neurobiological processes, including underlying molecular and cellular mechanisms. The pathophysiology of BD comprises networks of interconnected limbic, striatal, and fronto-cortical neurotransmitter circuits that involve interactions between cholinergic, catecholaminergic, and serotonergic neurotransmitter systems (Manji, Quiroz et al. 2003). For example, the monoamine neurotransmitter systems mediate complex behavioral effects of BD, including dysregulated behavior, circadian rhythms, sleep, and neuroendocrine and biochemical processes (Manji and Lenox 2000, Goodwin and Jamison 2007). Specifically, abnormalities in noradrenergic systems contribute to levels of depression and mania; reductions in serotonergic systems contribute to levels of depression, impulsivity, aggression, and suicide attempts; reductions in dopaminergic systems contribute to levels of depression, anhedonia, and abnormal incentive motivational behavior; and abnormalities in cholinergic systems contribute to levels of depression and mania (Manji, Quiroz et al. 2003). Abnormalities in signaling pathways have also been implicated in the pathophysiology of BD through their regulation of mood, appetite, and wakefulness (Manji 1992, Milligan and Wakelam 1992, Manji, Quiroz et al. 2003, Spiegel 2012). Specifically, abnormalities in the Gs/cAMP generating signaling pathway contribute to cyclic affective episodes; abnormalities in the protein kinase C signaling pathway contribute to levels of mania; and abnormalities in calcium signaling have also been observed in individuals with BD (Manji, Quiroz et al. 2003). These molecular and

cellular mechanisms all contribute to other abnormalities in BD, such as reduced gray matter volumes via reduced cortex volume, glial cell counts, and neuronal densities and sizes in subgenual prefrontal, orbital, and dorsal anterolateral prefrontal cortical regions (Drevets 2001, Manji, Quiroz et al. 2003). More specifically, reduced gray matter has been observed in orbital and medial PFC regions, the ventral striatum, and the hippocampus (Drevets 2001). These underlying processes all contribute to the development of structural and functional abnormalities that are observed in neural circuitries. There are three circuitries that are particularly important for understanding the neural mechanisms that underlie the vulnerability of youth at risk for BD to develop dimensional or categorical psychopathology. Two such circuitries are *emotion processing* and *emotion regulation*, as BD is characterized by emotional over-reactivity and emotional dysregulation (Goodwin and Jamison 2007). Emotion regulation circuitry incorporates several executive function domains, including voluntary and automatic subprocesses (Phillips, Ladouceur et al. 2008). Voluntary subprocesses include voluntary behavioral control (e.g. suppressing emotional expression), voluntary attentional control (e.g. selective attention, overcoming interference from emotional distractors, and inhibiting emotional motor responses), and voluntary cognitive change (e.g. reappraising anticipation of forthcoming events) (Phillips, Ladouceur et al. 2008). Automatic subprocesses include automatic behavioral change (e.g. extinction and behavioral regulation), automatic attentional control (e.g. cognitive disengagement and repressive and avoidant personality styles), and automatic cognitive change (e.g. covert appraisal and reappraisal, cover response (e.g. error) monitoring, and covert learning that automatically adjusts behavior) (Phillips, Ladouceur et al. 2008). A third circuitry is *reward processing*, as BD is also characterized by heightened reward sensitivity (Alloy, Bender et al.

2012, Ibanez, Cetkovich et al. 2012, Mason, O'Sullivan et al. 2012). Regions that are important to these circuitries will be discussed in detail, below.

These neurobiological processes all contribute to certain behaviors. For example, in youth at risk for BD, abnormalities in emotion processing circuitry contribute to greater emotional reactivity. This may manifest as abnormal hypersensitivity to the processing of emotional stimuli and may predispose to deficits in social processing. Additionally, abnormalities in emotion regulation circuitry contribute to greater emotional dysregulation. This may manifest as abnormally reduced abilities to regulate emotions while either voluntarily or automatically attending to non-emotional stimuli. Furthermore, abnormalities in reward processing contribute to greater impulsive sensation seeking. This may manifest as prematurely elicited behavior with little to no regard for the consequences, as well as an abnormally greater desire to engage in risky behavior. Furthermore, abnormalities in any of these circuitries may contribute to greater symptom severity. A recent study identified four symptoms as the strongest dimensions of psychopathology associated with BD risk: depression, mania, affective lability, and anxiety (Hafeman, Merranko et al. 2016). They found that OBP with high levels of these symptoms (i.e. all four measures being one standard deviation above the mean) had a 24-fold increased risk than OBP with low levels of these symptoms (i.e. all four measures being one standard deviation below the mean) of developing a new-onset bipolar spectrum disorder, over follow-up (Hafeman, Merranko et al. 2016). Specifically, they found that the predicted chance of conversion was 49% in OBP with high symptom levels and only 2% in OBP with low symptom levels (Hafeman, Merranko et al. 2016). Thus, these symptoms of depression, mania, affective lability, and anxiety are important predictors of new-onset bipolar spectrum in populations of youth at risk for BD (Hafeman, Merranko et al. 2016).

Finally, these predisposing factors, neurobiological processes, and behaviors result in a set of outcomes in youth at risk for BD. One such outcome may be the development of a mood or anxiety disorder, such as BD (Hafeman, Merranko et al. 2016), MDD, ADHD, and/or an Anxiety Disorder (Birmaher, Axelson et al. 2009). Furthermore, offspring may develop comorbidities between these disorders (Merikangas, Akiskal et al. 2007). Additionally, these outcomes may include functional impairments, such as in social or occupational functioning (American Psychiatric Association 2013).

1.3 NEURAL CIRCUITRIES IMPORTANT TO BD AND BD RISK

1.3.1 Neural Regions

Several major themes that have been elucidated from functional neuroimaging studies in BD include abnormally increased amygdala and decreased prefrontal cortical (PFC) activity during emotion processing and regulation, as well as abnormally increased PFC activity during reward processing (Phillips and Swartz 2014). More specifically, emotion processing (Phillips, Drevets et al. 2003) and regulation (Dolcos, Iordan et al. 2011) circuitries primarily involve the amygdala, anterior cingulate cortex (ACC), ventrolateral prefrontal cortex (vlPFC), and dorsolateral prefrontal cortex (dlPFC) (Phillips, Drevets et al. 2003, Phillips, Ladouceur et al. 2008, Dolcos, Iordan et al. 2011). Reward processing circuitry primarily involves the amygdala, ACC, vlPFC, orbitofrontal cortex (OFC), and ventral striatum (VS) (Kumar, Waiter et al. 2008, Grabenhorst and Rolls 2011, Phillips and Swartz 2014). A rough, conceptual illustration of the

location of these regions is presented in Figure 1. These regions will be described in detail, below.

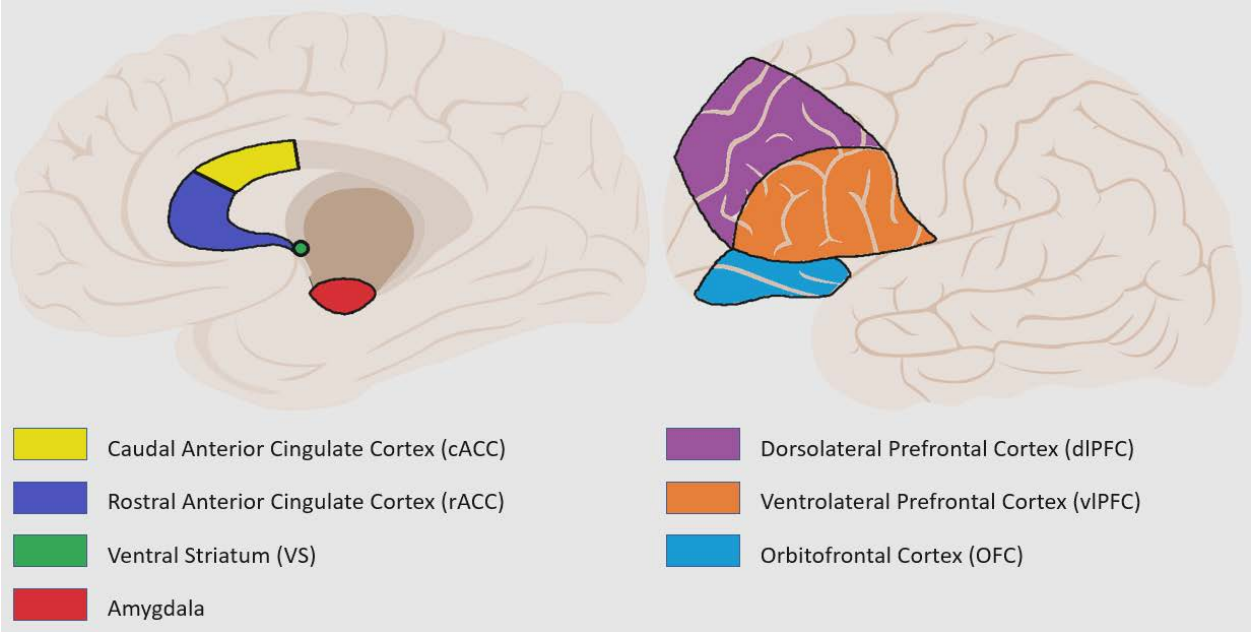

Figure 2: Neural Regions Implicated in Emotion Processing, Emotion Regulation, and Reward Processing Neural Circuitries

1.3.1.1 Amygdala

The amygdala is an important neural region of the limbic system (Swanson 2003), which is a functional anatomical system composed of the medial portions of the frontal, parietal, and temporal lobes that has important roles in learning, memory, and emotions (Kötter and Meyer 1992). It is strongly connected to the ACC and OFC (Ghashghaei, Hilgetag et al. 2007). Connections between the amygdala and the first and second cortical layers of the ACC and OFC may be interpreted as an implication in the focus of attention to motivationally relevant stimuli

(Ghashghaei, Hilgetag et al. 2007). Specifically, projections from the amygdala to the middle layers of these regions may provide information about emotional salience or external sensory stimuli (Ghashghaei, Hilgetag et al. 2007). The amygdala also has projections to the vlPFC (Carmichael and Price 1995). Specifically, studies have postulated that disturbed amygdala-vlPFC connectivity may be related to symptoms of anxiety (Hariri, Mattay et al. 2003).

The amygdala has well established roles in generating fear and anxiety responses, assigning emotional salience to external stimuli, and coordinating affective, autonomic, and behavioral responses to such stimuli (Davis 1997, Paré, Quirk et al. 2004, Pape and Pare 2010). The amygdala is also a key component of emotion processing, emotion regulation, and reward processing neural circuitries. In emotion circuitry, the amygdala is involved in regulating internal emotional states, cognitively evaluating the emotional content of complex perceptual cues, and processing information about emotions that are conveyed by complex perceptual cues (Gallagher and Chiba 1996). In reward processing circuitry, the amygdala is involved in associating stimuli with their reward values (Baxter and Murray 2002).

Many studies have examined the role of the amygdala in BD. Functional abnormalities in emotion processing and regulation neural circuitries in youth and adults with BD, compared with healthy controls (Phillips and Swartz 2014), include greater amygdala activity to emotional stimuli (Lawrence, Williams et al. 2004, Blumberg, Donegan et al. 2005) and lower amygdala-vlPFC FC (Altshuler, Bookheimer et al. 2008, Kalmar, Wang et al. 2009, Ladouceur, Farchione et al. 2011, Strakowski, Eliassen et al. 2011, Delvecchio, Fossati et al. 2012, Foland-Ross, Bookheimer et al. 2012, Garrett, Reiss et al. 2012, Kim, Thomas et al. 2012, Passarotti, Ellis et al. 2012, Townsend, Bookheimer et al. 2012, Townsend, Torrisi et al. 2013). Cross-sectional studies of youth at risk for BD have shown that, compared with OHP, OBP showed lower

amygdala-vlPFC FC to fearful faces during emotion regulation (Ladouceur, Diwadkar et al. 2013) and greater amygdala activity during facial emotion processing (Phillips, Ladouceur et al. 2008, Olsavsky, Brotman et al. 2012, Tseng, Bones et al. 2015, Chan, Sussmann et al. 2016), specifically to fearful faces (Olsavsky, Brotman et al. 2012). The few neuroimaging studies comparing OBP and OCP have found patterns of activity and FC in the amygdala and vlPFC that distinguish OBP from OCP (Manelis, Ladouceur et al. 2015, Manelis, Ladouceur et al. 2016, Soehner, Bertocci et al. 2016). Comparing all three groups during emotional face processing, OBP and OCP have shown greater right amygdala activity to all emotional faces compared with OHP, while OBP have shown lower right amygdala-ACC FC to all emotional faces and greater right amygdala-left vlPFC FC to happy faces compared with OCP and OHP (Manelis, Ladouceur et al. 2015). In reward circuitry, specific findings in relatives of adults with BD include greater amygdala activity during reward reversal compared with healthy controls (Linke, King et al. 2012). Thus, in youth at risk for BD, greater amygdala may reflect a higher arousal to emotions and reward, while lower connectivity between the amygdala and other PFC regions might reflect a reduced ability to regulate other regions that are important to emotion processing. These findings may also reflect an underlying attentional bias to positive emotional stimuli, specifically, in BD, which may predispose to symptoms of mania (Phillips and Swartz 2014).

1.3.1.2 Anterior Cingulate Cortex (ACC)

The ACC is another component of the limbic system which is involved in cognitive and emotional tasks (Bush, Luu et al. 2000). It is a part of the ventromedial PFC which covers the medial wall and ventral surface of the frontal cortex and develops relatively early in life (Fuster 2002, Phillips, Ladouceur et al. 2008). The ACC is divided into an anterior/ventral, or rostral (rACC), division and a posterior/dorsal, or caudal (cACC), division, which are interconnected

with each other (Musil and Olson 1988, Van Hoesen, Morecraft et al. 1993). FC studies have provided insight into the division of the ACC into rostral and caudal portions (Das, Kemp et al. 2005). Specifically, studies have suggested that the rACC shows an inverse modulation of the thalamus-sensory cortex pathway in response to emotionally salient stimuli while the cACC shown a positive relationship (Das, Kemp et al. 2005). This suggests that there is a functional differentiation between these ACC divisions that may contribute to dynamic functional relationships between the ACC and thalamo-amygdala regions (Das, Kemp et al. 2005, Phillips, Ladouceur et al. 2008).

As mentioned above, there are established connections between the ACC and the amygdala. Projections from the ACC to the amygdala may reflect the involvement of the ACC in conveying information to the amygdala about internalized emotions (Phillips, Ladouceur et al. 2008). Specifically, FC has been observed between the amygdala and the rACC (Van Hoesen, Morecraft et al. 1993, Carmichael and Price 1995). Studies have shown that the rACC projects to the amygdala which, in turn, regulates other regions, such as the hypothalamus (Bechara, Tranel et al. 1995). Other studies have postulated that increased rACC activity may lead to a reduction in amygdala activity, which may have a role in the reduction of emotional responsivity, particularly when resolving emotional conflict (Etkin, Egner et al. 2006). FC between the amygdala and the cACC has also been identified. Specifically, connections go from the amygdala to the subgenual part of the cACC (Brodmann's Area (BA) 25) to the supragenual part of the cACC (BA32) and then back to the amygdala (Paus 2001, Ghashghaei and Barbas 2002, Phillips, Drevets et al. 2003, Meyer-Lindenberg, Hariri et al. 2005, Pezawas, Meyer-Lindenberg et al. 2005). This relationship has been specifically implicated in the processing of fearful and angry emotions (Stein, Wiedholz et al. 2007). The ACC also has connections with the VS.

While, in general, the strongest projections to the VS are from the rACC (Kunishio and Haber 1994, Haber, Kunishio et al. 1995, Parvizi, Van Hoesen et al. 2006), studies have also identified projections from the cACC (specifically the supragenual part, BA32) to the VS (specifically the rostral pole of the caudate nucleus) (Haber, Kim et al. 2006). Studies have primarily implicated the latter relationships in tasks related to impulsivity and gambling (Jung, Schulte et al. 2013, van Holst, Chase et al. 2014).

The function of the rACC is generally characterized as more affective in nature (i.e. involved in assessing the salience of emotional and motivational information and regulating emotional responses), while the cACC is generally characterized as more evaluative or attentional in nature (Vogt, Finch et al. 1992, Bush, Luu et al. 2000). The ACC, as a whole, is also involved in emotion processing, emotion regulation, and reward processing neural circuitries (Phillips, Drevets et al. 2003, Phillips and Swartz 2014). Regarding emotion circuitries, lesion studies of the ACC have produced symptoms of emotional instability, apathy, and inattention (Tow and Whitty 1953, Kennard 1955, Corkin, Twitchell et al. 1979). Regarding reward processing, the ACC is involved in cost-benefit decision-making and associating actions with rewards (Walton, Kennerley et al. 2006, Croxson, Walton et al. 2009, Rushworth, Noonan et al. 2011).

Studies have reported lower ACC activity during facial emotion processing (Blumberg, Donegan et al. 2005), as well as during reward anticipation (Chase, Nusslock et al. 2013), in adults with BD. Lower ACC activity has also been reported in in youth at risk for BD during facial emotion processing (Chan, Sussmann et al. 2016). In a study comparing OBP, OCP, and OHP during emotional face processing, OBP showed lower positive FC between the right amygdala and ACC to all emotional faces than OCP and OHP (Manelis, Ladouceur et al. 2015).

During reward processing, findings in youth at risk for BD include lower cACC (BA32) activity and greater cACC-right vlPFC FC during the anticipation of loss, as well as lower cACC-right vlPFC FC during the anticipation of reward (Singh, Kelley et al. 2014). In general, these findings suggest that the ACC contributes to more diminished responses to emotional and rewarding stimuli in youth at risk for BD compared with control groups.

1.3.1.3 Ventrolateral Prefrontal Cortex (vlPFC)

The vlPFC is a part of the lateral PFC which develops relatively late in life and is principally involved in higher executive functions (Fuster 2002). The vlPFC is composed of the pars opercularis (BA44, located anterior to the premotor cortex (BA6) and on the lateral surface, inferior to BA9), the pars triangularis (BA45, located on the lateral surface, inferior to BA9 and adjacent to BA46), and the pars orbitalis and lateral orbitofrontal cortex (BA47, located below areas BA10 and BA45 and beside BA11) (Hooker and Knight 2006, Badre and Wagner 2007). Studies have shown functional connections between the vlPFC and several other regions, including the OFC, amygdala, and VS. Specifically, FC studies have suggested that the OFC may mediate an inhibitory role of the right vlPFC, specifically, upon the amygdala (Hariri, Bookheimer et al. 2000, Lange, Williams et al. 2003, Lieberman, Hariri et al. 2005, Lieberman, Eisenberger et al. 2007). Additionally, rodent studies have shown that the vlPFC has excitatory afferent connections with the VS (Sesack and Grace 2010).

The vlPFC has many different functions, including having roles in motor inhibition (Aron, Robbins et al. 2004), spatial attention (Corbetta and Shulman 2002, Corbetta, Patel et al. 2008), and processing information related to negative life experiences (Shin, Whalen et al. 2001, Markowitsch, Vandekerckhove et al. 2003, Dresler, Attar et al. 2012, Morey and Brown 2012). This region is also involved in emotion processing, emotion regulation, and reward processing

neural circuitries (Phillips, Drevets et al. 2003, Phillips and Swartz 2014). Regarding emotion, the vlPFC is implicated in the evaluation and effortful regulation of emotional behavior (Phillips, Drevets et al. 2003, Buhle, Silvers et al. 2014, Kohn, Eickhoff et al. 2014). Regarding reward, the vlPFC is involved in encoding values of choices and decision-making options (Walton, Behrens et al. 2011).

Functional abnormalities in emotion processing and regulation circuitries in youth and adults with BD (Phillips and Swartz 2014) include lower vlPFC activity (Phillips, Drevets et al. 2003, Phillips, Ladouceur et al. 2008, Hafeman, Bebko et al. 2014) and lower amygdala-vlPFC FC (Altshuler, Bookheimer et al. 2008, Kalmar, Wang et al. 2009, Ladouceur, Farchione et al. 2011, Strakowski, Eliassen et al. 2011, Delvecchio, Fossati et al. 2012, Foland-Ross, Bookheimer et al. 2012, Garrett, Reiss et al. 2012, Kim, Thomas et al. 2012, Passarotti, Ellis et al. 2012, Townsend, Bookheimer et al. 2012, Townsend, Torrisi et al. 2013) during emotion processing and regulation tasks. Findings in reward circuitry in adults with BD include greater left vlPFC activity during reward anticipation (Bermpohl, Kahnt et al. 2010, Nusslock, Almeida et al. 2012, Chase, Nusslock et al. 2013) and lower vlPFC-VS FC during processing of reward outcomes (Trost, Diekhof et al. 2014). Cross-sectional studies of youth at risk for BD have reported that, compared with OHP, OBP showed greater vlPFC activity to happy faces and lower right vlPFC-left amygdala FC to fearful faces during emotion regulation (Ladouceur, Diwadkar et al. 2013). Comparing all three groups during emotional face processing, OBP showed and greater right amygdala-left vlPFC FC to happy faces than OCP and OHP (Manelis, Ladouceur et al. 2015). Reward findings in youth at risk for BD include greater cACC-right vlPFC FC during loss anticipation, and lower cACC-right vlPFC FC during reward anticipation (Singh, Kelley et al. 2014). Only one study to date has compared reward circuitry activation in OBP, OCP, and

OHP (Manelis, Ladouceur et al. 2016). In this study, OBP had more negative bilateral VS-right vlPFC FC compared with both OCP and OHP during the processing of receipt of both reward and loss (Manelis, Ladouceur et al. 2016). These findings suggest that, in youth at risk for BD, the vlPFC significantly contributes to abnormal emotion regulation and reward processing both individually as well as through its connections with other prefrontal cortical and subcortical regions.

1.3.1.4 Dorsolateral Prefrontal Cortex (dlPFC)

The dlPFC is a lateral prefrontal cortical region that is comprised of BA9 and BA46, two regions that constitute the lower half of the mid-dorsolateral frontal cortex (Petrides and Pandya 1999). It is densely connected to many other prefrontal cortical and subcortical structures, including the OFC, thalamus, dorsal striatum, hippocampus, and secondary cortical association areas such as the posterior temporal, parietal, and occipital areas (Procyk and Goldman-Rakic 2006). It is a key component of neural circuitries that are involved in higher executive functions, such as effortful attentional and cognitive processes, including working memory and response inhibition (Fuster 2002, Dolcos, Iordan et al. 2011). The dlPFC is also involved in emotion processing and regulation neural circuitries. For example, this region has been consistently implicated in voluntary emotion regulation (Phillips, Ladouceur et al. 2008), including the voluntary behavioral control of both positive and negative emotions (Beauregard, Levesque et al. 2001, Lévesque, Eugene et al. 2003).

Studies in adults with BD have found lower dlPFC activity during memory tasks designed to implicitly evoke affective change (Malhi, Lagopoulos et al. 2007) and tasks of voluntary attentional control (Monks, Thompson et al. 2004, Lagopoulos, Ivanovski et al. 2007), but greater dlPFC activity during voluntary attentional control of emotion, specifically to sad and

happy distractors (Elliott, Ogilvie et al. 2004), and automatic attentional control (Gruber, Rogowska et al. 2004). In children and adolescents with BD, studies have shown greater dlPFC activity during voluntary attentional control (Chang, Adleman et al. 2004). Studies in youth at risk for BD have found lower dlPFC activity during emotional face processing (Tseng, Bones et al. 2015), as well as lower right vlPFC-left dlPFC FC during emotion regulation (Ladouceur, Diwadkar et al. 2013). These findings suggest that the dlPFC contributes to an abnormally reduced ability for youth at risk for BD to process and regulate emotions.

1.3.1.5 Orbitofrontal Cortex (OFC)

The OFC is a prefrontal cortical region that can be defined as BAs 11-14, the medial part of BA47, the dorsomedial PFC (BA10/32), and parts of the ACC (Ongur and Price 2000). In this dissertation, the OFC was defined as BA11. The OFC is a part of the orbital prefrontal network which has connections with subcortical limbic structures, such as with the ventral medial part of the basal nucleus of the amygdala, as well as with the striatum, thalamus, hypothalamus, and brainstem (Ongur and Price 2000). This network interacts with the medial prefrontal network to facilitate emotional behavior regulation by converging sensorimotor integration and visceromotor control when processing emotionally salient information (Phillips, Ladouceur et al. 2008). The OFC also has extensive and reciprocal connections with the amygdala and dlPFC (Stein, Wiedholz et al. 2007), which suggests that the OFC may mediate connections between higher-order dorsolateral prefrontal regions and subcortical limbic regions during emotion regulation (Phillips, Ladouceur et al. 2008).

The OFC receives information from ventral processing visual stream, taste, olfactory, and somatosensory inputs (Rolls 2004). It is also anatomically connected to regions such as the amygdala and cingulate cortex (Insausti, Amaral et al. 1987, Ongur and Price 2000). It is

primarily involved in reward processing neural circuitries. More specifically, this region is involved in encoding reward values, comparing values of different options (Boorman, Behrens et al. 2009), learning about the rewarding nature of stimuli, and rapid stimulus-reinforcement association learning (Rolls 2004). Relationships between the OFC and other regions are also important in reward circuitry. For example, coordinated activation of the ACC and OFC may help enable reward-based incentives (Haber 2011).

Studies have shown abnormalities in reward circuitry in youth and adults with, and at risk for, BD compared with healthy controls. Findings in adults with BD include greater right OFC activity during reward anticipation (Bermpohl, Kahnt et al. 2010, Nusslock, Almeida et al. 2012, Chase, Nusslock et al. 2013) and greater left OFC activity during reward reversal (Linke, King et al. 2012). Findings in youth at risk for BD include greater left lateral OFC activity during feedback of successful rewards (Singh, Kelley et al. 2014), which suggests that youth at risk for BD have an increased attempt to encode rewarding values of choice and have a greater attunement to rewarding stimuli.

1.3.1.6 Ventral Striatum (VS)

The VS is a subcortical structure that includes the nucleus accumbens as well as the broad continuity between the caudate nucleus and putamen (Haber and McFARLAND 1999). Its afferent projections from regions such as the amygdala, ACC, and OFC mediate different aspects of reward and emotional processing (Haber and Knutson 2010). Projections from the VS go to the ventral pallidum and substantia nigra and are then transferred to the ACC and OFC via the mediodorsal nucleus of the thalamus (Haber 2011). Coordinated activation of terminals in the striatum from regions such as the ACC and OFC may, together, enable reward-based incentives that drive impacts on long-term strategic planning (Haber 2011). More specifically, the VS is

involved in activations preceding and following rewards (Schultz, Tremblay et al. 2000), expecting positive incentive values (Knutson, Adams et al. 2001), processing reward prediction errors (Pagnoni, Zink et al. 2002), coding stimulus-reward values (O'Doherty 2004), and immediate reward prediction (Tanaka, Doya et al. 2004).

Studies showing abnormalities in reward circuitry in adults with BD include greater VS activity during reward anticipation (Nusslock, Almeida et al. 2012, Caseras, Lawrence et al. 2013, Phillips and Kupfer 2013), lower VS activity during reward receipt (Abler, Greenhouse et al. 2008, Trost, Diekhof et al. 2014), and lower vlPFC-VS FC during the processing of reward outcomes (Trost, Diekhof et al. 2014). In the one study to date that compared reward circuitry activation in OBP, OCP, and OHP, OBP had more negative bilateral VS-right vlPFC FC compared with both OCP and OHP during the processing of both reward and loss receipt (Manelis, Ladouceur et al. 2016). This finding suggests that, in OBP, the formation of associations between reward values and corresponding visual stimuli in the VS may inhibit the evaluation of reward and loss encoded by the vlPFC (Manelis, Ladouceur et al. 2016).

1.3.2 White Matter Tracts (WMTs)

Abnormalities in the structure of several WMTs have also been identified in youth with, and at risk for, BD. Specific tracts implicated in the pathophysiology of BD include the cingulum, forceps minor of the corpus callosum, superior longitudinal fasciculus, and uncinate fasciculus (Figure 2). Structural abnormalities in all of these tracts primarily include lower FA, which likely reflects lower collinearity of longitudinally-aligned fibers (Versace, Almeida et al. 2008), and greater RD, which likely reflects abnormal myelination, more obliquely oriented fibers, and/or local inflammation (Song, Yoshino et al. 2005, Mahon, Burdick et al. 2010).

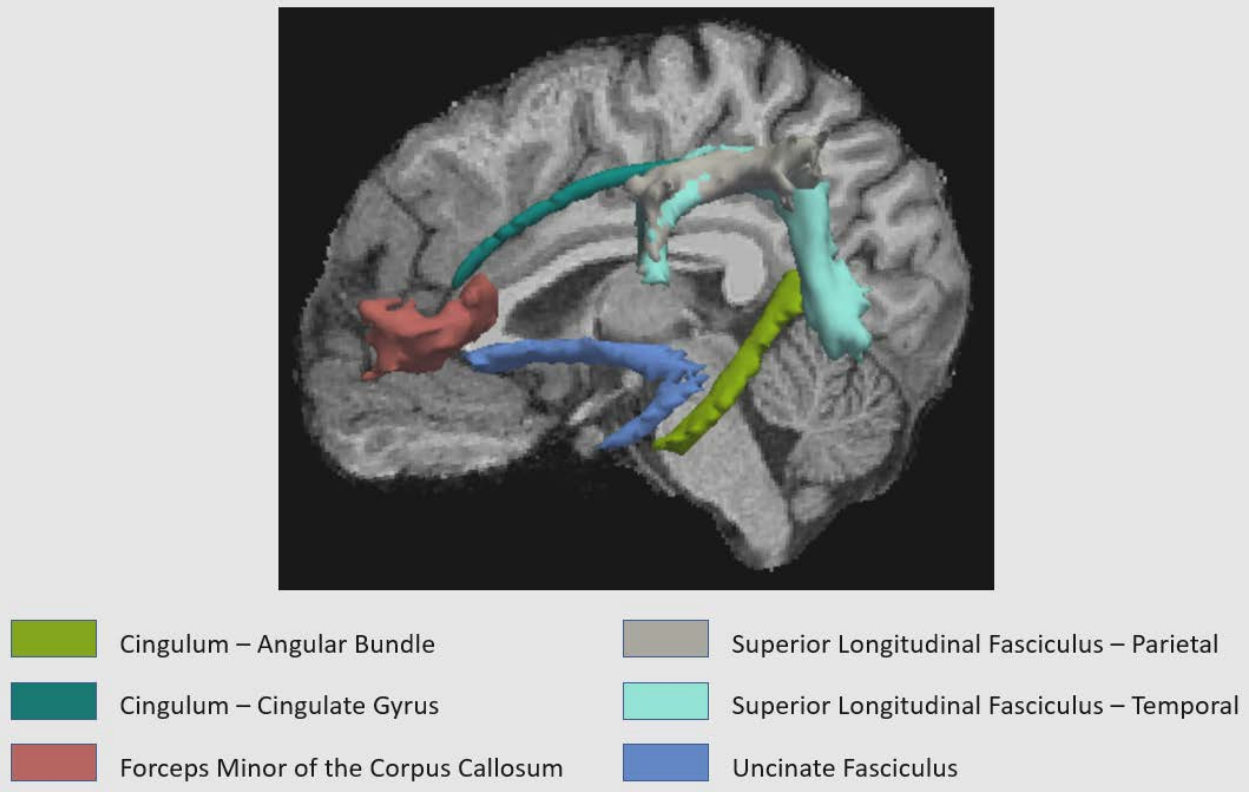

Figure 3: White Matter Tracts Implicated in Bipolar Disorder Pathophysiology

1.3.2.1 Cingulum

The cingulum is a white matter tract that is further divided into the angular bundle and the bundle of the cingulate gyrus (Wakana, Caprihan et al. 2007). It lies beneath the cortex of the cingulate gyrus and forms the white matter core of this region and the limbic lobe (Bruni and Montemurro 2009). Its trajectory follows the curve of the cingulate gyrus from the frontal lobe to the temporal lobe, encircling the corpus callosum (Bruni and Montemurro 2009). Its association fibers reciprocally connect medial cortical areas of the frontal and parietal lobes with the medial cortical areas of the temporal lobe (Bruni and Montemurro 2009). The cingulum has an essential role in emotion regulation, with the anterior portion connecting the ACC to the OFC (Papez 1937, Mufson and Pandya 1984). Abnormalities in youth and adults with BD include lower FA

and greater RD, likely reflecting cingulum demyelination without axonal loss that parallel clinical changes across illness phases in BD (Benedetti, Yeh et al. 2011, Versace, Andreazza et al. 2014).

1.3.2.2 Forceps Minor of the Corpus Callosum

The corpus callosum is the largest WMT in the brain and is situated on the floor of the interhemispheric fissure in between the cerebral hemispheres (Bruni and Montemurro 2009). It interconnects widespread areas of the neopallia association cortex and integrates sensory and motor information between the two hemispheres (Bruni and Montemurro 2009). The genu of the corpus callosum gives rise to the forceps minor, the subdivision of the tract that sweeps forward on both sides of the midline, anteriorly (Bruni and Montemurro 2009). The role of the forceps minor is to integrate language, attention, emotion, and sensorimotor functions (Sarrazin, d'Albis et al. 2015). In youth and adults with BD, lower FA and greater RD has also been shown in the forceps minor, and lower forceps minor FA has been associated with psychotic features and impulsivity (Wang, Jackowski et al. 2008, Wang, Kalmar et al. 2008, Chaddock, Barker et al. 2009, Benedetti, Yeh et al. 2011, Haller, Xekardaki et al. 2011, Versace, Andreazza et al. 2014, Sarrazin, d'Albis et al. 2015).

1.3.2.3 Superior Longitudinal Fasciculus

The superior longitudinal fasciculus is the largest association fiber bundle and is positioned laterally beneath the frontal, parietal, and temporal opercula (Bruni and Montemurro 2009). Its fibers are most compact in its mid portion and fan out forward and backward into the frontal, parietal, occipital, and temporal lobe association cortices, connecting regions in the frontal lobe (e.g. the vlPFC and dlPFC) and temporo-parietal lobe cortices (Bruni and Montemurro 2009).

The two most notable subdivisions of the superior longitudinal fasciculus are the parietal and temporal subdivisions (Bruni and Montemurro 2009). This tract supports roles of executive functioning, emotion regulation, and language processing (Versace, Andreazza et al. 2014). Similar to the above tracts, studies in youth and adults with BD have found lower FA and greater RD in the superior longitudinal fasciculus (Chaddock, Barker et al. 2009, van der Schot, Vonk et al. 2010, Versace, Almeida et al. 2010, Benedetti, Yeh et al. 2011, Versace, Andreazza et al. 2014).

1.3.2.4 Uncinate Fasciculus

The uncinate fasciculus, along with the inferior occipitofrontal fasciculus and the inferior longitudinal fasciculus, belongs to a large WMT network that connects fronto-temporal regions with the occipital cortex (Bruni and Montemurro 2009). The fibers of the uncinate fasciculus curve around the lateral fissure and interconnect the cortices of the middle, inferior frontal, orbital gyri, anterior temporal lobe gyri, parahippocampal gyri, and hippocampal gyri (Bruni and Montemurro 2009). This tract has also been implicated in emotion processing and regulation, as it connects key regions in emotion neural circuitry, including the amygdala, ACC, vlPFC, and OFC (Petrides and Pandya 2007), as well as prefrontal and anterior temporal cortices (Craig, Catani et al. 2009). As with the aforementioned tracts, lower FA and greater RD has also been shown in the uncinate fasciculus in youth and adults with BD (Versace, Almeida et al. 2008, Benedetti, Yeh et al. 2011, Linke, King et al. 2013, Versace, Andreazza et al. 2014).

1.3.3 Contribution to the Current Model of BD Risk

Given these findings, we can see how these abnormalities directly contribute to the neurobiological processes in the current model of BD risk. In emotion processing circuitry, key findings in youth at risk for BD include greater right amygdala activity to all emotional faces (Manelis, Ladouceur et al. 2015), lower ACC activity during facial emotion processing (Chan, Sussmann et al. 2016), lower dlPFC activity during facial emotion processing (Tseng, Bones et al. 2015), lower right amygdala-ACC FC to all emotional faces (Manelis, Ladouceur et al. 2015), greater right amygdala-left vlPFC FC to happy faces (Manelis, Ladouceur et al. 2015), lower collinearity in the forceps minor of the corpus callosum (Wang, Jackowski et al. 2008, Wang, Kalmar et al. 2008, Chaddock, Barker et al. 2009, Benedetti, Yeh et al. 2011, Haller, Xekardaki et al. 2011, Versace, Andreazza et al. 2014, Sarrazin, d'Albis et al. 2015), and lower collinearity in the uncinate fasciculus (Versace, Almeida et al. 2008, Benedetti, Yeh et al. 2011, Linke, King et al. 2013, Versace, Andreazza et al. 2014) (Figure 4).

For Figure 4, as well as similar figures: a green upward arrow within a region indicates greater activity; a red downward arrow within a region indicates lower activity; a green arrow connecting regions indicates greater FC between the seed and target region; and a red arrow connecting regions indicates lower FC between the seed and target region.

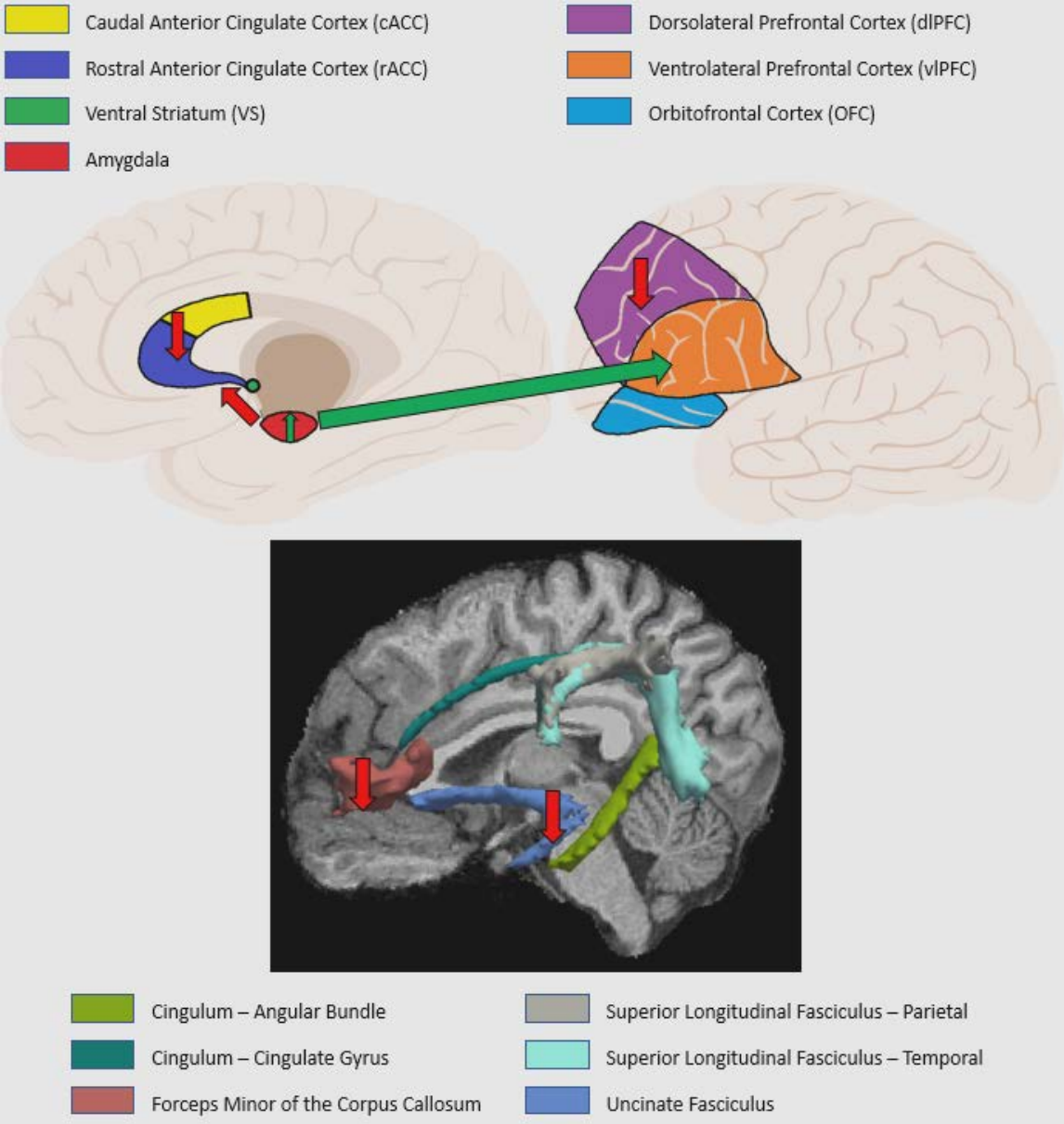

Figure 4: Current Model of BD Risk - Emotion Processing

In emotion regulation circuitry, key findings in youth at risk for BD include greater vlPFC activity when regulating attention away from happy faces (Ladouceur, Diwadkar et al. 2013), lower right vlPFC-left amygdala FC when regulating attention away from fearful faces (Ladouceur, Diwadkar et al. 2013), lower right vlPFC-left dlPFC FC during emotion regulation

(Ladouceur, Diwadkar et al. 2013), lower collinearity in the cingulum (Benedetti, Yeh et al. 2011, Versace, Andreazza et al. 2014), lower collinearity in the forceps minor of the corpus callosum (Wang, Jackowski et al. 2008, Wang, Kalmar et al. 2008, Chaddock, Barker et al. 2009, Benedetti, Yeh et al. 2011, Haller, Xekardaki et al. 2011, Versace, Andreazza et al. 2014, Sarrazin, d'Albis et al. 2015), lower collinearity in the superior longitudinal fasciculus (Chaddock, Barker et al. 2009, van der Schot, Vonk et al. 2010, Versace, Almeida et al. 2010, Benedetti, Yeh et al. 2011, Versace, Andreazza et al. 2014), and lower collinearity in the uncinate fasciculus (Versace, Almeida et al. 2008, Benedetti, Yeh et al. 2011, Linke, King et al. 2013, Versace, Andreazza et al. 2014) (Figure 5).

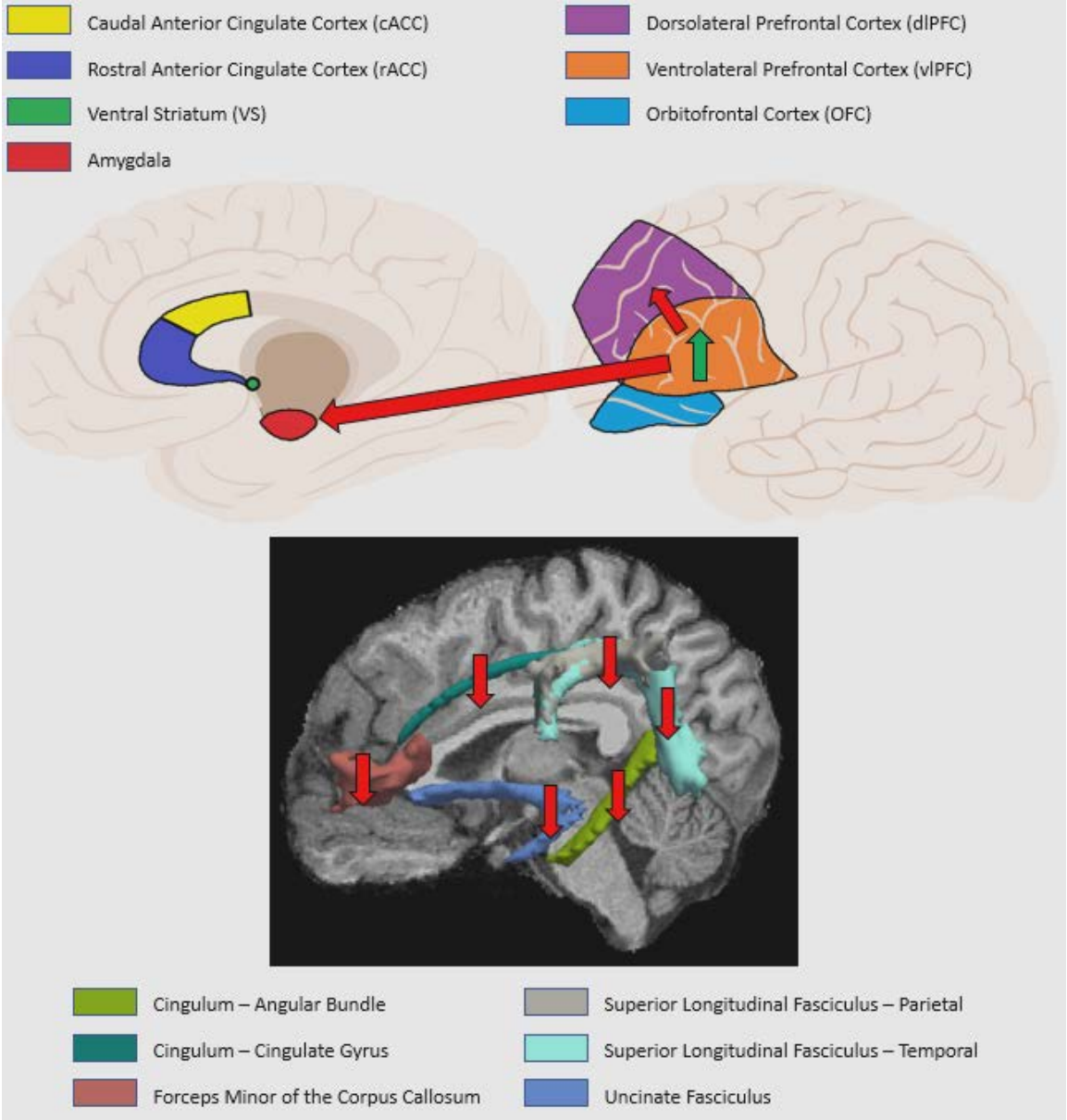

Figure 5: Current Model of BD Risk - Emotion Regulation

Finally, in reward processing circuitry, key findings in youth at risk for BD include greater amygdala activity during reward reversal (Linke, King et al. 2012), greater left OFC activity during reward reversal and receipt (Linke, King et al. 2012, Singh, Kelley et al. 2014), lower cACC activity during loss anticipation (Singh, Kelley et al. 2014), more negative bilateral

VS-right vlPFC FC during the processing of both reward and loss receipt (Manelis, Ladouceur et al. 2016), greater cACC-right vlPFC FC during loss anticipation (Singh, Kelley et al. 2014), and lower cACC-right vlPFC FC during reward anticipation (Singh, Kelley et al. 2014) (Figure 6).

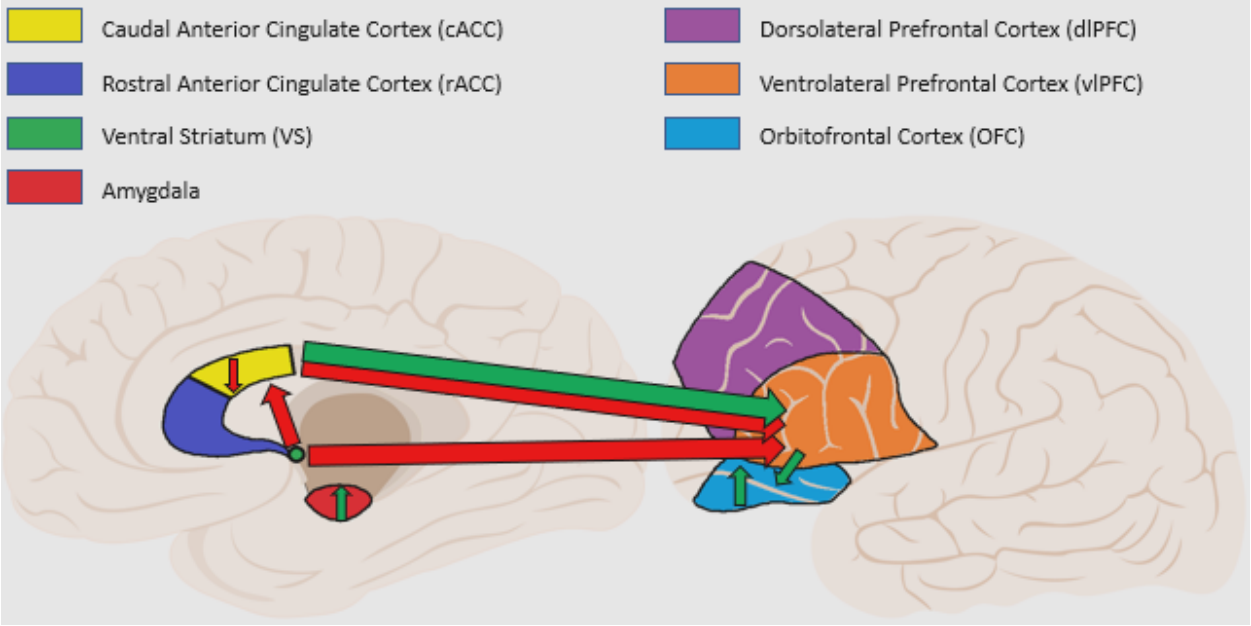

Figure 6: Current Model of BD Risk - Reward Processing

1.4 NEUROIMAGING TECHNIQUES

Using neuroimaging methods to identify neural abnormalities in youth at familial risk for BD may elucidate biological markers that may help distinguish specific risk for BD from risk for other psychiatric disorders. Furthermore, focusing on youth at risk for BD who are not yet unaffected by the disorder may identify markers of BD before illness onset. Functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) are neuroimaging methods which

can be used to assess neural function and structure, respectively, in youth at risk for BD (Matthews and Jezzard 2004).

1.4.1 Functional Magnetic Resonance Imaging (fMRI)

1.4.1.1 Basic Principles of fMRI

fMRI is noninvasive, widely-used neuroimaging technique that can examine cerebral physiology and pathophysiology by detecting regional hemodynamic responses to stimulation tasks (Bogusławska, Romanowski et al. 1999). Specifically, fMRI detects effects of neural activity on local blood volume, blood flow, and blood oxygen saturation (Bogusławska, Romanowski et al. 1999). This technique is based on the premise that localized changes in cerebral blood flow, cerebral blood volume, oxygen content, oxygen metabolism, oxygen extraction, glucose metabolism, and lactate concentration occur during neural activation (Bogusławska, Romanowski et al. 1999). Based on the relationships between these localized changes and anatomical areas of neural activation, we may use fMRI to visualize changes within activated brain tissue and map activity in the human brain (Bogusławska, Romanowski et al. 1999).

At rest, there is a strong special correlation between blood flow and glucose and oxygen metabolism (Bogusławska, Romanowski et al. 1999). After the onset of a stimulus, there is an initial rise in oxygen and glucose delivery to the neural regions that are activated, with glucose metabolism and cerebral blood flow increasing more robustly than oxygen metabolism (Bogusławska, Romanowski et al. 1999). Because of this, it is likely that non-oxidative, rather than oxidative, glycolysis largely supports physiological increases in neural activity (Fox and Raichle 1986, Fox, Raichle et al. 1988, Bogusławska, Romanowski et al. 1999). When cerebral blood flow greatly increases and oxygen metabolism only minimally increases, this uncoupling

results in a significant decrease in the oxygen extraction fraction during neural activation (Bogusławska, Romanowski et al. 1999). This decrease in the oxygen extraction fraction during local metabolism results in altered concentrations of oxyhemoglobin and deoxyhemoglobin in the neural region that is being activated (Bogusławska, Romanowski et al. 1999). This is the underlying principle of the blood-oxygen-level dependent (BOLD) effect (Bogusławska, Romanowski et al. 1999). As neural activity continues, the elevation of cerebral blood flow and glucose consumption persists, and oxidative metabolism progressively upregulates, causing regional cerebral blood oxygen levels to return to baseline (Bogusławska, Romanowski et al. 1999). Once neural activity ceases, there is a rapid normalization of cerebral blood flow with persisting elevated oxygen consumption, resulting in a transient oxygenation undershoot that occurs before returning to baseline (Frahm, Kleinschmidt et al. 1996, Bogusławska, Romanowski et al. 1999).

While studies have shown that the metabolic demands of neural activity do not regulate regional cerebral blood flow, there is nonetheless a tight association between neural activity and cerebral blood flow (Bogusławska, Romanowski et al. 1999). There are several mediators that have been identified that contribute to this association (Bogusławska, Romanowski et al. 1999). Neural activation results in increases in synaptic transmission and dendritic propagation of electrical impulses which, in turn, induce local increases in concentrations of mediators such as potassium, adenosine, nitric acid, and vasoactive neurotransmitters (Bogusławska, Romanowski et al. 1999). This then results in a cascade of changes in regional blood flow response during neural activation (Bogusławska, Romanowski et al. 1999).

The origin of the fMRI signal change is based on the relative change in concentrations of oxyhemoglobin and deoxyhemoglobin within capillary and small venule beds during task

activation (Bogusławska, Romanowski et al. 1999). Oxyhemoglobin does not have any free electrons and is diamagnetic, while deoxyhemoglobin has four unpaired electrons and is paramagnetic (Bogusławska, Romanowski et al. 1999). The free electrons of deoxyhemoglobin cause a local magnetic field distortion (Bogusławska, Romanowski et al. 1999). This results in a shortening effect of T2 (i.e. the transverse relaxation time that determines the rate at which excited protons either reach equilibrium or go out of phase with each other), but not a shortening effect of T1 (i.e. the longitudinal relaxation time that determines the rate at which excited protons return to equilibrium) (Bogusławska, Romanowski et al. 1999). During task activation, there is a relative decrease in deoxyhemoglobin within the capillary and venous beds that results in an increase in BOLD signal (Bogusławska, Romanowski et al. 1999). This BOLD signal also demonstrates an approximate 5-8 second delay of the hemodynamic response to task activation (Bogusławska, Romanowski et al. 1999). Overall, this method allows for an image spatial resolution on the order of several millimeters and a temporal resolution of several seconds (Matthews and Jezzard 2004).

1.4.1.2 Functional Connectivity (FC) Analyses

Using fMRI, we are also able to study task-related regional brain responses and task-dependent connectivity (McLaren, Ries et al. 2012). Functional connectivity (FC) is a statistical relationship that shows correlations among measurements of neuronal activity in different regions that are associated across time (Friston 2011). This method is based on the premise that strongly correlated patterns of neural activity among brain regions may be interpreted as evidence for inter-regional communication, likely due to reciprocal excitatory neurotransmission, and gives us insight into neural networks (Tononi, Edelman et al. 1998, Bressler and Kelso 2001, Fingelkurts, Fingelkurts et al. 2005). It is quantified with metrics such as correlation, covariance, and mutual

information between the time series of different neural regions (Hutchison, Womelsdorf et al. 2013). FC data may be acquired either during rest or during a task (Stevens 2016). A common way of performing FC analyses is to choose a seed brain region and use cross-correlation techniques to determine the association of this region with the time courses of other target regions (Stevens 2016).

One of the most popular types of FC analyses is known as a psychophysiological interactions (PPI) analysis (McLaren, Ries et al. 2012). PPI methods allow for the study of how brain regions interact in a task-dependent manner (Dodel, Golestani et al. 2005, Schmitz and Johnson 2006, Kim and Horwitz 2008, Minnebusch, Suchan et al. 2009, Chee, Tan et al. 2010, Snijders, Petersson et al. 2010). They provide information about functional integration of the brain and allow us to elucidate the psychological or behavioral significance of these integrations (Friston, Buechel et al. 1997, McLaren, Ries et al. 2012). The goal of PPI is to determine which target brain regions, or voxels, fluctuate in the same way as a given seed region in a specific context, such as during a behavioral task (O'Reilly, Woolrich et al. 2012). In doing so, PPI can identify regions whose activity depends on an interaction between a given task (i.e. psychological factors) and the time course of specific regions of interest (i.e. physiological factors) (O'Reilly, Woolrich et al. 2012). If an effect is observed, reflected by a task-specific increase in the relationship between brain regions, then this effect would suggest that the BOLD activity in these regions fluctuate similarly in response to a given task (O'Reilly, Woolrich et al. 2012).

In standard PPI implementation, a psychophysiological term is formed by the interaction of neural activity and a difference vector of two tasks (Friston, Buechel et al. 1997, Gitelman, Penny et al. 2003, McLaren, Ries et al. 2012). The goal of PPI methods is to infer condition-

specific functional integration by identifying regions that differ in connectivity by context or condition in fMRI studies that use block designs (Friston, Buechel et al. 1997, McLaren, Ries et al. 2012). There are several limitations to standard PPI methods, however. Such limitations include the inability to identify regional effects that are related to similarities between psychological contrasts, as well as the inability to span the space of all conditions, limiting standard PPI approaches to experiments with no more than two conditions (McLaren, Ries et al. 2012). This latter limitation is due to the fact that standard PPI methods assume that regional connectivity across conditions varies symmetrically around 0, which would affect the interpretation of analyses using more than two conditions (McLaren, Ries et al. 2012).

A generalized form of PPI (gPPI) has been developed to address several limitations of this standard approach (McLaren, Ries et al. 2008, Higo, Mars et al. 2011). In this approach, analyses begin with the identification of ON times for each condition which are then separately convolved with the canonical hemodynamic response function (McLaren, Ries et al. 2012). This forms a set of task, or psychological, regressors to allow for the correlation of neural signals and experimental conditions (McLaren, Ries et al. 2012). Next, BOLD signals are extracted from regions of interest (ROIs), and any effects of noise are removed using motion regressors (McLaren, Ries et al. 2012). This adjusted signal is then deconvolved in order to obtain an estimate of neural activity (Gitelman, Penny et al. 2003, McLaren, Ries et al. 2012). Finally, the estimated neural activity is multiplied by the condition ON times for each condition, separately, and then convolved with the hemodynamic response function (McLaren, Ries et al. 2012).

There are several advantages to using gPPI over standard PPI approaches (McLaren, Ries et al. 2012). For one, gPPI is expandable to an infinite number of conditions, as long as there are enough trials and time points (McLaren, Ries et al. 2012). It is important to note, however, that a

greater number of conditions require a greater number of regressors in the model, causing the accuracy of the estimates to decrease (McLaren, Ries et al. 2012). Second, gPPI allows for the investigation of how two neural regions interact and affect a third region (McLaren, Ries et al. 2012). Third, gPPI has been shown to reduce both false positives and false negatives, particularly for experiments that involve more than two conditions (McLaren, Ries et al. 2012). Altogether, gPPI is a well-validated method that enables the investigation of the brain's functional integration and its psychological or behavioral significance (McLaren, Ries et al. 2012). It was thus the method used in the FC analyses laid out in this dissertation (Chapters 3-4).

1.4.2 Diffusion Tensor Imaging (DTI)

DTI is a noninvasive neuroimaging technique that is used to characterize microstructural properties of soft tissue (Jones and Leemans 2011). It uses the diffusion of water to investigate subtle changes in white matter microstructural organization (Versace, Almeida et al. 2008). It adds diffusion-encoding gradients to standard magnetic resonance pulse sequences to sensitize MRI signals to the diffusion of water molecules (Stejskal and Tanner 1965). The anisotropic diffusion of water molecules along the dominant fiber orientation of white matter provides insights into its microstructural organization (Moseley, Cohen et al. 1990, Jones and Leemans 2011). Fiber orientation can be determined from the direction of the diffusion-weighted signal with the greatest attenuation which can then be used to reconstruct white matter trajectories (Conturo, Lori et al. 1999, Jones, Simmons et al. 1999, Mori, Crain et al. 1999, Basser, Pajevic et al. 2000, Parker, Haroon et al. 2003).

Several measures of diffusion can aid in the interpretation of white matter tract (WMT) structure. One of the most commonly used measures is fractional anisotropy (FA), which is an

index ratio of diffusional anisotropy in longitudinal versus oblique directions (Versace, Almeida et al. 2008, Huisman 2010). Greater FA has been associated with greater fiber myelination, a greater number of myelinated fibers, and greater longitudinal directional alignment of fibers versus oblique alignment (Versace, Almeida et al. 2008, Huisman 2010). Conversely, lower FA may reflect local edema, the presence of cerebrospinal fluid, compromised myelin structure, changes in axonal structure, or altered spacing of fibers (Arfanakis, Haughton et al. 2002, Beaulieu 2002, Mukherjee, Miller et al. 2002, Thomalla, Glauche et al. 2004, Concha, Beaulieu et al. 2005). A second measure is known as longitudinal or axial diffusivity (AD), which is a measure of water diffusion along the principal direction that has been associated with a greater number of longitudinally aligned fibers or greater axonal diameters (Versace, Almeida et al. 2008). A third measure is known as radial diffusivity (RD), which is a measure of water diffusion along oblique directions that has been associated with abnormal myelination, a greater number of obliquely oriented fibers, and local inflammation (Song, Yoshino et al. 2005). Another metric that can be used to assess WMT structure is length. Greater length may be interpreted as an attempt to enhance interhemispheric connectivity to better achieve functional integration (Kumar, Sundaram et al. 2009, Hong, Ke et al. 2011). On the other hand, greater length has also been associated with structural reductions in fiber diameter, myelin, or numbers of fibers, all of which may contribute to lower fiber collinearity (Lewis, Theilmann et al. 2013). Finally, a fifth measure that can be used in the study of white matter is tract volume, which may reflect fiber density (Brecheisen, Vilanova et al. 2009).

DTI is one of the most commonly used methods to examine changes in WMT structure due to its abilities to allow for robust estimation of parameters and be sensitive to microstructural changes while being time efficient and relatively simple to implement (Pierpaoli, Jezzard et al.

1996, Scholz, Klein et al. 2009, Fields 2010, Zatorre, Fields et al. 2012, Beaulieu 2014). There are other types of diffusion imaging techniques in addition to DTI, however. For example, diffusion spectrum imaging (DSI) and Q-ball imaging (QBI) use probability density functions instead of single tensors, allowing them to describe the diffusion process in multiple direction at each voxel (Soares, Marques et al. 2013). These techniques require longer acquisition times, however, as well as more encoding directions (Tournier, Mori et al. 2011). Diffusion kurtosis imaging (DKI) attempts to address some limitations of DTI, such as its reduced ability to resolve intra-voxel fiber crossing, by providing additional measures of tissue heterogeneity and resolving multiple tracts within each voxel (Henriques, Correia et al. 2015). Similar to DSI and QBI, DKI also has relatively long image acquisition times, and it has a more complex model whose parameters are still unclear (Steven, Zhuo et al. 2014). Another technique, known as neurite orientation dispersion and density imaging (NODDI), is a robust and time-efficient method that estimates parameters that represent axon density and dispersion (Zhang, Schneider et al. 2012). Some limitations of NODDI include its inability to formally represent perpendicularly crossing fibers (Jeurissen, Leemans et al. 2013) and the fact that pathological neural processes and/or non-healthy appearing WMTs may undermine its underlying assumptions (Pasternak, Sochen et al. 2009, Jelescu, Veraart et al. 2015, Guglielmetti, Veraart et al. 2016). DTI methods were used to examine WMT structure in this dissertation (Chapter 5).

1.4.3 White Matter Tract – Neural Activity Relationships

Given that the structural integrity of white matter is key for ensuring the intact functioning of a given neural circuitry, studying relationships between WMT structure and activity may provide a more comprehensive understanding of BD. Combining DTI and fMRI techniques has become

increasingly important in fields of cognitive and clinical neuroscience (Zhu, Zhang et al. 2014). Such studies have examined relationships between WMT structure and either BOLD activity (Conturo, Lori et al. 1999, Werring, Clark et al. 1999, Olesen, Nagy et al. 2003, Toosy, Ciccarelli et al. 2004, Baird, Colvin et al. 2005, Madden, Spaniol et al. 2007, Ystad, Hodneland et al. 2011, O'Donnell, Rigolo et al. 2012) or FC (Koch, Norris et al. 2002, Guye, Parker et al. 2003, van den Heuvel, Mandl et al. 2008, Greicius, Supekar et al. 2009, Supekar, Uddin et al. 2010, Calamante, Masterton et al. 2013). These studies have demonstrated that benefits to combining these methods include the facilitation of studies of structural connectivity, the examination of relationships between neural structure and function, and the guidance of neurosurgical interventions (Rykhlevskaia, Gratton et al. 2008). Thus, studying structure-function relationships has the potential to contribute to our understanding of mechanisms underlying multiple pathophysiological conditions, including psychiatric disorders.

There are three main ways in which such combinations are done (Zhu, Zhang et al. 2014). The first is fMRI-assisted DTI, including fMRI guided fiber tracking or filtering and fMRI-based validation (Zhu, Zhang et al. 2014). The second is DTI-assisted fMRI, including functional analyses based on DTI-derived networks and the inference of functional roles from structural connectivity (Zhu, Zhang et al. 2014). The third is the joint fusion of DTI and fMRI, including joint analyses and joint modeling (Zhu, Zhang et al. 2014). In joint DTI/fMRI fusion, both modalities are considered to have equally important roles (Zhu, Zhang et al. 2014). In joint analysis, specifically, the results of analyzing the different modalities are derived, separately, and then combined when performing statistical analyses (Zhu, Zhang et al. 2014). Such statistical analyses often include analysis of variance (ANOVA), Pearson correlation, linear regression, and/or principal component analyses to examine the interactions between the two techniques

(Zhu, Zhang et al. 2014). This latter method was used in the WMT-activity analyses presented in this dissertation (Chapter 5).

An important topic related to the study of WMT-activity relationships, as well as to individual structural and functional analyses, is that of native space. Performing tractographic analyses in each individual's own native space allows for the reconstruction of tracts connecting specific cortical and subcortical regions using individually-based neuroanatomy (Adluru, Zhang et al. 2013). This is in contrast to other methods that use standard group-level analyses, such as voxel-based analyses and tract-based spatial statistics (Adluru, Zhang et al. 2013). Voxel-based analyses are limited in power due to the need to address multiple comparisons, and the focal effects of tract-based spatial statistics may be obscured due to the fact that regional mapping of measures is based upon the local maximum FA (Adluru, Zhang et al. 2013). Thus, performing tractographic analyses in native space better accounts for anatomical inter-subject variability, which provides greater specificity in the study of neural structure and function, as well as the relationships between them (Adluru, Zhang et al. 2013). Additionally, performing fMRI analyses in native space particularly helps identify relationships between structural and functional connectivity, whereas normalization to MNI space and smoothing might reduce this ability (Razlighi, Habeck et al. 2014). All analyses throughout this dissertation were thus performed in native space (Chapters 3-5).

1.5 GOALS OF DISSERTATION RESEARCH

While much is known about BD risk, there are still several gaps in knowledge that need to be addressed. For one, studies comparing OBP to both OCP and OHP in emotion processing,

emotion regulation, and reward processing neural circuitries are limited. More studies are needed to either confirm or add to this body of knowledge. Second, it is still unclear whether these neural measures are markers of risk for the future development of BD. Examination of longitudinal follow-up of both neural and symptom measures in OBP compared with OCP and OHP is needed to help determine whether these neural measures are markers of specific risk for BD. Third, while structural and functional abnormalities in these circuitries have been identified, separately, little is known about the relationships between them and their implications in BD risk. Exploration of WMT-activity relationships may provide greater insight into the mechanisms that underlie BD risk in at-risk youth.

Given the current literature regarding BD risk, as well as the gaps in knowledge that have yet to be understood, we sought to identify abnormalities in neural measures and symptomatology that distinguish youth at risk for BD from youth at risk for other psychiatric disorders and healthy control groups. In this dissertation, we describe a series of studies that employed both cross-sectional and longitudinal analyses to examine activity, FC, and symptom measures in emotion processing and emotion regulation neural circuitries (Chapter 3), as well as in reward processing neural circuitry (Chapter 4), in OBP compared with OCP and OHP. We also explored relationships between WMT structure and activity in emotion processing neural circuitry, as well as symptomatology, in OBP compared with control groups (Chapter 5). Taken together, our results identify several neural and symptomatic abnormalities that uniquely distinguish youth at risk for BD and that have the potential to be objective neural markers of BD risk. These findings contribute to our understanding of the pathophysiology that underlies BD risk and have significant implications for the improved diagnosis and treatment of BD in at-risk youth.

2.0 GENERAL METHODS

This chapter provides descriptions of the methods that are relevant to all of the studies that are subsequently described in this dissertation.

2.1 PARTICIPANTS

2.1.1 Recruitment

Most OBP and OCP, as well as some OHP, were recruited from the Bipolar Offspring Study (BIOS) (Birmaher, Axelson et al. 2009). BIOS is a longitudinal study that aims to identify objective neural markers of BD risk by comparing emotion processing, emotion regulation, and reward neural circuitries in OBP and OCP. Specifically, BIOS follows the clinical, psychosocial, neurocognitive, and neural trajectories of at-risk youth from childhood into adulthood and examines prodromal symptoms of BD in these youth. The ultimate goal of BIOS is to use these findings to improve our understanding of prodromal symptoms associated with BD risk and eventually lead to enhanced early identification and preventative treatment for youth at risk for BD. Most OHP, as well as some OBP and OCP, were also recruited from the healthy control group of the Longitudinal Assessment of Manic Symptoms (LAMS) study (Findling, Youngstrom et al. 2010, Horwitz, Demeter et al. 2010). LAMS is a parallel study to BIOS which

examines neurocognitive and neural circuitry functioning in youth with behavioral and emotional dysregulation. The goals of LAMS are to document the rate of elevated symptoms of mania in children, describe the longitudinal course and diagnostic evolution of elevated symptoms of mania from childhood into adolescence, and identify childhood risk factors that may predict poor functional outcomes in children and adolescents with elevated symptoms of mania.

2.1.2 Inclusion and Exclusion Criteria

OBP had at least one parent with BD; OCP had at least one parent with a non-BD psychiatric disorder (i.e. MDD, ADHD, and/or an Anxiety Disorder); and OHP had parents with no psychiatric disorders. All offspring were between the ages of 8 and 17 years in order to identify youth at familial risk for BD in whom symptoms that often predate BD onset can emerge (Axelson, Birmaher et al. 2003). Exclusion criteria included: a personal history of a serious medical illness, head injury, or neurological disorder; an IQ < 70, assessed with Wechsler Abbreviate Scale of Intelligence (Wechsler 1999); a personal diagnosis of BD, as we were interested in identifying neural markers of BD risk prior to illness onset; a personal diagnosis of autism or schizophrenia, as these disorders have wide spectrums of symptoms, and having such diagnoses would make it difficult to understand whether or not emerging symptoms pertain to the familial load of these disorders rather than BD; a contraindication to magnetic resonance imaging (MRI), including pregnancy or having metal in the body; substance use on the day of the scan or a substance abuse disorder in the last three months; and emotional face n-back task accuracy < 70%. For OHP, additional exclusion criteria included a personal history of a DSM-IV disorder. Before participation, parents and guardians provided written informed consent, and youth provided written informed assent. Participants received monetary compensation.

2.1.3 Clinical Assessments Used to Assess Symptomatology

Several clinical assessments were used in the studies laid out in this dissertation. Psychiatric diagnoses were confirmed by a licensed psychiatrist or psychologist prior to scanning. The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS)–Present and Lifetime Version is a well-validated and accepted measure that was used to confirm psychiatric diagnoses in offspring (Kaufman, Birmaher et al. 1997). To confirm psychiatric diagnoses in parents, the well-validated and accepted Structural Clinical Interview for DSM-IV (SCID) (First 1996) and Family History Screen (Weissman, Wickramaratne et al. 2000) were used in BIOS and LAMS, respectively. SES was assessed by the well-validated and accepted Hollingshead Four Factor Index of Social Status (Hollingshead 1975).

Both the Mood and Feelings Questionnaire (MFQ) (Sund, Larsson et al. 2001) and the K-SADS Depression Rating Scale (KDRS) (Kaufman, Birmaher et al. 1997) are well-validated and accepted measures used to assess symptoms of depression. The K-SADS Mania Rating Scale (KMRS) is a well-validated and accepted measure used to assess symptoms of mania (Axelson, Birmaher et al. 2003). The Children's Affective Lability Scale (CALS) is a well-validated and accepted measure used to assess symptoms of affective lability (Gerson, Gerring et al. 1996). The Screen for Child Anxiety Related Disorders (SCARED) is a well-validated and accepted measure used to asses symptoms of anxiety (Birmaher, Khetarpal et al. 1997, Birmaher, Brent et al. 1999). Both parent-reported (-P) and child-reported (-C) versions of MFQ, CALS, and SCARED were administered on the day of the scan. Summary assessments, which are based on both parent-reported and child-reported information, of KDRS and KMRS were administered, on average, two months after the scan.

2.1.4 Power Calculations

Power calculations are in line with those in BIOS. For standard regression analyses, with n = 28-35 youth per group, we have 75-84% power to detect a significant main effect of group on neuroimaging dependent variables (medium effect size f = 0.25, up to 10 covariates per model) (Cohen 1988). For multivariate multiple regression analyses that involve variable selection, such as elastic net regression analyses, power calculations are impractical (Cohen 2003).

2.2 NEUROIMAGING DATA ACQUISITION

2.2.1 Scanners

Two scanners were used throughout the following studies. Images were acquired either using a Siemens Magnetom TrimTrio 3T MRI system with a Siemens 32 radiofrequency channel receiver coil or with a Siemens Magnetom Prisma system with a 64-channel head coil. All participants were scanned at least one time. Because BIOS is an ongoing longitudinal study, several participants were also scanned for a second time at the time that these studies were conducted. Information regarding which participants were scanned on each scanner and duration between scans is detailed in the studies, below. Scanner was a covariate in analyses in which participants were scanned using different scanners.

Axial 3D magnetization prepared rapid gradient echo (MPRAGE) sequences acquired T1-weighted volumetric anatomical images covering the whole brain. A reverse interleaved gradient echo planar imaging (EPI) sequence acquired T2-weighted BOLD images covering the

whole cerebrum and most of the cerebellum. Diffusion-weighted images were acquired using a single-shot spin-echo planar imaging sequence, parallel to the Anterior-Posterior Commissure line using 61 optimized non-collinear diffusion gradient directions. Sixty-one non-coplanar b = 1000 sec / mm^2 (diffusion-weighting b value) images were acquired, along with seven b = 0 (no-diffusion weighting) images. Scanner parameters can be found in Table 1.

Table 1: Scanner Parameters

	MPRAGE		EPI		DTI	
	TrimTrio	Prisma	TrimTrio	Prisma	TrimTrio	Prisma
Slices	192	176	38	38	64	64
Slice Thickness	1 mm	1 mm	3.1 mm	3.1 mm	2 mm	2 mm
Flip Angle (FA)	9 deg	9 deg	90 deg	90 deg		
Field of View (FOV)	256 mm	256 mm	205 mm	205 mm	256 mm	256 mm
TR	2300 msec	2300 msec	2000 msec	2000 msec	9900 msec	9900 msec
TE	3.93 msec	2.88 msec	28 msec	28 msec	98 msec	70 msec
TI	900 msec	900 msec				
Phase Encoding	A >> P	A >> P	P >> A	P >> A	P >> A	P >> A
Slice Order	Interleaved	Interleaved	Interleaved	Interleaved	Interleaved	Interleaved
Fat Suppression	None	None	Fat Sat	Fat Sat	Fat Sat	Fat Sat
Shimming	Standard	Standard	Standard	Standard	Standard	Standard
Gradient Mode	Normal	Fast	Fast	Performance	Fast	Performance

2.2.2 fMRI Tasks

Every participant performed a series of fMRI tasks that were set in the following order: (1) emotional face processing task, (2) reward task, (3) DTI acquisition, (4) emotional face n-back task, (5) resting state. In each study, we examined performance on one or more of these tasks. We will now provide descriptions of the emotional face processing, emotional face n-back, and

reward tasks. The specific task contrasts used in each study are detailed in the study chapters, below.

2.2.2.1 Emotional Face Processing Task

The emotional face processing task, known as the dynamic faces task (DFT), is a 12.5-min long fMRI task (Figure 7) (Phillips, Ladouceur et al. 2008, Almeida, Kronhaus et al. 2011, Perlman, Almeida et al. 2012). In emotional trials, stimuli comprise faces from the NimStim set for positive (i.e. happy) and negative (i.e. angry, fearful, and sad) emotions (Tottenham, Tanaka et al. 2009). For each trial, one face is collated into a one-sec long movie, morphing in 5% increments from neutral (0% emotion) to 100% emotion. In control trials, movies comprise a simple shape (a dark oval) superimposed onto a light-grey oval with similar structural characteristics to the faces, which subsequently morphs into a larger shape, approximating the movement of the morphed faces. There are three blocks for each of the four emotional conditions (i.e. happy, angry, fearful, and sad), with twelve stimuli per block, and six control blocks with six stimuli per block. Emotional and control blocks are presented in a pseudorandomized order so that no two blocks of any condition are presented sequentially. Participants are asked to use one of three fingers to press a button indicating the color of a semi-transparent foreground color flash (i.e. orange, blue, or yellow) that appears during the mid-200–650 msec of the one-sec presentation of the dynamically-changing face. Emotional faces are task-irrelevant and, thus, processed implicitly (Tottenham, Tanaka et al. 2009).

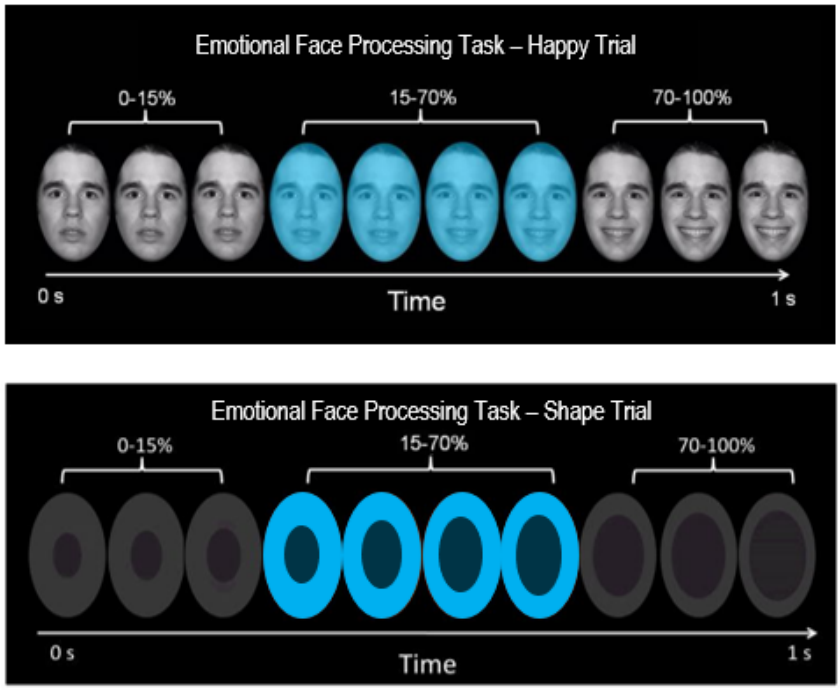

Figure 7: Emotional Face Processing Task – Example Happy and Shape Trials

2.2.2.2 Emotional Face N-Back Task

The emotional face n-back task is a modified version of an n-back working memory task (Figure 8) (Ladouceur, Silk et al. 2009). In this task, participants are asked to respond to a pre-specified letter out of a pseudorandom sequence of letters visually presented on a computer screen. It includes a 0-back no-memory load condition (EF-0-BACK; e.g., press the button to a specific letter (ex. "M")) and a 2-back high-memory load condition (EF-2-BACK; e.g., press the button whenever the current letter is identical to the letter presented two trails back (ex. "G-N-G")). The letters are flanked by fearful, happy, or neutral face distracters (Tottenham, Tanaka et al. 2009) with a no-face condition controlling for the interference related to presenting a face distractor. There are eight stimulus blocks: two memory-load conditions (EF-0-BACK and EF-2-BACK), each with one of four face distractor conditions (fearful, happy, neutral, or no face). The task

comprises three 7-min 4-sec runs for a total of 24 blocks presented in a pseudorandomized order. Each block includes twelve 500 msec trials that comprise a letter flanked with either identical pictures of an actor's facial expression or no pictures. Jittered inter-trial intervals (mean duration = 3500 msec) comprise a fixation cross (flanked with faces). Participants are asked to respond as quickly as possible with their index fingers to the target letter. Brief instructions are presented on the screen for 4000 msec at the beginning of each block. Detailed instructions are provided during task practice prior to the scanning session.

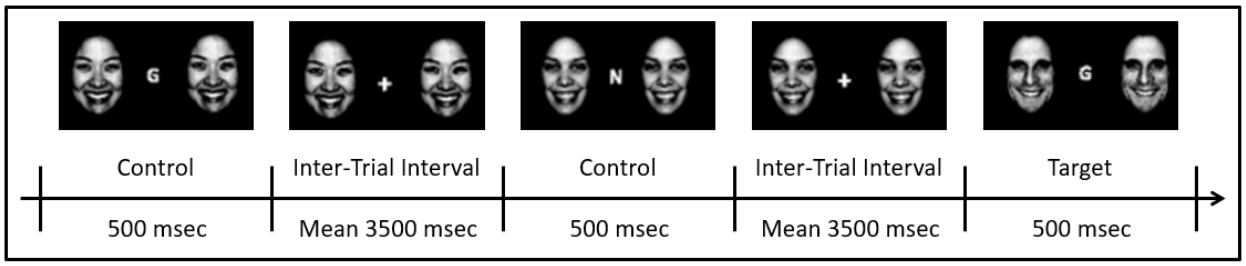

Figure 8: Emotional Face N-Back Task – Example 2-Back Happy Trial

2.2.2.3 Reward Processing Task

The reward processing task is a well-validated card guessing task with both reward and loss receipt components (Figure 9) (Forbes, Hariri et al. 2009, Bebko, Bertocci et al. 2014). This task comprises guessing and control trials. For guessing trials, participants view instructions to guess a number (2000 msec) and then press a button to guess whether the value of the card will be higher or lower than "5" (3000 msec). This is followed by the actual value of the card (between 1-9; 500 msec), outcome feedback (Reward: green upward-facing arrow, Loss: red downward-facing arrow; 500 msec), and a fixation cross (3000 msec). For control trials, participants press a

button to the letter "X" (3000 msec), followed by an asterisk (500 msec), a yellow circle (500 msec), and a fixation cross (3000 msec). The entire task lasts approximately 6 minutes. The task is a block design with 3 reward (80% reward, 20% loss trials), 3 loss (80% loss, 20% reward trials), and 3 control (no change in reward/loss) blocks. Each guessing block consists of 5 trials presented in an oddball format (Reward: reward, reward, reward, loss, reward; Loss: loss, loss, reward, loss, loss); each control block consists of 6 control trials. Participants are misled into believing that task performance determined outcome.

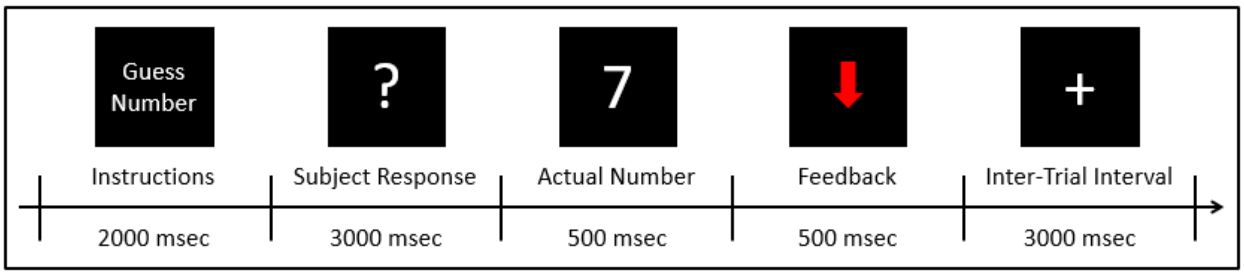

Figure 9: Reward Processing Task – Example Loss Trial

2.3 NEUROIMAGING DATA ANALYSES

Functional images were preprocessed using realignment and unwarping steps in Statistical Parametric Mapping (SPM8) (http://www.fil.ion.ucl.ac.uk/spm/doc/). First-level fixed effect models were created for activity and/or FC with trials modelled as epochs with design matrix regressors (Ashburner and Friston 2005), including 6 directions of motion artifact regressors (Satterthwaite, Elliott et al. 2013). Participants with excessive movement of translation > 4 mm were excluded, followed by despiking for all remaining participants

(http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dDespike.html). For each participant, the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Linear Image Registration Tool (FLIRT) in FMRIB Software Library (FSL) was used to coregister despiked functional images into structural space using each participant's own segmentation and cortical parcellation volume aparc+aseg.mgz (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki).

ROIs were created for each participant, individually, using each participant's own aparc+aseg.mgz file using the Center for Morphometric Analysis standard labels in FreeSurfer (https://surfer.nmr.mgh.harvard.edu/). See Table 2 for information from the FreeSurferColorLUT text file about each ROI used throughout this dissertation. Unless otherwise stated, the left vlPFC comprised the left lateral orbitofrontal cortex, left pars opercularis, left pars orbitalis, and left pars triangularis, together, and the right vlPFC comprised the right lateral orbitofrontal cortex, right pars opercularis, right pars orbitalis, and right pars triangularis, together. ROI masks were resampled into 2x2x2 mm^3 fMRI voxel dimensions. The fslmeants command in FSL was used to extract raw BOLD and/or FC signals (threshold: p = 1) in each subject's native space. Signals were extracted from each ROI for each contrast for each task for each subject. The specific ROIs used in each study, including seed and target regions for each gPPI analysis, are described in the studies, below.

Table 2: Region of Interest Information

Region of Interest		#No.	Label Name
Amygdala	Left	18	Left-Amygdala
	Right	54	Right-Amygdala
Anterior Cingulate Cortex (ACC)	Left Caudal	1002	ctx-lh-caudalanteriorcingulate
	Left Rostral	1026	ctx-lh-rostralanteriorcingulate
	Right Caudal	2002	ctx-rh-caudalanteriorcingulate
	Right Rostral	2026	ctx-rh-rostralanteriorcingulate
Dorsolateral Prefrontal Cortex (dlPFC)	Left	1003	ctx-lh-caudalmiddlefrontal
	Right	2003	ctx-rh-caudalmiddlefrontal
Orbitofrontal Cortex (OFC)	Left	1014	ctx-lh-medialorbitofrontal
	Right	2014	ctx-rh-medialorbitofrontal
Ventral Striatum (VS)	Left	26	Left-Accumbens-area
	Right	58	Right-Accumbens-area
Ventrolateral Prefrontal Cortex (vlPFC)	Left Lateral Orbitofrontal Cortex	1012	ctx-lh-lateralorbitofrontal
	Left Pars Opercularis	1018	ctx-lh-parsopercularis
	Left Pars Orbitalis	1019	ctx-lh-parsorbitalis
	Left Pars Triangularis	1020	ctx-lh-parstriangularis
	Right Lateral Orbitofrontal Cortex	2012	ctx-rh-lateralorbitofrontal
	Right Pars Opercularis	2018	ctx-rh-parsopercularis
	Right Pars Orbitalis	2019	ctx-rh-parsorbitalis
	Right Pars Triangularis	2020	ctx-rh-parstriangularis

2.4 ELASTIC NET REGRESSION ANALYSES

Elastic net regression analyses with k = 10-fold cross-validation and $\alpha = 0.5$ were used for data selection and reduction in each study using GLMNET in R (Friedman 2014). Elastic net is a statistical technique that has been used in genetic, clinical, and fMRI studies (Tibshirani 1996, Kohannim, Hibar et al. 2012, Kohannim, Hibar et al. 2012, Christensen, Zoetmulder et al. 2014, Friedman 2014, Luo, McShan et al. 2015, Wang, Xu et al. 2015, Yan, Tsurumi et al. 2015, Zemmour, Bertucci et al. 2015, Bertocci, Bebko et al. 2016, Bertocci, Bebko et al. 2017, Bertocci, Bebko et al. 2017). This technique allows for the testing of a large number of potential predictor variables, relative to the number of participants, while minimizing model error and the

risk of overfitting (Bertocci, Bebko et al. 2016). Elastic net is a variant of the modified least-squares Least Absolute Shrinkage and Selection Operator (LASSO) regression which penalizes complex models with a regularization parameter (λ) (Tibshirani 1996). Compared to LASSO, which uses a penalty term of $\alpha = 1$, elastic net uses an adjusted penalty term of $\alpha = 0.5$ to allow for a greater extent of correlation among predictor variables, rendering these analyses more sensitive to correlated variables (Zou and Hastie 2005, Bertocci, Bebko et al. 2017). Elastic net method shrinks coefficients toward zero and eliminates unimportant terms entirely, thereby minimizing prediction error, reducing the chance of overfitting, and enforcing recommended sparsity in the solution (Tibshirani 1996, Friedman, Hastie et al. 2010, Friedman 2014).

GLMNET uses an algorithm that involves cyclical coordinate descent and regularization (Wu and Lange 2008). In other words, this method optimizes each parameter separately, while holding all other parameters fixed until the coefficients stabilize, and then adds constraints to the problem in order to avoid overfitting (Wu and Lange 2008, Bertocci, Bebko et al. 2016). Further, GLMNET uses cross-validation to identify the optimal penalty term (λ) that minimizes mean cross-validated model error for the model while guarding against Type III errors (i.e. testing hypotheses suggested by the data) (Wu and Lange 2008, Bertocci, Bebko et al. 2016). A test statistic or p-value for elastic net that has a simple and exact asymptotic null distribution is still under development (Lockhart, Taylor et al. 2014). Thus, throughout our studies, significance was determined in all other statistical analyses. Please refer to Chapter 2.1.4 for the power computations for more conventional regression analyses.

In each elastic net regression used throughout the studies, below, demographic measures were included as predictor variables: age, sex, intelligence quotient (IQ), socioeconomic status (SES), handedness, and highest parental education. Categorical outcomes (i.e. sex, SES,

handedness, and highest parental education) were entered into the model as dummy-coded variables. For example, for a variable with 2 possible outcomes (e.g. sex: male or female), this variable would be entered into the model as a single variable with one possible outcome coded with the value of 1 and the other possible outcome coded with the value of 0. Longitudinal follow-up was not examined using elastic net regression analyses and was, instead, examined in exploratory analyses.

3.0 ACTIVITY AND FUNCTIONAL CONNECTIVITY IN EMOTION PROCESSING AND REGULATION NEURAL CIRCUITRIES IN OFFSPRING AT RISK FOR BD

This chapter is a modified version of the following manuscript that is currently in press:

Acuff HE, Versace A, Bertocci MA, Ladouceur CD, Hanford LC, Manelis A, Monk K, Bonar L, McCaffrey A, Goldstein BI, Goldstein TR, Sakolsky D, Axelson D, Birmaher B, Phillips ML. Activity and functional connectivity in emotion processing and regulation neural circuitries in offspring at risk for bipolar disorder. *JAMA Psychiatry*. (In Press)

3.1 INTRODUCTION

Emotion processing and emotion regulation neural circuitries are very important to the study of BD risk. More work is needed, however, to determine whether abnormalities in these circuitries may be used to identify youth at familial risk for BD who are likely to develop the disorder in the future. Two previous BIOS studies examined activity and FC using emotion processing and regulation tasks, separately (Ladouceur, Diwadkar et al. 2013, Manelis, Ladouceur et al. 2015). No studies, however, have used both cross-sectional *and* longitudinal analyses to examine how measures of activity and FC in emotion processing and emotion regulation neural circuitries distinguish OBP from control groups.

Specific functional abnormalities in these circuitries in adults and youth with and at risk for BD have been discussed previously (Chapter 1.3.1). Key findings in youth at risk for BD during emotion processing include greater amygdala activity to all emotional faces (Manelis, Ladouceur et al. 2015), lower ACC activity during facial emotion processing (Tseng, Bones et al. 2015, Chan, Sussmann et al. 2016), lower dlPFC activity during facial emotion processing (Tseng, Bones et al. 2015), lower right amygdala-ACC FC to all emotional faces (Manelis, Ladouceur et al. 2015), and greater right amygdala-left vlPFC FC to happy faces (Manelis, Ladouceur et al. 2015). Findings during emotion regulation include greater vlPFC activity when regulating attention away from happy faces (Ladouceur, Diwadkar et al. 2013), lower amygdala-vlPFC FC when regulating attention away from fearful faces (Ladouceur, Diwadkar et al. 2013), and lower dlPFC-vlPFC FC during emotion regulation (Ladouceur, Diwadkar et al. 2013). More studies, and particularly ones that additionally examine changes in neural measures over follow-up, are needed to identify abnormalities in emotion processing and regulation neural circuitries that are specific to OBP.

Additionally, relationships between neural measures in emotion processing and regulation neural circuitries and symptoms associated with BD risk (i.e. depression, mania, affective lability, and anxiety (Hafeman, Merranko et al. 2016)) remain relatively unexamined. In emotionally dysregulated youth, worsening affective lability and depression severity were associated with greater right amygdala and left vlPFC activity, worsening anxiety with lower right amygdala and greater left vlPFC activity, and worsening mania with greater right amygdala and lower left vlPFC activity over time (Bertocci, Bebko et al. 2017). In OCP, right amygdala-ACC FC positively correlated with affective lability, depression, and anxiety severity (Manelis, Ladouceur et al. 2015). Such studies have yet to find significant relationships between

functioning in emotion processing and regulation neural circuitries and symptom severity in OBP, however. Examining these relationships can improve our understanding of BD development in youth and may enhance early identification of BD risk in, and guide novel interventions for, OBP.

Given studies showing differences between OBP and both OCP and OHP in emotion processing and regulation neural circuitries, and the importance of relating these measures to symptoms associated with BD risk both at baseline and over follow-up, we hypothesized that:

1. Greater amygdala and/or lower PFC activity and abnormal amygdala-PFC FC in emotion processing and regulation neural circuitries would distinguish OBP from OCP and OHP.
2. Magnitudes of these abnormal neural measures would be positively associated with elevated depression, mania, affective lability, and/or anxiety severity in OBP compared with control groups.

In exploratory analyses, we examined whether changes in neural measures over follow-up were significantly associated with changes in symptom severity in all offspring.

3.2 MATERIALS AND METHODS

3.2.1 Participants

Thirty-one OBP (mean (SD) age = 13.87 (2.42), 15 female), twenty-eight OCP (mean (SD) age = 14.48 (2.01), 10 female), and twenty-one OHP (mean (SD) age = 14.20 (1.48), 10 female) were examined in this analysis (Table 3). In this and all future tables and figures, an asterisk indicates a p-value less than 0.05. Of the original thirty-seven OBP, forty OCP, and thirty-one OHP that

were recruited: three OBP, six OCP, and eight OHP were excluded due to excessive motion (translation > 4 mm); two OBP and one OCP were excluded due to missing data; and one OBP, five OCP, and two OHP were excluded due to poor emotional face n-back task performance (< 70% accuracy on any block for either task). Overall emotional face n-back task performance for the remaining subjects were as follows: OBP, mean (SD) = 93.67% (0.04%), range = 81.25-99.48%; OCP, mean (SD) = 95.13% (0.03%), range = 83.85-99.48%; OHP, mean (SD) = 96.48% (0.03%), range = 86.98-99.48%. Twenty-six OBP, twenty-one OCP, and nineteen OHP were also included in a related BIOS paper (Manelis, Ladouceur et al. 2015).

Twelve OBP had at least one non-BD diagnosis: three had MDD, three had an Anxiety Disorder, five had ADHD, one had Oppositional Defiant or Conduct Disorder, and one had an Eating Disorder. Fourteen OCP had at least one non-BD diagnosis: three had MDD, five had an Anxiety Disorder, eight had ADHD, three had Oppositional Defiant or Conduct Disorder, and one had Obsessive Compulsive Disorder. Five OBP and six OCP were taking antidepressant, antipsychotic, stimulant, and/or non-stimulant medications for non-BD disorders. Symptom assessments included SCARED-P, SCARED-C, CALS-P, CALS-C, MFQ-P, MFQ-C, KDRS, and KMRS (Chapter 2.1.3).

Table 3: Exp 1. Offspring of Bipolar, Comparison and Healthy Offspring

	OBP n = 31 M(SD) or Total	OCP n = 28 M(SD) or Total	OHP n = 21 M(SD) or Total	Statistic	p =
Demographic Information					
Age	13.87(2.42)	14.48(2.01)	14.20(1.48)	F = 0.648	.526
Sex (females)	15	10	10	χ^2 = 1.133	.567
IQ	101.13(15.55)	101.75(14.84)	105.71(12.18)	F = 0.692	.503
Socioeconomic Status				χ^2 = 13.986	.082
Very Low (8-19)	7	5	1		
Low (20-29)	8	1	4		
Medium (30-39)	6	4	1		
High (40-54)	7	10	9		
Very High (55-66)	3	8	6		
Handedness				χ^2 = 5.050	.282
Right	26	26	19		
Left	2	2	2		
Mixed	3	0	0		
Highest Parental Education				χ^2 = 5.960	.428
High School Graduate or Lower	5	1	4		
Partial College or Specialized Training	13	8	8		
Standard College or University Graduate	7	11	5		
Graduate Professional Training	6	8	4		
Clinical Measures					
Diagnosis	12	14	0	F = 8.569	**< .001***
Major Depressive Disorder	3	3	0	F = 1.156	.320
Anxiety Disorder	3	5	0	F = 2.164	.122
Attention Deficit/Hyperactivity Disorder	5	8	0	F = 3.807	**.027***
Oppositional Defiant or Conduct Disorder	1	3	0	F = 1.623	.204
Obsessive Compulsive Disorder	0	1	0	F = 0.927	.400
Eating Disorder	1	0	0	F = 0.786	.459
Psychotropic Medication Use	5	6	0	F = 2.608	.080
Scan Day Assessments					
SCARED-P	9.84(6.92)	9.50(11.14)	4.62(4.69)	F = 2.932	**.023***
SCARED-C	12.81(14.95)	8.00(12.16)	9.36(11.86)	F = 1.029	.250
CALS-P	8.19(9.19)	4.64(4.84)	1.62(2.71)	F = 6.464	**.001***
CALS-C	10.32(12.48)	5.32(8.76)	6.19(13.96)	F = 1.504	.117
MFQ-P	6.55(9.08)	4.48(5.00)	1.38(2.13)	F = 3.909	**.011***
MFQ-C	8.41(10.87)	7.84(10.95)	5.29(11.03)	F = 0.536	.293
Assessment Closest to Scan					
KMRS	1.77(2.69)	0.54(1.04)	0.05(0.23)	F = 6.223	**.002***
KDRS	2.58(5.26)	2.00(3.74)	0.26(0.56)	F = 2.005	.072

3.2.2 Neuroimaging Data Acquisition and Analyses

All scan 1 and fifteen scan 2 images (for one OBP and fourteen OHP) were acquired using the Siemens Magnetom TrimTrio 3T MRI system, and fifteen scan 2 images (for eight OBP and seven OCP) were acquired using a Siemens Magnetom Prisma system (Chapter 2.2.1). Participants completed the emotional face processing task (DFT) (Chapter 2.2.2.1) and the emotional face n-back task with 0-back (EF-0-BACK) and 2-back (EF-2-BACK) conditions (Chapter 2.2.2.2). Neuroimaging data analyses were performed as previously described (Chapter 2.3). ROIs included the amygdala, cACC, rACC, vlPFC, and dlPFC (Table 2). gPPI analyses assessed task-related connectivity (McLaren, Ries et al. 2012). Seed regions included the bilateral amygdala. Target regions included, separately: the left and right cACC, left and right rACC, left and right vlPFC, and left and right dlPFC. Task stimulus contrasts included, separately: happy, angry, fearful, and sad faces versus shapes for DFT; fearful, happy, and neutral versus no faces, and fearful and happy versus neutral faces, for EF-0-BACK and EF-2-BACK; and EF-2-BACK versus EF-0-BACK for fearful, happy, neutral, and no faces.

3.2.3 Primary Analyses

A single elastic net regression analysis, including OBP, OCP, and OHP, was used for data selection and reduction. This single model contained 2 dummy-coded outcome variables: BD risk (OBP versus OCP/OHP) and general psychiatric disorder risk (OBP/OCP versus OHP). The number of dummy-coded variables for a given category is equal to one less than the total number of possible options (e.g. one variable to code for the two possible options of OBP and OCP/OHP). This one model also contained 336 predictor variables. Twelve of these predictor

variables were demographic measures: age, sex, IQ, SES, handedness, and highest parental education (Table 4).

Table 4: Exp 1. Elastic Net Regression Predictor Variables: Demographic

12 DEMOGRAPHIC VARIABLES	
Variable	**Possible Options for Dummy-Coded Variables**
Age	
Sex	
IQ	
SES	Very Low Low Medium High Very High
Handedness	Right Left Mixed
Highest Parental Education	High School Graduate or Lower Partial College or Specialized Training Standard College or University Graduate Graduate Professional Training

One hundred eighty of these predictor variables were activity measures in each ROI for each contrast, separately (Table 5).

Table 5: Exp 1. Elastic Net Regression Predictor Variables: Activity Measures

180 NEUROIMAGING VARIABLES: Activity Measures		
Contrast	**10 Regions of Interest for Each Contrast**	
Happy Faces vs. Shapes	Left Amygdala	Right Amygdala
Angry Faces vs. Shapes	Left cACC	Right cACC
Fearful Faces vs. Shapes	Left rACC	Right rACC
Sad Faces vs. Shapes	Left vlPFC	Right vlPFC
EF-2-BACK Fearful vs. Neutral Faces	Left dlPFC	Left dlPFC
EF-2-BACK Fearful vs. No Faces		
EF-2-BACK Happy vs. Neutral Faces		
EF-2-BACK Happy vs. No Faces		
EF-2-BACK Neutral vs. No Faces		
EF-0-BACK Fearful vs. Neutral Faces		
EF-0-BACK Fearful vs. No Faces		
EF-0-BACK Happy vs. Neutral Faces		
EF-0-BACK Happy vs. No Faces		
EF-0-BACK Neutral vs. No Faces		
Fearful Faces EF-2-BACK vs. EF-0-BACK		
Happy Faces EF-2-BACK vs. EF-0-BACK		
Neutral Faces EF-2-BACK vs. EF-0-BACK		
No Faces EF-2-BACK vs. EF-0-BACK		

One hundred forty-four of these predictor variables were FC measures with a bilateral amygdala seed region and target regions in each ROI for each contrast, separately (Table 6).

Table 6: Exp 1. Elastic Net Regression Predictor Variables: Functional Connectivity Measures with Amygdala Seed

144 NEUROIMAGING VARIABLES: FC Measures with Bilateral Amygdala Seed Region		
Contrast	**8 Target Regions of Interest for Each Contrast**	
Happy Faces vs. Shapes	Left cACC	Right cACC
Angry Faces vs. Shapes	Left rACC	Right rACC
Fearful Faces vs. Shapes	Left vlPFC	Right vlPFC
Sad Faces vs. Shapes	Left dlPFC	Right dlPFC
EF-2-BACK Fearful vs. Neutral Faces		
EF-2-BACK Fearful vs. No Faces		
EF-2-BACK Happy vs. Neutral Faces		
EF-2-BACK Happy vs. No Faces		
EF-2-BACK Neutral vs. No Faces		
EF-0-BACK Fearful vs. Neutral Faces		
EF-0-BACK Fearful vs. No Faces		
EF-0-BACK Happy vs. Neutral Faces		
EF-0-BACK Happy vs. No Faces		
EF-0-BACK Neutral vs. No Faces		
Fearful Faces EF-2-BACK vs. EF-0-BACK		
Happy Faces EF-2-BACK vs. EF-0-BACK		
Neutral Faces EF-2-BACK vs. EF-0-BACK		
No Faces EF-2-BACK vs. EF-0-BACK		

In this analysis, the resulting model was chosen based on the corrected Akaike information criterion (AICc) to address smaller sample sizes and potential overfitting (McQuarrie and Tsai 1998, Claeskens and Hjort 2008, Giraud 2014):

$$AICc = AIC + \frac{2k^2+2k}{n-k-1}$$

In the above equation, k = the number of parameters and n = the number of subjects. Change in AICc (ΔAICc) compared the AICc of each model ($AICc_i$) with the model with the next greatest number of parameters ($AICc_j$), representing the information lost using the i^{th} versus j^{th} model (Burnham and Anderson 2004):

$$\Delta AICc_i = AICc_j - AICc_i$$

The model having the most substantial support was the one that had the fewest parameters with a ΔAICc < 2 (Burnham and Anderson 2004).

Post-hoc pseudo r-squared analyses examined the proportion of variance in dependent variables explained by the non-zero predictor variables observed with elastic net. ANOVAs and post-hoc t-tests examined between-group differences in neuroimaging measures for all non-zero predictors and symptom measures. Correlation analyses examined relationships among neuroimaging and symptom measures.

3.2.4 Exploratory Analyses

Longitudinal follow-up analyses were performed in nine OBP (mean (SD) age = 15.17 (1.89), 3 female), eleven OCP (mean (SD) age = 16.99 (1.81)), 2 female), and fourteen OHP (mean (SD) age = 15.78 (1.39), 5 female) who had completed second scans (mean (SD) inter-scan interval = 2.24 (1.03) years). One OBP and two OCP were taking medications. In these follow-up subjects, correlation and linear regression analyses examined relationships between changes in symptoms and changes in neuroimaging measures showing between group differences in the above analyses. All analyses were repeated removing medicated youth. Additional analyses included: exploring group differences in reaction times; examining relationships between age and neuroimaging measures; comparing age to pubertal development measures using the Peterson Pubertal Development Scale (Petersen, Crockett et al. 1988); and comparing neuroimaging measures in offspring with and without non-BD psychiatric disorders.

3.3 RESULTS

3.3.1 Hypothesis Testing

Of the initial 336 predictors described in Tables 4-6, above, 12 variables, together, optimized model fit (ΔAICc = 1.811, λ = 0.553; Figure 10). Plots A-B represent variable fit for BD risk (OBP versus OCP/OHP; Figure 10A) and general psychiatric disorder risk (OBP/OCP versus OHP; Figure 10B). 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. In these figures, Lambda.min (λ = 0.553) corresponds to the λ of the selected model with 12 predictor variables. Plot C represents the non-zero variable fit after cross-validation (Figure 10C). In this figure, Lambda.min corresponds to the λ which minimizes mean squared error, and Lambda.1se corresponds to the λ that is one standard error away from the Lambda.min.

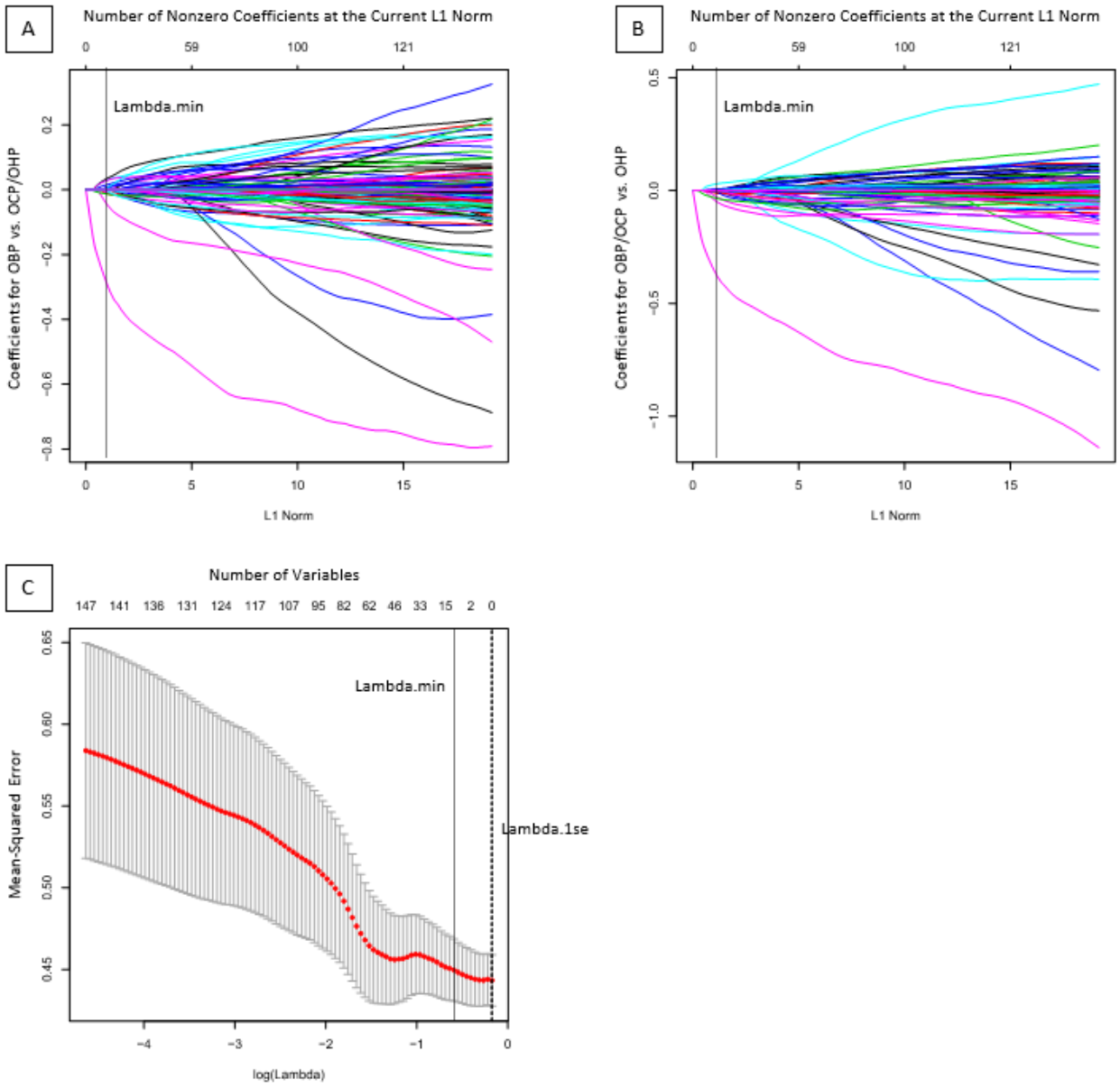

Figure 10: Exp 1. Elastic Net Plots

A pseudo r-squared, calculated containing the 12 non-zero predictors from the model versus an intercept-only model, indicated that 51.39% of the variance in group was explained by these predictors. All predictors were neuroimaging measures variables (Table 7).

Table 7: Exp 1. Between-Group Differences in Neuroimaging Measures

	ANOVA		Bonferroni Sig. Test for Multiple Comparisons		
Neuroimaging Measure	F =	p =	OBP vs. OCP p =	OBP vs. OHP p =	OCP vs. OHP p =
DFT: Amygdala-Left dlPFC FC to Sad Faces vs. Shapes	3.010	.055	.768	.049	.526
DFT: Left dlPFC Activity to Angry Faces vs. Shapes	5.522	**.006***	1.00	**.005***	.057
EF-2-BACK: Amygdala-Left cACC FC to Fearful vs. No Faces	4.352	**.016***	**.014***	.289	.985
EF-2-BACK: Amygdala-Left cACC FC to Happy vs. No Faces	6.110	**.003***	**.002***	.337	.352
EF-2-BACK: Amygdala-Left cACC FC to Neutral vs. No Faces	7.413	**.001***	**.001***	.784	.068
EF-2-BACK: Amygdala-Right vlPFC FC to Happy vs. Neutral Faces	2.007	.141	.822	.152	1.00
EF-2-BACK: Right rACC Activity to Happy vs. No Faces	4.458	**.015***	**.011***	.591	.477
EF-0-BACK: Amygdala-Left dlPFC FC to Happy vs. No Faces	3.368	**.040***	1.00	.100	.053
EF-0-BACK: Amygdala-Left rACC FC to Happy vs. Neutral Faces	2.254	.112	.551	.126	1.00
EF-0-BACK: Left rACC Activity to Happy vs. Neutral Faces	5.643	**.005***	.716	.071	**.004***
EF-0-BACK: Right rACC Activity to Happy vs. Neutral Faces	5.039	**.009***	1.00	**.025***	**.014***
EF-2-BACK vs. EF-0-BACK: Amygdala-Left rACC FC to Happy Faces	3.247	**.044***	.074	.146	1.00

An ANOVA and post-hoc t-tests, Bonferroni-corrected for three between-group parallel tests, examined all twelve neuroimaging measures that were significant non-zero predictors of group (Figure 11). Compared with OHP, OBP had lower DFT left dlPFC activity to angry faces versus shapes (mean (SD) difference = 0.108 (0.033), p = 0.005; Figure 11A). Compared with OCP, OBP had greater EF-2-BACK bilateral amygdala-left cACC FC to fearful (mean (SD) difference = 0.493 (0.169), p = 0.014), happy (mean (SD) difference = 0.516 (0.148), p = 0.002), and neutral (mean (SD) difference = 0.604 (0.159), p = 0.001) versus no faces (Figure 11B), and greater EF-2-BACK right rACC activity to happy versus no faces (mean (SD) difference = 0.744 (.249), p = 0.011; Figure 11C). Compared with OHP, OCP had lower EF-0-BACK left (mean

(SD) difference = 0.802 (0.241), p = 0.004) and right (mean (SD) difference = 0.691 (0.236), p = 0.014) rACC activity to happy versus neutral faces, and OBP had lower EF-0-BACK right rACC activity to happy versus neutral faces (mean (SD) difference = 0.626 (.231), p = 0.025) (Figure 11D). No significant group differences were found for the remaining measures.

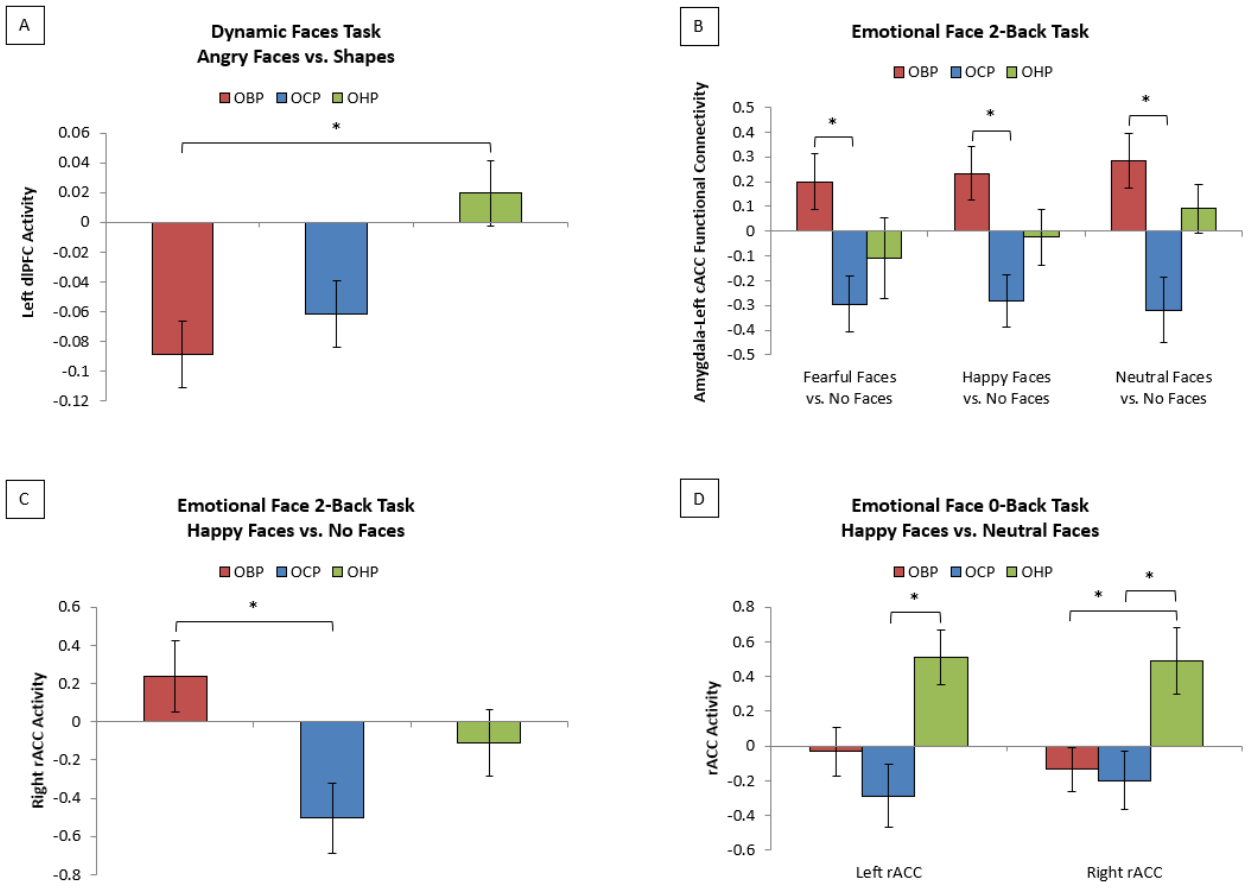

Figure 11: Exp 1. Group Differences in Neuroimaging Measures

ANOVAs examined effects of group on all symptom measures (Table 8). For ANOVAs, additional Bonferroni corrections are presented in parentheses.

Table 8: Exp 1. Between-Group Differences in Symptom Measures

Symptom Measure	ANOVA		Bonferroni Sig. Test for Multiple Comparisons		
	F =	p =	OBP vs. OCP p =	OBP vs. OHP p =	OCP vs. OHP p =
SCARED-P	2.932	.059	1.00	.084	.131
SCARED-C	1.029	.362	.504	1.00	1.00
CALS-P	6.464	**.003* (.024*)**	.123	**.002***	.343
CALS-C	1.504	.229	.320	.652	1.00
MFQ-P	3.909	**.024*** (.192)	.730	.020	.328
MFQ-C	0.536	.588	1.00	.966	1.00
KMRS	6.223	**.003* (.024*)**	**.032***	**.005***	1.00
KDRS	2.005	.142	1.00	.155	.451

Bonferroni corrections for eight parallel tests revealed two significant findings: CALS-P ($F(2,77) = 6.464$, $p = 0.003$ (0.024, corrected)) and KMRS ($F(2,75) = 6.223$, $p = 0.003$ (0.024, corrected)). Bonferroni-corrected post-hoc t-tests revealed that OBP had greater CALS-P severity than OHP (mean (SD) difference = 6.575 (1.853), $p = 0.002$), and greater KMRS severity than OHP (mean (SD) difference = 1.722 (0.529), $p = 0.005$) and OCP (mean (SD) difference = 1.238 (0.473), $p = 0.032$) (Figure 12).

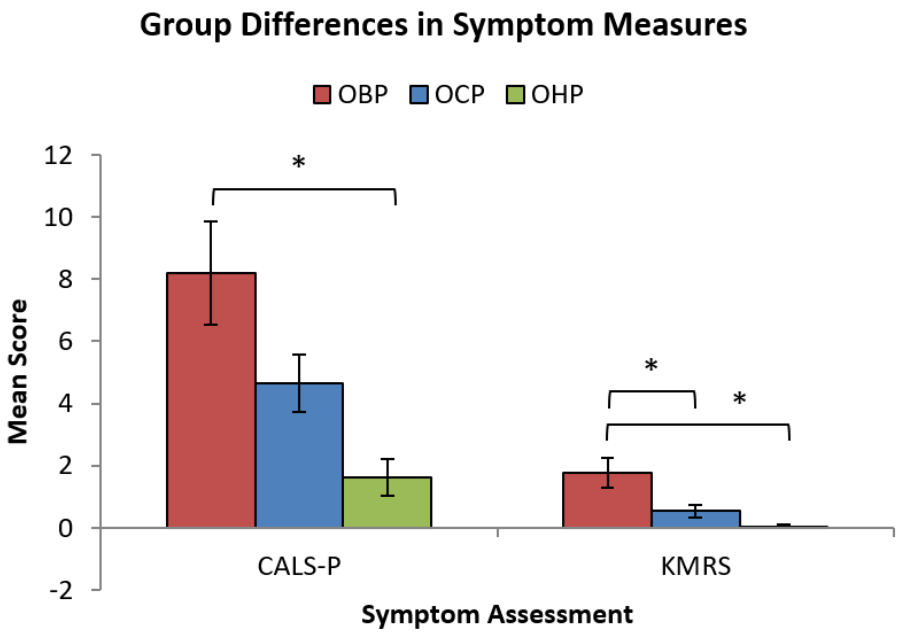

Figure 12: Exp 1. Group Differences in Symptom Measures

Bivariate Spearman's rank-order correlation analyses examined relationships among all seven neuroimaging measures and both symptom measures that showed significant group differences, above. Across all subjects, one significant relationship was found: baseline CALS-P severity positively correlated with EF-2-BACK right rACC activity to happy faces ($\rho = 0.304$, $p = 0.006$; Figure 13). This just missed significance using Bonferroni corrections for fourteen tests ($p < 0.004$).

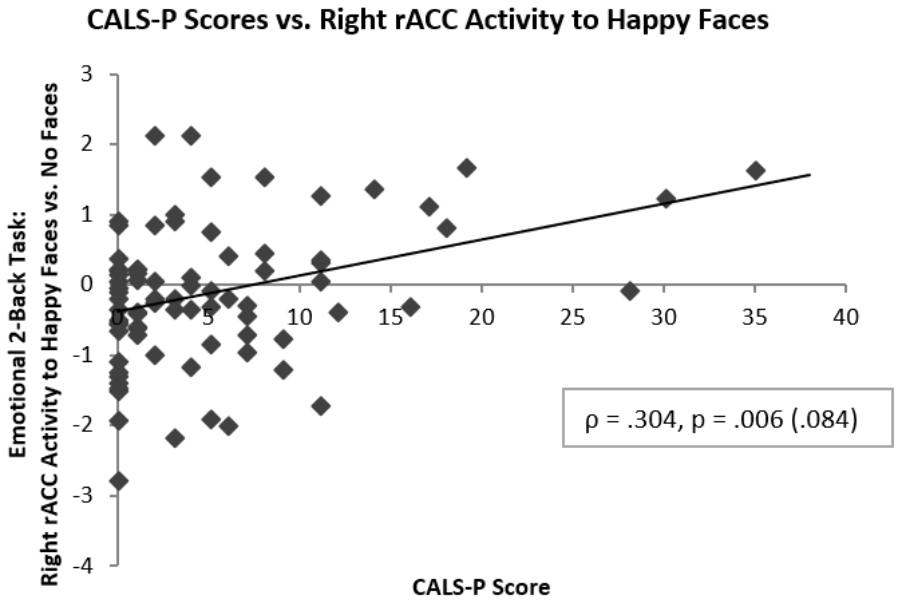

Figure 13: Exp 1. Relationships between Symptom and Neuroimaging Measures at Baseline

3.3.2 Exploratory Analyses

3.3.2.1 Longitudinal Follow-Up Analyses

Bivariate Pearson's correlation analyses examined relationships among changes over follow-up in all seven neuroimaging and both symptom measures that showed significant group differences, above. Across all follow-up subjects, one significant (Bonferroni-corrected) relationship was found: an increase in CALS-P severity was significantly positively correlated with an increase in EF-2-BACK bilateral amygdala-left cACC FC to fearful faces ($r = 0.541$, $p = 0.003$ (0.042, corrected); Figure 14). A linear regression, with five covariates (age, gender, IQ, time between scans, and scanner) showed that change in CALS-P scores significantly predicted change in bilateral amygdala-left cACC FC to fearful faces ($R^2 = 0.423$, $F(6,21) = 2.569$, $p = 0.050$).

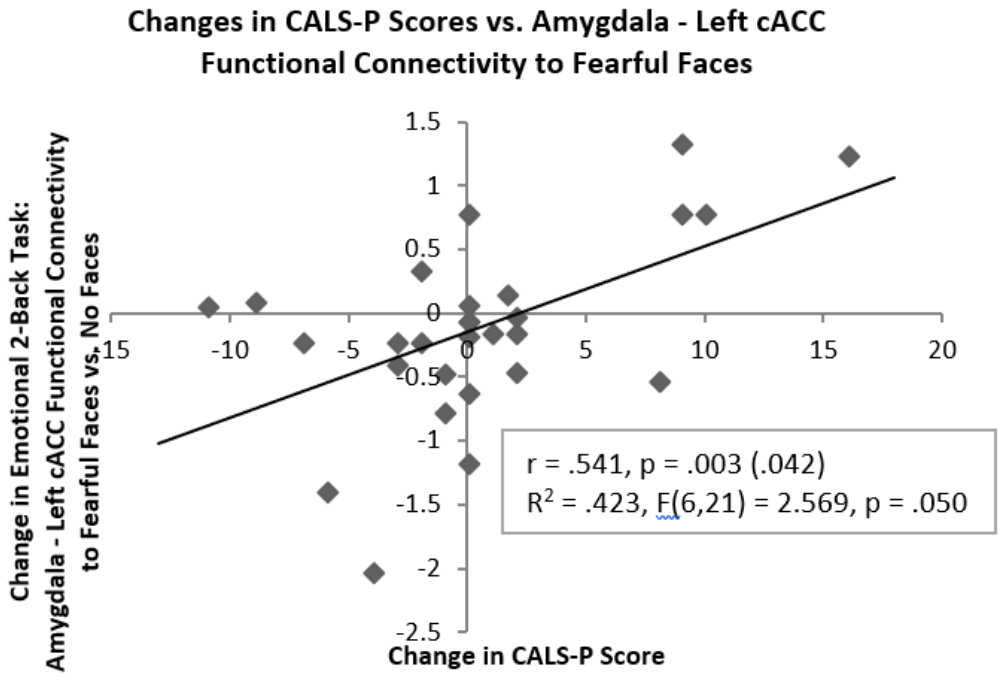

Figure 14: Exp 1. Relationships between Symptom and Neuroimaging Measures over Follow-Up

3.3.2.2 Repeated Analyses Removing Medicated Youth

When analyses were repeated removing medicated youth, OBP no longer had significantly greater right rACC activity to EF-2-BACK happy faces (mean (SD) difference = 0.408 (.275), p = 0.432) and showed borderline significantly greater bilateral amygdala-left cACC FC to fearful faces (mean (SD) difference = 0.454 (.188), p = 0.056) versus OCP. In follow-up analyses, the relationship between change in CALS-P score and change in EF-2-BACK bilateral amygdala-left cACC FC to fearful faces remained significant (r = 0.597, p = 0.002); the linear regression model just missed significance (R^2 = 0.442, F(6,18) = 2.378, p = 0.072). No other findings changed by removing medicated youth.

3.3.2.3 Symptom Comparison in Offspring Taking and Not Taking Medications

We compared symptom measures in offspring taking and not taking psychotropic medications. In OBP (Table 9), independent sample t-tests did not reveal any significant differences between offspring taking versus not taking medications for SCARED-P, SCARED-C, CALS-C, MFQ-P, MFQ-C, KMRS, or KDRS. Medicated OBP had greater CALS-P severity than unmedicated OBP (mean (SD) difference = 8.853 (3.916), p = 0.031 (0.248, corrected)), but this significance did not survive Bonferroni corrections.

Table 9: Exp 1. Comparison of Symptom Measures in Medicated and Unmedicated Offspring of Bipolar Parents

	t-test for Equality of Means						
						95% Confidence Interval of the Difference	
Symptom Measure	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
SCARED-P	-0.321	29	0.75	-1.027	3.194	-7.558	5.505
SCARED-C	0.475	29	0.638	3.273	6.886	-10.809	17.356
CALS-P	-2.261	29	**0.031*** (0.248)	-8.853	3.916	-16.862	-0.845
CALS-C	-1.214	29	0.235	-6.833	5.631	-18.349	4.683
MFQ-P	-1.134	3.086	0.337	-10.96	9.669	-41.25	19.33
MFQ-C	-0.457	3.192	0.677	-4.74	10.379	-36.672	27.192
KMRS	0.107	29	0.915	0.133	1.245	-2.412	2.679
KDRS	-1.052	5.286	0.339	-4.24	4.031	-14.435	5.955

In OCP (Table 10), independent sample t-tests did not reveal any significant differences between offspring taking versus not taking medications for SCARED-P, SCARED-C, CALS-P, CALS-C, MFQ-P, MFQ-C, or KDRS. Medicated OCP had greater KMRS severity than unmedicated OCP (mean (SD) difference = 1.105 (.443), p = 0.030 (0.240, corrected)), but this significance also did not survive Bonferroni corrections.

Table 10: Exp 1. Comparison of Symptom Measures in Medicated and Unmedicated Offspring of Comparison Parents

	t-test for Equality of Means						
						95% Confidence Interval of the Difference	
Symptom Measure	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
SCARED-P	-1.209	26	0.237	-6.152	5.088	-16.609	4.306
SCARED-C	-0.829	26	0.415	-4.667	5.632	-16.243	6.909
CALS-P	-0.107	26	0.916	-0.242	2.271	-4.911	4.426
CALS-C	-0.262	26	0.795	-1.076	4.106	-9.516	7.365
MFQ-P	0.937	23	0.358	2.35	2.507	-2.836	7.536
MFQ-C	-0.622	23	0.540	-3.45	5.548	-14.927	8.027
KMRS	-2.289	26	**0.030*** (0.240)	-1.015	0.443	-1.927	-0.104
KDRS	-0.732	26	0.471	-1.273	1.738	-4.846	2.300

3.3.2.4 Effects of Non-BD Psychiatric Disorders

We compared neuroimaging measures in OBP with and without non-BD psychiatric disorders (Table 11). Independent sample t-tests did not reveal any significant differences between offspring with versus without non-BD psychiatric disorders for the following measures: DFT bilateral amygdala-left dlPFC FC to sad faces versus shapes; DFT left dlPFC activity to angry faces versus shapes; EF-2-BACK bilateral amygdala-left cACC FC to fearful, happy, or neutral versus no faces; EF-2-BACK amygdala-right vlPFC FC to happy versus neutral faces; EF-2-BACK right rACC activity to happy versus no faces; EF-0-BACK bilateral amygdala-left rACC FC to happy versus neutral faces; EF-0-BACK left or right rACC activity to happy versus neutral faces; or EF-2-BACK versus EF-0-BACK bilateral amygdala-left rACC FC to happy faces. The difference between offspring with versus without non-BD psychiatric disorders for EF-0-BACK bilateral amygdala-left dlPFC FC to happy versus no faces was significant but did not survive Bonferroni corrections (mean (SD) difference = 0.239 (0.116), p = 0.049 (0.588, corrected)).

Table 11: Exp 1. Comparison of Neuroimaging Measures in Offspring of Bipolar Parents With versus Without Non-Bipolar Disorders

Neuroimaging Measure	t-test for Equality of Means						
	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
						Lower	Upper
DFT: Amygdala-Left dlPFC FC to Sad Faces vs. Shapes	-0.737	29	0.467	-0.09704	0.13175	-0.36651	0.17242
DFT: Left dlPFC Activity to Angry Faces vs. Shapes	-0.137	29	0.892	-0.00641	0.046688	-0.1019	0.089075
EF-2-BACK: Amygdala-Left cACC FC to Fearful vs. No Faces	0.188	29	0.852	0.04422	0.23569	-0.43781	0.52625
EF-2-BACK: Amygdala-Left cACC FC to Happy vs. No Faces	-0.082	29	0.935	-0.01844	0.22427	-0.47712	0.44024
EF-2-BACK: Amygdala-Left cACC FC to Neutral vs. No Faces	-0.267	16.153	0.793	-0.06855	0.2571	-0.61316	0.47607
EF-2-BACK: Amygdala-Right vlPFC FC to Happy vs. Neutral Faces	0.39	29	0.700	0.0399	0.10237	-0.16946	0.24926
EF-2-BACK: Right rACC Activity to Happy vs. No Faces	0.315	29	0.755	0.12229	0.38794	-0.67114	0.91571
EF-0-BACK: Amygdala-Left dlPFC FC to Happy vs. No Faces	-2.064	26	**0.049*** (0.588)	-0.23942	0.11598	-0.47781	-0.00102
EF-0-BACK: Amygdala-Left rACC FC to Happy vs. Neutral Faces	0.288	29	0.775	0.07862	0.27309	-0.47991	0.63714
EF-0-BACK: Left rACC Activity to Happy vs. Neutral Faces	-0.903	29	0.374	-0.25935	0.28735	-0.84706	0.32835
EF-0-BACK: Right rACC Activity to Happy vs. Neutral Faces	-0.546	29	0.589	-0.1429	0.26153	-0.67778	0.39199
EF-2-BACK vs. EF-0-BACK: Amygdala-Left rACC FC to Happy Faces	-0.532	29	0.599	-0.14289	0.26874	-0.69253	0.40674

In addition, we repeated ANOVAs for each significant neuroimaging finding pertaining to OBP twice: once in OBP and OCP without non-BD disorders, and once in OBP and OCP with non-BD disorders (Table 12). Only one finding survived Bonferroni corrections for 7 tests: EF-2-BACK bilateral amygdala-left cACC FC to neutral versus no faces in youth without non-BD disorders (mean (SD) difference = 0.643 (0.169), p = 0.001 for OBP vs. OCP; mean (SD) difference = 0.475 (0.165), p = 0.018 for OCP vs. OHP). No other findings survived Bonferroni corrections in youth with or without non-BD disorders.

Table 12: Exp 1. Repeated Analyses in Offspring With and Without Non-Bipolar Disorders

	Youth Without Non-BD Disorders					Youth With Non-BD Disorders				
	ANOVA		Bonferroni Sig. Test for Multiple Comparisons			ANOVA		Bonferroni Sig. Test for Multiple Comparisons		
Neuroimaging Measure	F =	p =	OBP vs. OCP p =	OBP vs. OHP p =	OCP vs. OHP p =	F =	P =	OBP vs. OCP p =	OBP vs. OHP p =	OCP vs. OHP p =
DFT: Left dlPFC Activity to Angry Faces vs. Shapes	4.383	**0.018*** (0.126)	1.000	0.017	0.224	4.492	**0.017*** (0.119)	1.000	0.033	0.079
EF-2-BACK: Amygdala-Left cACC FC to Fearful vs. No Faces	2.056	0.138	0.206	0.355	1.000	1.966	0.152	0.161	0.832	0.824
EF-2-BACK: Amygdala-Left cACC FC to Happy vs. No Faces	2.787	0.071	0.070	0.497	0.838	3.375	**0.043*** (0.301)	0.039	0.588	0.370
EF-2-BACK: Amygdala-Left cACC FC to Neutral vs. No Faces	7.55	**0.001* (0.007*)**	**0.001***	0.820	**0.018***	2.392	0.103	0.110	1.000	0.459
EF-2-BACK: Right rACC Activity to Happy vs. No Faces	2.769	0.072	0.070	0.574	0.738	1.82	0.174	0.200	1.000	0.636
EF-0-BACK: Left rACC Activity to Happy vs. Neutral Faces	4.46	**0.016*** (0.112)	1.000	0.080	0.026	4.747	**0.014*** (0.098)	0.568	0.444	0.011
EF-0-BACK: Right rACC Activity to Happy vs. Neutral Faces	4.031	**0.024*** (0.168)	1.000	0.050	0.071	3.562	**0.037*** (0.259)	1.000	0.207	0.051

3.3.2.5 Group Differences in Reaction Time

We explored group differences in reaction times for both tasks (Table 13). For the DFT, no significant group differences in reaction times were found for the happy, sad, angry, fearful, or shape contrasts. For the emotional face n-back task, no significant group differences in reaction times were found for the 0-back fearful, 0-back happy, 0-back neutral, 0-back no face, 2-back fearful, 2-back happy, 2-back neutral, or 2-back no face contrasts.

Table 13: Exp 1. Comparison of Reaction Times in All Subjects

	ANOVA			
	df			
Task Contrast	Between Groups	Within Groups	F	p
Dynamic Faces Task				
Happy Faces	2	74	0.346	0.709
Sad Faces	2	74	0.034	0.967
Angry Faces	2	74	0.796	0.455
Fearful Faces	2	74	0.062	0.940
Shapes	2	74	0.060	0.942
Emotional Face N-Back Task				
EF-0-BACK				
Fearful Faces	2	77	1.669	0.195
Happy Faces	2	77	1.814	0.170
Neutral Faces	2	77	1.303	0.278
No Faces	2	77	2.268	0.110
EF-2-BACK				
Fearful Faces	2	77	0.182	0.834
Happy Faces	2	77	1.246	0.293
Neutral Faces	2	77	0.418	0.660
No Faces	2	77	1.266	0.288

3.3.2.6 Relationships between Age and Neuroimaging Measures

We examined relationships between age and neuroimaging measures (Table 14). Across all subjects, bivariate Pearson's correlation analyses did not reveal any significant correlations between age and DFT bilateral amygdala-left dlPFC FC to sad faces versus shapes; EF-2-BACK bilateral amygdala-left cACC FC to fearful, happy, or neutral versus no faces; EF-2-BACK amygdala-right vlPFC FC to happy versus neutral faces; EF-2-BACK right rACC activity to happy versus no faces; EF-0-BACK bilateral amygdala-left dlPFC FC to happy versus no faces; EF-0-BACK bilateral amygdala-left rACC FC to happy versus neutral faces; EF-0-BACK left or right rACC activity to happy versus neutral faces; or EF-2-BACK versus EF-0-BACK bilateral amygdala-left rACC FC to happy faces. The correlation between age and DFT left dlPFC

activity to angry faces versus shapes was significant but did not survive Bonferroni corrections (r = 0.225, p = 0.045 (0.540, corrected)).

Table 14: Exp 1. Correlations between Neuroimaging Measures and Age

	Age	
Neuroimaging Measure	Pearson Correlation	Sig. (2-tailed)
DFT: Amygdala-Left dlPFC FC to Sad Faces vs. Shapes	0.032	0.779
DFT: Left dlPFC Activity to Angry Faces vs. Shapes	.225	**0.045*** (0.540)
EF-2-BACK: Amygdala-Left cACC FC to Fearful vs. No Faces	-0.168	0.137
EF-2-BACK: Amygdala-Left cACC FC to Happy vs. No Faces	-0.051	0.651
EF-2-BACK: Amygdala-Left cACC FC to Neutral vs. No Faces	0.139	0.219
EF-2-BACK: Amygdala-Right vlPFC FC to Happy vs. Neutral Faces	-0.092	0.419
EF-2-BACK: Right rACC Activity to Happy vs. No Faces	0.024	0.834
EF-0-BACK: Amygdala-Left dlPFC FC to Happy vs. No Faces	-0.084	0.461
EF-0-BACK: Amygdala-Left rACC FC to Happy vs. Neutral Faces	-0.058	0.612
EF-0-BACK: Left rACC Activity to Happy vs. Neutral Faces	-0.081	0.473
EF-0-BACK: Right rACC Activity to Happy vs. Neutral Faces	0.089	0.434
EF-2-BACK vs. EF-0-BACK: Amygdala-Left rACC FC to Happy Faces	0.128	0.258

3.3.2.7 Relationships between Age and Pubertal Status

We ran additional analyses comparing age to pubertal development measures using the Peterson Pubertal Development Scale (Table 15) (Petersen, Crockett et al. 1988). Overall pubertal development scores were computed by summing across the five items for boys (body hair, facial hair, voice change, skin change, and growth spurt) and girls (body hair, breast growth, menarche, skin change, and growth spurt), separately. At baseline, bivariate Pearson's correlation analyses revealed a significant correlation between age and overall pubertal development in all subjects (r = 0.687, p < 0.001), as well as in OBP (r = 0.698, p < 0.001), OCP (r = 0.682, p < 0.001), and OHP (r = 0.710, p < 0.001), separately.

Table 15: Exp 1. Correlations between Age and Peterson Pubertal Development

	Age	
	Pearson Correlation	Sig. (2-tailed)
All Offspring	0.687	**< 0.001***
Offspring of Bipolar Parents	0.698	**< 0.001***
Offspring of Comparison Parents	0.682	**< 0.001***
Offspring of Healthy Parents	0.710	**< 0.001***

3.3.2.8 Elastic Net Regression Analysis Including Clinical Variables

We ran an additional elastic net regression analysis that included clinical variables (i.e. medications, diagnoses, and symptom measures) as additional predictor variables. When compared to the original model, this additional model identified diagnoses (present versus not present), CALS-P scores, and KMRS scores as additional predictors. Furthermore, all neuroimaging measures that were identified in the original model as showing significant differences between OBP and OCP and/or OHP remained significant in this additional model: DFT left dlPFC activity to angry faces versus shapes, EF-2-BACK bilateral amygdala-left cACC FC to fearful versus no faces, EF-2-BACK bilateral amygdala-left cACC FC to happy versus no faces, EF-2-BACK bilateral amygdala-left cACC FC to neutral versus no faces, EF-2-BACK right rACC activity to happy versus no faces, and EF-0-BACK right rACC activity to happy versus neutral faces. Psychotropic medication (i.e. taking versus not taking) was not a significant predictor of group.

3.3.2.9 Determination of Variance in Group Explained by Neuroimaging and Symptom Measures that Differed Significantly Among Groups

In order to identify the relative contribution of each of these neuroimaging and symptom measures to the determination of group membership, we used a stepwise linear regression to

determine the variance in group explained by each individual neuroimaging and symptom measure. DFT left dlPFC activity to angry faces versus shapes explained 4.6% of the variance ($p = 0.033$). CALS-P score explained 3.9% of the variance ($p = 0.050$). KMRS score explained 2.8% of the variance ($p = 0.093$). EF-2-BACK bilateral amygdala-left cACC FC to fearful versus no faces explained 1.4% of the variance ($p = 0.239$). EF-0-BACK right rACC activity to happy versus neutral faces explained 0.8% of the variance ($p = 0.360$). EF-2-BACK right rACC activity to happy versus no faces explained 0.5% of the variance ($p = 0.474$). EF-2-BACK bilateral amygdala-left cACC FC to happy versus no faces explained 0.2% of the variance ($p = 0.644$). EF-2-BACK left rACC activity to happy versus neutral faces explained 0.1% of the variance ($p = 0.719$). EF-2-BACK bilateral amygdala-left cACC FC to neutral versus no faces did not explain any additional variance ($p = 0.852$).

3.4 DISCUSSION

3.4.1 Summary of Findings

In order to identify neural markers of future BD risk in OBP, we examined baseline and follow-up measures of activity and FC in amygdala-PFC circuitry during emotion processing and regulation that distinguished OBP from OCP and OHP, and the extent to which these measures were associated with symptom severity.

OBP showed greater right rACC activity to happy faces during EF-2-BACK performance than OCP. The rACC is the “affective division” of the ACC with connections to affective neural regions (e.g. amygdala) (Van Hoesen, Morecraft et al. 1993, Carmichael and Price 1995) and

roles in processing emotional conflict and integrating emotion and cognition (Vogt, Finch et al. 1992, Devinsky, Morrell et al. 1995, Bush, Luu et al. 2000, Bishop, Duncan et al. 2004, Bissière, Plachta et al. 2008). rACC recruitment may help resolve emotional conflict by suppressing amygdala activity, leading to reduced emotional responsivity and blunted sympathetic autonomic responses to incongruent emotional distracters (Etkin, Egner et al. 2006). Greater right rACC activity to happy faces also positively correlated with greater parent-reported affective lability severity, a precursor of BD in OBP (Hafeman, Merranko et al. 2016). Affective lability is defined as "a predisposition to marked, rapidly reversible shifts in affective states, extremely sensitive to meaningful environmental events that might induce more modest emotional responses in normal individuals" (Siever and Davis 1991, Henry, Van den Bulke et al. 2008). We may speculate that these findings reflect inefficient recruitment of the rACC to downregulate amygdala activity, leading to affective lability and, potentially, risk for future BD in OBP. The relationship with parent-reported, versus child-reported, affective lability may reflect the greater reliability of parental reports of child symptoms, as these are considered more useful than child reports in diagnosing BD in children (Youngstrom, Findling et al. 2004).

OBP and OCP showed lower rACC activity than OHP to happy faces during EF-0-BACK performance. Similarly, OBP had lower dlPFC activity than OHP to angry faces during the DFT, another face emotion processing task with no working memory component. These findings suggest that both OBP and OCP fail to recruit, to a normal extent, PFC regions (i.e. the rACC and dlPFC) that are important for the processing of emotional stimuli. In addition, OBP, alone, showed abnormal recruitment of the rACC when regulating attention away from positive emotional stimuli. Differential patterns of aberrant recruitment of PFC regions for the processing

and regulation emotional stimuli in different contexts is thus a potential neural mechanism that distinguishes OBP from OCP and confers risk for BD in OBP.

OBP also showed greater bilateral amygdala-left cACC FC to fearful, happy, and neutral faces during EF-2-BACK performance compared with OCP. Changes in bilateral amygdala-left cACC FC to fearful faces positively correlated with changes in parent-reported affective lability severity over follow-up. Along with the rACC, the cACC is implicated in implicit emotion regulation (Kober, Barrett et al. 2008, Phillips, Ladouceur et al. 2008, Kim, Loucks et al. 2011, Goodkind, Gyurak et al. 2013, Frank, Dewitt et al. 2014). The cACC is part of the central executive control network, however, and has a more specific role than the rACC in attentional task performance (Van Veen and Carter 2002, Haas, Omura et al. 2006, Margulies, Kelly et al. 2007). Our findings thus suggest that greater bilateral amygdala-left cACC FC to emotional face distracters, as well as increasing bilateral amygdala-left cACC FC over time to fearful face distracters, may reflect a compensatory, but inefficient, neural mechanism to redirect attention away from emotional face distracters during attentional tasks. This, in turn, may predispose to increasing affective lability and BD in at-risk youth.

Removing medicated youth reduced the significance of the differences between right rACC activity to happy faces and bilateral amygdala-left cACC FC to fearful faces during EF-2-BACK performance in OBP versus OCP, as well as the relationship between change in the latter measure and change in affective lability over follow-up. Medicated OBP had greater affective lability severity than unmedicated OBP, however, and thus reflected a particularly high-risk subset of OBP. Furthermore, removing medicated youth from these analyses affected the significance only of neural measures that showed significant relationships with affective lability severity. Additionally, medication was not a predictor of group in an additional elastic net

regression model that included medication and all clinical variables, as well as all neuroimaging and demographic measures, as predictors. Thus, greater right rACC activity to happy faces, and greater bilateral amygdala-left cACC FC to fearful faces, during EF-2-BACK performance may represent markers of BD risk in higher-risk OBP who are more affectively labile and more likely to be medicated, but psychotropic medication use, in itself, is not a predictor of risk for BD in youth.

Previous studies reported that OBP show greater amygdala and PFC activity during emotion processing and regulation (Olsavsky, Brotman et al. 2012, Ladouceur, Diwadkar et al. 2013, Manelis, Ladouceur et al. 2015). While OBP showed greater right rACC activity to happy faces during EF-2-BACK versus OCP, OBP also showed lower left dlPFC activity to angry faces and lower right rACC activity to EF-0-BACK happy faces versus OHP. This is more consistent with studies of patients with BD showing lower activity in PFC regions supporting emotion regulation (Phillips, Drevets et al. 2003, Phillips, Ladouceur et al. 2008, Hafeman, Bebko et al. 2014). Previous studies also reported mixed results of either greater (Manelis, Ladouceur et al. 2015) or lower (Abler, Greenhouse et al. 2008, Bermpohl, Kahnt et al. 2010, Linke, King et al. 2012, Nusslock, Almeida et al. 2012, Caseras, Lawrence et al. 2013, Chase, Nusslock et al. 2013, Ladouceur, Diwadkar et al. 2013) amygdala-PFC FC in OBP. In comparison to findings in other studies that focused on amygdala-vlPFC FC, our findings additionally implicated a relationship between the amygdala and cACC. Furthermore, our DFT findings of lower left dlPFC activity add to those in BIOS showing greater amygdala activity, lower amygdala-ACC FC, and greater amygdala-vlPFC FC in OBP compared with OHP (Manelis, Ladouceur et al. 2015). Together, our findings suggest differential patterns of functional abnormalities in circuitries associated with emotion processing and regulation in OBP compared with OCP and OHP.

3.4.2 Conclusions

This is the first study to employ both cross-sectional and longitudinal analyses of emotion processing and regulation neural circuitries in youth at risk for BD versus comparative at-risk and healthy control groups. We show that greater right rACC activity to happy faces and greater bilateral amygdala-left cACC FC to fearful faces during attentional task performance with high-memory load conditions significantly distinguish OBP from OCP, at the group level, and these measures have significant relationships with affective lability, a precursor of BD. We conclude that greater right rACC activity and greater amygdala-cACC FC during emotion regulation are candidate objective markers of BD risk in youth. Our findings are an important step toward identifying neural markers of BD risk to aid in enhanced early identification, and guide interventions for, youth at risk for BD.

4.0 BASELINE AND FOLLOW-UP ACTIVITY AND FUNCTIONAL CONNECTIVITY IN REWARD NEURAL CIRCUITRY IN OFFSPRING AT RISK FOR BIPOLAR DISORDER

This chapter is a modified version of the following manuscript that is currently in preparation: Acuff HE, Versace A, Bertocci MA, Ladouceur CD, Hanford LC, Manelis A, Monk K, Bonar L, McCaffrey A, Goldstein BI, Goldstein TR, Sakolsky D, Axelson D, Birmaher B, Phillips ML. Baseline and follow-up activity and functional connectivity in reward neural circuitries in offspring at risk for bipolar disorder. *In Preparation.*

4.1 INTRODUCTION

One neural circuitry that is important to the study of BD is reward processing, which has strong associations with impulsive sensation seeking (Chase, Fournier et al. 2017). This is a personality trait that comprises impulsivity (i.e. often prematurely elicited behavior with little to no forethought, reflection, or consideration of the consequences (Evenden 1999)) and sensation seeking (i.e. the inclination and desire to seek and take risks for new and intense sensations and experiences (Zuckerman 2013)). Impulsive sensation seeking is also associated with the future development of BD (Meyer, Johnson et al. 1999, Meyer, Johnson et al. 2001, Alloy, Abramson et al. 2008, Harmon-Jones, Abramson et al. 2008, Urošević, Abramson et al. 2008). Studies have

reported positive associations between impulsive sensation seeking and greater probabilities of developing BD in adolescents and young adults (Meyer, Johnson et al. 1999, Giovanelli, Hoerger et al. 2013), as well as between this trait and mania severity in young adults who are at risk for developing the disorder (Alloy, Bender et al. 2012). Such findings implicate high levels of this trait as a potential risk factor for BD (Chase, Fournier et al. 2017). Identifying abnormalities in reward circuitry that are associated with impulsive sensation seeking in youth at familial risk for BD may thus elucidate biological markers of specific risk for future BD in at-risk populations.

Specific functional abnormalities in reward circuitry in adults and youth with and at risk for BD have been discussed previously (Chapter 1.3.1). Key findings in youth at risk for BD include greater amygdala activity during reward reversal (Linke, King et al. 2012), greater vlPFC activity during loss anticipation (Singh, Kelley et al. 2014), greater left OFC activity during reward reversal (Linke, King et al. 2012), lower cACC activity (Singh, Kelley et al. 2014), more negative bilateral VS-right vlPFC FC during the processing of both reward and loss receipt (Manelis, Ladouceur et al. 2016), greater vlPFC-ACC FC during loss anticipation (Singh, Kelley et al. 2014), and lower vlPFC-ACC FC during reward anticipation (Singh, Kelley et al. 2014). The findings of more negative bilateral VS-right vlPFC FC remained after removing youth who had non-BD psychiatric disorders and who were taking psychotropic medications, suggesting that these measures likely reflected trait-level neural markers that confer risk for, or protect against, BD in at-risk youth (Manelis, Ladouceur et al. 2016).

Our primary goal in this present study was to expand upon our previous findings by further investigating differences between OBP, OCP, and OHP in reward processing circuitry, both at baseline and at follow-up, and by examining whether these findings reflected trait-or state-level markers of risk for BD versus risk for other psychiatric illnesses in OBP. To achieve

this goal, we wished to identify OBP-specific abnormalities in reward processing neural circuitry that were independent of non-BD psychopathology and psychotropic medication use. Elucidating such abnormalities would be a step toward identifying candidate neural markers of risk for BD versus risk for other psychiatric disorders. As described above, previous findings indicate predominantly greater amygdala and PFC activity, lower ACC activity, and either greater or lower FC between PFC regions in individuals at risk for BD relative to OHP and/or OCP, present largely to reward and loss receipt. Previous findings also indicate the stability of these patterns of neural activity and FC when removing youth with psychiatric disorders and medications. We thus hypothesized:

1. OBP would show greater amygdala and PFC activity, lower ACC activity, and either greater or lower FC between PFC regions to reward and loss receipt compared with OCP and OHP.
2. These findings would be unaffected by non-BD psychopathology and psychotropic medications.

In exploratory analyses, we examined relationships among neural measures and symptomatology, both at baseline and follow-up. Together, these OBP-specific abnormalities in reward processing neural circuitry that are independent of non-BD psychopathology, medication use, and symptom severity would be candidate, trait-level neural markers of risk for BD versus risk for other psychiatric disorders in youth.

4.2 MATERIALS AND METHODS

4.2.1 Participants

Thirty-two OBP (mean (SD) age = 13.95 (2.43), 16 female), thirty-six OCP (mean (SD) age = 14.09 (2.32), 14 female), and thirty-nine OHP (mean (SD) age = 13.90 (1.81), 18 female) were examined in this analysis (Table 16). Of the original thirty-six OBP, forty-two OCP, and forty-one OHP that were recruited: two OBP, five OCP, and one OHP were excluded due to excessive motion (translational > 4 mm); and two OBP, one OCP, and one OHP were excluded due to missing data. Twenty-seven OBP, twenty-five OCP, and twenty-three OHP were also included in a related BIOS paper (Manelis, Ladouceur et al. 2016).

Thirteen OBP had at least one non-BD diagnosis: four had MDD, four had an Anxiety Disorder, eight had ADHD, one had Oppositional Defiant or Conduct Disorder, and two had an Eating Disorder. Fifteen OCP had at least one non-BD diagnosis: three had MDD, seven had an Anxiety Disorder, six had ADHD, three had Oppositional Defiant or Conduct Disorder, and two had Obsessive Compulsive Disorder. Six OBP and eight OCP were taking antidepressant, antipsychotic, mood stabilizer, stimulant, and/or non-stimulant medications for non-BD disorders. Symptom assessments included SCARED-P, SCARED-C, CALS-P, CALS-C, MFQ-P, MFQ-C, KDRS, and KMRS (Chapter 2.1.3).

Table 16: Exp 2. Offspring of Bipolar, Comparison, and Healthy Offspring

	OBP n = 32 M(SD) or Total	OCP n = 36 M(SD) or Total	OHP n = 39 M(SD) or Total	Statistic	p =
Demographic Information					
Age	13.95(2.43)	14.09(2.32)	13.90(1.81)	F = 0.071	.932
Sex (females)	16	14	18	χ^2 = 0.887	.642
IQ	100.00(15.83)	102.08(14.91)	104.15(13.58)	F = 0.701	.498
Socioeconomic Status				χ^2 = 21.059	**.007***
Very Low (8-19)	9	8	4		
Low (20-29)	8	1	1		
Medium (30-39)	6	6	9		
High (40-54)	6	10	12		
Very High (55-66)	3	11	13		
Handedness				χ^2 = 5.019	.285
Right	27	33	35		
Left	2	2	4		
Mixed	3	1	0		
Highest Parental Education				χ^2 = 8.572	.380
Partial High School	0	1	1		
High School Graduate or Lower	5	3	6		
Partial College or Specialized Training	13	11	11		
Standard College or University Graduate	8	14	7		
Graduate Professional Training	6	7	14		
Clinical Measures					
Diagnosis	13	15	0	F = 13.275	**< .001***
Major Depressive Disorder	4	3	0	F = 2.430	.093
Anxiety Disorder	4	7	0	F = 4.155	**.018***
Attention Deficit/Hyperactivity Disorder	8	6	0	F = 5.523	**.005***
Oppositional Defiant or Conduct Disorder	1	3	0	F = 1.842	.164
Obsessive Compulsive Disorder	0	2	0	F = 2.030	.137
Eating Disorder	2	0	0	F = 2.430	.093
Psychotropic Medication Use	6	8	0	F = 5.019	**.008***
Scan Day Assessments					
SCARED-P	10.19(6.64)	9.87(10.65)	3.77(4.00)	F = 8.542	**< .001***
SCARED-C	13.03(14.70)	8.86(11.90)	8.35(9.88)	F = 1.515	.225
CALS-P	9.94(10.83)	5.14(7.02)	1.85(2.51)	F = 10.707	**< .001***
CALS-C	10.03(12.29)	7.17(9.86)	4.69(10.51)	F = 2.122	.125
MFQ-P	7.12(9.64)	4.57(8.11)	1.36(2.60)	F = 5.690	**.005***
MFQ-C	7.81(10.49)	7.56(10.00)	4.51(8.75)	F = 1.320	.272
Assessment Closest to Scan					
KDRS	3.22(5.81)	2.14(3.66)	0.21(0.53)	F = 5.558	**.005***
KMRS	1.97(2.82)	1.08(3.25)	0.03(0.16)	F = 5.530	**.005***

4.2.2 Neuroimaging Data Acquisition and Analyses

All scan 1 and nineteen scan 2 images (for nineteen OHP) were acquired using a Siemens Magnetom TrimTrio 3T MRI system, and twenty-two scan 2 images (for fourteen OBP and eight OCP) were acquired using a Siemens Magnetom Prisma system (Chapter 2.2.1). Participants completed the reward processing task (Chapter 2.2.2.3). Neuroimaging data analyses were performed as previously described (Chapter 2.3). ROIs included the amygdala, cACC, rACC, vlPFC, OFC, and VS (Table 2). gPPI analyses assessed task-related connectivity. Seed regions included, separately, the bilateral VS, bilateral pars opercularis, bilateral pars orbitalis, bilateral pars triangularis, and bilateral lateral orbitofrontal cortex. These seed regions were chosen due to the particularly high associations between activity in both the VS and vlPFC and impulsive sensation seeking (Caseras, Lawrence et al. 2013, Chase, Fournier et al. 2017). Target regions for the bilateral VS seed region included, separately: the left and right amygdala, left and right cACC, left and right rACC, left and right OFC, and left and right vlPFC. Target regions for the bilateral vlPFC seed regions included, separately: the left and right amygdala, left and right cACC, left and right rACC, left and right OFC, and left and right VS. Task stimulus contrasts included, separately: reward versus control and loss versus control.

4.2.3 Statistical Analyses

A single elastic net regression analysis, including OBP, OCP, and OHP, was used for data selection and reduction. This single model contained 2 dummy-coded outcome variables: BD risk (OBP versus OCP/OHP) and general psychiatric disorder risk (OBP/OCP versus OHP). This one model also contained 117 predictor variables. Thirteen of these predictor variables were

demographics measures: age, sex, IQ, SES handedness, and highest parental education (Table 17).

Table 17: Exp 2. Elastic Net Regression Predictor Variables: Demographic

13 DEMOGRAPHIC VARIABLES	
Variable	**Possible Options for Dummy-Coded Variables**
Age	
Sex	
IQ	
SES	Very Low Low Medium High Very High
Handedness	Right Left Mixed
Highest Parental Education	Partial High School High School Graduate or Lower Partial College or Specialized Training Standard College or University Graduate Graduate Professional Training

Twenty-four of these predictor variables were activity measures in each ROI for each contrast, separately (Table 18).

Table 18: Exp 2. Elastic Net Regression Predictor Variables: Activity Measures

24 NEUROIMAGING VARIABLES: Activity Measures		
Contrast	**12 Regions of Interest for Each Contrast**	
Reward vs. Control	Left Amygdala	Right Amygdala
	Left cACC	Right cACC
	Left rACC	Right rACC
Loss vs. Control	Left OFC	Right OFC
	Left vlPFC	Right vlPFC
	Left VS	Right VS

Twenty of these predictor variables were FC measures with a bilateral VS seed region and target regions in each ROI for each contrast, separately (Table 19).

Table 19: Elastic Net Regression Variables: Functional Connectivity Measures with Ventral Striatum Seed

20 NEUROIMAGING VARIABLES: FC Measures with Bilateral VS Seed Region		
Contrast	**10 Regions of Interest for Each Contrast**	
Reward vs. Control	Left Amygdala	Right Amygdala
	Left cACC	Right cACC
	Left rACC	Right rACC
Loss vs. Control	Left OFC	Right OFC
	Left vlPFC	Right vlPFC

Sixty of these predictor variables were FC measures with a bilateral vlPFC seed region (separated into the pars orbitalis, pars opercularis, and pars triangularis) and target regions in each ROI for each contrast, separately (Table 20).

Table 20: Exp 2. Elastic Net Regression Predictor Variables: Functional Connectivity Measures with Ventrolateral Prefrontal Cortex Seed

60 NEUROIMAGING VARIABLES: FC Measures with Bilateral vlPFC Seed Region			
Contrast	**Seed Region**	**10 Regions of Interest for Each Contrast and Seed Region**	
Reward vs. Control	Pars Orbitalis	Left Amygdala	Right Amygdala
	Pars Opercularis	Left cACC	Right cACC
	Pars Triangularis	Left rACC	Right rACC
Loss vs. Control	Pars Orbitalis	Left OFC	Right OFC
	Pars Opercularis	Left VS	Right VS
	Pars Triangularis		

Post-hoc pseudo r-squared analyses examined the proportion of variance in dependent variables explained by the non-zero predictor variables observed with elastic net. ANOVAs and Tukey HSD-corrected post-hoc t-tests examined: between-group differences in neuroimaging measures for all non-zero predictors and effects of youth with versus without non-BD disorders. Additional analyses included ANOVAs and post-hoc t-tests to examine effects of psychotropic medications, and correlation analyses to examine effects of age, on non-zero predictor neuroimaging measures showing significant effects of group.

ANOVAs and post-hoc t-tests examined between-group differences in baseline symptom measures. Correlation analyses examined relationships between neuroimaging and symptom measures, both at baseline and at follow-up, and relationships between changes in neuroimaging and symptom measures between baseline and follow-up, for all measures showing significant between-group differences at baseline. Follow-up analyses occurred in fourteen OBP (mean (SD) age = 17.48 (2.85), 6 female), eight OCP (mean (SD) age = 17.47 (1.89), 5 female), and nineteen OHP (mean (SD) age = 15.17 (1.65), 8 female) who had completed second scans (mean (SD)

inter-scan interval = 2.70 (1.22) years). Two OBP and one OCP were taking medications. Findings were corrected using Bonferroni corrections to account for the number of multiple tests.

4.3 RESULTS

4.3.1 Hypothesis Testing 1

4.3.1.1 Identification of Non-Zero Predictors

Of the initial 117 predictors, 26 variables, together optimized model fit using the minimum λ (λ = 0.224) identified by cross-validation (Figure 15). Plots A-B represent variable fit for BD risk (OBP versus OCP/OHP; Figure 15A) and general psychiatric disorder risk (OBP/OCP versus OHP; Figure 15B). Each curve corresponds to an independent variable in the full model prior to optimization. Plot C represents the non-zero variable fit after cross-validation (Figure 15C).

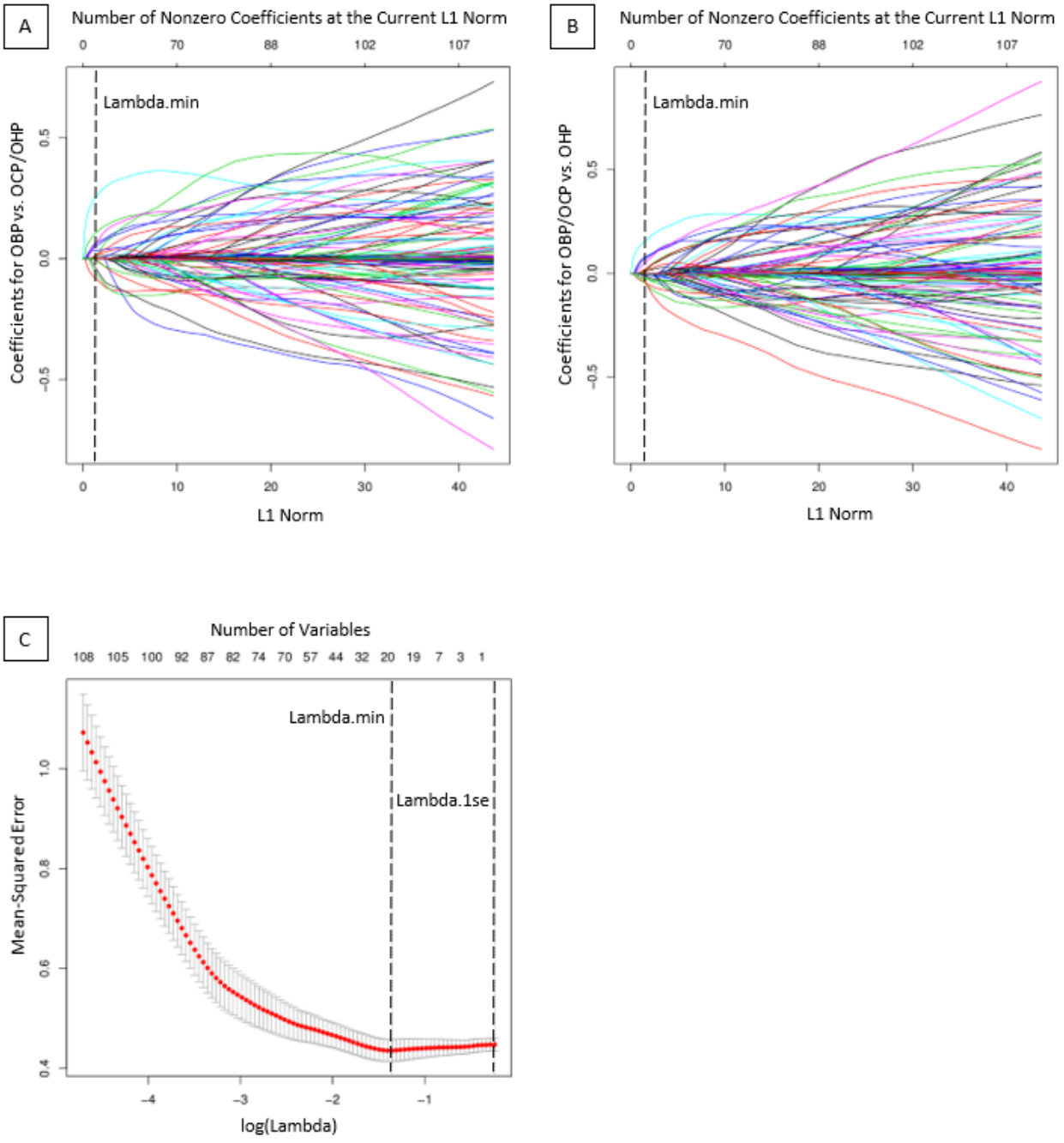

Figure 15: Exp 2. Elastic Net Plots

A pseudo r-squared, calculated containing the 26 non-zero predictors from the model versus an intercept-only model, indicated that 34.24% of the variance in group was explained by these predictors (Table 21). Twenty-two neuroimaging variables predicted 40.90% of the total explained variance: 2 activity variables to reward (left and right OFC); 10 FC variables to reward (bilateral VS-left cACC, bilateral VS-right rACC, bilateral lateral orbitofrontal cortex-left amygdala, bilateral lateral orbitofrontal cortex-left rACC, bilateral lateral orbitofrontal cortex-left VS, bilateral pars opercularis-right OFC, bilateral pars orbitalis-left OFC, bilateral pars orbitalis-right cACC, bilateral pars orbitalis-right OFC, and bilateral pars triangularis-right VS); and 10 FC variables to loss (bilateral VS-left cACC, bilateral VS-right rACC, bilateral lateral orbitofrontal cortex-left amygdala, bilateral lateral orbitofrontal cortex-left rACC, bilateral pars orbitalis-left rACC, bilateral pars orbitalis-right amygdala, bilateral pars orbitalis-right cACC, bilateral pars triangularis-left rACC, bilateral pars triangularis-right amygdala, and bilateral pars triangularis-right OFC). Four demographic variables predicted 83.00% of the total explained variance: IQ, SES (very low and low), and highest parental education (standard college/university graduate).

Table 21: Exp 2. Elastic Net Regression Non-Zero Coefficients

	Elastic Net Derived Coefficient		Exponentiated Coefficient		Percent Variance Explained	
	OBP	OBP or OCP	OBP	OBP or OCP	Individual	Group
Neuroimaging Variables						
Activity to Reward Trials						
Left OFC	-0.001	-0.002	0.999	0.998	0.1%	
Right OFC	-0.003	-0.007	0.997	0.993	0.8%	
Functional Connectivity to Reward Trials						
VS – Left cACC	-0.007	-0.002	0.993	0.998	0.4%	
VS – Right rACC	-0.082	-0.019	0.921	0.981	0.3%	
Lateral Orbitofrontal Cortex – Left Amygdala	-0.207	-0.315	0.813	0.730	8.3%	
Lateral Orbitofrontal Cortex – Left rACC	-0.024	-0.020	0.977	0.980	3.0%	
Lateral Orbitofrontal Cortex – Left VS	0.038	0.138	1.038	1.148	7.1%	
Pars Opercularis – Right OFC	-0.002	-0.010	0.998	0.990	1.2%	
Pars Orbitalis – Left OFC	0.037	-0.014	1.038	0.986	0.7%	
Pars Orbitalis – Right cACC	0.043	0.048	1.044	1.050	1.1%	
Pars Orbitalis – Right OFC	0.157	-0.034	1.170	0.967	2.4%	40.90%
Pars Triangularis – Right VS	-0.047	-0.062	0.954	0.940	1.5%	
Functional Connectivity to Loss Trials						
VS – Left cACC	-0.124	-0.070	0.883	0.932	2.7%	
VS – Right rACC	-0.111	-0.076	0.895	0.927	1.0%	
Lateral Orbitofrontal Cortex – Left Amygdala	-0.007	-0.011	0.993	0.989	1.5%	
Lateral Orbitofrontal Cortex – Left rACC	0.055	0.039	1.057	1.039	2.0%	
Pars Orbitalis – Left rACC	0.001	0.001	1.001	1.001	1.2%	
Pars Orbitalis – Right Amygdala	0.109	0.084	1.116	1.088	3.2%	
Pars Orbitalis – Right cACC	0.074	0.094	1.077	1.099	2.6%	
Pars Triangularis – Left rACC	0.141	0.121	1.151	1.129	8.5%	
Pars Triangularis – Right Amygdala	0.024	0.025	1.025	1.025	0.3%	
Pars Triangularis – Right OFC	0.001	-0.001	1.001	0.999	2.4%	
Demographic Variables						
IQ	-0.002	-0.002	0.998	0.998	5.3%	
Very Low Socioeconomic Status	0.087	0.100	1.090	1.105	2.0%	
Low Socioeconomic Status	0.325	0.210	1.384	1.233	6.7%	83.00%
Highest Parental Education: Standard College / University Graduate	-0.001	0.043	0.999	1.044	2.1%	

4.3.1.2 Between-Group Differences in Neuroimaging Predictors

A one-way between subjects ANOVA examined the effects of group on all non-zero predictors identified through elastic net (Table 22).

Table 22: Exp 2. Between-Group Differences in Neuroimaging Measures

	ANOVA		Tukey HSD Sig. Test for Multiple Comparisons		
	F =	p =	OBP vs. OCP p =	OBP vs. OHP p =	OCP vs. OHP p =
Neuroimaging Variables					
Activity to Reward Trials					
Left OFC	2.375	0.098	0.804	0.336	0.090
Right OFC	1.990	0.142	0.961	0.286	0.158
Functional Connectivity to Reward Trials					
VS – Left cACC	2.382	0.097	0.091	0.258	0.822
VS – Right rACC	2.850	0.062	0.061	0.177	0.841
Lateral Orbitofrontal Cortex – Left Amygdala	3.333	**0.040***	1.000	0.079	0.069
Lateral Orbitofrontal Cortex – Left rACC	0.461	0.632	0.976	0.640	0.758
Lateral Orbitofrontal Cortex – Left VS	2.048	0.134	0.952	0.284	0.147
Pars Opercularis – Right OFC	1.080	0.343	0.525	0.967	0.346
Pars Orbitalis – Left OFC	7.181	**0.001***	**0.001***	0.197	0.080
Pars Orbitalis – Right cACC	1.799	0.171	0.557	0.145	0.660
Pars Orbitalis – Right OFC	8.457	**< 0.001***	**< 0.001***	0.165	**0.046***
Pars Triangularis – Right VS	1.975	0.144	0.577	0.121	0.581
Functional Connectivity to Loss Trials					
VS – Left cACC	4.173	**0.018***	**0.025***	**0.049***	0.942
VS – Right rACC	2.558	0.082	0.138	0.107	0.996
Lateral Orbitofrontal Cortex – Left Amygdala	1.061	0.350	0.974	0.382	0.489
Lateral Orbitofrontal Cortex – Left rACC	2.213	0.114	0.295	0.105	0.852
Pars Orbitalis – Left rACC	1.807	0.169	0.577	0.144	0.636
Pars Orbitalis – Right Amygdala	1.191	0.308	0.520	0.292	0.914
Pars Orbitalis – Right cACC	1.788	0.172	0.910	0.182	0.345
Pars Triangularis – Left rACC	1.918	0.152	0.321	0.146	0.903
Pars Triangularis – Right Amygdala	1.161	0.317	0.714	0.284	0.735
Pars Triangularis – Right OFC	3.233	**0.043***	**0.033***	0.401	0.380
Demographic Variables					
IQ	0.701	0.498	0.830	0.466	0.816
Socioeconomic Status	6.771	**0.002***	**0.032***	**0.001***	0.560
Highest Parental Education: Standard College / University Graduate	0.409	0.666	0.789	0.655	0.975

There was a significant effect ($p < 0.05$) of group on bilateral VS-left cACC FC to loss ($F(2,104) = 4.173$, $p = 0.018$), bilateral pars orbitalis-left ($F(2,104) = 7.181$, $p = 0.001$) and -right ($F(2,104) = 8.457$, $p < 0.001$) OFC FC to reward, bilateral pars triangularis-right OFC FC to loss ($F(2,104) = 3.233$, $p = 0.043$), bilateral lateral orbitofrontal cortex-left amygdala FC to reward ($F(2,104) = 3.333$, $p = 0.040$), and SES ($F(2,104) = 6.771$, $p = 0.002$). Post-hoc comparisons using the Tukey HSD test indicated that: OBP had significantly lower bilateral VS-left cACC FC

to loss versus OCP (p = 0.025) and OHP (p = 0.049) (Figure 16A); OBP had greater bilateral pars orbitalis-left (p = 0.001) and -right (p < 0.001) OFC FC to reward versus OCP; OCP had lower bilateral pars orbitalis-right OFC FC to reward versus OHP (p = 0.046); and OBP had greater bilateral pars triangularis-right OFC FC to loss versus OCP (p = 0.033) (Figure 16B).

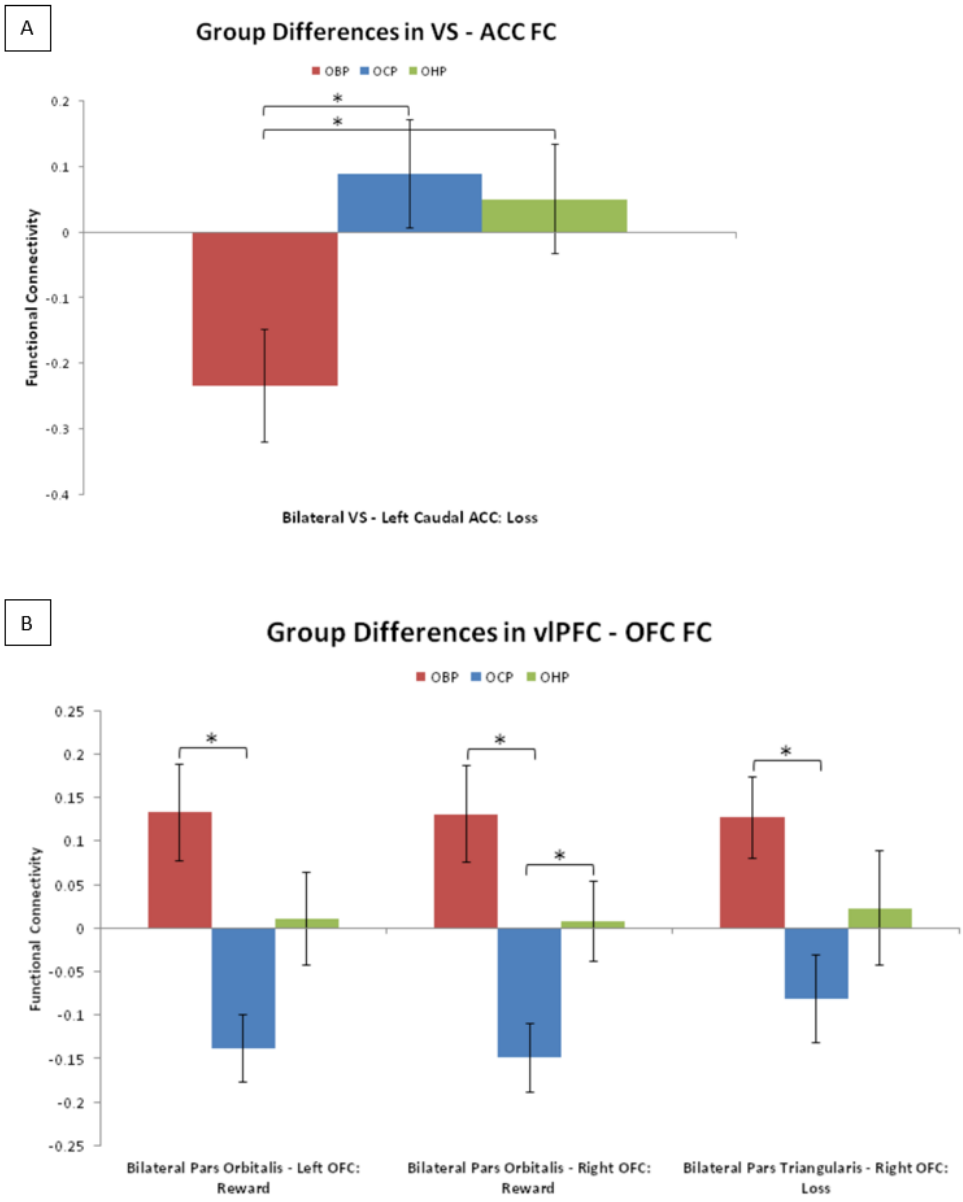

Figure 16: Exp 2. Between-Group Differences in Neuroimaging Measures

Additionally, OBP had lower SES versus OCP ($p = 0.032$) and OHP ($p = 0.001$) (Figure 17).

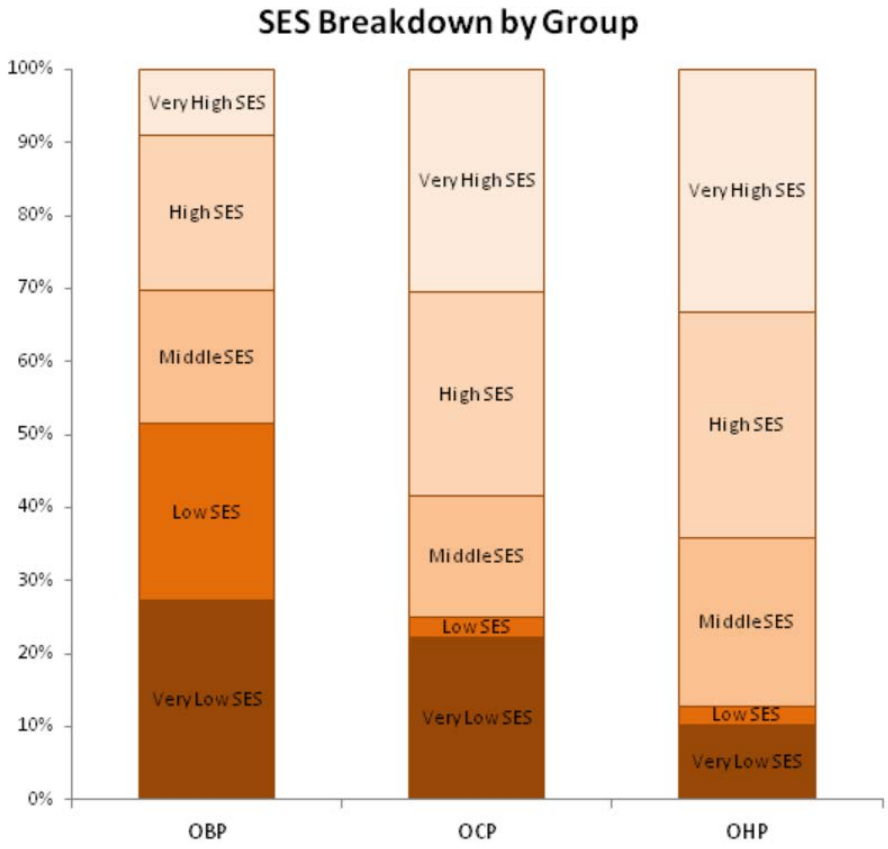

Figure 17: Exp 2. Between-Group Differences in Demographic Measures

4.3.1.3 Exploratory Effects of Left- versus Right-Sided Regions

Once the above FC findings were identified that significantly distinguished OBP from OCP and/or OHP, we additionally explored the nature of the laterality of the seed regions. Two one-way between subjects ANOVAS (Bonferroni-corrected for 2 tests) and post-hoc t-tests (Tukey HSD-corrected) examined between-group differences in bilateral VS-left cACC FC to loss,

bilateral pars orbitalis-left and -right OFC FC to reward, and bilateral pars triangularis-right OFC FC to loss using left-sided and right-sided seed regions, separately (Figure 18). Regarding right-sided seed regions, there was a main effect of group on *right* VS-left cACC FC to loss ($F(2,104) = 4.857$, $p = 0.010$) and *right* pars orbitalis-left ($F(2,104) = 6.140$, $p = 0.003$) and -right ($F(2,104) = 7.552$, $p = 0.001$) OFC FC to reward. OBP had lower right VS-left cACC FC to loss versus OCP ($p = 0.028$) and OHP ($p = 0.015$) but greater right pars orbitalis-left ($p = 0.003$ vs. OCP, $p = 0.036$ vs. OHP) and -right ($p = 0.001$ vs. OCP, $p = 0.038$ vs. OHP) OFC FC to reward versus OCP and OHP, respectively. Regarding left-sided seed regions, there was also a main effect of group on *left* pars orbitalis-left ($F(2,104) = 6.427$, $p = 0.002$) and -right ($F(2,104) = 6.283$, $p = 0.003$) OFC FC to reward. OBP showed greater FC versus OCP, but not versus OHP, for the left ($p = 0.002$) and right ($p = 0.002$) OFC, respectively. OCP additionally had significantly lower *left* pars orbitalis-left OFC FC to reward versus OHP ($p = 0.045$).

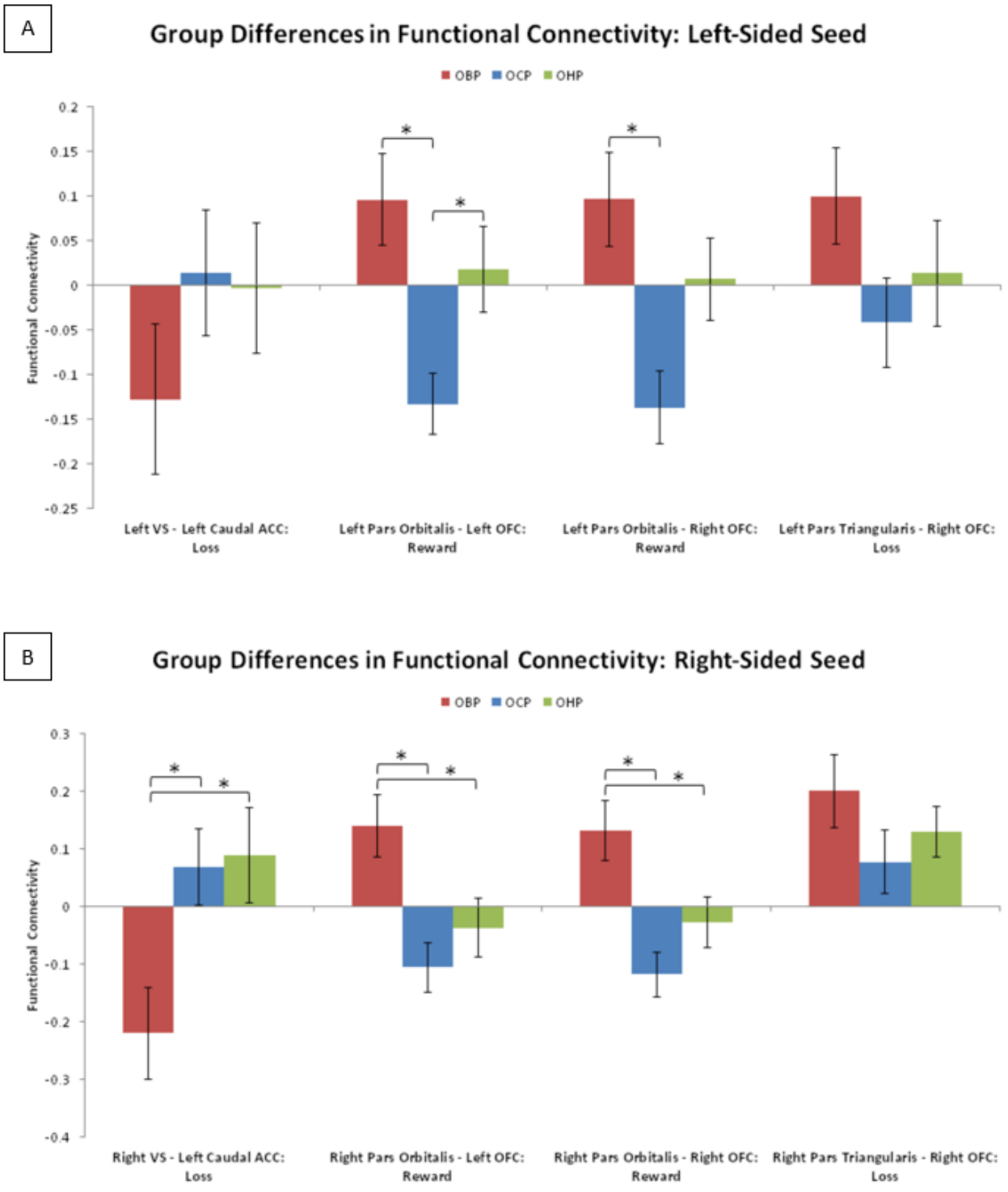

Figure 18: Exp 2. Between-Group Differences in Left- versus Right-Sided Neuroimaging Measures

In summary, OBP significantly differed from both OCP and OHP for three measures: right VS-left cACC FC to loss, right pars orbitalis-left OFC FC to reward, and right pars orbitalis-right OFC FC to reward. These were thus the focus of all future analyses.

4.3.2 Hypothesis Testing 2: Effects of Non-BD Disorders

Two one-way between subjects ANOVAS (Bonferroni-corrected for 2 tests) and post-hoc t-tests (Tukey HSD-corrected) examined between-group differences in the above three neuroimaging measures that significantly distinguished OBP from both OCP and OHP in youth with versus without non-BD disorders. OBP significantly differed from OCP and OHP only when examining youth *without* non-BD disorders for the right VS-left cACC ($F(2,76) = 4.105$, $p = 0.020$) and right pars orbitalis-left ($F(2,76) = 4.218$, $p = 0.018$) and -right ($F(2,76) = 5.051$, $p = 0.009$) OFC FC findings. In these youth, OBP had lower right VS-left cACC ($p = 0.034$ vs. OCP, $p = 0.033$ vs. OHP) and greater right pars orbitalis-left ($p = 0.031$ vs. OCP, $p = 0.030$ vs. OHP) and -right ($p = 0.008$ vs. OCP, $p = 0.037$ vs. OHP) OFC FC versus OCP and OHP, respectively. No significant between-group differences were found in youth *with* non-BD disorders.

No differences in the above findings were found when removing youth taking psychotropic medications. No significant correlations were found between age and any significant neuroimaging measures.

4.3.3 Exploratory Analyses: Between-Group Differences in Baseline Symptom Measures

A one-way between subjects ANOVA compared the effects of group on 8 baseline symptom measures (Figure 19). There was a significant effect ($p < 0.006$, Bonferroni corrected for 8 tests)

of group on SCARED-P ($F(2,103) = 8.542$, $p < 0.001$), CALS-P ($F(2,103) = 10.707$, $p < 0.001$), MFQ-P ($F(2,103) = 5.690$, $p = 0.005$), KDRS ($F(2,103) = 5.558$, $p = 0.005$), and KMRS ($F(2,103) = 5.530$, $p = 0.005$) scores. No significant effects of group were found for child-reported measures. Post-hoc comparisons using the Tukey HSD test indicated that: compared with OCP, OBP had significantly greater CALS-P scores ($p = 0.024$); compared with OHP, OBP had significantly greater SCARED-P ($p = 0.002$), CALS-P ($p < 0.001$), MFQ-P ($p = 0.003$), KDRS ($p = 0.004$), and KMRS ($p = 0.004$) scores; and, compared with OHP, OCP had significantly greater SCARED-P ($p = 0.002$) scores.

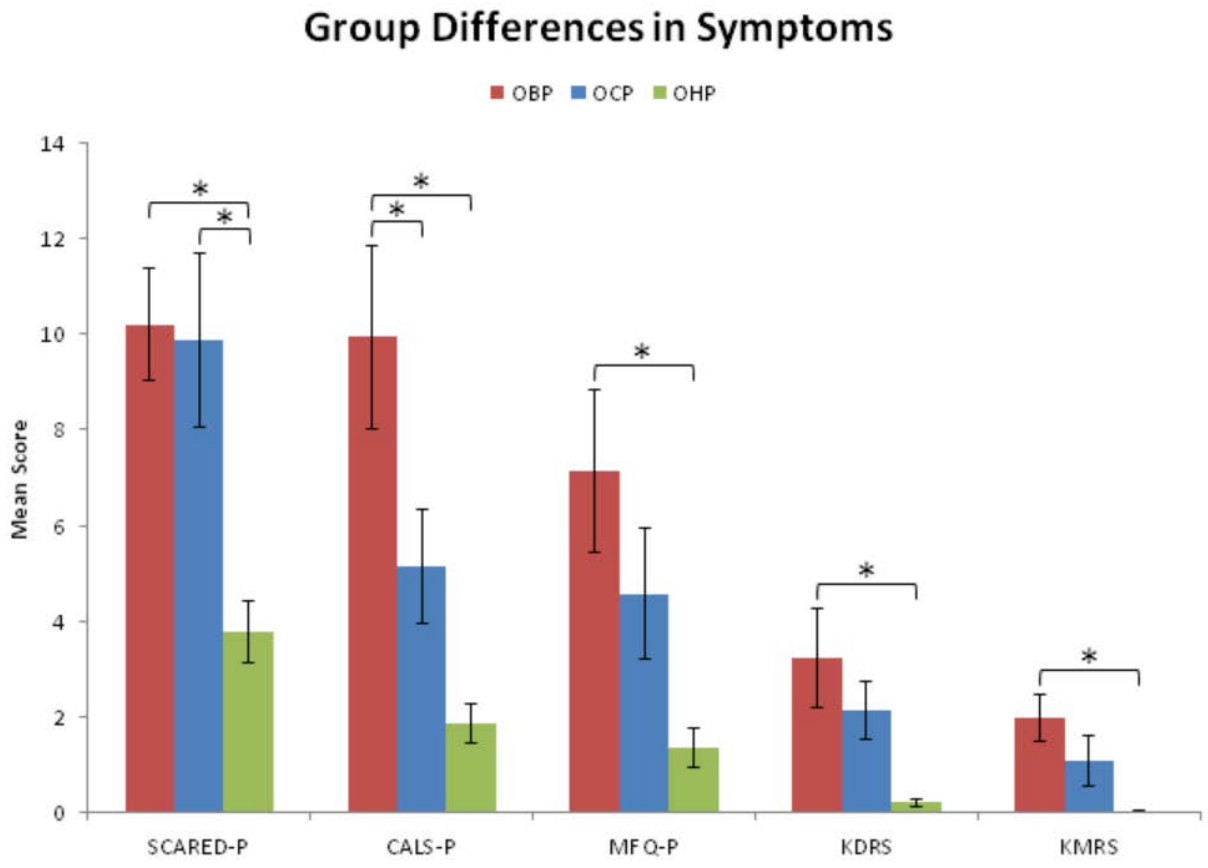

Figure 19: Exp 2. Between-Group Differences in Symptom Measures

No significant correlations were found when examining relationships between the above neuroimaging (right VS-left cACC, right pars orbitalis-left and -right OFC FC) and symptom (SCARED-P, CALS-P, MQ-P, KDRS, KMRS) measures that significantly differed among all groups at baseline (Table 23).

Table 23: Exp 2. Correlations between Neuroimaging and Symptom Measures at Baseline

	Right VS – Left cACC FC to Loss		Right Pars Orbitalis – Left OFC FC to Reward		Right Pars Orbitalis – Right OFC FC to Reward	
	r =	p =	r =	p =	r =	p =
SCARED-P	-.193	**.049*** (.735)	.033	.740	-.033	.739
CALS-P	-.142	.148	.029	.769	-.091	.352
MFQ-P	-.031	.755	.006	.955	-.163	.096
KDRS	-.08	.420	-.053	.592	-.104	.289
KMRS	-.061	.535	.126	.198	.101	.302

Similarly, no significant correlations were found when examining relationships between the above neuroimaging and symptom measures at follow-up (Table 24).

Table 24: Exp 2. Correlations between Neuroimaging and Symptom Measures at Follow-Up

	Right VS – Left cACC FC to Loss		Right Pars Orbitalis – Left OFC FC to Reward		Right Pars Orbitalis – Right OFC FC to Reward	
	r =	p =	r =	p =	r =	p =
SCARED-P	.216	.242	.027	.884	.048	.797
CALS-P	.144	.438	.028	.881	.046	.804
MFQ-P	.005	.980	-.268	.138	-.139	.447
KDRS	.142	.383	.097	.552	.103	.526
KMRS	.379	**.016*** (.240)	-.065	.690	-.070	.669

Furthermore, no significant correlations were found when examining relationships between changes in the above neuroimaging and symptom measures, over time (Table 25).

Table 25: Exp 2. Correlations between Changes in Neuroimaging and Symptom Measures Over Time

	Right VS – Left cACC FC to Loss		Right Pars Orbitalis – Left OFC FC to Reward		Right Pars Orbitalis – Right OFC FC to Reward	
	r =	p =	r =	p =	r =	p =
SCARED-P	-.045	.812	.046	.809	.149	.431
CALS-P	.048	.801	-.196	.298	-.041	.831
MFQ-P	-.102	.584	-.360	**.047*** (.705)	-.269	.143
KDRS	.088	.588	-.029	.858	.013	.936
KMRS	.316	**.047*** (.705)	-.199	.219	-.152	.349

Neuroimaging and symptom measures also did not significantly differ between first and second scans (Table 26).

Table 26: Exp 2. Differences in Neuroimaging and Symptom Measures between First and Second Scans

	t-test for Equality of Means						
	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
						Lower	Upper
Neuroimaging Measures							
Right VS – Left cACC FC: Loss	.957	81	.341	.107	.111	-.115	.328
Right Pars Orbitalis – Left OFC FC: Reward	-.794	81	.430	-.057	.072	-.200	.086
Right Pars Orbitalis – Right OFC FC: Reward	-1.449	81	.151	-.090	.062	-.213	.033
Symptom Measures							
SCARED-P	2.010	62.32	**.049*** (.392)	2.912	1.449	.016	5.809
CALS-P	.411	70	.683	.538	1.309	-2.074	3.149
MFQ-P	.487	71	.628	.702	1.443	-2.174	3.579
KDRS	-1.076	81	.285	-1.391	1.294	-3.965	1.182
KMRS	-1.240	81	.219	-.679	.548	-1.769	.411

4.4 DISCUSSION

4.4.1 Summary of Findings

The goal of this study was to identify measures of activity and FC in reward processing neural circuitry that distinguished OBP from OCP and OHP and determine whether these measures represented trait- or state-level neural markers in OBP. Our primary findings indicated that OBP had lower FC between the right VS-left cACC to loss but greater FC between the right pars orbitalis and both the left and right OFC to reward. These findings were not affected by non-BD psychopathology, psychotropic medication use, or symptomatology. Additionally, these neural measures remained stable at follow-up.

The VS and ACC have established connections that are important to reward neural circuitries (Jung, Schulte et al. 2013). Projections from the VS go to the ventral pallidum and substantia nigra and are then transferred to the ACC and OFC via the mediodorsal nucleus of the thalamus (Haber 2011). Coordinated activation of terminals in the striatum from regions such as

the ACC and OFC may, together, enable reward-based incentives that drive impacts on long-term strategic planning (Haber 2011). Several studies have examined the relationship between the VS and ACC during decision-making and reward tasks. In one study, the left cACC was shown to have significant FC with both the left *and* right VS during resting state and decision-making tasks (Jung, Schulte et al. 2013). This study found that greater left cACC-VS FC was associated with greater use of coping strategies and lower non-planning impulsiveness (Jung, Schulte et al. 2013). Another study found that more severe gambling problems were significantly correlated with lower FC between the right VS and left ACC (van Holst, Chase et al. 2014). Our findings of lower right VS-left cACC FC to loss in OBP parallel these findings and further suggest that lower FC between the VS and cACC may be related to impaired regulation of response to loss or reward receipt during reward and/or gambling tasks in youth at risk for BD. This may further reflect difficulty learning from punishment or failure, which may manifest as symptoms of impulsivity or impulsive sensation seeking. Specifically, individuals may continue to engage in risky situations with the potential for reward receipt despite evidence that these attempts may be futile or detrimental. The fact that this finding distinguished OBP from both OCP and OHP additionally suggests that abnormally reduced right VS-left cACC FC to loss may be a marker of risk for future development of BD in youth.

While it is well established that the vlPFC and OFC are involved in reward processing individually, less is known about the relationship between these two important regions in reward circuitry. In the present study, the vlPFC was defined as the lateral orbitofrontal cortex (Hooker and Knight 2006), pars orbitalis (BA47), pars opercularis (BA44), and pars triangularis (BA45) (Badre and Wagner 2007), and the OFC was defined as the medial orbitofrontal cortex (BA11). Anatomically, BA47 is dorsolaterally adjacent to, and interconnected with, BA11 (Kelly, Uddin

et al. 2010, de Schotten, Dell'Acqua et al. 2012, Yeterian, Pandya et al. 2012, Snow 2016), and both regions coactivate during reward tasks (Zald, McHugo et al. 2012). Both regions are integrally involved in reward processing circuitry, with BA47 primarily having roles in reward-related decision-making (Dixon and Christoff 2014), and BA11 having roles in encoding reward values and comparing values of different options (Rushworth, Noonan et al. 2011). Many studies in youth and adults with, and at risk for, BD found that these individuals show greater activity, bilaterally, in both regions during reward processing compared with control groups (Bermpohl, Kahnt et al. 2010, Linke, King et al. 2012, Nusslock, Almeida et al. 2012, Chase, Nusslock et al. 2013, Singh, Kelley et al. 2014). It is thus unsurprising that we identified greater FC between the pars orbitalis (BA47) and OFC (BA11) during reward trials in OBP relative to both OCP and OHP, likely reflecting greater encoding of, and decision-making about, reward value in OBP. While we found that this relationship distinguished OBP from both groups when examining FC only with the *right* pars orbitalis, OBP were also significantly differentiated from OCP when examining FC with the *left* pars orbitalis. The fact that OBP were not significantly distinguished from OHP, as well, might reflect an issue with power. Thus, we may speculate the relationship between the *bilateral* pars orbitalis and *bilateral* OFC might be an additional neural marker of risk for BP in OBP. Future studies with increased sample sizes are necessary to determine this.

Our findings parallel previous findings that highlighted the importance of the VS and vlPFC in distinguishing OBP from OCP and OHP during reward processing (Manelis, Ladouceur et al. 2016). A previous study, which used standard group-level analyses as opposed to analyses in native space, found that OBP had lower bilateral VS-right vlPFC FC to reward and loss trials (Manelis, Ladouceur et al. 2016), similar to our findings of decreased bilateral (and right) VS-left cACC FC to loss. Additionally, these vlPFC findings were primarily right-sided

(Manelis, Ladouceur et al. 2016), as in our study. While this previous study showed that the vlPFC had lower connectivity with the VS (Manelis, Ladouceur et al. 2016), we showed greater vlPFC-OFC to reward receipt, suggesting a greater encoding of reward values and attunement to reward stimuli in OBP. This highlights the vlPFC as a key region with multiple roles in reward processing circuitry that uniquely distinguish OBP. Additionally, main findings remained significant when excluding youth with non-BD psychopathology and psychotropic medications, as in previous studies (Manelis, Ladouceur et al. 2016). Furthermore, no relationships were found between main neural findings and symptomatology, either at baseline or at follow-up, and all of these measures remained stable over follow-up. Altogether, these findings suggest that our main findings of lower right VS-left cACC FC to loss and greater right pars orbitalis-OFC FC to reward may be *trait*-level neural markers of future BD risk in OBP. This is an important step toward understanding the mechanisms underlying the neural basis of familial risk for BD.

Additional findings from our study were that OBP had lower SES compared with OCP and OHP. Several studies have shown that low SES is associated with an increased risk for BD (Weissmann, Bruce et al. 1991, Kessler, Rubinow et al. 1997, Tsuchiya, Agerbo et al. 2004). This further suggests that our sample of OBP may be at greater risk for developing BD in the future. An additional finding from this study was that OBP had greater bilateral pars triangularis-right OFC FC to loss compared with OCP. However, this finding did not remain significant when separating the pars triangularis into left and right regions. It is possible that this region of the vlPFC has less of a role in reward processing circuitry compared with its other functions, such as verbal semantic retrieval (Buckner 1996).

4.4.2 Conclusions

This is the first study to employ both cross-sectional and longitudinal analyses of reward processing neural circuitry in youth at risk for BD versus comparative at-risk and healthy control groups. We show that lower right VS-left cACC FC to loss and greater right pars orbitalis-OFC FC to reward significantly distinguish OBP from both OCP and OHP. These findings are independent of non-BD psychopathology, psychotropic medication use, and symptomatology, and they remain stable at follow-up. This renders these findings likely trait-level neural markers that may reflect either risk for BD in at-risk youth. Our findings comprise an important step toward identifying neural markers of BD risk to aid in enhanced early identification, and guide interventions for, youth at risk for BD.

5.0 WHITE MATTER – EMOTION PROCESSING ACTIVITY RELATIONSHIPS IN YOUTH OFFSPRING OF BIPOLAR PARENTS

This chapter is a modified version of the following manuscript that is currently under revision:

Acuff HE, Versace A, Bertocci MA, Hanford LC, Ladouceur CD, Manelis A, Monk K, Bonar L, McCaffrey A, Goldstein BI, Goldstein TR, Sakolsky D, Axelson D, LAMS Consortium, Birmaher B, Phillips ML. White matter – emotion processing activity relationships in youth offspring of bipolar parents. *Under Revision.*

5.1 INTRODUCTION

Relationships between neural structure and function is an important, yet relatively unexamined, topic in the study of BD. Given that the structural integrity of white matter is key for ensuring the intact functioning of a given neural circuitry, studying relationships between WMT structure and neural activity may provide a more comprehensive understanding of BD risk. More specifically, neuroimaging studies can identify markers of risk for BD by detecting abnormal structure and activity in neural circuitries that are important for processes aberrant in individuals with BD, such as emotion processing (Phillips and Swartz 2014). In addition, studying relationships between these structural and functional abnormalities may provide greater insight

into mechanisms that underlie the pathophysiology of BD risk in comparison to risk for other psychiatric disorders.

Specific structural and functional abnormalities in emotion processing circuitry in adults and youth with and at risk for BD have been discussed previously (Chapters 1.3.1-2). Key structural findings in youth with, and at risk for, BD include lower collinearity in the cingulum (Benedetti, Yeh et al. 2011, Versace, Andreazza et al. 2014), forceps minor of the corpus callosum (Wang, Jackowski et al. 2008, Wang, Kalmar et al. 2008, Chaddock, Barker et al. 2009, Benedetti, Yeh et al. 2011, Haller, Xekardaki et al. 2011, Versace, Andreazza et al. 2014, Sarrazin, d'Albis et al. 2015), superior longitudinal fasciculus (Chaddock, Barker et al. 2009, van der Schot, Vonk et al. 2010, Versace, Almeida et al. 2010, Benedetti, Yeh et al. 2011, Versace, Andreazza et al. 2014), and uncinate fasciculus (Versace, Almeida et al. 2008, Benedetti, Yeh et al. 2011, Linke, King et al. 2013, Versace, Andreazza et al. 2014). Functional findings in youth at risk for BD during emotion processing include greater amygdala activity to all emotional faces (Manelis, Ladouceur et al. 2015), lower ACC activity during facial emotion processing (Tseng, Bones et al. 2015, Chan, Sussmann et al. 2016), lower dlPFC activity during facial emotion processing (Tseng, Bones et al. 2015), lower right amygdala-ACC FC to all emotional faces (Manelis, Ladouceur et al. 2015), and greater right amygdala-left vlPFC FC to happy faces (Manelis, Ladouceur et al. 2015).

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 familial risk for the disorder (Phillips, Ladouceur et al. 2008, Versace, Ladouceur et al. 2010, Olsavsky, Brotman et al. 2012, Ladouceur, Diwadkar et al. 2013, Singh and Chang 2013, Singh, Kelley et al. 2014, Tseng, Bones et al. 2015).

Focusing on youth at risk for BD unaffected by the disorder may allow us to identify markers of BD before illness onset. Additionally, of the studies that examined youth at risk for BD, few compared youth at familial risk for BD to those at risk for other disorders (Manelis, Ladouceur et al. 2015, Manelis, Ladouceur et al. 2016, Soehner, Bertocci et al. 2016). It thus remains difficult to determine the extent to which neural findings represent markers of specific risk for BD.

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 fMRI techniques has become increasingly important in fields of cognitive and clinical neuroscience (Zhu, Zhang et al. 2014). Such studies have examined relationships between WMT structure and either BOLD activity (Conturo, Lori et al. 1999, Werring, Clark et al. 1999, Olesen, Nagy et al. 2003, Toosy, Ciccarelli et al. 2004, Baird, Colvin et al. 2005, Madden, Spaniol et al. 2007, Ystad, Hodneland et al. 2011, O'Donnell, Rigolo et al. 2012) or FC (Koch, Norris et al. 2002, Guye, Parker et al. 2003, van den Heuvel, Mandl et al. 2008, Greicius, Supekar et al. 2009, Supekar, Uddin et al. 2010, Calamante, Masterton et al. 2013). Both types of structure-function relationships have the potential to contribute to our understanding of mechanisms that underlie psychiatric disorders. No studies to date in youth at risk for BD, however, have employed multimodal neuroimaging techniques in attempts to identify markers of specific risk for BD.

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

imaging to study WMT-activity relationships and their relationships with symptoms in youth at risk for BD.

Furthermore, while non-BD disorders may confound neural findings, these disorders are common in youth at risk for BD. 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 neural findings distinguishing OBP from OCP remained even after excluding youth with non-BD disorders (Manelis, Ladouceur et al. 2015, Manelis, Ladouceur et al. 2016). 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 familial 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 (i.e. cingulum, forceps minor, superior longitudinal fasciculus, uncinate fasciculus) fiber collinearity and greater amygdala and/or lower prefrontal (i.e. 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.

In additional analyses, we examined: how these relationships compared to 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.

5.2 MATERIALS AND METHODS

5.2.1 Participants

Thirty-two OBP (mean (SD) age = 13.81 (2.45), 15 female), thirty OCP (mean (SD) age = 13.98 (2.30), 12 female), and twenty-four OHP (mean (SD) age = 13.80 (1.72), 10 female), were examined in this analysis (Table 27). Of the original thirty-eight OBP, thirty-seven OCP, and twenty-seven OHP that were recruited: one OBP and five OCP were excluded due to excessive motion (translation > 4 mm); five OBP, two OCP, and three OHP were excluded due to missing data. Twenty-seven OBP, twenty-six OCP, and twenty-two OHP were also included in a related BIOS paper (Manelis, Ladouceur et al. 2015).

Fourteen OBP had at least one non-BD diagnosis: four had MDD, four had an Anxiety Disorder, seven had ADHD, two had Oppositional Defiant or Conduct Disorder, and two had an Eating Disorder. Fifteen OCP had at least one non-BD diagnosis: four had MDD, six had an Anxiety Disorder, seven had ADHD, three had Oppositional Defiant or Conduct Disorder, and two had Obsessive Compulsive Disorder. Six OBP and six OCP were taking antidepressant, antipsychotic, mood stabilizer, stimulant, and/or non-stimulant medications for non-BD disorders. Symptom assessments included SCARED-P, SCARED-C, CALS-P, CALS-C, MFQ-P, MFQ-C, and KMRS (Chapter 2.1.3).

Table 27: Exp 3. Offspring of Bipolar, Comparison, and Healthy Offspring

	OBP n = 32 M(SD) or Total	OCP n = 30 M(SD) or Total	OHP n = 24 M(SD) or Total	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	χ^2 = 0.324	.851
IQ	99.97(15.80)	102.97(14.22)	104.00(13.60)	F = 0.591	.556
Socioeconomic Status				χ^2 = 7.037	.134
Low or Very Low (8-29)	16	7	7		
Medium (30-39)	6	5	3		
High or Very High (40-66)	10	18	14		
Handedness				χ^2 = 5.987	.200
Right	27	28	21		
Left	2	2	3		
Mixed	3	0	0		
Highest Parental Education				χ^2 = 6.765	.343
High School Graduate or Lower	5	3	6		
Partial College or Specialized Training	13	8	11		
Standard College or University Graduate	8	11	4		
Graduate Professional Training	6	8	3		
Clinical Measures					
Diagnosis	14	15	0	t = -0.486	.629
Major Depressive Disorder	4	4	0	t = -0.096	.924
Anxiety Disorder	4	6	0	t = -0.793	.431
Attention Deficit/Hyperactivity Disorder	7	7	0	t = -0.135	.893
Oppositional Defiant or Conduct Disorder	2	3	0	t = -0.534	.595
Obsessive Compulsive Disorder	0	2	0	t = -1.439	.161
Eating Disorder	2	0	0	t = 1.438	.161
Psychotropic Medication Use	3	0	0	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	**< .001***

5.2.2 Neuroimaging Data Acquisition and Analyses

All images were acquired using a Siemens Magnetom TrimTrio 3T MR system (Chapter 2.2.1). Participants completed the emotional face processing task (DFT) (Chapter 2.2.2.1). Neuroimaging data analyses were performed as previously described (Chapter 2.3). ROIs included the amygdala, vlPFC, cACC, and rACC (Table 2). In this analysis, the pars triangularis was excluded from the vlPFC because it cytoarchitectonically belongs to Broca's area and is more implicated in various aspects of linguistic functioning (Saito, Muragaki et al. 2016), as opposed to emotion processing. Task stimulus contrasts of interest included, separately: positive emotional faces (i.e. happy) versus shapes and negative emotional faces (i.e. angry, fearful, and sad, averaged together) versus shapes.

FreeSurfer was used to define the end regions for global probabilistic tractography (Fischl 2012). ExploreDTI was used to ensure image quality and to correct for motion artifacts and current distortions (Leemans and Jones 2009, Klein, Staring et al. 2010). A B-spline cubic interpolation reduced the EPI distortions and registered the mean b0 image to the structural, native space (Wu, Chang et al. 2008). TRActs Constrained by UnderLying Anatomy (TRACULA), based on a Bayesian framework, was used to determine the probabilistic distributions of 18 white matter tracts and extract FA, RD, AD, length, and volume for each tract (Yendiki, Panneck et al. 2011). Advantages of probabilistic tractography over deterministic methods include the ability to explicitly represent uncertainty in the data (Behrens, Woolrich et al. 2003, Behrens, Berg et al. 2007, Berman, Chung et al. 2008).

5.2.3 Statistical Analyses

Two elastic net regression analyses, including OBP and OCP, only, were used for variable selection and reduction. The first model contained the following 6 outcome variables: activity in the left and right amygdala, left and right vlPFC, bilateral cACC, and bilateral rACC to positive (i.e. happy) emotional faces. The second model contained the following 6 outcome variables: activity in the left and right amygdala, left and right vlPFC, bilateral cACC, and bilateral rACC to negative (i.e. angry, fearful, and sad, averaged together) emotional faces. Both models contained the same 163 predictor variables. Nineteen of these predictor variables were demographic and clinical measures: age, gender, IQ, SES, handedness, and highest parental education, and diagnoses (Table 28).

Table 28: Exp 3. Elastic Net Regression Predictor Variables: Demographic and Clinical

19 DEMOGRAPHIC AND CLINICAL VARIABLES	
Variable	**Possible Options for Dummy-Coded Variables**
Group	
Age	
Sex	
IQ	
SES	Very Low Low Medium High Very High
Handedness	Right Left Mixed
Highest Parental Education	High School Graduate or Lower Partial College or Specialized Training Standard College or University Graduate Graduate Professional Training
Diagnoses	Mood Disorder Anxiety Disorder Attention Deficit/Hyperactivity Disorder Oppositional Defiant Disorder Obsessive Compulsive Disorder Eating Disorder

One hundred forty-four of these predictor variables were main effects of WMT measures (RD, AD, length, and volume of the forceps major, forceps minor, left and right anterior thalamic radiation, left and right cingulum-angular bundle, left and right cingulum-cingulate gyrus, left and right corticospinal tract, left and right inferior longitudinal fasciculus, left and right superior longitudinal fasciculus-parietal, left and right superior longitudinal fasciculus-temporal, and left and right uncinate fasciculus, separately) and GROUP(OBP,OCP)xWMT measure interactions to examine between-group differences in WMT-activity relationships (Table 29).

Table 29: Exp 3. Elastic Net Regression Predictor Variables: Diffusion Tensor Imaging Measures

144 NEUROIMAGING VARIABLES: WMT Measures		
DTI Measure	**18 WMTs for Each DTI Measure**	
Radial Diffusivity	Forceps Major	Forceps Minor
Axial Diffusivity	Left Anterior Thalamic Radiation	Right Anterior Thalamic Radiation
Length	Left Cingulum – Angular Bundle	Right Cingulum – Angular Bundle
Volume	Left Cingulum – Cingulate Gyrus	Right Cingulum – Cingulate Gyrus
Radial Diffusivity Group Interaction	Left Corticospinal Tract	Right Corticospinal Tract
Axial Diffusivity Group Interaction	Left Inferior Longitudinal Fasciculus	Right Inferior Longitudinal Fasciculus
Length Group Interaction	Left Superior Longitudinal Fasciculus – Parietal	Right Superior Longitudinal Fasciculus – Parietal
Volume Group Interaction	Left Superior Longitudinal Fasciculus – Temporal	Right Superior Longitudinal Fasciculus – Temporal
	Left Uncinate Fasciculus	Right Uncinate Fasciculus

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.

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 TRACULA (Yendiki, Panneck et al. 2011). While FA is the most widely used invariant measure of anisotropy used in diffusion tensor imaging, it is calculated from a combination of AD, RD, and mean diffusivity measures (Alexander, Lee et al. 2007). This 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.

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 the following equation (Paternoster, Brame et al. 1998):

$$Z = \frac{Slope_{OBP} - Slope_{OCP}}{\sqrt{SE_{OBP}^2 + SE_{OCP}^2}}$$

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, de Una-Alvarez 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-Rodriguez, de Una-Alvarez 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-Rodriguez, de Una-Alvarez et al. 2009). Thus, it is an important tool for multitest adjustment when working with high-dimensional biological data (Carvajal-Rodriguez, de Una-Alvarez et al. 2009), rendering it well-suited for the large number of multiple comparison adjustments performed in this study.

5.2.4 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 measures moderated WMT-activity relationships by determining whether there were significant interactions between symptom severity and WMT measures on neural activity.

5.3 RESULTS

5.3.1 Analyses Testing Hypotheses

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 in the amygdala, vlPFC, and ACC when processing negative emotions. Thus, we will hereafter focus on findings pertaining to the processing of positive (i.e. happy) emotional faces.

Of the initial 163 predictors, 14 predictors, together, optimized model fit using the minimum λ (λ=1.436) identified by cross-validation when examining responses to happy faces in all ROIs (Figure 20). Plots A-F represent variable fit for activity in response to happy faces in the left amygdala (Figure 20A), right amygdala (Figure 20B), left vlPFC (Figure 20C), right vlPFC (Figure 20D), bilateral cACC (Figure 20E), and bilateral rACC (Figure 20F). Plot G represents the non-zero variable fit after cross validation (Figure 20G).

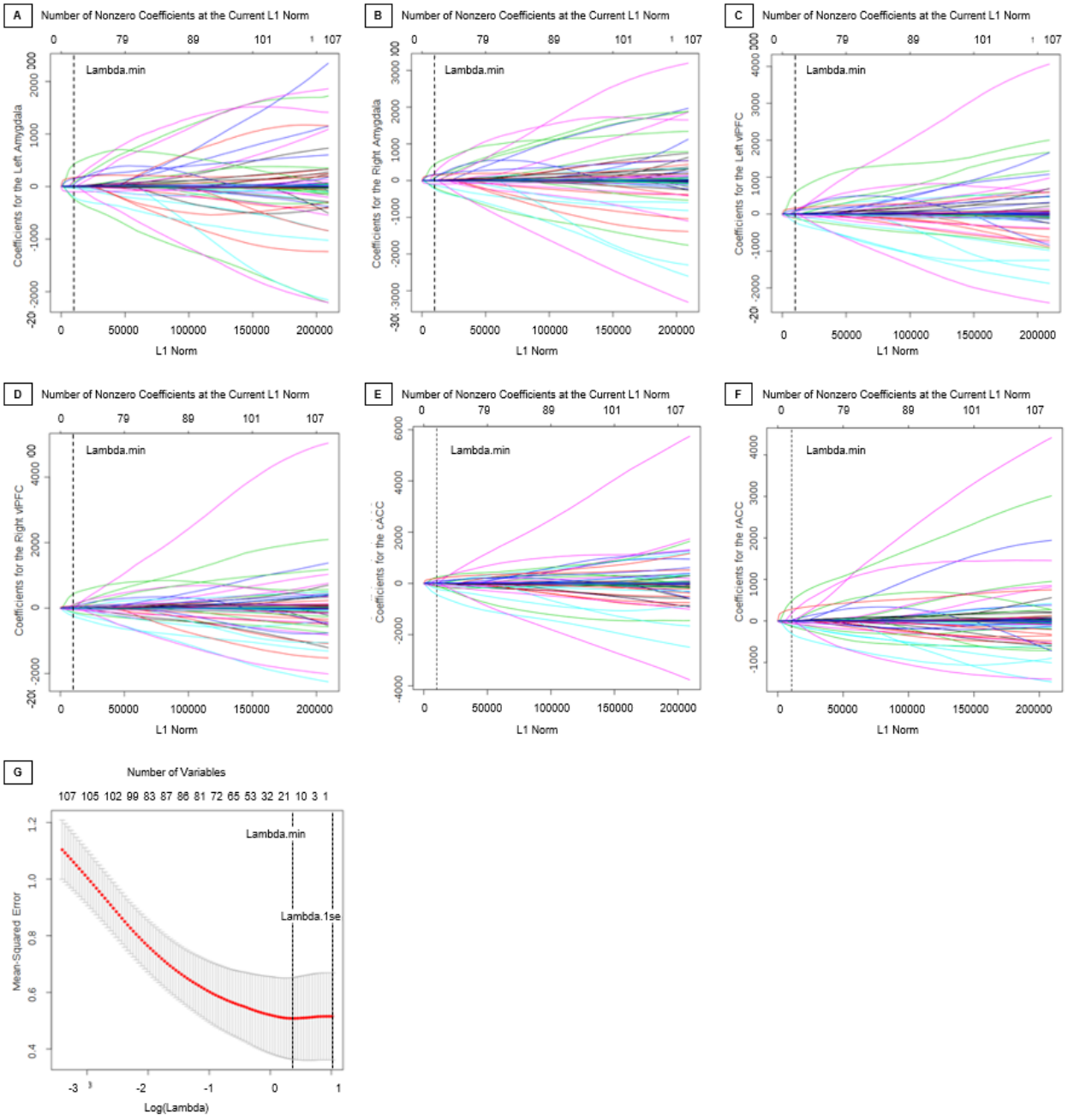

Figure 20: Exp 3. Elastic Net Plots

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. (Table 30)

Table 30: Exp 3. Elastic Net Coefficients and Explained Variance

	Elastic Net Derived Coefficient						Exponentiated Coefficient						Percent Variance Explained
	Left Amygdala	Right Amygdala	Left vlPFC	Right vlPFC	cACC	rACC	Left Amygdala	Right Amygdala	Left vlPFC	Right vlPFC	cACC	rACC	
Group Interaction Variables													
Forceps Minor Radial Diffusivity	-0.42	-0.35	-0.27	-0.18	-0.31	-0.07	0.66	0.71	0.77	0.83	0.73	0.93	.013
Right Cingulum-Cingulate Gyrus Volume	-2.14	-1.53	-1.35	-0.49	-1.07	-0.22	0.12	0.22	0.26	0.61	0.34	0.80	.064
Right Inferior Longitudinal Fasciculus Length	-0.02	-0.01	-0.01	-0.01	-0.02	-0.00	0.98	0.98	0.99	0.99	0.99	1.00	.003
Right Cingulum-Cingulate Gyrus Length	-0.01	-0.01	-0.01	-0.01	-0.01	-0.00	0.99	0.99	0.99	0.99	0.99	1.00	.030
Left Cingulum-Angular Bundle Volume	-67.52	-61.37	-51.84	-29.99	-50.52	-33.33	4.73×10^{-30}	2.22×10^{-27}	3.05×10^{-23}	9.44×10^{-14}	1.15×10^{-22}	3.35×10^{-15}	.042
Forceps Major Volume	-2.37	-2.22	-1.41	-1.02	-1.82	-0.22	0.09	0.11	0.24	0.36	0.16	0.80	.038
Left Superior Longitudinal Fasciculus-Parietal Axial Diffusivity	-1.37	-1.16	-0.87	-0.64	-1.06	-0.24	0.26	0.31	0.42	0.53	0.35	0.78	.011
Forceps Major Radial Diffusivity	-0.10	-0.09	-0.06	-0.04	-0.07	-0.01	0.90	0.92	0.94	0.96	0.93	0.99	.051
Other Variables													
Left Cingulum-Cingulate Gyrus Volume	100.15	87.77	89.70	39.22	103.26	141.06	3.11×10^{43}	1.32×10^{38}	9.07×10^{38}	1.08×10^{17}	7.01×10^{44}	1.83×10^{61}	.063
Left Superior Longitudinal Fasciculus-Temporal Volume	28.70	31.28	20.63	8.71	17.44	2.64	2.71×10^{12}	3.85×10^{13}	9.08×10^{8}	6.08×10^{3}	3.77×10^{7}	1.40×10^{1}	.043
Left Superior Longitudinal Fasciculus-Temporal Length	10.70	7.92	7.31	5.79	10.44	10.53	4.45×10^{4}	2.75×10^{3}	1.49×10^{3}	3.27×10^{2}	3.41×10^{4}	3.76×10^{4}	.231
Medium SES	-0.00	-0.01	-0.01	-0.01	-0.01	-0.01	1.00	0.99	0.99	0.99	0.99	0.99	.090
Right Handedness	-0.01	-0.01	-0.01	-0.01	-0.01	-0.02	0.99	0.99	0.99	0.99	0.99	0.98	.009
Left Handedness	0.03	-0.02	0.02	0.03	0.03	0.01	1.03	1.02	1.02	1.03	1.03	1.01	.046

A pseudo r-squared, calculated containing the 14 non-zero predictors from the model versus an intercept only model, indicated that 16.5% of the variance in activity to happy faces in all ROIs was explained by these predictors. Eight of these predictors were GROUPxWMT

interaction variables (Figure 21). This heat map represents color-coded exponentiated coefficients for GROUPxWMT interaction variables in the elastic net model. Each row represents a variable with a 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 were associated with activity, are depicted with increased coefficients ranging from white to green, representing the least and greatest coefficient observed of these variables in this model, respectively.

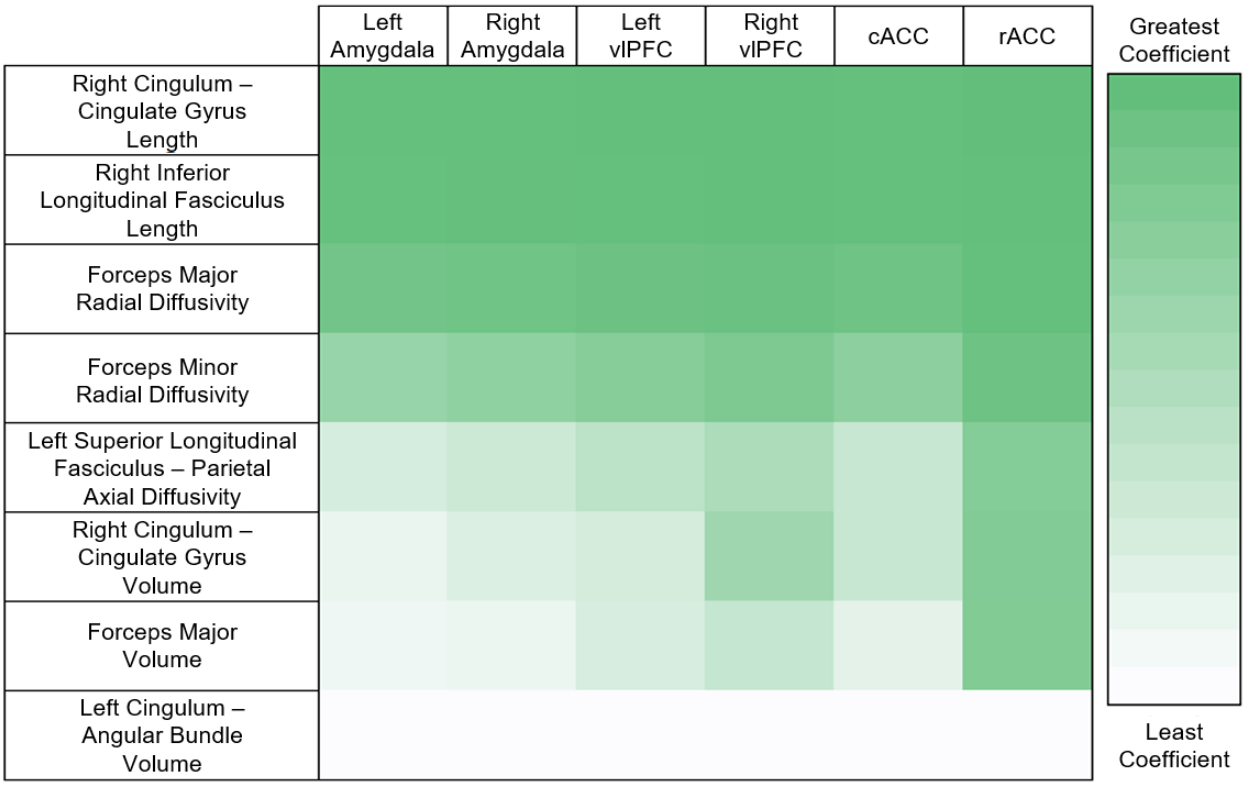

Figure 21: Exp 3. Heat Map of Select Exponentiated Coefficients

Of these interactions, the slopes of 2 WMT-activity relationships significantly differed between OBP and OCP after correcting for multiple comparisons (Table 31).

Table 31: Exp 3. Slope Comparisons between Offspring of Bipolar and Comparison Parents

Predictor Variable	Outcome Variable	Z	p =	Predictor Variable	Outcome Variable	Z	p =
Right Cingulum-Cingulate Gyrus Length	Right Amygdala	-2.17	.030 (.451)	Left Superior Longitudinal Fasciculus-Parietal AD	Left Amygdala	-1.62	.105
	Right vlPFC	-1.38	.168		Left vlPFC	-1.59	.112
	cACC	-2.26	**.024 (.054)**		cACC	-2.07	.038 (1.00)
	rACC	-0.72	.472		rACC	-2.20	.028 (.173)
Right Inferior Longitudinal Fasciculus Length	Right Amygdala	-0.95	.342	Right Cingulum-Cingulate Gyrus Volume	Right Amygdala	-0.27	.787
	Right vlPFC	-0.71	.478		Right vlPFC	0.65	.516
	cACC	-1.28	.201		cACC	-0.30	.764
	rACC	-1.01	.312		rACC	0.08	.936
Forceps Major RD	Left Amygdala	-1.68	.093	Forceps Major Volume	Left Amygdala	-0.55	.582
	Right Amygdala	-1.80	.072		Right Amygdala	-1.08	.280
	Left vlPFC	-0.29	.772		Left vlPFC	0.41	.682
	Right vlPFC	-0.86	.390		Right vlPFC	-0.47	.638
	cACC	-0.45	.653		cACC	-0.73	.465
	rACC	-0.17	.865		rACC	0.00	1.00
Forceps Minor RD	Left Amygdala	-2.07	.038 (.941)	Left Cingulum-Angular Bundle Volume	Left Amygdala	0.91	.363
	Right Amygdala	-1.89	.059		Left vlPFC	0.90	.368
	Left vlPFC	-1.56	.119		cACC	0.49	.624
	Right vlPFC	-1.37	.171		rACC	1.45	.147
	cACC	-1.80	.072				
	rACC	-2.47	**.014 (.014)**				

These significant relationships were between right cingulum-cingulate gyrus length and cACC activity (p = 0.024 (0.054, corrected)) and between forceps minor RD and rACC activity (p = 0.014 (0.014, corrected)) (Figure 22). 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.

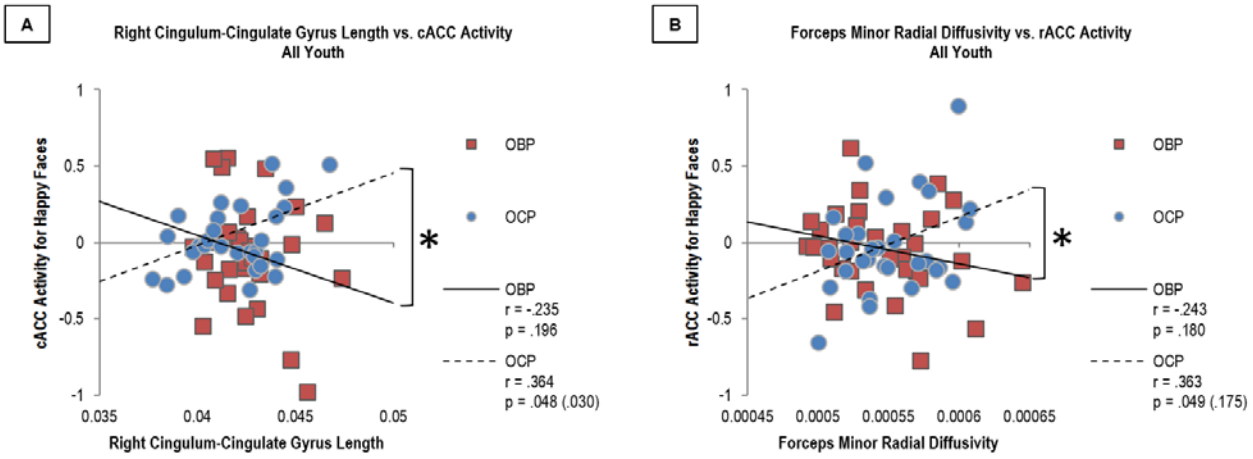

Figure 22: Exp 3. Comparison of White Matter Tract-Activity Relationships in Offspring of Bipolar and Comparison Parents

These WMT-activity relationships for right cingulum-cingulate gyrus length-cACC activity and forceps minor RD-rACC activity remained significantly different between OBP and OCP only in youth without non-BD disorders ($p = 0.023$ (0.002, corrected) and $p = 0.017$ (< 0.001, corrected), respectively; Figures 23A-B). These relationships did not remain significantly different between OBP and OCP in youth with non-BD disorders ($p = 0.276$ and $p = 0.204$, respectively; Figures 23C-D).

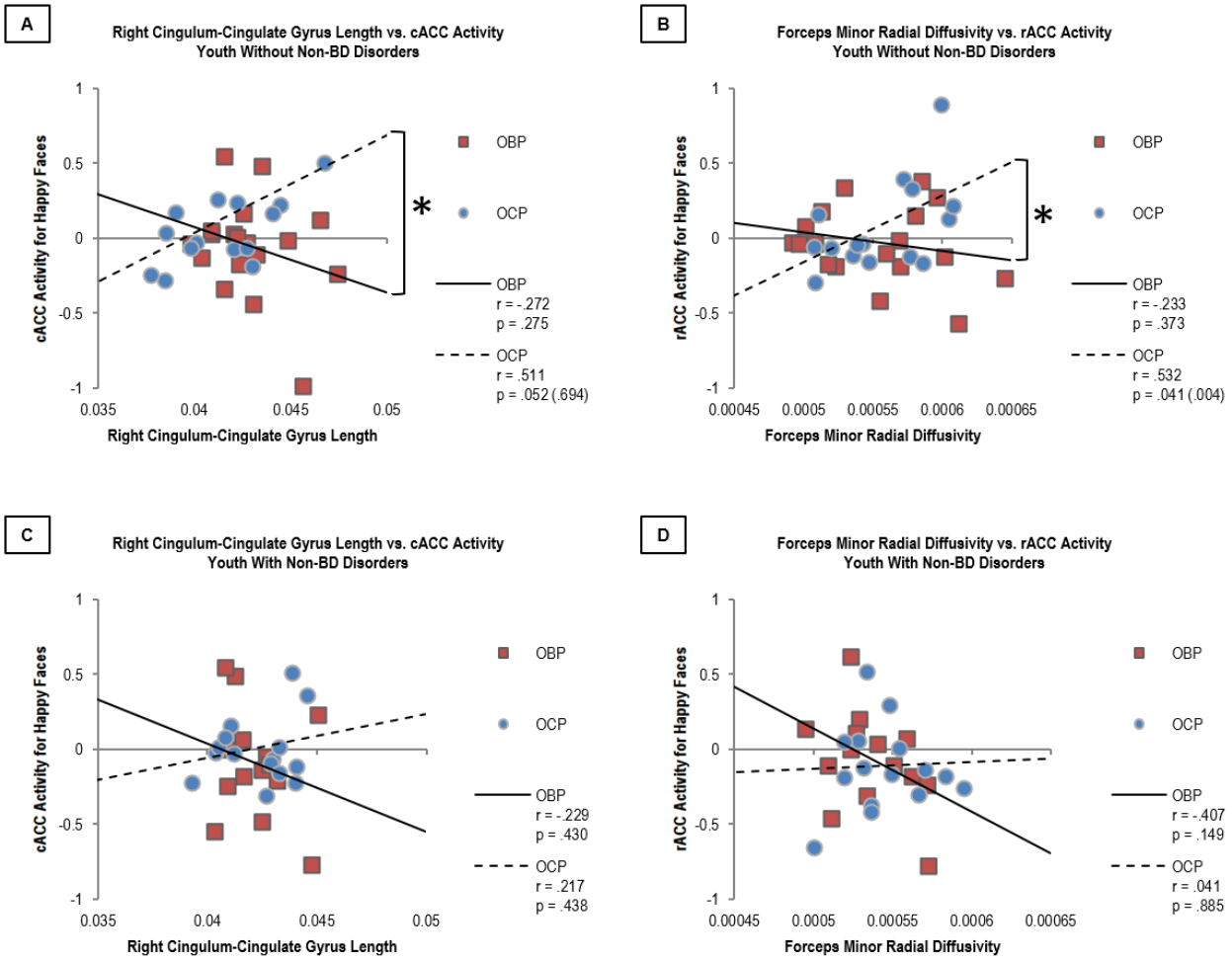

Figure 23: Exp 3. Comparison of White Matter Tract-Activity Relationships in Offspring of Bipolar and Comparison Parents With and Without Non-Bipolar Disorders

5.3.2 Additional Analyses

The relationships for OHP were in between those of OBP and OCP (Figure 24). These relationships did not significantly differ, however, between OHP and either OBP ($p = 0.401$ for right cingulum-cingulate gyrus length-cACC activity, $p = 0.258$ for forceps minor RD-rACC

activity) or OCP (p = 0.126 for right cingulum-cingulate gyrus length-cACC activity, p = 0.107 for forceps minor RD-rACC activity).

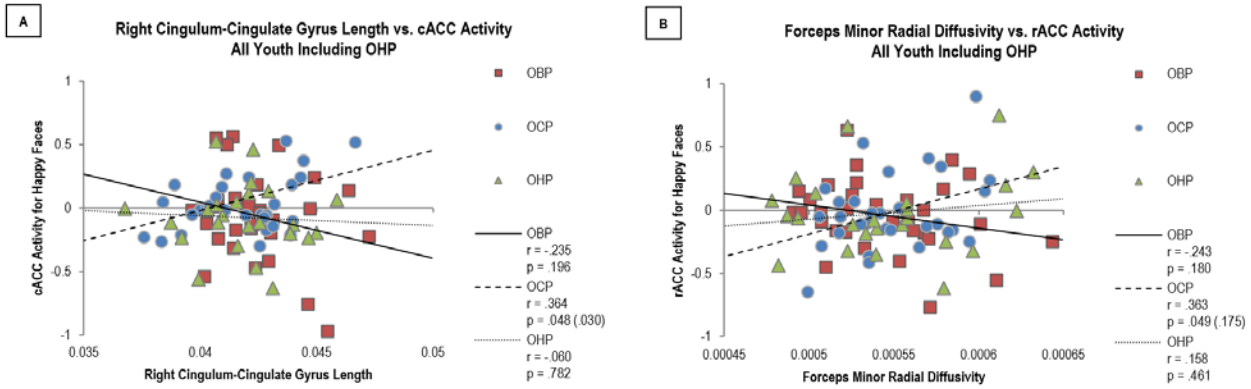

Figure 24: Exp 3. Comparison of White Matter Tract-Activity Relationships in Offspring of Bipolar, Comparison, and Healthy Offspring

Removing youth who were taking psychotropic medications did not affect the significance of either the right cingulum-cingulate gyrus length-cACC activity relationship (p = 0.018 (0.014, corrected)) or the significance of the forceps minor RD-rACC activity relationship (p = 0.003 (< 0.001, corrected)) in all OBP and OCP (Figure 25).

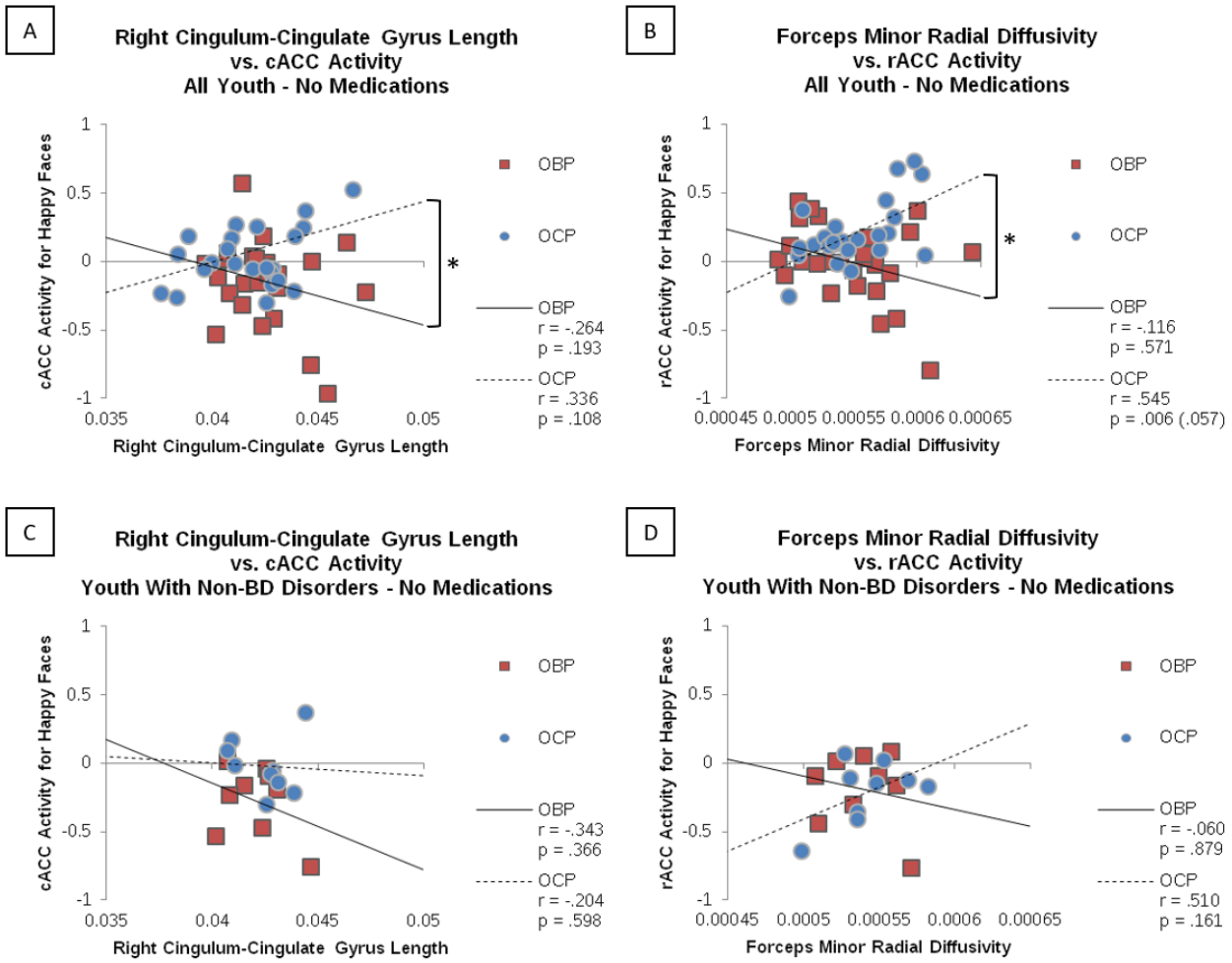

Figure 25: Exp 3. Comparison of White Matter Tract-Activity Relationships in Unmedicated Offspring of Bipolar and Comparison Parents

Greater right cingulum-cingulate gyrus length was significantly associated with lower right cingulum-cingulate gyrus FA ($p = 0.001$ (0.002, corrected)). Additionally, greater forceps minor RD was significantly associated with lower forceps minor FA ($p < 0.001$ (< 0.001, corrected)). (Table 32)

Table 32: Exp 3. Correlations between Neuroimaging Measures and Fractional Anisotropy

		Right Cingulum-Cingulate Gyrus		
		Fractional Anisotropy	Axial Diffusivity	Radial Diffusivity
Right Cingulum-Cingulate Gyrus Length	Pearson Correlation	-.423	-.055	.375
	Significance	.001* (.002*)	.672	.003* (.027*)

		Forceps Minor	
		Fractional Anisotropy	Axial Diffusivity
Forceps Minor Radial Diffusivity	Pearson Correlation	-.836	-.108
	Significance	<.001* (<.001*)	.405

Age was not significantly associated with right cingulum-cingulate gyrus length, forceps minor RD, cACC activity, or rACC activity in either OBP or OCP (Figure 26).

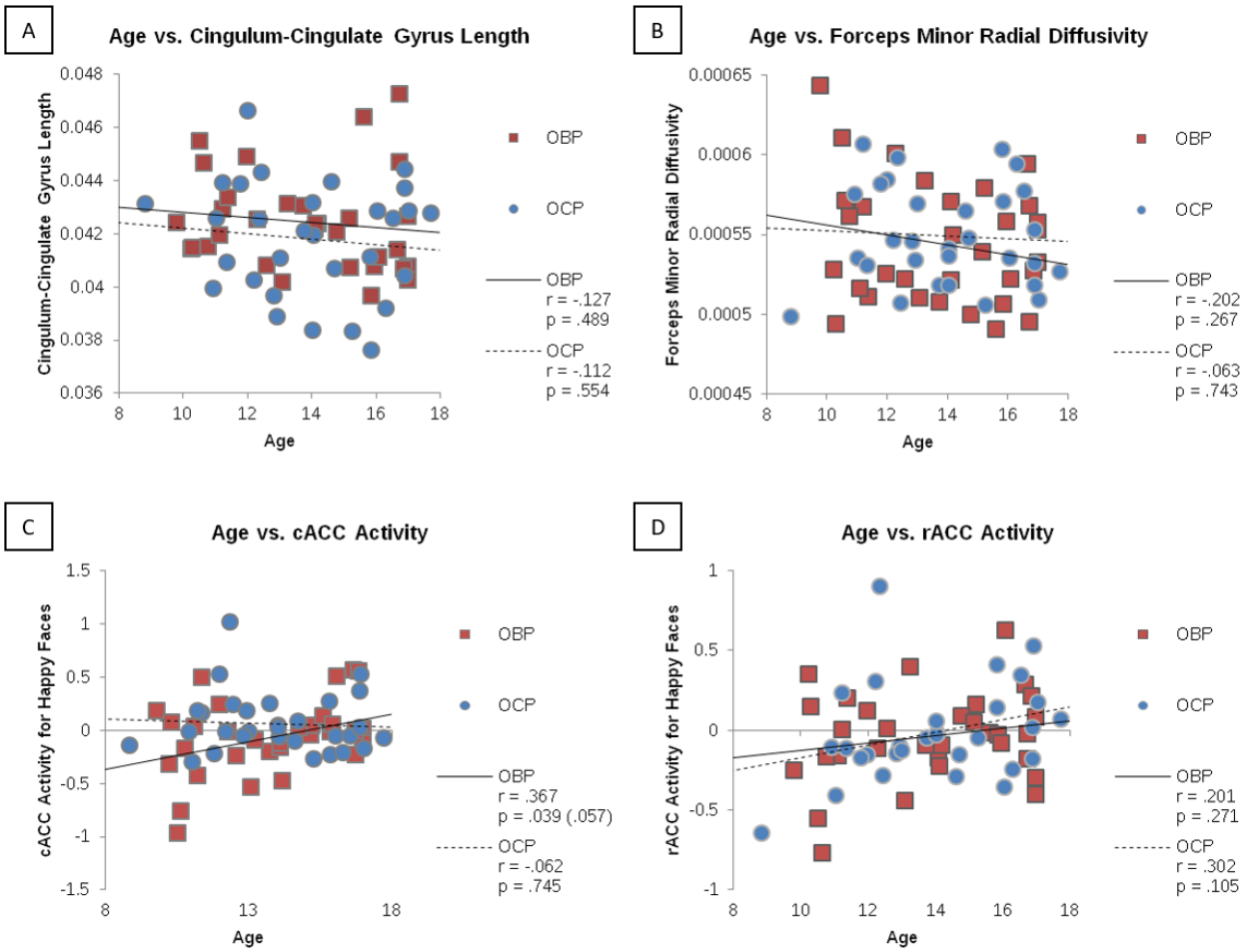

Figure 26: Exp 3. Relationships between Age and Measures of White Matter Tracts and Activity

When comparing individual WMT and activity measures in all OBP and OCP, no group differences were found (Table 33).

Table 33: Exp 3. Between-Group Differences in Neuroimaging Measures

Region	Youth	Group	Mean	SD	t	df	p =	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
										Lower	Upper
Right Cingulum-Cingulate Gyrus Length	All	OBP	$4.24x10^{-2}$	$1.83x10^{-3}$	1.261	60	.212	$6.40x10^{-4}$	$5.10x10^{-4}$	$-3.70x10^{-4}$	$1.65x10^{-3}$
		OCP	$4.18x10^{-2}$	$2.15x10^{-3}$							
	Without Disorders	OBP	$4.27x10^{-2}$	$2.09x10^{-3}$	1.625	31	.114	$1.32x10^{-3}$	$8.10x10^{-4}$	$-3.40x10^{-4}$	$2.97x10^{-3}$
		OCP	$4.14x10^{-2}$	$2.57x10^{-3}$							
	With Disorders	OBP	$4.21x10^{-2}$	$1.44x10^{-3}$	-0.205	27	.839	$-1.20x10^{-4}$	$5.70x10^{-4}$	$-1.29x10^{-3}$	$1.05x10^{-3}$
		OCP	$4.22x10^{-2}$	$1.62x10^{-3}$							
Forceps Minor Radial Diffusivity	All	OBP	$5.44x10^{-4}$	$3.78x10^{-5}$	-0.520	60	.605	$-4.60x10^{-6}$	$8.83x10^{-6}$	$2.20x10^{-5}$	$1.31x10^{-5}$
		OCP	$5.49x10^{-4}$	$3.12x10^{-5}$							
	Without Disorders	OBP	$5.52x10^{-4}$	$4.50x10^{-5}$	-0.192	31	.849	$-2.80x10^{-6}$	$1.44x10^{-5}$	$3.20x10^{-5}$	$2.66x10^{-5}$
		OCP	$5.54x10^{-4}$	$3.59x10^{-5}$							
	With Disorders	OBP	$5.35x10^{-4}$	$2.41x10^{-5}$	-0.913	27	.369	$-8.50x10^{-6}$	$9.29x10^{-6}$	$-2.80x10^{-5}$	$1.06x10^{-5}$
		OCP	$5.44x10^{-4}$	$2.58x10^{-5}$							
cACC Activity	All	OBP	-.062	.345	-1.592	60	.117	-.128	.080	-.288	.033
		OCP	.066	.281							
	Without Disorders	OBP	-.043	.335	-1.45	31	.157	-1.68	.116	-.405	.068
		OCP	.126	.328							
	With Disorders	OBP	-.087	.369	-0.830	27	.414	-.093	.112	-.322	.137
		OCP	.006	.219							
rACC Activity	All	OBP	-.041	.283	-0.356	60	.723	-.027	.075	-.176	.123
		OCP	-.014	.306							
	Without Disorders	OBP	-.026	.250	-1.161	31	.254	-.111	.096	-.306	.084
		OCP	.085	.300							
	With Disorders	OBP	-.059	.329	0.469	27	.643	.054	.115	-.181	.289
		OCP	-.113	.288							

ANOVAS examined group differences in SCARED, CALS, MFQ, and KMRS measures (Table 34).

Table 34: Exp 3. Between-Group Differences in Symptom Measures

Clinical Assessment	Group	Mean	SD	t	df	p =	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference Lower	Upper
SCARED-P	OBP	9.625	6.435	0.061	59.000	.951	0.142	2.315	-4.490	4.775
	OCP	9.483	11.224							
SCARED-C	OBP	12.469	14.624	1.089	60.000	.281	3.802	3.492	-3.183	10.787
	OCP	8.667	12.729							
CALS-P	OBP	8.520	9.933	2.309	42.498	**.026* (.044*)**	4.551	1.971	0.574	8.527
	OCP	3.970	4.516							
CALS-C	OBP	9.750	12.176	1.142	60.000	.258	3.250	2.847	-2.445	8.945
	OCP	6.500	10.058							
MFQ-P	OBP	6.520	9.376	1.445	36.647	.157	2.710	1.875	-1.092	6.511
	OCP	3.810	3.555							
MFQ-C	OBP	8.030	10.701	-0.259	55.000	.797	-0.744	2.878	-6.513	5.024
	OCP	8.780	11.015							
KMRS	OBP	2.000	2.806	3.333	34.544	**.002* (.004*)**	1.700	0.510	0.664	2.736
	OCP	0.300	0.651							

OBP had significantly greater CALS-P (p = 0.026 (0.044, corrected)) and KMRS (p = 0.002 (0.004, corrected)) scores compared with OCP (Figure 27).

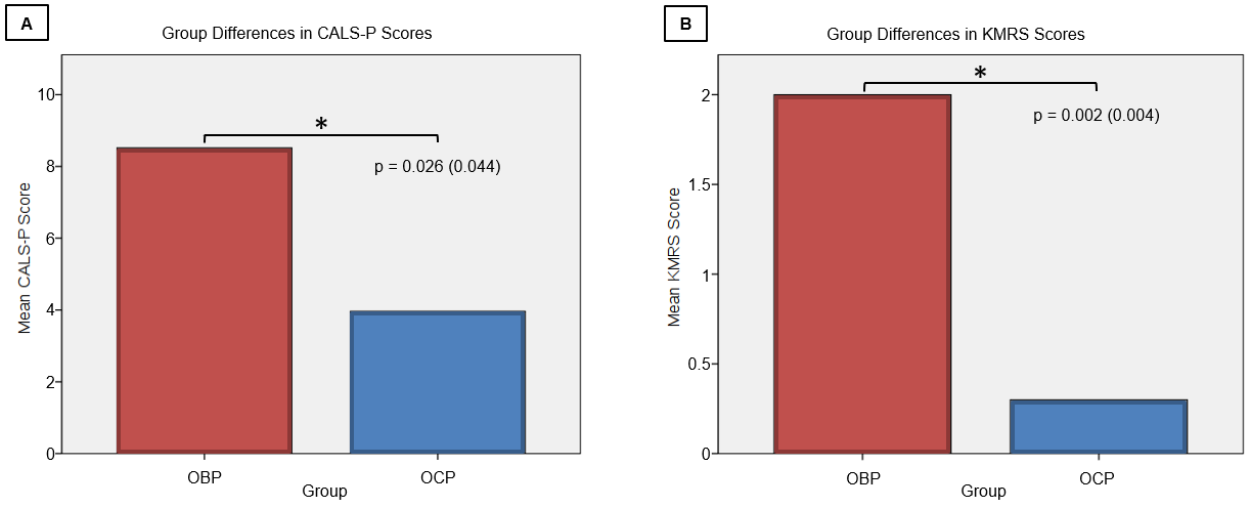

Figure 27: Exp 3. Between-Group Differences in Symptom Measures

When examining the moderating effect of symptom measures on WMT-activity relationships, regression analyses showed a significant interaction between CALS-P scores and forceps minor RD on rACC activity in OBP ($F(1,29) = 5.566$, $p = 0.025$ (0.036, corrected)) (Table 35).

Table 35: Exp 3. Interaction Analyses between Symptoms and White Matter Tract-Activity Relationships

OBP								
			cACC Activity				rACC Activity	
			F	p =			F	p =
Right Cingulum-Cingulate Gyrus Length	X	SCARED-P	0.784	.383	Forceps Minor Radial Diffusivity	X SCARED-P	0.421	.521
		SCARED-C	2.815	.104		SCARED-C	3.656	.065
		CALS-P	2.010	.167		CALS-P	5.566	.025* (.036*)
		CALS-C	0.001	.975		CALS-C	0.193	.664
		MFQ-P	4.541	.042 (.733)		MFQ-P	5.438	.027 (.196)
		MFQ-C	0.398	.533		MFQ-C	0.142	.709
		KMRS	1.192	.284		KMRS	0.361	.552

OCP								
			cACC Activity				rACC Activity	
			F	p =			F	p =
Right Cingulum-Cingulate Gyrus Length	X	SCARED-P	0.154	.698	Forceps Minor Radial Diffusivity	X SCARED-P	1.270	.270
		SCARED-C	0.346	.561		SCARED-C	0.985	.329
		CALS-P	0.054	.817		CALS-P	0.226	.639
		CALS-C	0.013	.911		CALS-C	0.000	1.00
		MFQ-P	0.947	.340		MFQ-P	0.349	.560
		MFQ-C	0.818	.375		MFQ-C	0.020	.888
		KMRS	1.239	.275		KMRS	1.017	.322

Separating OBP into those with higher and lower CALS-P scores, based on a median split, revealed that those with higher CALS-P scores (mean (SD) = 15.33 (10.52), $r = -0.214$, $p = 0.443$) had greater inverse WMT-activity relationships than those with lower scores (mean (SD) = 2.13 (2.00), $r = -0.181$, $p = 0.503$) (Figure 28).

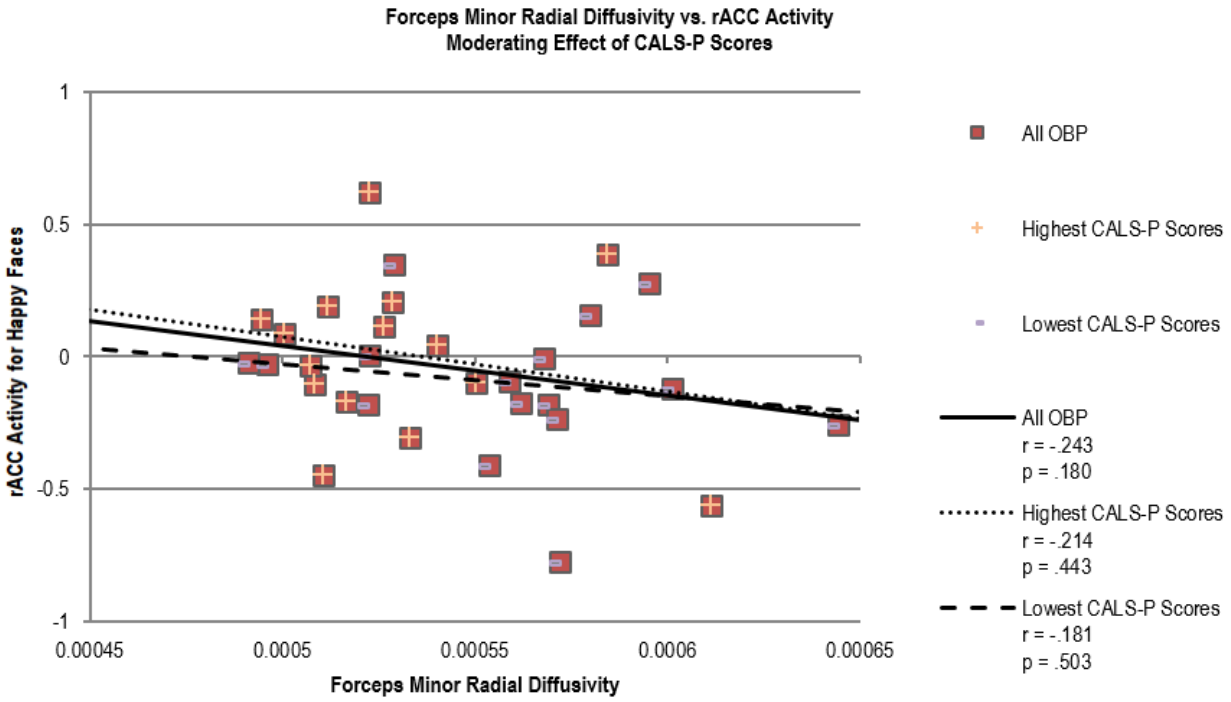

Figure 28: Exp 3. Effects of Symptom Measures on White Matter Tract-Activity Relationships

5.4 DISCUSSION

5.4.1 Summary of Findings

To our knowledge, this is the first study to use multimodal neuroimaging techniques to identify WMT-activity relationships that distinguish youth at familial 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 markers 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 PFC 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. Greater right cingulum-cingulate gyrus length was associated with lower cACC activity to happy faces in OBP but greater activity in OCP. Similarly, greater forceps minor RD was associated with lower rACC activity to happy faces in OBP but greater activity in OCP. Neither relationship significantly differentiated either at-risk group from OHP, however.

Greater WMT length has been associated with structural reductions in fiber diameter, myelin, or numbers of fibers (Lewis, Theilmann et al. 2013). Similarly, greater WMT RD has been associated with abnormal myelination, a greater number of obliquely oriented fibers, and local inflammation (Song, Yoshino et al. 2005). Furthermore, additional analyses revealed that both greater right cingulum-cingulate gyrus length and forceps minor RD were associated with lower FA and, thus, lower fiber collinearity. This suggests that, in OBP alone, lower fiber collinearity in the right cingulum-cingulate gyrus and forceps minor was significantly associated

with lower activity in the cACC and rACC, respectively. When comparing these WMT-activity relationships in youth with and without non-BD disorders, the between-group differences in these relationships remained significant only in OBP and OCP without disorders. Furthermore, removing youth taking psychotropic medications did not affect the significance of either WMT-activity relationship. Together, these findings indicate that the key WMT-activity relationships differentiating OBP from OCP were the right cingulum-cingulate gyrus length-cACC activity and forceps minor RD-rACC activity relationships when processing positive emotions, which remained evident when excluding youth who had non-BD psychiatric disorders and who were taking medications.

Previous neuroimaging studies of youth and adults with BD provide similar findings regarding WMT and activity abnormalities, separately, during emotion processing. Studies have reported that individuals with, and at risk for, BD have abnormally low ACC activity (Phillips, Drevets et al. 2003, Blumberg, Donegan et al. 2005, Dolcos, Iordan et al. 2011, Chan, Sussmann et al. 2016) and abnormally low fiber collinearity in the cingulum (Benedetti, Yeh et al. 2011, Linke, King et al. 2013, Versace, Andreazza et al. 2014) and forceps minor (Wang, Kalmar et al. 2008, Chaddock, Barker et al. 2009, Benedetti, Yeh et al. 2011, Haller, Xekardaki et al. 2011, Versace, Andreazza et al. 2014). Our findings add to this literature by showing that, in OBP, lower fiber collinearity in the cingulum and forceps minor were associated with lower activity to happy faces in the cACC and rACC, respectively. The cingulum is the WMT that forms the white matter core of the cingulate gyrus and has an essential role in emotion regulation (Papez 1937, Mufson and Pandya 1984, Wang, Jackowski et al. 2008, Bruni and Montemurro 2009). 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, Cao et al. 2015, Sarrazin, d'Albis et al. 2015). The cACC is a part of the central executive network with specific roles in attentional task performance (Van Veen and Carter 2002, Haas, Omura et al. 2006, Margulies, Kelly et al. 2007). 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, Morrell et al. 1995, Zimmerman, DelBello et al. 2006). Thus, the inverse relationships between right cingulum-cingulate gyrus length and cACC activity, as well as 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 cingulum and forceps minor may contribute to lower activity in the ACC by reducing the integrity of connections between regions that are important to positive emotional processing and regulation (Morgan, Mishra et al. 2009).

Conversely, the relationships between right cingulum-cingulate gyrus length and cACC activity, as well as between forceps minor RD and rACC activity, were positive in OCP such that lower fiber collinearity in the cingulum and forceps minor contributed to greater ACC activity in this group. Additionally, while not statistically significant, these WMT-activity relationships for OHP were intermediate between those of OBP and OCP. 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 neural marker preceding BD illness. Given the significantly greater familial risk for BD in OBP versus OCP, however, we may speculate that the right cingulum-cingulate gyrus-cACC activity and forceps minor RD-rACC activity relationships suggest diverging pathophysiological mechanisms in OBP versus OCP. Further study, including larger

sample sizes and longitudinal analyses, is needed to understand the implications of these main findings 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. Specifically, greater affective lability was associated with a greater inverse WMT-activity relationship. Affective lability is defined as "a predisposition to marked, rapidly reversible shifts in affective states, extremely sensitive to meaningful environmental events that might induce more modest emotional responses in normal individuals" (Siever and Davis 1991, Henry, Van den Bulke et al. 2008). Given that affective lability is a precursor of BD in OBP (Hafeman, Merranko 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). All of 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 participants 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 of the significant findings were specific to happy faces, reflecting the importance of positive emotion processing abnormalities in the development of BD. A common theme that has been observed in 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 greater amygdala, striatal, and medial PFC activity in response to positive emotional stimuli in individuals affected with BD (Lawrence, Williams et al. 2004, Blumberg, Donegan et al. 2005). Several studies have shown that adults with BD have abnormally increased amygdala and medial PFC activity (Surguladze, Marshall et al. 2010, Keener, Fournier et al. 2012), as well as abnormally decreased positive bilateral OFC-amygdala effective connectivity (Almeida, Versace et al. 2009), to emotional faces, and 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, mania and/or hypomania.

5.4.2 Conclusions

In this study, we showed that the relationships between right cingulum-cingulate gyrus length-cACC activity when processing happy faces, as well as between forceps minor RD and rACC activity when processing happy faces, significantly differentiated youth at familial risk for BD from youth at risk for non-BD psychiatric disorders. These relationships were evident in youth unaffected by psychiatric disorders and medications. Additionally, the relationship between forceps minor RD and rACC activity was moderated by symptoms of affective lability. Given these findings, it is possible that these WMT-activity relationships reflect underlying neural 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 neural measures of BD risk that may help improve the accuracy in identifying and intervening for youth most at risk for future BD.

6.0 GENERAL DISCUSSION

6.1 SUMMARY OF FINDINGS

In this dissertation, we first sought to determine measures of activity and FC in emotion processing and regulation neural circuitries that distinguished youth at risk for BD from youth at risk for other psychiatric disorders and healthy controls. We found that OBP showed greater right rACC activity when regulating attention away from happy faces and greater bilateral amygdala-left cACC FC when regulating attention away from fearful faces, both of which had significant relationships with affective lability (Chapter 3). These findings contribute to the model of emotion regulation in BD risk which previously consisted of greater vlPFC activity when regulating attention away from happy faces (Ladouceur, Diwadkar et al. 2013), lower right vlPFC-left amygdala FC when regulating attention away from fearful faces (Ladouceur, Diwadkar et al. 2013), lower right vlPFC-left dlPFC FC during emotion regulation (Ladouceur, Diwadkar et al. 2013), lower collinearity in the cingulum (Benedetti, Yeh et al. 2011, Versace, Andreazza et al. 2014), lower collinearity in the forceps minor of the corpus callosum (Wang, Jackowski et al. 2008, Wang, Kalmar et al. 2008, Chaddock, Barker et al. 2009, Benedetti, Yeh et al. 2011, Haller, Xekardaki et al. 2011, Versace, Andreazza et al. 2014, Sarrazin, d'Albis et al. 2015), lower collinearity in the superior longitudinal fasciculus (Chaddock, Barker et al. 2009, van der Schot, Vonk et al. 2010, Versace, Almeida et al. 2010, Benedetti, Yeh et al. 2011,

Versace, Andreazza et al. 2014), and lower collinearity in the uncinate fasciculus (Versace, Almeida et al. 2008, Benedetti, Yeh et al. 2011, Linke, King et al. 2013, Versace, Andreazza et al. 2014) (Figure 29).

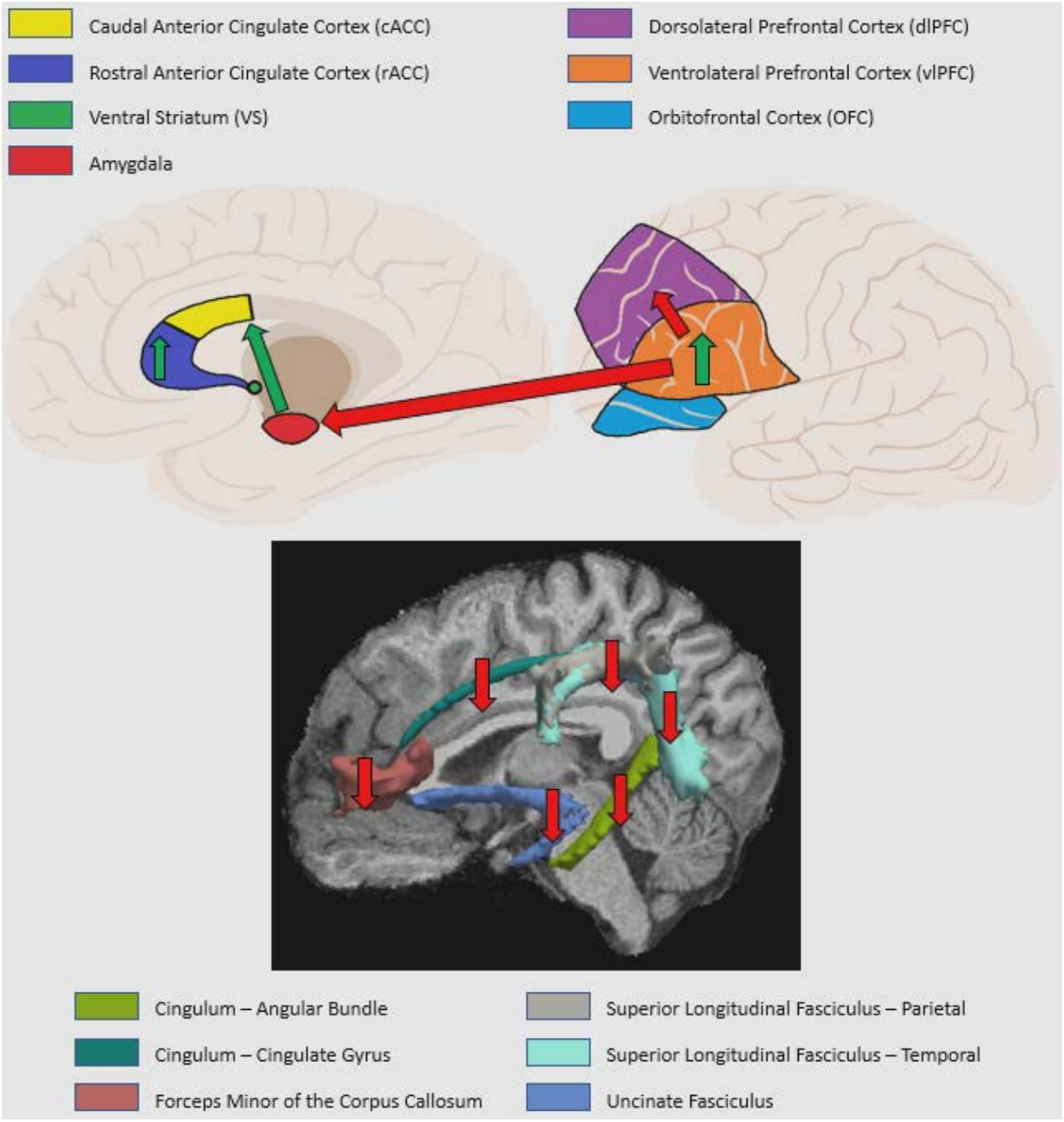

Figure 29: Updated Model of BD Risk - Emotion Regulation

Next, we took a similar approach to identify measures of activity and FC in reward neural circuitry that uniquely distinguished OBP from control groups. We observed that OBP had lower right VS-left cACC FC to loss and greater right pars orbitalis-OFC FC to reward, and these findings were independent of present non-BD psychopathology, psychotropic medication use, and symptomatology (Chapter 4). These findings contribute to the model of reward processing in BD risk which previously consisted of greater amygdala activity during reward reversal (Linke, King et al. 2012), greater left OFC activity during reward reversal and receipt (Linke, King et al. 2012, Singh, Kelley et al. 2014), lower cACC activity during loss anticipation (Singh, Kelley et al. 2014), more negative bilateral VS-right vlPFC FC during the processing of both reward and loss receipt (Manelis, Ladouceur et al. 2016), greater cACC-right vlPFC FC during loss anticipation (Singh, Kelley et al. 2014), and lower cACC-right vlPFC FC during reward anticipation (Singh, Kelley et al. 2014) (Figure 30).

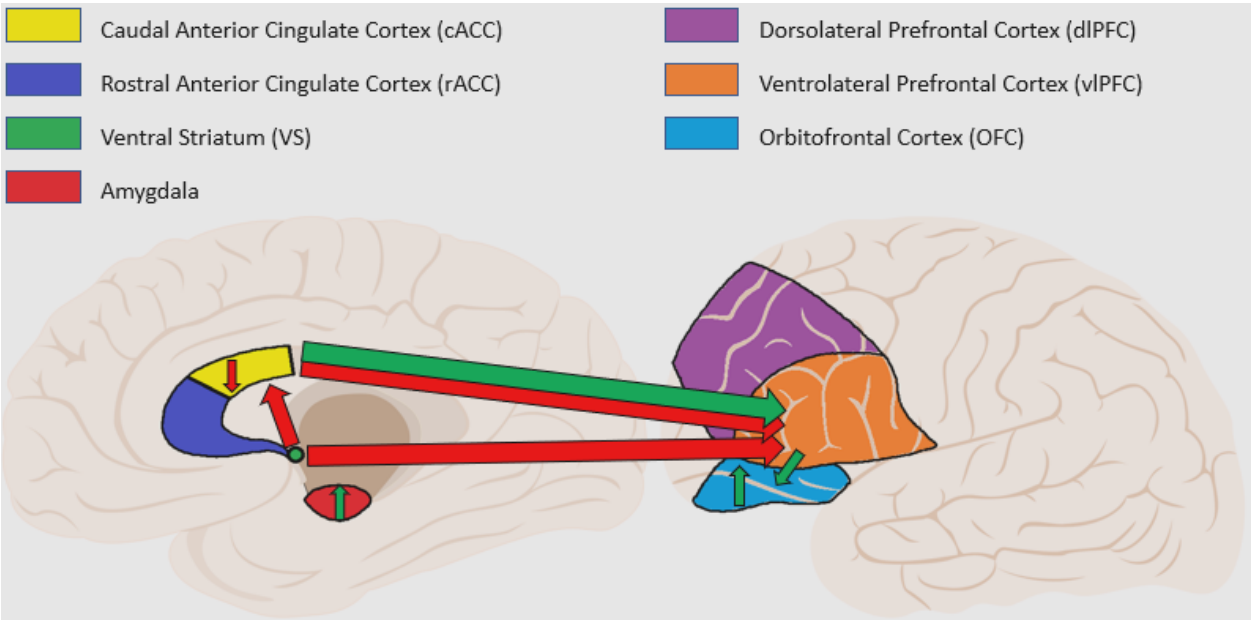

Figure 30: Updated Model of BD Risk - Reward Processing

Finally, we explored relationships between WMT structure and activity in emotion processing neural circuitry in youth at risk for BD. We found that the relationships between right cingulum-cingulate gyrus length and cACC activity, as well as between forceps minor RD and rACC activity, when processing happy faces significantly differentiated OBP from OCP (Chapter 5). These findings were evident in youth unaffected by non-BD psychopathology, and the latter finding was moderated by symptoms of affective lability. These findings contribute to the model of emotion processing in BD risk which previously consisted of greater right amygdala activity to all emotional faces (Manelis, Ladouceur et al. 2015), lower ACC activity during facial emotion processing (Chan, Sussmann et al. 2016), lower dlPFC activity during facial emotion processing (Tseng, Bones et al. 2015), lower right amygdala-ACC FC to all emotional faces (Manelis, Ladouceur et al. 2015), greater right amygdala-left vlPFC FC to happy faces (Manelis, Ladouceur et al. 2015), lower collinearity in the forceps minor of the corpus callosum (Wang, Jackowski et al. 2008, Wang, Kalmar et al. 2008, Chaddock, Barker et al. 2009, Benedetti, Yeh et al. 2011, Haller, Xekardaki et al. 2011, Versace, Andreazza et al. 2014, Sarrazin, d'Albis et al. 2015), and lower collinearity in the uncinate fasciculus (Versace, Almeida et al. 2008, Benedetti, Yeh et al. 2011, Linke, King et al. 2013, Versace, Andreazza et al. 2014) (Figure 31).

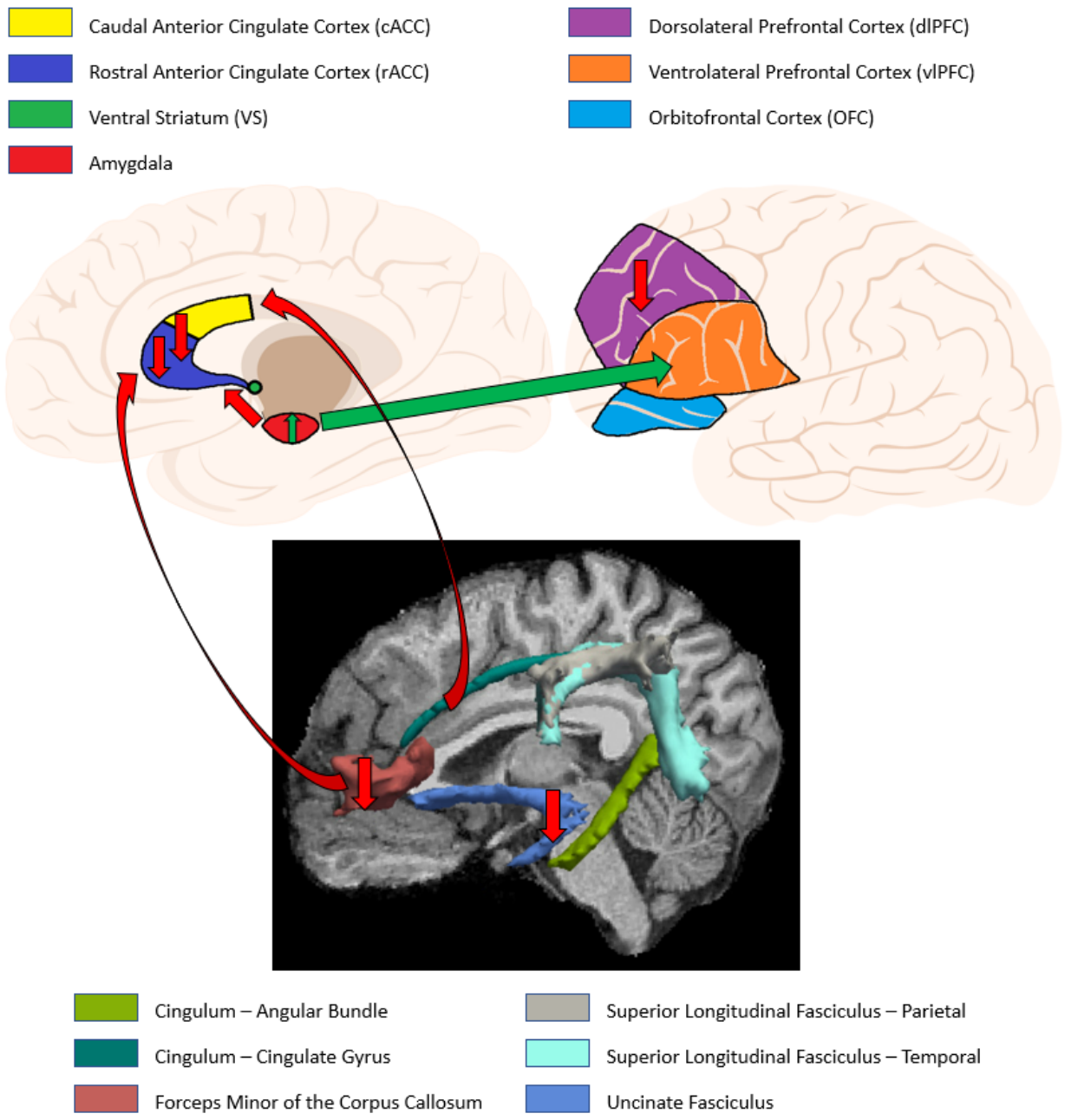

Figure 31: Updated Model of BD Risk - Emotion Processing

We will now discuss the implications of these findings for the pathophysiology underlying BD risk and possible targets for improved diagnostic and treatment interventions for youth at risk for BD.

6.2 CONTRIBUTIONS TO THE NEURAL MODEL OF BD RISK

The primary aim of this dissertation was to examine emotion processing, emotion regulation, and reward neural circuitries both at baseline and at follow-up, as well as relationships between white matter structure and neural activity, in order to contribute to the neural model of BD risk. In addition to furthering our understanding of specific neural regions and tracts, other goals of this work included: examining relationships between neural measures and symptomatology, determining state- versus trait-dependent natures of these neural circuitries, and exploring effects of non-BD psychopathology, medications, and age. A summary of the main contributions of this dissertation to the neural model of BD risk can be found in red in Figure 32.

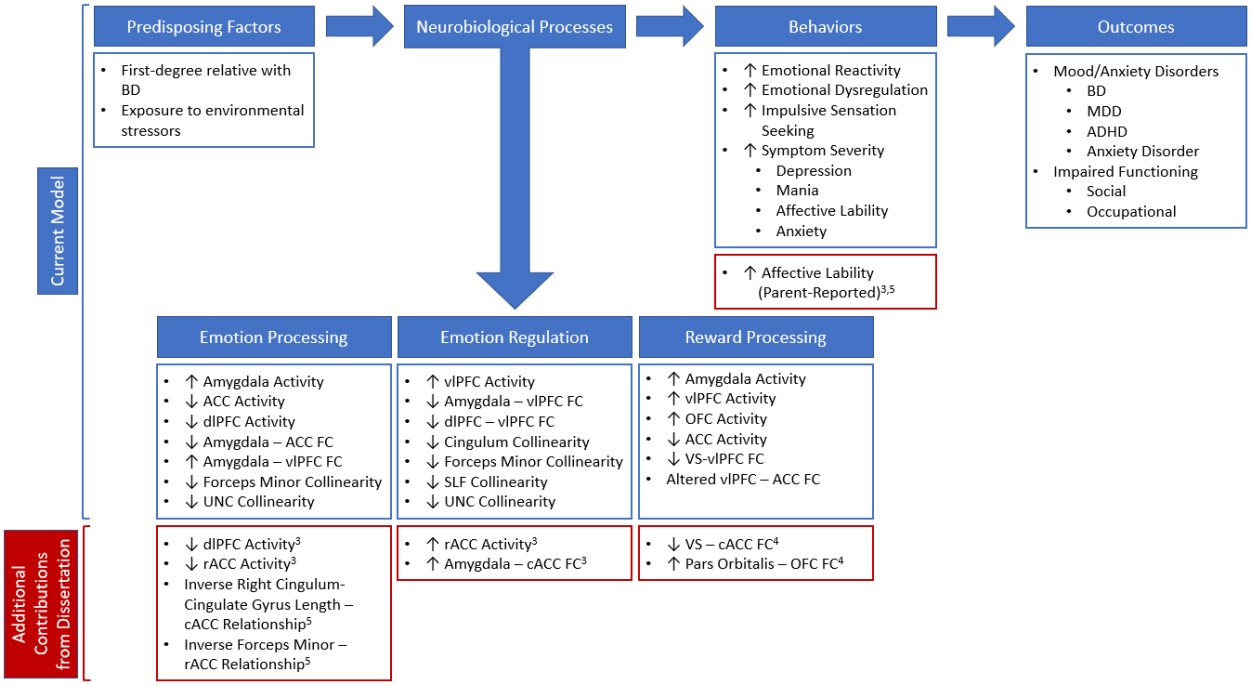

Figure 32: Contributions to the Neural Model of Bipolar Disorder Risk with Chapter Numbers in Superscripts

6.2.1 Additional Understanding of Specific Neural Regions and Tracts

6.2.1.1 Caudal and Rostral Anterior Cingulate Cortex

Some of the most substantial and consistent findings to arise from this dissertation pertain to the ACC. It is the only neural region that had significant implications in all three studies laid out in this work. When examining emotion processing and regulation neural circuitry, we showed greater right rACC activity to happy versus no faces in OBP compared with OCP during EF-2-BACK performance, lower right rACC activity to happy versus neutral faces in OBP and OCP compared with OHP during EF-0-BACK performance, and greater bilateral amygdala-left cACC FC to fearful, happy, and neutral versus no faces in OBP compared with OCP during EF-2-BACK performance. When examining reward processing neural circuitry, we showed lower right VS-left cACC FC to loss in OBP compared with both OCP and OHP. When examining relationships between WMT structure and activity in emotion processing neural circuitry, we showed inverse relationships between right cingulum-cingulate gyrus length and bilateral cACC activity when processing happy faces versus shapes, as well as between forceps minor RD and bilateral rACC activity when processing happy faces versus shapes, which differed significantly from the positive relationships in OCP.

The primary contribution of these findings to the current model of BD risk pertain to the division of the ACC into rostral and caudal regions. The ACC, as a whole, has been well established in the literature as a region involved in both emotional and cognitive tasks (Bush, Luu et al. 2000). The rACC, specifically, has been found to have more affective roles in processing emotional conflict and integrating emotion and cognition (Vogt, Finch et al. 1992, Van Hoesen, Morecraft et al. 1993, Carmichael and Price 1995, Devinsky, Morrell et al. 1995, Bush, Luu et al. 2000, Bishop, Duncan et al. 2004, Bissière, Plachta et al. 2008). Conversely, the

cACC has been shown to be a part of the central executive control network with roles pertaining more to attentional task performance (Van Veen and Carter 2002, Haas, Omura et al. 2006, Margulies, Kelly et al. 2007). While these separate functions have been identified, little work has been done to determine the roles and implications of these separate regions in the pathophysiology of BD and BD risk.

For example, in emotion processing neural circuitry, studies have found lower ACC activity (Tseng, Bones et al. 2015, Chan, Sussmann et al. 2016) and lower amygdala-ACC FC (Manelis, Ladouceur et al. 2015) in youth at risk for BD. None of these studies, however, determined whether these findings were specific to the rostral or caudal portion of the ACC. In accordance with previous studies showing lower activity in the ACC, as a whole, we found that activity in the right rACC was lower compared with OHP during EF-0-BACK performance, a task that is similar to the emotional face processing task (DFT) in that participants are asked to attend to a task with no working memory component while emotional faces are simultaneously presented. Similarly, bilateral rACC activity when processing happy faces was inversely correlated with forceps minor RD, and this relationship significantly differentiated OBP from OCP. In line with previous studies characterizing the rACC as more affective in nature (Vogt, Finch et al. 1992, Bush, Luu et al. 2000), our findings further suggest that the *rostral* ACC is the primary portion of the ACC implicated in emotion processing neural circuitry in youth at risk for BD. We did, however, find one additional role of the cACC in emotion processing neural circuitry. Specifically, we found that the relationship between right cingulum-cingulate gyrus length and cACC activity when processing happy faces also distinguished OBP from OCP. Thus, while the rACC appears to be more heavily implicated in the processing of emotions, the cACC may also have a contributing role in this neural circuitry.

In addition to identifying the portion of the ACC primarily implicated in emotion processing neural circuitry, our findings also suggest that lower rACC activity is primarily observed when OBP are processing happy faces. It has been suggested that a deficit in depressed individuals may reflect negative bias when perceiving emotional faces such that happy faces are interpreted as neutral faces (Schaefer, Baumann et al. 2010). A decrease in activity in the rACC (and cACC) may thus contribute to an abnormal perception of happy faces in patients with and at risk for BD, and perhaps particularly those who are in depressed states. The mechanism by which this occurs might pertain to the role of the rACC in suppressing amygdala activity when participants are attempting to resolve emotional conflict (Etkin, Egner et al. 2006). Indeed, abnormally greater amygdala activity has been shown in individuals with BD when processing positive emotional stimuli (Lawrence, Williams et al. 2004, Blumberg, Donegan et al. 2005, Surguladze, Marshall et al. 2010, Keener, Fournier et al. 2012). Thus, we may postulate that, in youth at risk for BD, abnormally lower activity in the rACC, specifically, may reflect inefficient recruitment of this region to downregulate amygdala activity, leading to abnormally greater amygdala activity when processing positive emotional stimuli, such as happy faces. This would implicate the rACC as a key region in emotional processing neural circuitry in youth at risk for BD.

The circuitry of emotion regulation, on the other hand, more clearly has roles for both the rostral and caudal portions of the ACC. Compared to studies examining emotion and reward processing neural circuitries, previous studies investigating emotion regulation in youth at risk for BD have produced little regarding the role of the ACC. In our studies, we found that greater rACC activity when regulating attention away from positive emotions and greater bilateral amygdala-left cACC FC when regulating attention away from all emotions (i.e. fearful, happy,

and neutral faces) during EF-2-BACK performance distinguished OBP from OCP. The 2-back condition of the emotional face n-back task, compared to the 0-back condition, introduces a difficult working memory component that is not present when simply processing emotions. Thus, it is not surprising that both the "affective" rACC and the "attentional" cACC are recruited in OBP during a task that requires the ability to regulate emotions while simultaneously attending to a working memory task. We may speculate about a pathophysiological process in OBP that underlies their attempt to regulate emotions during attentional tasks. On one hand, greater rACC activity may correspond with an attempt to downregulate amygdala activity when resolving emotional conflict. On the other hand, greater FC between the cACC and the amygdala may reflect an attempt on the part of the cACC to upregulate amygdala activity, or this may reflect a failure of the cACC to downregulate amygdala activity. Altogether, this may reflect a compensatory, but ultimately inefficient, mechanism in the ACC to regulate amygdala activity while redirecting attention away from emotional face distracters during an attentional task in youth at risk for BD.

Conversely, in reward processing neural circuitry, the *caudal* ACC appears to be the portion of the ACC that is primarily implicated. One previous study showed that OBP had lower cACC activity and greater vlPFC-cACC FC when anticipating loss, as well as lower vlPFC-cACC FC when anticipating rewards (Singh, Kelley et al. 2014). In line with these findings, we found that FC between the bilateral (and right) VS and the left cACC when experiencing loss was lower in OBP compared to both OCP and OHP. While such findings have not been shown in individuals with or at risk for BD, they are consistent with studies showing lower connectivity between the left cACC and both the bilateral and right VS during tasks related to gambling and decision-making, specifically correlating with decreases in impulsive behavior strategies (Jung,

Schulte et al. 2013, van Holst, Chase et al. 2014). Thus, our work here may have uncovered a unique role of the left cACC, and its FC with the VS, in abnormal processing of loss in youth at risk for BD. Specifically, we may speculate that an abnormal connection between the left cACC and the VS in youth at risk for BD may negatively affect their ability to properly use behavioral and/or coping strategies when faced with either ambiguous or risky decisions that have outcomes pertaining to loss. Additionally, this may further reflect difficulty learning from punishment or failure, which may manifest as symptoms of impulsivity or impulsive sensation seeking. Specifically, individuals may continue to engage in risky situations with the potential for reward receipt despite evidence that these attempts may be futile or detrimental.

In summary, the findings presented in this dissertation support and add to the existing literature regarding the role of the ACC in emotion processing, emotion regulation, and reward processing neural circuitries (Figure 33). These roles primarily include abnormally lower ACC recruitment during the processing of emotions and rewards, as well as abnormally greater ACC recruitment during the regulation of emotions. More specifically, we observed three main findings. First, while both the rACC and cACC are implicated in circuitries related to emotion, the rACC appears to have a greater role in the processing of positive emotions while the cACC has a greater role in the processing and regulation of both positive and negative emotions. This is consistent with the literature suggesting that the rACC is generally characterized as more affective in nature, while the cACC is generally characterized as more evaluative or attentional in nature (Vogt, Finch et al. 1992, Bush, Luu et al. 2000). Second, the cACC appears to have a greater role in reward processing neural circuitry than the rACC. Third, abnormalities in the rACC appear to pertain more to activity, on its own, while abnormalities in the cACC appear to pertain more to FC between this and other regions, potentially implicating the cACC more in

roles that involve modulation or regularization between regions in emotion and reward neural circuitries. Together, this suggests that there is a failure to recruit the rACC during the processing of predominantly happy emotional faces but greater recruitment of the ACC, as a whole, during more explicit emotion regulation. The combination of these processes likely reflects an ineffective neural mechanism to process and regulate emotions in OBP that likely involves aberrant connections between both the rostral and caudal ACC and the amygdala. Furthermore, there might be a laterality effect and a somatotopic organization of the ACC such that the *right* ACC is may be more involved when processing and regulating positive emotions while the *left* ACC may be more involved when processing and regulating negative emotions and stimuli pertaining to loss. Thus, our findings correspond with previous studies that implicate the rACC in more affective roles and the cACC in more attentional roles and altogether highlight the ACC as a key region that is important to the underlying pathophysiology predisposing to BD risk.

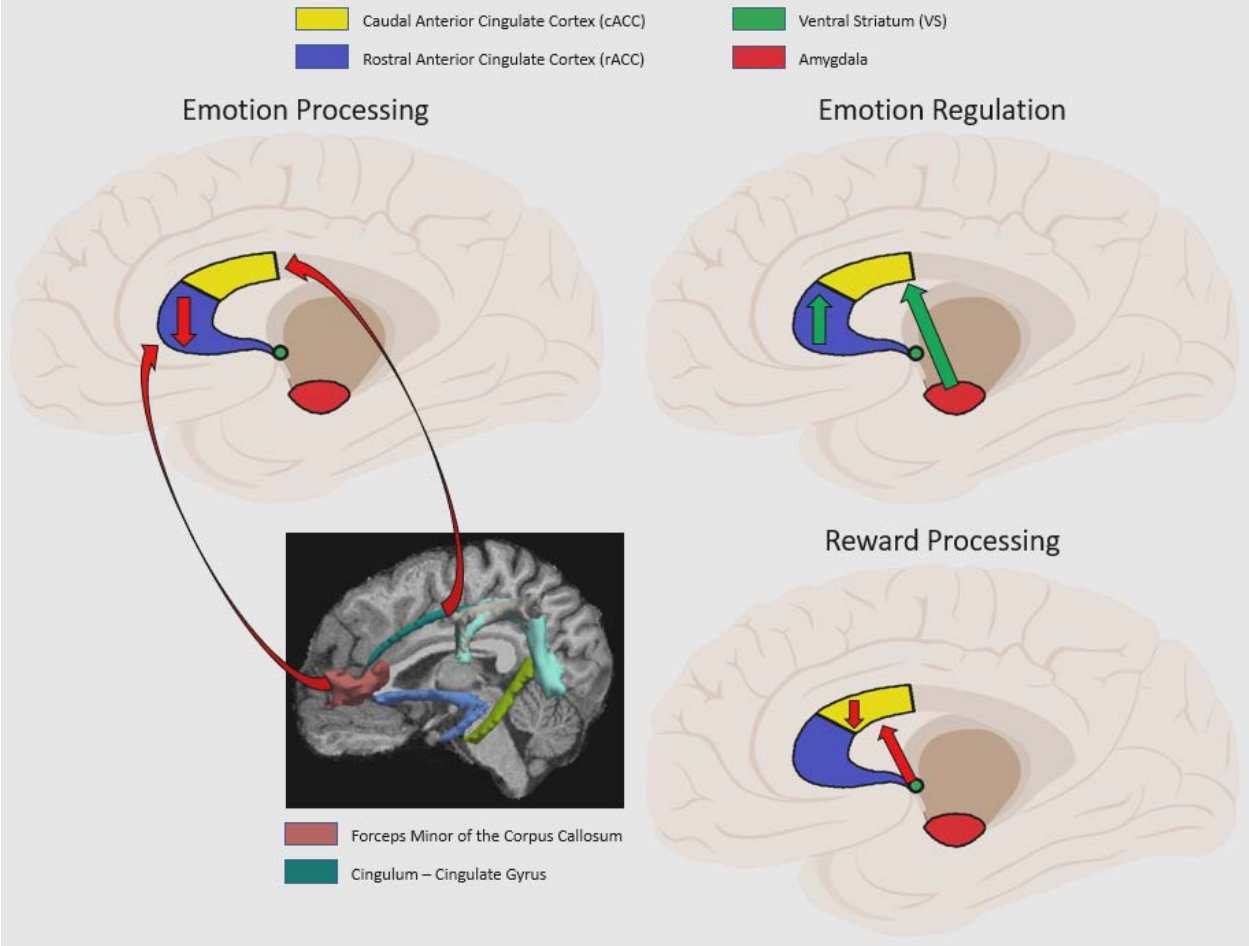

Figure 33: Neural Model of BD Risk - Anterior Cingulate Cortex

6.2.1.2 Additional Neural Regions and Tracts

While the majority of our contributions to the current model of BD risk pertain to the ACC, we observed several findings in other neural regions that also add to and support this model. Such observations were found for all other regions that we examined throughout our studies, including the amygdala, VS, vlPFC, OFC, and dlPFC.

Our main finding pertaining to the amygdala, as mentioned above, was that OBP showed greater bilateral amygdala-left cACC FC to fearful, happy, and neutral versus no faces during

emotion regulation. The most comparable findings in previous studies have shown greater amygdala activity when processing emotional faces (Phillips, Ladouceur et al. 2008, Olsavsky, Brotman et al. 2012, Tseng, Bones et al. 2015, Chan, Sussmann et al. 2016), specifically fearful faces (Olsavsky, Brotman et al. 2012), and lower amygdala-vlPFC FC to fearful faces during emotion regulation (Ladouceur, Diwadkar et al. 2013). Regarding its role in emotion regulation neural circuitry, the amygdala is involved in regulating internal emotional states, cognitively evaluating the emotional content of complex perceptual cues, and processing information about emotions that are conveyed by complex perceptual cues (Gallagher and Chiba 1996). Similarly, as mentioned above, the cACC is involved in implicit emotion regulation with specific roles in attentional task performance (Van Veen and Carter 2002, Haas, Omura et al. 2006, Margulies, Kelly et al. 2007, Kober, Barrett et al. 2008, Phillips, Ladouceur et al. 2008, Kim, Loucks et al. 2011, Goodkind, Gyurak et al. 2013, Frank, Dewitt et al. 2014). In contrast to the lower connectivity between the amygdala and vlPFC, which may reflect the modulatory role that the vlPFC plays on amygdala activation in the context of emotional distracters (Ladouceur, Diwadkar et al. 2013), abnormally greater connectivity between the amygdala and cACC may suggest an inefficient compensatory mechanism of two neural regions with roles in emotion regulation during attentional control. Further, while lower amygdala-ACC FC has been shown while processing emotional faces (Manelis, Ladouceur et al. 2015), we alternatively show greater amygdala-ACC FC while regulating attention away from emotional faces. This parallels the findings presented above in which lower rACC activity was observed during emotion processing but greater rACC activity was observed during emotion regulation. This suggests that greater recruitment of the amygdala and ACC is necessary when difficult working memory or attentional tasks are added to the relatively simpler processing of emotional faces.

A second additional finding pertained to the VS. We observed lower right VS-left cACC FC when experiencing loss in OBP compared with OCP and OHP. The VS has established connections with the ACC which may enable reward-based incentives that drive impacts on long-term strategic planning (Haber 2011). As mentioned above, previous studies have found that lower connectivity between these regions is related to increases in gambling behavior and reductions in behavioral strategies important for coping with reward-related decision-making tasks (Jung, Schulte et al. 2013, van Holst, Chase et al. 2014). The fact that lower FC between the VS and the vlPFC when processing the receipt of both reward and loss has also been shown in OBP suggests that the VS may have a primarily inhibitory role when evaluating reward-related stimuli and forming associations between such stimuli and reward values (Manelis, Ladouceur et al. 2016), thus contributing to aberrant reward and loss processing in youth at risk for BD.

A third additional finding was that of greater FC between the right vlPFC and both the left and right OFC to reward in OBP compared with OCP and OHP. Greater vlPFC activity (Singh, Kelley et al. 2014) and greater OFC activity (Singh, Kelley et al. 2014) during reward processing are findings that have been established in previous studies of youth at risk for BD. The vlPFC is important for encoding values of choices and decision-making options (Walton, Behrens et al. 2011), while the OFC is important for encoding reward values, comparing values of different options (Boorman, Behrens et al. 2009), learning about the rewarding nature of stimuli, and rapid stimulus-reinforcement association learning (Rolls 2004). Less is known, however, about the relationship between these regions, the specific parts of these regions that are involved, and their implications for BD risk. In our studies, the specific parts of these regions that were functionally connected were the right pars orbitalis (BA47) and both the left and right

OFC (BA11). These specific regions are anatomically connected and have been shown to coactivate during reward tasks (Kelly, Uddin et al. 2010, de Schotten, Dell'Acqua et al. 2012, Yeterian, Pandya et al. 2012, Zald, McHugo et al. 2012, Snow 2016). Thus, we showed that greater FC between BA47 and BA11, specifically, are neural measures that distinguish youth at risk for BD from control groups. The specific mechanism by which this occurs may be an increased attempt to encode rewarding values of choice and decision-making options, suggesting a greater attunement to reward stimuli in OBP.

In parallel with previous studies, our findings primarily implicated the *right* vlPFC in reward processing circuitry in OBP. Studies have shown that relatives of individuals with BD, as well as younger adults in early stages of the disorder, have abnormally increased right vlPFC gray matter volume (Hajek, Cullis et al. 2013). This is in contrast to adults with BD in whom smaller right vlPFC gray matter volume was associated with longer illness duration (Hajek, Cullis et al. 2013). These findings suggest that right vlPFC volumes may decrease as BD progresses (Kalmar, Wang et al. 2009). Over time, we may thus speculate that OBP who are going to develop BD in the future will have progressively reduced right vlPFC volume, and this may potentially lead to a reduction in activity and/or FC with the OFC as BD develops.

Another additional finding was that OBP had lower dlPFC activity when processing angry faces versus shapes compared with OHP. This directly correlates previous studies showing lower dlPFC activity during emotional face processing (Tseng, Bones et al. 2015). Furthermore, the dlPFC is a key component of neural circuitries involved in emotion processing and regulation, as it has many connections with other prefrontal cortical and subcortical structures such as the OFC, thalamus, dorsal striatum, hippocampus, and secondary cortical association areas such as the posterior temporal, parietal, and occipital areas (Procyk and Goldman-Rakic

2006). Together, our findings correspond with the existing literature and suggest that OBP are less able to recruit the dlPFC, and potentially other prefrontal cortical and subcortical regions, when attempting to process angry emotions.

The final findings from our studies pertained to the right cingulum-cingulate gyrus and the forceps minor of the corpus callosum. As mentioned above, for the first time in the literature, we found that inverse WMT-activity relationships between right cingulum-cingulate gyrus length and cACC activity, as well as between forceps minor RD and rACC activity, when processing positive emotions distinguished OBP from OCP. The cingulum is the WMT that forms the white matter core of the ACC and has an essential role in emotion regulation (Papez 1937, Mufson and Pandya 1984, Wang, Jackowski et al. 2008, Bruni and Montemurro 2009). The rACC is located around the genu of the corpus callosum (Paus 2001), the part of the tract that gives rise to the forceps minor, which integrates emotion with language, attention, and sensorimotor functions (Bruni and Montemurro 2009, Sarrazin, d'Albis et al. 2015). This role is directly related to that of the rACC in integrating functions of emotion and cognition (Vogt, Finch et al. 1992, Devinsky, Morrell et al. 1995, Bush, Luu et al. 2000, Bishop, Duncan et al. 2004, Bissière, Plachta et al. 2008). The related anatomical and functional properties of the cingulum, forceps minor, and ACC thus come together to form WMT-activity relationships that uniquely distinguish OBP from OCP. Specifically, lower fiber collinearity in these WMTs was associated with lower activity in the ACC when processing happy faces. This may indicate that, in youth at risk for BD, abnormal myelination and/or more obliquely oriented fibers in the cingulum and forceps minor may contribute to lower activity in the ACC by reducing the integrity of connections between regions that are important to positive emotional processing (Morgan, Mishra et al. 2009). We may further speculate that the above patterns of greater activity in, and FC with, the ACC during

emotion regulation may reflect altered fiber alignment in prefrontal WMTs. This may contribute to why the rACC does not appear to be recruited to a normal extent during emotion processing but is then recruited ineffectively during more explicit emotion regulation. Altogether, this may reflect a failed compensatory mechanism in OBP that distinguishes them from the potentially less disadvantaged OCP who show increased ACC recruitment with lower WMT collinearity.

6.2.2 Relationships between Neural Measures and Symptomatology

Symptoms of depression, mania, affective lability, and anxiety have been identified as the strongest dimensions of psychopathology associated with BD risk (Hafeman, Merranko et al. 2016). It was thus important to relate significant neural findings to these symptoms to better understand the implications of these measures to the pathophysiology underlying risk for BD. In the studies laid out in this dissertation, our primary findings pertained to parent-reported affective lability and its relationship with the ACC.

Our analyses highlighted two main findings relating affective lability severity to activity in the rACC. In our first study, we found that greater right rACC activity when regulating attention away from happy faces positively correlated with greater parent-reported affective lability severity. In our third study, we identified a significant interaction between parent-reported affective lability severity and forceps minor RD on rACC activity to processing happy faces in OBP such that greater affective lability was associated with a greater inverse WMT-activity relationship. Our analyses also found a relationship between affective lability severity and the cACC. In our first study, we showed that changes in bilateral amygdala-left cACC FC to fearful faces positively correlated with changes in parent-reported affective lability severity over an approximate 2-year follow-up in all offspring. Together, these findings suggest a relationship

between affective lability symptoms and abnormal activity and/or FC in both the rostral and caudal ACC during tasks of emotion processing and regulation.

Affective lability is defined as "a predisposition to marked, rapidly reversible shifts in affective states, extremely sensitive to meaningful environmental events that might induce more modest emotional responses in normal individuals" (Siever and Davis 1991, Henry, Van den Bulke et al. 2008). Studies have postulated that one of the core abnormalities that is observed in individuals with BD is a hyperreactivity to environmental stimuli, which may lead to symptoms of affective lability (Henry, Van den Bulke et al. 2008). Affective lability has been shown to characterize individuals with BD during euthymic periods, suggesting that such emotional features characterize BD in between mood episodes (Henry, Van den Bulke et al. 2008). In addition, the stress reactivity to environmental factors that is characteristic of affective lability may also influence and increase the rate of relapses of depressive and manic episodes (Ellicott, Hammen et al. 1990). Individuals with BD may experience perpetual emotional lability because they feel emotions with higher intensities when faced with daily emotional stimuli (Henry, Van den Bulke et al. 2008). This global emotional hyperreactivity, even during euthymic periods, may facilitate relapses (Henry, Van den Bulke et al. 2008). Furthermore, affective lability may also underlie clinical states that are associated with BD, such as subclinical bipolarity, cyclothymia, ultra-rapid cycling, or even temperaments (Henry, Van den Bulke et al. 2008).

Studies have also suggested that symptoms of affective lability may underlie psychobiological dysregulation that contributes to the development of psychiatric illnesses (Siever and Davis 1991). Correlations have been observed between affective dimensions and early age of onset for BD, suggesting that symptoms of affective lability may be associated with the genetic heterogeneity that underlies BD (Bellivier, Golmard et al. 2001, Bellivier, Golmard et

al. 2003, Henry, Van den Bulke et al. 2008). Additionally, symptoms associated with affective lability have been found in unaffected relatives of individuals with BD, suggesting that this dimension may be a clinical risk marker predisposing to the development of affective disorders (Clayton, Ernst et al. 1994, Henry, Van den Bulke et al. 2008). Indeed, affective and emotional lability has been shown to be strong risk factors for the development of BD (Hafeman, Merranko et al. 2016).

In studies of BD, patients with early-onset BD have been shown to be more responsive to both positive and negative emotional stimuli than older patients (Leibenluft, Charney et al. 2003). In our analyses, we specifically identify relationships between affective lability and activity in the rACC when processing and regulating attention away from positive emotional stimuli (i.e. happy faces). As previously described, the rACC is the "affective division" of the ACC with roles in processing emotional conflict, integrating emotion and cognition (Vogt, Finch et al. 1992, Devinsky, Morrell et al. 1995, Bush, Luu et al. 2000, Bishop, Duncan et al. 2004, Bissière, Plachta et al. 2008), and suppressing amygdala activity, leading to reduced emotional responsivity (Etkin, Egner et al. 2006). The finding of greater right rACC activity when regulating attention away from happy faces may reflect abnormal recruitment of the rACC to downregulate amygdala activity, leading to increased symptoms of affective lability. Similarly, modulation of the inverse relationship between forceps minor RD and rACC activity by affective lability severity likely suggests that 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, Mishra et al. 2009). Taken together, it is thus possible that abnormal rACC activity when

processing and/or regulating attention away from positive emotions may represent a neural basis for affective lability severity as a clinical risk marker in youth at risk for BD.

Furthermore, a relationship between affective lability and the cACC was also identified in our analyses. As previously stated, the cACC is a part of the central executive control network with a more specific role in attentional task performance (Van Veen and Carter 2002, Haas, Omura et al. 2006, Margulies, Kelly et al. 2007). In comparison to the findings pertaining to the rACC when processing and regulating attention away from positive emotions, the relationship between changes in affective lability severity and changes in bilateral amygdala-left cACC FC, over time, was found when regulating attention away from negative (i.e. fearful) emotions. Given that patients with BD may be more affectively labile and more responsive to either positive or negative emotions (Leibenluft, Charney et al. 2003), we may further speculate that the rACC is implicated more in the processing and/or regulation of positive emotions, while the cACC is implicated more in the regulation of negative emotions. Together, abnormal activity and FC in and between these divisions of the ACC are likely important markers of a predisposition to greater affective lability severity in youth at risk for BD.

6.2.3 State-Dependent versus Trait-Dependent Neural Circuitries and Regions

Another way in which these analyses contribute to our understanding of BD risk is by examining whether the neural circuitries of emotion processing, emotion regulation, and reward processing are primarily state-dependent or trait-dependent. State-dependent neural circuitries would be expected to be differentially affected by mood states, such as during euthymic, depressed, and manic episodes (Van der Schot, Kahn et al. 2010). Trait-dependent circuitries, on the other hand, would be expected to remain stable across these different affective states (Van der Schot, Kahn

et al. 2010). Differentiating state-dependent and trait-dependent neural circuitries and regions would allow us to better understand the underlying pathophysiology of BD, and BD risk, and how these mechanisms either change or remain stable throughout mood states.

Previous studies have examined the state- and trait-dependent nature of neural regions and symptoms associated with emotion processing, emotion regulation, and reward processing neural circuitries. State-dependent findings have included results pertaining to amygdala activity during emotion processing and regulation (Van der Schot, Kahn et al. 2010, Townsend and Altshuler 2012), dlPFC activity during emotion processing (Van der Schot, Kahn et al. 2010), ACC activity during cognitive tasks (Strakowski, Delbello et al. 2005), left amygdala-OFC FC when viewing sad stimuli and amygdala-OFC FC when viewing happy stimuli (Versace, Thompson et al. 2010), and activity in limbic subcortical structures when examining cerebral metabolism (Strakowski, Delbello et al. 2005). Trait-dependent findings have included results pertaining to OFC activity during emotion processing (Van der Schot, Kahn et al. 2010), right amygdala-OFC FC when viewing sad stimuli (Versace, Thompson et al. 2010), abnormal ventral ACC, OFC, and VS activity when processing happy and neutral stimuli (Liu, Blond et al. 2012), PFC activity during emotion processing and regulation (Van der Schot, Kahn et al. 2010, Townsend and Altshuler 2012), vlPFC activity during a Stroop task (Blumberg, Leung et al. 2003), activity and choline concentrations in the striatum (Strakowski, Delbello et al. 2005), and symptoms of impulsivity (Swann, Pazzaglia et al. 2003, Swann, Dougherty et al. 2004, Najt, Perez et al. 2007, Peluso, Hatch et al. 2007, Swann, Lijffijt et al. 2009).

While the state- and trait-dependent natures of some of the above circuitries and regions overlap, several general themes can be noted. For example, regions such as the amygdala, ACC, and dlPFC tend to have more state-dependent properties during emotional processing and

regulation, while regions such as the vlPFC, OFC, and VS tend to have more trait-dependent properties during tasks pertaining to cognition or reward. The findings from our analyses directly parallel these broad themes. Because we were examining youth at risk for BD and not individuals who had already been diagnosed with BD, we were not able to examine neural structure and function in youth who were in different mood states (i.e. euthymic, depressed, or manic). We did, however, explore relationships between significant neural findings and symptoms. In doing so, we only found relationships between symptomatology (i.e. affective lability) and neural measures in emotion processing and regulation neural circuitry (i.e. right rACC activity when regulating attention away from happy faces, inverse relationships between right cingulum-cingulate gyrus length-cACC activity and forceps minor RD-rACC activity when processing happy faces, and changes in bilateral amygdala-left cACC FC when regulating attention away from fearful faces). Conversely, no relationships were found between symptomatology and neural measures in reward processing neural circuitry (i.e. right VS-left cACC FC to loss and right pars orbitalis-OFC FC to reward). Thus, our findings correspond with and contribute to the existing literature by suggesting that neural regions implicated in emotion processing and regulation neural circuitries, such as the ACC, are primarily state-dependent in nature, while neural regions implicated in reward processing neural circuitries, such as the VS, vlPFC, and OFC, are more trait-dependent.

Possible implications for such findings include more targeted diagnostic and treatment interventions in youth with, and at risk for, BD. For example, interventions related to emotion processing and regulation neural circuitries may be more effective when patients are in a particular mood state, such as when a patient is depressed, manic, euthymic, or experiencing particularly high levels of a symptom such as affective lability. Interventions pertaining to

reward processing neural circuitry, on the other hand, may be effective at any time during the course of a patient's illness because this circuitry is more reflective of traits that are intrinsic to BD and BD risk, regardless of mood state.

6.2.4 Presence of Non-BD Psychopathology

Another aspect of BD risk that was examined throughout these analyses was that of non-BD psychopathology. As previously discussed, OBP are at great familial risk for developing BD (Smoller and Finn 2003, Merikangas, Akiskal et al. 2007, Singh and Chang 2013, Phillips and Swartz 2014), but they are also at an increased risk for other non-BD mood and anxiety disorders (Chang, Steiner et al. 2000). While it is possible that these non-BD disorders may confound neural findings, these disorders are common in youth at risk for BD and were thus important additional factors to consider when performing our studies. By including both at-risk youth with and without these disorders and performing analyses on each group, separately, we attempted to determine the extent to which significant neural findings were confounded, or not, by present psychopathology.

In all of our studies, we repeated analyses of main findings separating youth into those with and without non-BD disorders. In the analysis examining activity and FC in emotion processing and regulation neural circuitries, group differences in greater bilateral amygdala-left cACC FC to neutral faces was only observed in at-risk youth who *did not* have non-BD disorders. Similarly, when examining activity and FC in reward processing neural circuitry, group differences in lower right VS-left cACC FC and greater right pars orbitalis-OFC FC were only observed in at-risk youth who *did not* have non-BD disorders. Likewise, when exploring WMT-activity relationships, group differences in right cingulum-cingulate gyrus length-cACC

activity and forceps minor RD-rACC activity when processing happy faces were also only observed in at-risk youth who *did not* have non-BD disorders. None of the main findings in any of these three studies were observed in at-risk youth who *did* have non-BD disorders.

There are several possible explanations for why these main findings were only observed in youth without non-BD psychopathology. One explanation is that these measures are potential markers of risk for the future development of BD. In support of this claim, we may speculate that OBP who have already developed a non-BD psychiatric disorder at the time of these studies are less likely to additionally develop BD. OBP without non-BD disorders, on the other hand, have yet to develop any psychiatric disorders, and they are still at great familial risk for developing BD. Thus, it is possible that these main neural findings are markers of risk for BD in these presently healthy at-risk youth. This claim would be further supported by the fact that worsening symptoms of affective lability were associated with several of these main findings, as described previously.

A second explanation, however, is that these measures represent markers of resilience that protect against the development of BD. Support for this claim includes the fact that comorbidities in patients with BD are common. For example, in one study, 80% of children with BD had a comorbid diagnosis of ADHD (Chang, Steiner et al. 2000). Thus, it is also possible that OBP with non-BD disorders are more at risk for developing a comorbid diagnosis of BD in the future, while OBP without non-BD disorders represent a group of presently healthy offspring who will continue to remain resilient to a BD diagnosis. Indeed, in our sample of follow-up youth, 2 OBP have developed a diagnosis of BD since their first scan: one was previously in the sample of youth without non-BD disorders, and one was previously in the sample of youth with a non-BD disorder, having had previous diagnoses of MDD and an Eating Disorder. More

longitudinal data are thus needed to definitively determine whether these neural findings are markers of risk or resilience in at-risk youth.

6.2.5 Potential Confounding Factors of Medications

Another topic that is worth noting is that of medications. Medication exposure may be a potential confound in neuroimaging studies of BD and BD risk, as medications have direct effects on neural function in order to alter the course of disease and treat psychiatric symptoms (Hafeman, Chang et al. 2012). While a recent review determined that the effects of psychotropic medications do not appear to provide alternative explanations for differences in neural structure or function when comparing patients with BD to healthy controls (Hafeman, Chang et al. 2012), we nonetheless wanted to examine potential effects of medication on our findings.

When examining activity and FC in emotion processing and regulation neural circuitries, we found that removing five medicated OBP and six medicated OCP from the analyses affected the significance of the findings that showed relationships with affective lability severity. Specifically, significance was reduced for the differences between right rACC activity when regulating attention away from happy faces and bilateral amygdala-left cACC FC when regulating attention away from fearful faces during EF-2-BACK performance in OBP versus OCP, as well as the relationship between change in the latter measure and change in affective lability over follow-up. When we compared affective lability severity in medicated and unmedicated OBP, however, we found that medicated OBP had greater symptom severity. Thus, by removing medicated youth from the analyses, we were no longer examining some of the most affectively labile OBP who were potentially at some of the greatest risk for developing BD in the future. This led us to hypothesize that greater right rACC activity when regulating attention away

from happy faces and greater bilateral amygdala-left cACC FC when regulating attention away from fearful faces may represent markers of BD risk in higher-risk OBP who are more affectively labile. We were not able, however, to determine the exact nature of the potential effects that medications had on these neural measures.

When examining activity and FC in reward processing neural circuitry, we did not find any significant differences in findings when we removed the six OBP and eight OCP taking antidepressant, antipsychotic, mood stabilizer, stimulant, and non-stimulant medications. Thus, the findings of right VS-left cACC FC to loss and right pars orbitalis-OFC FC to reward did not appear to be affected by medication effects. Similarly, when examining WMT-activity relationships in emotion processing neural circuitry, we did not find any significant differences in findings when we removed the six OBP and six OCP taking medications. Thus, the relationships of right cingulum-cingulate gyrus length-cACC activity and forceps minor RD-rACC activity when processing happy faces also did not appear to be affected by medication effects.

In summary, medications affected only our main findings that pertained to emotion regulation neural circuitry, while medication effects were not observed for any main findings pertaining to emotion processing or reward processing neural circuitries. Review studies have generally found that psychotropic medications do not provide alternative explanations for differences in neural structure or function when comparing patients with BD to healthy controls (Hafeman, Chang et al. 2012). Thus, the few medication effects that were observed in our study of emotion regulation may reflect the high-risk nature of the offspring. By taking these high-risk individuals out of the analyses, we likely removed youth at risk for BD whose neural abnormalities differed the most from control groups. Therefore, the fact that medication effects

were observed in this analysis may, in fact, support our hypothesis that these neural measures are potential markers of risk for the future development of BD. The effects of medication in youth at risk for BD and other psychiatric disorders is complex, however, and warrants continued examination when studying the underlying pathophysiology of BD and BD risk.

6.2.6 Influence of Age and Development

6.2.6.1 Discussion of Typical Brain Development

In neuroimaging studies that examine children and adolescents, it is important to consider the potential implications of brain development. Throughout childhood and adolescence, increases in white matter volumes (likely reflecting increasing myelination) occur globally with specific increases occurring in the frontal, parietal, and occipital cortices (Sowell, Trauner et al. 2002). Conversely, gray matter volumes peak at about 12 years of age in frontal and parietal cortices and then decrease from early childhood to post-adolescence in a nonlinear manner, likely reflecting the pruning of neural connections (Huttenlocher 1979, Reiss, Abrams et al. 1996, Giedd, Blumenthal et al. 1999, Courchesne, Chisum et al. 2000). Such developmental changes may be related to a refinement or increased efficiency in connections between prefrontal and subcortical regions throughout childhood and adolescence in typically-developing youth (Herba and Phillips 2004). This developmental perspective may shed light on important implications for emotion and reward circuitry in youth at risk for BD.

For example, in a typically-developing brain, ventromedial areas of the PFC (e.g. ACC, OFC) develop relatively earlier than lateral PFC regions (e.g. vlPFC, dlPFC) (Fuster 2002). These former regions are primarily involved in the control of emotional behaviors, while the latter regions are more involved in higher executive functions (Fuster 2002). Additionally, the

explicit processing of emotional faces continues to develop from early childhood into adolescence (Camras and Allison 1985, Chung and Thomson 1995, De Sonneville, Verschoor et al. 2002). Together, these findings suggest that neural systems that are implicated in emotion processing and regulation neural circuitries may not be fully mature into adulthood (Phillips, Ladouceur et al. 2008). Additionally, this may contribute to the reason why children and adolescents are often unable to regulate their emotions, leading to behavioral disturbances that occur without insight or subjective awareness (Goodwin and Jamison 2007). Furthermore, studies have shown that the accumbens develops relatively earlier than PFC regions such as the OFC (Galvan, Hare et al. 2006). These findings suggest that, as subcortical systems mature, they may become disproportionately activated relative to top-down control systems that mature later in development (Galvan, Hare et al. 2006). This may bias adolescents toward seeking immediate versus long-term gains and, ultimately, may underlie risk-taking behavior (Galvan, Hare et al. 2006).

There are several considerations to note when examining children and adolescents at risk for BD. For example, youth with BD have been shown to develop decreased volumes in the amygdala, ACC, dlPFC, OFC, and nucleus accumbens (Blumberg, Fredericks et al. 2005, Dickstein, Milham et al. 2005, Gogtay, Ordonez et al. 2007). These studies have suggested that such abnormal patterns of cortical development may reflect affective dysregulation (Gogtay, Ordonez et al. 2007). Altogether, studies of brain development in youth highlight the fact that many structural changes are occurring throughout childhood and adolescents. Thus, while studies have suggested mechanisms that may underlie emotional dysregulation and impulsive or risk-taking behavior in typically-developing youth, atypical brain development in offspring at risk for BD during these critical periods may predispose them to even more severe behavioral problems

that may then lead to detrimental outcomes, such as the development of mood or anxiety disorders.

Alternatively, the fact that it is normal for children and adolescents to exhibit behaviors related to abnormal emotion and reward function may also suggest that abnormalities seen in offspring at risk for BD may reflect compensatory, rather than vulnerability, mechanisms. In this way, abnormalities that are observed in OBP that parallel those in typically-developing individuals may indicate that the way in which their brains are developing may be attempting to compensate for their genetic predisposition to psychopathy and, in fact, protect against the future development of psychiatric disorders. Longitudinal studies of neural structure and function that additionally examine developmental patterns in typically-developing and at-risk youth are necessary to fully understand how brain maturation leads to the development of, or protection against, BD in at-risk offspring.

6.2.6.2 Additional Analyses Examining Effects of Age

In all of our studies, we examined the effects of age and pubertal development on significant findings through correlation analyses. In doing so, we did not find any significant correlations between age and any significant neural or symptom measure in any of our three analyses. With a participant age range of 8-17 years, however, we wanted to further examine whether or not OBP showed similar patterns of neural and symptom measures with increasing age when compared to OCP and OHP. To do this, we explored age-by-group interactions for all significant findings in each study. For each finding, we performed a linear regression with the neural or symptom measure as the outcome measure and age, group, and an age X group interaction term as predictor measures (Tables 36-38). This was done separately for each group pair (i.e. OBP versus OCP, OBP versus OHP, and OCP versus OHP).

No significant age-by-group interactions were found for any of the main neural or symptom findings for our first study examining activity and FC in emotion processing and regulation neural circuitries. These findings included right rACC activity to happy faces during EF-2-BACK and EF-0-BACK performance, bilateral amygdala-left cACC FC to fearful, happy, and neutral faces during EF-2-BACK performance, left dlPFC activity to angry faces during the DFT, and CALS-P scores (Table 36).

Table 36: Exp 1. Group-by-Age Interactions

	OBP vs. OCP						OBP vs. OHP						OCP vs. OHP					
	Main Effect			Interactions			Main Effect			Interactions			Main Effect			Interactions		
	F	Sig.	R^2		t	Sig.	F	Sig.	R^2		t	Sig.	F	Sig.	R^2		t	Sig.
Right rACC Activity to Happy Faces (2-Back)	2.979	0.039*	0.14	Age	0.358	0.721	0.915	0.441	0.054	Age	0.574	0.568	0.773	0.515	0.049	Age	-0.063	0.95
				Group	-0.396	0.694				Group	-0.174	0.863				Group	0.129	0.898
				Age X Group	0.834	0.408				Age X Group	0.338	0.737				Age X Group	-0.295	0.769
Right rACC Activity to Happy Faces (0-Back)	0.285	0.836	0.015	Age	0.859	0.294	2.729	0.054	0.146	Age	0.475	0.637	2.55	0.068	0.145	Age	0.608	0.546
				Group	0.409	0.684				Group	-0.228	0.821				Group	-0.438	0.664
				Age X Group	-0.351	0.727				Age X Group	-0.099	0.922				Age X Group	0.133	0.895
Amygdala – Left cACC FC to Fearful Faces (2-Back)	4.534	0.007*	0.198	Age	-0.351	0.727	2.31	0.088	0.126	Age	-1.911	0.062	1.176	0.329	0.073	Age	-0.732	0.468
				Group	2.186	0.033*				Group	-0.359	0.721				Group	-1.706	0.095
				Age X Group	-1.755	0.085				Age X Group	0.538	0.593				Age X Group	1.607	0.115
Amygdala – Left cACC FC to Happy Faces (2-Back)	4.998	0.004*	0.214	Age	0.727	0.47	1.371	0.263	0.079	Age	-1.218	0.229	2.244	0.096	0.13	Age	0.05	0.961
				Group	2.243	0.029*				Group	-0.3	0.766				Group	-1.952	0.057
				Age X Group	-1.745	0.087				Age X Group	0.479	0.634				Age X Group	1.767	0.084
Amygdala – Left cACC FC to Neutral Faces (2-Back)	6.387	0.001*	0.258	Age	2.06	0.044*	0.615	0.609	0.037	Age	0.587	0.56	4.51	0.008*	0.231	Age	1.848	0.071
				Group	2.277	0.027*				Group	0.456	0.651				Group	-1.309	0.197
				Age X Group	-1.72	0.091				Age X Group	-0.309	0.758				Age X Group	1.015	0.315
Left dlPFC Activity to Angry Faces (DFT)	1.295	0.285	0.066	Age	1.767	0.083	4.333	0.009*	0.213	Age	1.371	0.177	3.432	0.025*	0.186	Age	1.776	0.082
				Group	0.45	0.655				Group	0.075	0.94				Group	-0.264	0.793
				Age X Group	-0.549	0.585				Age X Group	-0.454	0.652				Age X Group	-0.04	0.968
CALS-P	1.284	0.289	0.065	Age	0.509	0.613	3.501	0.022*	0.18	Age	0.564	0.576	2.183	0.103	0.127	Age	0.402	0.69
				Group	-0.157	0.876				Group	0.242	0.81				Group	0.599	0.552
				Age X Group	0.443	0.659				Age X Group	0.135	0.893				Age X Group	-0.321	0.75

Similarly, no age-by-group interactions were found for any of the main nerual or symptom findings for our third study examining WMT-activity relationships in emotion processing neural circuitry. These findings included right cingulum-cingulate gyrus length, bilateral cACC activity when processing positive emotions, forceps minor RD, bilateral rACC activity when processing positive emotions, and CALS-P scores (Table 37).

Table 37: Exp 3. Group-by-Age Interactions

	OBP vs. OCP						OBP vs. OHP						OCP vs. OHP					
	Main Effect			Interactions			Main Effect			Interactions			Main Effect			Interactions		
	F	Sig.	R^2		t	Sig.	F	Sig.	R^2		t	Sig.	F	Sig.	R^2		t	Sig.
Right Cingulum-Cingulate Gyrus Length	0.797	0.501	0.04	Age	-0.911	0.366	1.129	0.346	0.061	Age	0.716	0.477	0.551	0.65	0.032	Age	0.603	0.549
				Group	0.154	0.878				Group	1.553	0.127				Group	1.265	0.212
				Age X Group	0.047	0.962				Age X Group	-1.403	0.166				Age X Group	-1.28	0.206
cACC Activity to Happy Faces (DFT)	2.684	0.055	0.122	Age	1.319	0.192	1.852	0.149	0.097	Age	1.597	0.116	1.208	0.317	0.068	Age	0.245	0.807
				Group	-2.008	0.049*				Group	-0.76	0.451				Group	0.85	0.399
				Age X Group	1.771	0.082				Age X Group	0.785	0.436				Age X Group	-0.614	0.542
Forceps Minor RD	0.616	0.608	0.031	Age	-1.043	0.301	0.377	0.77	0.021	Age	-0.303	0.763	0.066	0.978	0.004	Age	0.081	0.936
				Group	0.496	0.622				Group	0.711	0.48				Group	0.404	0.688
				Age X Group	-0.597	0.553				Age X Group	-0.744	0.46				Age X Group	-0.377	0.708
rACC Activity to Happy Faces (DFT)	1.429	0.243	0.069	Age	2.009	0.049*	0.396	0.756	0.022	Age	0.658	0.513	0.884	0.456	0.05	Age	1.001	0.322
				Group	0.482	0.631				Group	-0.463	0.645				Group	-0.779	0.44
				Age X Group	-0.538	0.593				Age X Group	0.437	0.664				Age X Group	0.792	0.432
CALS-P	2.131	0.107	0.102	Age	0.897	0.373	4.05	0.012*	0.192	Age	0.836	0.407	1.706	0.178	0.095	Age	0.6	0.551
				Group	-0.282	0.779				Group	0.051	0.959				Group	0.541	0.591
				Age X Group	0.674	0.503				Age X Group	0.404	0.688				Age X Group	-0.253	0.801

For our second study examining activity and FC in reward processing neural circuitry, no age-by-group interactions were found for right VS-left cACC FC to loss during the reward task (Table 38).

Table 38: Exp 2. Group-by-Age Interactions

	OBP vs. OCP						OBP vs. OHP						OCP vs. OHP					
	Main Effect			Interactions			Main Effect			Interactions			Main Effect			Interactions		
	F	Sig.	R^2		t	Sig.	F	Sig.	R^2		t	Sig.	F	Sig.	R^2		t	Sig.
Right VS – Left cACC FC to Loss (Reward)	2.722	0.049*	0.085	Age	0.474	0.637	0.918	0.435	0.027	Age	-0.26	0.795	0.368	0.776	0.011	Age	0.409	0.683
				Group	0.453	0.652				Group	-0.163	0.871				Group	-0.49	0.625
				Age X Group	-0.954	0.343				Age X Group	-0.078	0.938				Age X Group	0.59	0.556
Right Pars Orbitalis – Left OFC FC to Winning (Reward)	6.104	0.001*	0.172	Age	2.523	0.013*	1.529	0.211	0.043	Age	0.563	0.574	3.668	0.015*	0.101	Age	2.603	0.011*
				Group	2.998	0.004*				Group	0.899	0.371				Group	-1.531	0.129
				Age X Group	-2.58	**0.012***				Age X Group	-0.608	0.544				Age X Group	1.426	0.157
Right Pars Orbitalis – Right OFC FC to Winning (Reward)	7.705	<0.001	0.208	Age	1.433	0.155	1.978	0.122	0.055	Age	-1.12	0.265	3.322	0.023*	0.092	Age	1.449	0.15
				Group	3.89	<0.001*				Group	0.677	0.5				Group	-2.397	0.018*
				Age X Group	-3.354	**0.001***				Age X Group	-0.345	0.731				Age X Group	2.23	**0.028***

There were, however age-by-group interactions found for the other two main findings in this analysis. For right pars orbitalis-left OFC FC to reward, age-by-group interactions were found between OBP and OCP ($F(3,88) = 2.722$, $p = 0.001$ (0.004, corrected), $R^2 = 0.172$; $t = -2.58$, $p = 0.012$ (0.048, corrected)) (Figure 33). The relationship between age and right pars

orbitalis-left OFC FC to reward was inverse in OBP and positive in OCP. The relationship for OHP fell in between those of OBP and OCP.

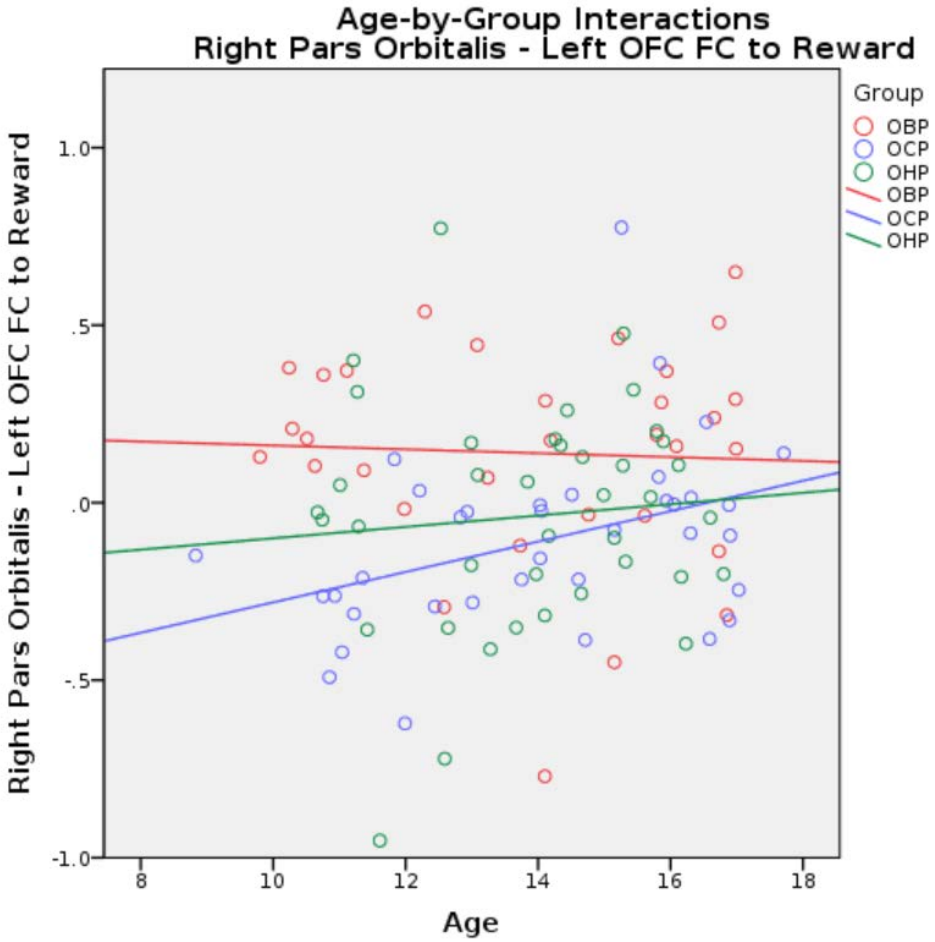

Figure 34: Age-by-Group Interactions for Right Pars Orbitalis-Left Orbitofrontal Cortex Functional Connectivity to Reward

For right pars orbitalis-right OFC FC to reward, age-by group interactions were also found between OBP and OCP ($F(3,88) = 7.705$, $p < 0.001$ (< 0.001, corrected), $R^2 = 0.208$; $t = -3.354$, $p = 0.001$ (0.004, corrected)), as well as between OCP and OHP ($F(3,98) = 3.322$, $p =$

0.023 (0.092, corrected), $R^2 = 0.092$; t = 2.23, p = 0.028 (0.112, corrected)) (Figure 34). Only the interaction between OBP and OCP survived Bonferroni corrections for 4 tests ($p < 0.013$), however. Similar to above, the relationship between age and right pars orbitalis-right OFC FC to reward was inverse in OBP and positive in OCP, and the relationship for OHP fell in between those of OBP and OCP.

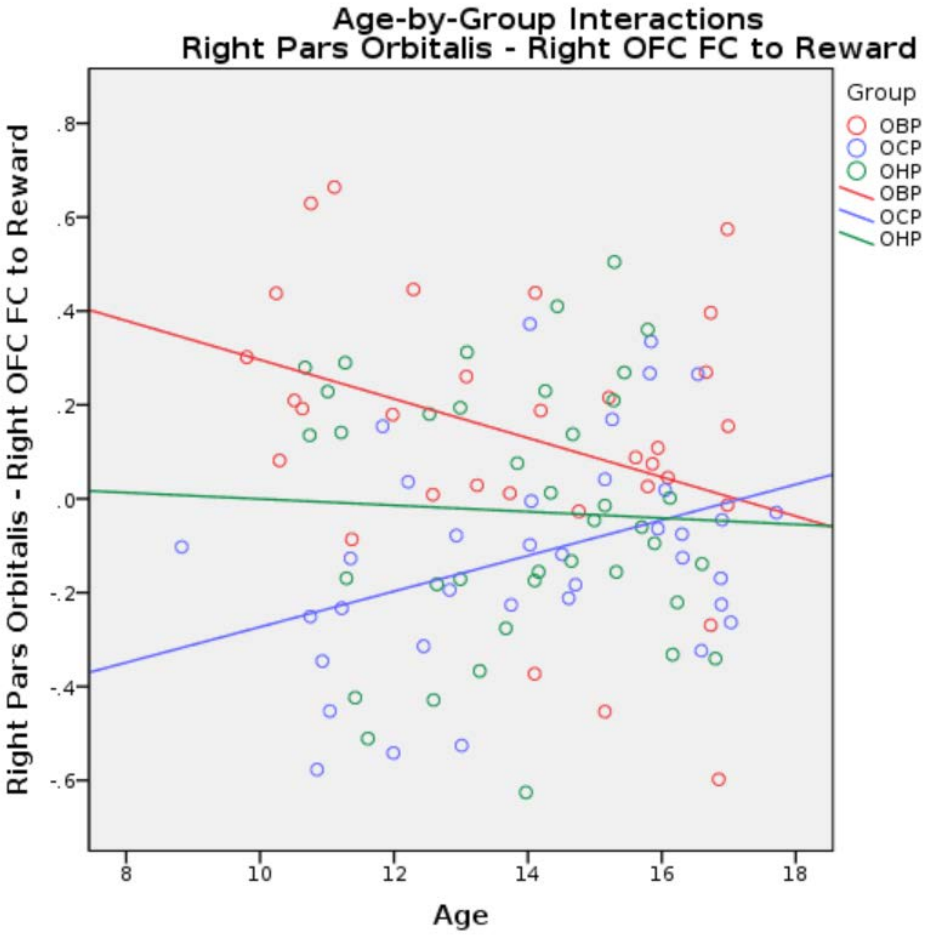

Figure 35: Age-by-Group Interactions for Right Pars Orbitalis-Right Orbitofrontal Cortex Functional Connectivity to Reward

There are several possible explanations for these findings. On one hand, these findings may suggest that FC between the right pars orbitalis and both the left and right OFC strengthens throughout development in OCP but weakens throughout development in OBP. This is particularly interesting given our findings that, in our current sample, OBP had increased FC between these regions compared with both OCP and OHP. Given these findings, in conjunction with the knowledge that the prefrontal cortex does not reach full maturity until the third decade of life (Gogtay, Giedd et al. 2004, O'Donnell, Noseworthy et al. 2005), we may postulate that, over time, right pars orbitalis-OFC FC will continue to weaken in OBP and continue to strengthen in OCP, causing these neural markers to converge to a pattern more similar to that of OHP. If this were the case, then this would suggest that the right pars orbitalis-OFC FC measures are more likely representative of resilient mechanisms that protect against the future development of psychopathology.

On the other hand, we may also speculate that younger OBP are more at risk for BD than older OBP because they have more time to develop the disorder. In contrast, the older an individual becomes without having developed BD, the less likely they may be to ever develop the disorder. If this were true, then the younger, more at-risk offspring may be driving the differences in right pars orbitalis-OFC FC that are observed between OBP and both OCP and OHP. This would then suggest that these neural measures may, in fact, be markers of risk for the future development of BD. More longitudinal data is necessary to determine which hypothesis is more likely.

6.2.7 Differences between BD and Other Psychiatric Disorders

It is worthy to mention differences in emotion and reward function between BD and other psychiatric disorders. For example, there are several differences to note between BD and MDD regarding emotion processing and regulation. In BD, structural and functional abnormalities in emotion circuitry lead to an oversensitive, but dysfunctional, neural system that identifies emotional significance and produces affective states with impairment in the regulation of subsequent emotional behavior (Phillips, Drevets et al. 2003). This results in mood lability, a greater tendency to enter into an affective state in response to environmental stimuli, and impaired emotional regulation (Phillips, Drevets et al. 2003). Conversely, in MDD, structural and functional neural abnormalities lead to a restricted emotional range with a bias toward the perception of negative emotions (Phillips, Drevets et al. 2003). This primarily results in symptoms of depressed mood and anhedonia (Phillips, Drevets et al. 2003). Taken together with our findings, these differences may contribute to why abnormal symptoms of affective lability, as opposed to symptoms of depression, were related to neural abnormalities that distinguished OBP from control groups.

Additionally, there are distinct differences between BD and MDD in reward processing circuitry. For example, in MDD, neural abnormalities in reward processing (such as reduced activation in the VS and ACC (Pizzagalli, Holmes et al. 2009)) lead to a reduced ability to modulate behavior in response to intermittent rewards (Pizzagalli, Iosifescu et al. 2008, Vrieze, Pizzagalli et al. 2013), as well as blunted processing of incentive salience, incentive motivation, and reinforcement learning (Whitton, Treadway et al. 2015). This may lead to symptoms of anhedonia and reduced reward-seeking behaviors (Rawal, Collishaw et al. 2013, Whitton, Treadway et al. 2015). Specific findings that distinguish BD from MDD include heightened

activation in the left vlPFC during reward anticipation (Chase, Nusslock et al. 2013), as well as heightened reward-related activation, specifically in regions such as the VS (Caseras, Lawrence et al. 2013, Mason, O'sullivan et al. 2014, Trost, Diekhof et al. 2014)). This may lead to symptoms of mania or hypomania and greater tendencies to seek risks and rewards in BD compared with MDD (Whitton, Treadway et al. 2015). These differences between BD and MDD specifically parallel our findings of greater FC between the vlPFC and OFC during reward processing in OBP.

6.2.8 Conceptualization of BD in Terms of Emotion and Reward Neural Circuitries

BD has been conceptualized as a disorder of abnormalities in prefrontal cortical-amygdala-centered emotion circuitry and prefrontal cortical-striatal-centered reward circuitry (Phillips and Swartz 2014). In particular, studies have highlighted the roles of functioning within and between the vlPFC and amygdala which contribute to emotion dysregulation (Hariri, Bookheimer et al. 2000, Davis and Whalen 2001, Swanson 2003, Goldin, McRae et al. 2008, Phillips, Ladouceur et al. 2008), as well as the roles of functioning within the (primarily left-sided) vlPFC and OFC which contribute to heightened reward sensitivity (Knutson and Wimmer 2007, Schmidt, Cléry-Melin et al. 2009, Sesack and Grace 2010, Grabenhorst and Rolls 2011). Taken together with studies hypothesizing that the left hemisphere is important for approach-related emotions (Davidson, Irwin et al. 2003), these left-sided neural findings in emotion and reward circuitries may predispose individuals with, and at risk for, BD to heightened emotion and reward processing, which may contribute to symptoms of mania or hypomania (Phillips and Swartz 2014). Taken together, these findings suggest that BD can be conceptualized as a disorder of dysfunctional bilateral prefrontal cortical-amygdala emotion circuits and overactive left-sided

prefrontal cortical-striatal reward circuits that, together, result in emotional lability, emotional dysregulation, and reward sensitivity, all of which characterize BD (Phillips and Swartz 2014).

Our findings contribute to this conception in several ways. First, we also observed abnormalities in the bilateral prefrontal cortex and amygdala in emotion circuitry. Specifically, we observed inverse relationships between *bilateral* rACC and cACC and prefrontal WMT structure when processing happy faces, greater *right* rACC activity when regulating attention away from happy faces, and greater *bilateral* amygdala-*left* cACC FC when regulating attention away from all emotional faces. Second, we also observed abnormalities in left-sided prefrontal cortical-striatal reward circuitry. Specifically, we observed FC between the right VS and the *left* cACC when processing loss, as well as between the right pars orbitalis and both the right and *left* OFC when processing reward. Additionally, differences in FC between the *left* pars orbitalis and both the right and *left* OFC were observed when comparing OBP to OCP. Thus, our findings parallel established conceptualizations of BD and further suggest that the ACC, and particularly the right rACC and left cACC, is a key region that is implicated in both abnormal emotion and reward circuitry in offspring at risk for BD. Abnormalities in the ACC, as well as other prefrontal cortical and subcortical regions, likely contribute to the emotional lability, emotional dysregulation, and reward sensitivity characteristics of BD that predispose individuals with, and at risk for, the disorder to greater symptoms of affective lability and mania.

6.2.9 Summary of Contributions

In summary, we contributed to the neural model of BD risk in several ways. First, we identified the ACC as a region with primary importance in emotion processing, emotion regulation, and reward processing neural circuitries. Specifically, the rACC appears to be implicated more in

processing and regulating positive emotions, and the cACC seems to have greater roles in processing and regulating both positive and negative emotions, as well as in processing loss. Second, we either found novel roles for, or supported existing literature regarding, other regions implicated in these circuitries, namely the amygdala, VS, vlPFC, OFC, and dlPFC. Third, we highlighted the importance of affective lability symptoms in youth at risk for BD and showed relationships between this symptom measure and activity in, and FC with, the ACC during emotion processing and regulation. Fourth, we provided additional support for the state-dependent nature of emotion processing and regulation neural circuitries in contrast to the more trait-dependent nature of reward processing circuitry. Fifth, we examined the effects of present non-BD psychopathology in at-risk youth and developed several hypotheses regarding the implications of these findings. Sixth, we explored the potential confounding factors of medications and determined that the few medication effects that were observed pertained primarily to emotion regulation neural circuitry and may have, in fact, provided additional support for the hypothesis that these neural findings are potential measures of risk for BD. Finally, we examined the influence of age and development on our main findings and found that the effects of age on right pars orbitalis-OFC FC may implicate these findings as measures of either protection against, or risk for, the future development of BD. Overall, the analyses laid out in this dissertation contribute significantly to our current understanding of the pathophysiology underling BD risk.

6.3 IMPLICATIONS FOR THE MANAGEMENT OF BD

There are several ways in which the findings from this dissertation may aid in the identification and management of patients with, and at risk for, BD. In this section, we will discuss current diagnostic and treatment strategies for BD and propose ways in which the findings presented above may improve upon these methods in at-risk youth.

6.3.1 Diagnosis of BD

6.3.1.1 Current Diagnostic Strategies for BD

The absence of objective markers of pathophysiological processes that underlie BD, as well as the heterogeneity within and overlap between BD and other psychiatric illnesses, causes great difficulty when attempting to diagnose BD in clinical practice (Phillips and Kupfer 2013). On average, it takes between 5 and 10 years to properly diagnose BD after illness onset (Baldessarini, Tondo et al. 2007). One of the most frequent misdiagnoses in patients with BD is unipolar depression. Reasons for this include the facts that patients with BD often have a higher prevalence of depressive symptoms, have less clear histories of mania or hypomania, spend more time in depressive episodes than in either manic or hypomanic episodes, and preferentially recognize and seek treatment for depressive versus manic or hypomanic symptoms (Hirschfeld, Lewis et al. 2003, Judd, Schettler et al. 2003, Goodwin and Jamison 2007, Phillips and Kupfer 2013). Studies have reported that only 20% of patients with BD are properly diagnosed with the disorder within the first year of them seeking treatment for depressive episodes (Hirschfeld, Lewis et al. 2003). The misdiagnosis of BD as unipolar depression can lead to serious consequences, such as the inappropriate prescription of drugs and poor clinical and functional

outcomes for patients (Hirschfeld, Lewis et al. 2003, Baldessarini, Salvatore et al. 2010, Goodwin 2012, Valentí, Pacchiarotti et al. 2012). It is thus very important to find ways to better diagnosis BD, particularly during its early stages, in order to prevent these consequences associated with misdiagnosis (Phillips and Kupfer 2013).

Several strategies currently exist to help improve the diagnosis of BD, including changes to the DSM-V which may help physicians more accurately diagnose BD during standard clinical assessments (Phillips and Kupfer 2013). One such change is the focus on using more dimensional measures when defining BD, including subthreshold symptoms associated with BD, which have been associated with shorter times to future relapse (De Dios, Ezquiaga et al. 2012, Phillips and Kupfer 2013). In accordance with this change, new clinical rating scales have been developed that include assessments of subthreshold symptoms, such as the Bipolar Inventory Symptoms Scale and the Hypomania Checklist (Angst, Adolfsson et al. 2005, Bowden, Singh et al. 2007). Another strategy is the use of neuroimaging methods to identify biological measures and potential neural markers which may help inform the diagnosis of BD (Phillips and Kupfer 2013). Using neuroimaging techniques to study structural and functional abnormalities in neural circuitries pertaining to emotion and cognition in at-risk populations has the potential to identify neural measures that distinguish BD from other, commonly misdiagnosed disorders, such as unipolar depression (Phillips and Vieta 2007, Craddock and Sklar 2013, Phillips and Kupfer 2013). Additionally, relating these neural measures to subthreshold symptomatology may better characterize the dimensional nature of BD, allowing for diagnostic strategies that focus on the underlying pathophysiological processes of the disorder (Phillips and Kupfer 2013). This is in direct correlation with the proposal by the Research Domain Criteria (RDoC) of the US National Institute of Mental Health that the classification of psychiatric illnesses should be based on

dimensions of such pathophysiological processes rather than phenomenological observations (Insel, Cuthbert et al. 2010).

Once these pathophysiological processes are better understood, pattern recognition approaches may be used to apply machine learning to the clinical diagnosis of BD. These approaches can aid in the development of algorithms to allow computers to classify patterns of neural activity which can then be used to help make decisions about clinical diagnoses (Haynes and Rees 2006, Phillips and Kupfer 2013). Several studies have applied the combination of pattern recognition with neuroimaging techniques to the diagnosis of BD. One study found that patterns of lower whole-brain neural activity to intense happy faces could distinguish BD type I from unipolar depression and healthy controls (Mourão-Miranda, Almeida et al. 2012). Another study determined that blood flow to the subgenual ACC at rest could distinguish BD type I from unipolar depression (Almeida, Mourao-Miranda et al. 2013). A third study found that structural MRI could be used to distinguish BD from schizophrenia and healthy controls (Schnack, Nieuwenhuis et al. 2014). While these studies focused on patients who already exhibited the symptoms associated with a BD diagnosis, few studies have attempted to use pattern recognition approaches to identify youth at risk for developing the diagnosis in the future. One study found that machine learning approaches combined with activity during the presentation of neutral faces helped predict which youth at risk for BD were at higher risk for developing a psychiatric mood or anxiety disorder (Mourão-Miranda, Oliveira et al. 2012). In this study, however, none of the at-risk individuals went on to develop a diagnosis of BD (Mourão-Miranda, Oliveira et al. 2012). Thus, more work is necessary to determine how machine learning can be combined with neuroimaging techniques to examine youth at risk for BD and predict which individuals will

eventually develop BD, allowing for earlier interventions and overall better outcomes for these individuals.

The identification of neural abnormalities in BD and risk for BD may also be combined with other techniques to aid in the diagnosis of the disorder. For example, lipid oxidative stress has been identified as a potential pathophysiological mechanism underlying WMT abnormalities in BD (Phillips and Kupfer 2013). In one study of BD, lower WMT collinearity was associated with increased serum measures of lipid oxidative stress (Versace, Andreazza et al. 2014). Elevated amounts of lipid oxidative stress have also been observed in neural regions important to emotion processing, emotion regulation, and reward processing neural circuitries, such as the ACC and prefrontal cortex, specifically BA10 (Wang, Shao et al. 2009, Andreazza, Shao et al. 2010). Thus, detecting oxidative stress by peripherally analyzing serum measures and relating these measures to specific WMTs and neural regions implicated in BD and BD risk may provide additional mechanisms by which BD can be diagnosed earlier and with greater accuracy.

6.3.1.2 Contribution of this Dissertation to Diagnostic Strategies for BD

The work presented in this dissertation can contribute to current diagnostic strategies for BD in several ways. The first pertains to clinical assessments, which are already used in clinical practice to aid in the diagnosis of BD. As mentioned above, affective lability is one of the four symptoms identified as the strongest dimensions of psychopathology associated with BD risk (Hafeman, Merranko et al. 2016). In our analyses, we found that affective lability is significantly associated with neural measures that distinguish youth at risk for BD from youth at risk for other disorders, specifically greater rACC activity when regulating attention away from happy faces, greater bilateral amygdala-left cACC FC when regulating attention away from fearful faces over follow-up, and more inverse forceps minor RD-rACC activity relationships when processing

happy faces. Additionally, these affective lability findings were specifically parent-reported. The fact that parent-reported assessments of affective lability were associated with these neural measures, compared with child-reported assessments, may reflect the greater reliability of parental reports of child symptoms, as these are considered more useful than child reports in diagnosing BD in children (Youngstrom, Findling et al. 2004). Thus, our findings would lead us to make two recommendations: (1) incorporate assessments of affective lability into standard clinical practices, such as the CALS (Gerson, Gerring et al. 1996), and (2) prioritize using parental reports, rather than child reports, as these may be more indicative of neural abnormalities in the ACC, specifically, that distinguish youth at risk for BD from youth at risk for other psychiatric disorders.

Another way in which the work presented in this dissertation can contribute to current diagnostic strategies for BD pertains to the application of a machine learning approach using pattern recognition. As mentioned above, several attempts have been made to use such approaches to enhance the accuracy of diagnosing BD, but no attempts have successfully led to the identification of at-risk individuals who are going to develop a BD diagnosis in the future. Thus, our suggestion is to develop a machine learning approach that distinguishes youth at risk for BD from youth at risk for other disorders and healthy controls that focuses on the findings presented in this dissertation. Possible approaches may include using Gaussian Process Classifiers (GPC), which assigns predictive probabilities of group membership to individual patients (Mourão-Miranda, Oliveira et al. 2012, Mourão-Miranda, Almeida et al. 2012), or support vector machine (SVM) analyses, which use training and testing phases to predict group membership based on subject features, such as neural activity (Almeida, Mourao-Miranda et al. 2013, Schnack, Nieuwenhuis et al. 2014). Using such approaches, patterns may be observed in

emotion processing and regulation neural circuitry (with specific focuses on rACC activity, dlPFC activity, and amygdala-cACC FC), as well as in reward processing circuitry (with specific focuses on VS-cACC and vlPFC-OFC FC), that may be used for the development of clinical markers of risk for BD in at-risk youth.

A final way in which the work presented in this dissertation can contribute to current diagnostic strategies for BD pertains to the potential development of serum biomarkers. As described above, elevated amounts of lipid oxidative stress have been associated with abnormalities in both WMTs and the ACC. Coincidentally, the two main findings from our WMT-activity analyses were inverse relationships between the right cingulum-cingulate gyrus and cACC, as well as between the forceps minor and rACC. Thus, our findings would lead us to suggest developing biomarkers reflecting oxidative stress, which may be detected by peripherally analyzing serum measures, that are associated with these specific tracts and regions that distinguish youth risk for BD. Altogether, we believe that the findings presented here may be applied to the improved diagnostic accuracy of BD in individuals at risk for the disorder through the development of more targeted clinical assessments, machine learning approaches, and serum biomarkers.

6.3.2 Treatment of BD

6.3.2.1 Current Treatment Strategies for BD

Treatment and management of BD is multi-faceted and complex. The two main focuses of BD treatment are acute stabilization, with the goal of bringing patients to a euthymic state, and maintenance, with the goals of preventing relapse, reducing symptoms, and enhancing overall functioning (Geddes and Miklowitz 2013). Even when treated, it has been reported that 37% of

patients with BD relapse into a depressive or manic episode within 1 year with 60% relapsing within 2 years (Gitlin, Swendsen et al. 1995). The identification of neural markers of BD and BD risk may provide biological targets for personalized treatment and for the development of new interventions for BD (Phillips and Kupfer 2013). The findings from this dissertation may thus also be used to improve upon such strategies for patients with, and at risk for, BD.

One of the primary ways to treat BD is with medications. Many medications target neurotransmitter and neurohormonal dysregulation (Geddes and Miklowitz 2013). For example, some medications target dopamine, which is associated with manic symptoms (Geddes and Miklowitz 2013). Antipsychotic agents block dopamine D2 receptors in attempts to reduce manic symptoms (Cousins, Butts et al. 2009, Cipriani, Barbui et al. 2011). Other medications target serotonin and glutamate, which are implicated more in depressive symptoms (Geddes and Miklowitz 2013). Selective serotonin reuptake inhibitors and atypical antipsychotics enhance serotonin activity (Stockmeier 2003), while medications such as valproate, lamotrigine, some antidepressants, and ketamine (used for rapid alleviation of symptoms) modulate glutamate transmission (Diazgranados, Ibrahim et al. 2010, Li, Frye et al. 2012, Zarate, Brutsche et al. 2012). There are other targets that pertain to intracellular signaling. For example, lithium, valproate, and carbamazepine target inositol monophosphatase, which is implicated in manic depression, by reducing its concentration and increasing neuronal growth (Agam, Shamir et al. 2002, Harwood 2005). Lithium also mediates neuroprotective effects by inhibiting GSK-3, an enzyme whose dysregulation impairs neural plasticity (Li, Frye et al. 2012, Andreazza and Young 2014). Protein kinase C activity is inhibited by lithium, valproate, and tamoxifen, which may help alleviate manic symptoms (Newberg, Catapano et al. 2008). Calcium channels are also associated with manic symptoms and are inhibited by lamotrigine and calcium channel blockers

(Andreazza and Young 2014). Some medications also regulate sleep and circadian rhythms, such as antipsychotics, lithium, and valproate, which can help stabilize mood (Malkoff-Schwartz, Frank et al. 1998, Frank, Kupfer et al. 2005, Harvey 2011).

In addition to medications, psychosocial treatments are key components of BD management. Indeed, treatment guidelines recommend integrating pharmacotherapy and psychotherapy in order to achieve an optimum management of BD (Goodwin and Psychopharmacology 2009, Yatham, Kennedy et al. 2013). Benefits of psychosocial interventions include: earlier identification of, and interventions for, warning signs of recurrences; increased illness acceptance; enhanced medication adherence; enhanced ability to cope with environmental stressors; stabilized sleep and wake routines; re-engagement with social, familial, and occupational roles; enhanced family relationships; and reduced misuse of drugs and/or alcohol (Geddes and Miklowitz 2013).

There are several specific evidence-based models of psychotherapy that are used to treat BD. *Cognitive-behavioral therapy* is based on the theory that recurrences of mood disorders arise from pessimistic thoughts in response to life events and core dysfunctional beliefs about the patient's self, world, and future (Beck, Rush et al. 1979). Sessions focus on modulation of these ways of thinking and can be used to treat both depressive and manic episodes (Lam, Hayward et al. 2005). *Family-focused therapy* is based on the association between relapses and both the criticism and hostility of caregivers (Hooley 2007). Sessions involve the patient and caregivers and incorporate psychoeducation as well as skills training in communication and problem-solving (Miklowitz 2010). *Interpersonal and social rhythm therapy* attempts to modulate the relationship between sleep and mood disturbances by encouraging patients to maintain and regulate both daily routines and sleep and wake rhythms (Frank, Kupfer et al. 2005). *Group*

psychoeducation follows a predesigned curriculum that focuses on illness awareness, treatment adherence, early detection of warning signs, and regulating sleep and wake rhythms (Colom, Vieta et al. 2003). *Functional remediation* uses memory, attention, problem solving, reasoning, and organization exercises to target patients' cognitive functioning (Torrent, Bonnin et al. 2013). Finally, *systematic care management* focuses on the combination of pharmacotherapy, group psychoeducation, and intensive monitoring of the patient by a nurse care manager (Geddes and Miklowitz 2013).

There are several other methods that are used for the management of BD. One is *electroconvulsive therapy (ECT)*, a treatment that involves oxygenation, anesthesia, brief pulses of electrical stimulation, and continuous physiological monitoring to achieve rapid and short-term improvement of severe symptoms (Husain, Rush et al. 2004, Health 2006). It is typically recommended only after an adequate trial of other treatment options has been deemed ineffective and/or when BD is considered to be potentially life-threatening (Health 2006). Such cases include a severe depressive episode, a prolonged or severe manic episode, and catatonia (Health 2006). Another treatment is *transcranial magnetic stimulation (TMS)*, a noninvasive procedure that uses magnetic fields to stimulate nerve cells and manipulate brain activity in spatially distinct cortical regions (Wassermann, Epstein et al. 2008). It has been used in patients with BD to treat bipolar depression (Dolberg, Dannon et al. 2002, Nahas, Kozel et al. 2003), and it has potentially comparable efficacy to ECT in treating catatonia (Wassermann, Epstein et al. 2008). As a generalization, TMS stimulation of the left prefrontal cortex is more effective at treating depressive symptoms (George, Wassermann et al. 1995, Pascual-Leone, Catala et al. 1996, Pascual-Leone, Rubio et al. 1996, George, Wassermann et al. 1997, Avery, Claypoole et al. 1999), while TMS stimulation of the right prefrontal cortex is more effective at treating manic

symptoms (Grisaru, Chudakov et al. 1998, Michael and Erfurth 2004). A third method is *transcranial direct current stimulation (tDCS),* a noninvasive neurostimulation technique in which a weak direct current is applied on the scalp to induce shifts in membrane resting potentials and either depolarize or hyperpolarize neurons (Nitsche, Fricke et al. 2003). While this technique has primarily been a promising emerging therapy for major depression (Boggio, Rigonatti et al. 2008, Rigonatti, Boggio et al. 2008, Ferrucci, Bortolomasi et al. 2009, Ferrucci, Bortolomasi et al. 2009), one study found that this method can also improve depressive symptoms in patients with BD (Brunoni, Ferrucci et al. 2011). Together, ECT, TMS, and tDCS comprise several other methods for treating BD in addition to medications and psychotherapy.

There are a number of considerations to note when treating BD in children and adolescents in comparison to adults. First, no medications are approved by the US Food and Drug Administration for children under the age of 10 (Washburn, West et al. 2011). Medications used to treat mania in pediatric BD include lithium, antiepileptic drugs with mood stabilizing effects (including carbamazepine, divalproex sodium, lamotrigine, and topiramate), and second-generation antipsychotics medications (including risperidone, olanzapine, aripiprazole, and quetiapine) (Hamrin and Iennaco 2010). Because over half of patients with pediatric BD do not respond sufficiently to one medication, it is common for youth with BD to be placed on more than one medication (Kafantaris, Coletti et al. 2001, Kafantaris, Dicker et al. 2001, DelBello, Kowatch et al. 2002, Washburn, West et al. 2011). As with adults, psychosocial treatments are necessary adjunctive treatments to pharmacologic interventions (McClellan, Kowatch et al. 2007). Specific therapies that have been used in pediatric BD include psychoeducational treatment, family-focused therapy that has been adapted for adolescents, interpersonal and social rhythm therapy for adolescents, child- and family-focused cognitive-behavioral therapy, and an

additional therapy known as dialectical behavior therapy for adolescents, which is specifically designed to treat borderline personality disorder and particularly address emotional dysregulation (Linehan 1993, Goldstein, Axelson et al. 2007, Washburn, West et al. 2011). Regarding other therapies, ECT has been considered highly efficient for treating several psychiatric disorders in adolescents, including BD (Lima, Nascimento et al. 2013). TMS has been used less frequently (Walter, Tormos et al. 2001), and little is known about the use of tDCS in pediatric BD. Besides these considerations, treatment of BD is similar across children, adolescents, and adults.

6.3.2.2 Contribution of this Dissertation to Treatment Strategies for BD

There are two primary ways in which the work from this dissertation may contribute to the improvement of treatment strategies for BD in at-risk youth. First, we identified several potential candidates of neural markers that may be used to identify youth who are more likely to develop BD in the future, as described above. In practice, if these measures can help identify youth who are likely to develop BD, then interventions in the form of psychosocial therapies may be started early in these individuals, prior to illness onset.

One therapy that may be started early is *psychoeducational treatment*. The goals of this treatment are to increase knowledge and understanding of BD and its treatment, improve upon the management of BD symptoms and associated conditions, improve upon communication and problem-solving skills, and increase the sense of support for the individual and his or her family (Washburn, West et al. 2011). Additionally, at-risk youth can begin to develop coping skills that can help them better manage their emotions, improve upon their communication skills, and control their impulses (Washburn, West et al. 2011). They may also learn healthy habits that focus on maintaining proper sleep hygiene, nutrition, and exercise activities (Washburn, West et al. 2011).

A second therapy that may be started early is *family-focused therapy for adolescents*. This treatment can involve the at-risk individual as well as parents and siblings (Washburn, West et al. 2011). This therapy has some goals that overlap with psychoeducational treatment, such as increasing awareness of coping skills, but also has a focus on issues pertaining to family, such as decreasing levels of familial expressed emotion and improving upon family problem-solving and communication skills (Washburn, West et al. 2011). The specific treatment components include: psychoeducation for the entire family about the symptoms, etiology, course, and treatment of BD; communication enhancement training, including the development of skills such as active listening, positive feedback, and constructive criticism; and problem-solving skills training to help identify and solve problems in daily life (Miklowitz, George et al. 2004, Washburn, West et al. 2011).

Dialectical behavior therapy for adolescents is another treatment that has components of both individual therapy and family skills training (Washburn, West et al. 2011). In individual therapy, patients focus on problem behaviors and are encouraged to work on skills with their coach (Goldstein, Axelson et al. 2007, Washburn, West et al. 2011). In family therapy, skills include psychoeducation, mindfulness, distress tolerance, emotion regulation, and interpersonal effectiveness (Washburn, West et al. 2011). Thus, psychoeducational treatment, family-focused therapy, and dialectical behavior therapy all have the potential to teach at-risk youth and their families valuable skills and habits that may help them prepare for and eventually manage BD if and when the disorder develops.

Child- and family-focused cognitive-behavioral therapy was specifically created for children between the ages of 8 and 12 years (Pavuluri, Graczyk et al. 2004, West, Jacobs et al. 2009). In comparison to the aforementioned therapies, this therapy includes additional intensive

work with the patient's parents that focuses on developing effective parenting techniques (Washburn, West et al. 2011). This intervention combines traditional cognitive-behavioral therapy methods with psychoeducation, interpersonal therapy, mindfulness, and positive psychology theories to address the potential impact of BD on a child's life (West, Henry et al. 2007, Washburn, West et al. 2011). Specific skills that can be learned and/or improved upon with this therapy include established routines, behavioral management, self-efficacy, reduced negative cognitions, social functioning, problem-solving, and social support (Washburn, West et al. 2011). Child- and family-focused cognitive-behavioral therapy is thus an additional valuable therapy that may be particularly useful in younger children who are determined to be at risk for developing BD.

Finally, *interpersonal and social rhythm therapy for adolescents* may also be helpful in at-risk youth. This treatment capitalizes on the knowledge that psychosocial stressors may disrupt social and sleep routines which may ultimately lead to the precipitation or exacerbation of BD (Washburn, West et al. 2011). Specific interventions for adolescents include stabilizing social and sleep routines through the exploration of relationships between stress and mood, as well as through an emphasis on addressing deficits in interpersonal functioning (Hlastala and Frank 2006, Washburn, West et al. 2011). Early establishment of proper sleep and wake routines may help regulate circadian rhythms and help alleviate some of the stressors that may eventually be associated with episodes of BD.

The second primary way in which the work from this dissertation may contribute to the improvement of treatment strategies for BD in at-risk youth is through more targeted interventions for methods such as ECT, TMS, and tDCS. The primary findings from our analyses indicated abnormalities in the ACC which had significant relationships with symptoms of

affective lability. Thus, we may suggest that interventions such as ECT, TMS, and tDCS can focus on targeting the ACC, both in at-risk individuals with severe symptoms of affective lability and in individuals who have gone on to develop a formal diagnosis of BD. Using these methods to stimulate the ACC may aid in the alleviation of symptoms associated with BD, particularly affective lability. Based on the existing literature regarding current clinical guidelines, we further suggest that ECT is the method of choice for attempting such interventions, as this method currently appears to be more widely used for the treatment of BD than either TMS or tDCS. However, future studies can consider using any of these three techniques in order to attempt to find more effective therapeutic techniques for youth with, and at risk for, BD. In summary, we believe that the findings presented in this dissertation may be applied to the improvement of therapeutic strategies for BD in individuals at risk for the disorder through earlier psychosocial therapy and more targeted approaches for treatments such as ECT.

6.4 LIMITATIONS

There were several limitations in the work presented in this dissertation. Throughout all of the studies, sample size was limited, particularly when comparing subsamples of youth who either had or did not have a non-BD disorder and when examining follow-up data. Future studies should aim to replicate and validate our findings with larger sample sizes. 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, Merranko et al. 2016). While medication impacted some findings, such as those pertaining to the ACC in emotion regulation neural circuitry, these effects may, in fact, reflect the medicated status of the most

affectively labile and high-risk OBP. Furthermore, medication was not a predictor of group in additional elastic net regression analyses performed in the first study, and medication did not have any significant effects on any other findings. Nonetheless, further study is needed to determine the nature of relationships between medications and emotion regulation neural circuitry functioning. Additionally, while we showed that age did not significantly correlate with any structural or functional main finding, we did observe age X group interactions for the FC between the right pars orbitalis and both the left and right OFC. Thus, pubertal development, as well as other environmental effects such as childhood adversity, cannot be entirely ruled out as contributing factors in our results. When examining relationships between neural and symptom measures, as well as between WMT and activity measures, we assumed linear models. While nonlinear models could be considered, the interpretation of findings based on non-linear models is significantly limited in studies with such complex designs (Marsh, McGlynn et al. 1994). 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 each scan. Recent studies have debated the possible inflation of predictions in neuroimaging studies in individuals with psychiatric disorders (Whelan and Garavan 2014). In response, we used a well-validated approach that penalizes complex models using regularization, cross-validation, and sparsity enforcement in model fit. Relatedly, it can be argued that the generalizability of our results may be limited due to the ways in which lambda was fit and regression parameters were estimated in our elastic net models. In response, we used cross-validation strategies which have been shown to be effective in avoiding overfitting because

the training sample is independent from the validation sample (Arlot and Celisse 2010). Another limitation was that 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 at-risk youth. Additionally, while we have speculated about possible distinct roles of the rostral and caudal divisions of the ACC and their unique roles in the pathophysiology underlying BD risk, future studies are necessary to determine directional associations that differ between these regions. Finally, at this point, we were only able to associate our main neural findings with group and then speculate as to the potential implications of these findings as neural markers of risk. Future studies that involve risk prediction tests are necessary to determine whether these neural findings are, in fact, neural markers that have predictive or diagnostic utility.

6.5 FUTURE DIRECTIONS

In light of the findings presented throughout this dissertation, there are several future directions that we wish to discuss. First, there is much more to be done regarding longitudinal follow-up. While we attempted to explore follow-up data for our subjects throughout several of our studies, we were only able to examine a subset of participants at this time. Once all subjects have returned for their second scans, we will be able to perform additional analyses with increased power to better understand how the main neural findings observed throughout these studies change over time and relate to worsening symptomatology. In addition, as these youth age into adulthood, we may be able to better discern which specific neural abnormalities predispose these

youth to worsening or new psychopathology, including BD, and which measures may protect against the development of psychiatric illnesses.

There is also much that is left to understand regarding relationships between WMT structure and function, as well as their implications for BD risk. While we chose to initially focus on relationships between WMT structure and activity measures in emotion processing neural circuitry, we can additionally examine relationships between WMT structure and other functional measures such as FC, cortical thickness, and gray matter volume. We can also examine such relationships in other neural circuitries, namely emotion regulation and reward processing. Further, exploration of longitudinal changes in these structure-function relationships, over time, may elucidate more findings pertaining to BD risk.

Additionally, there are many other approaches that we can take and analyses that we can perform to study BD risk. For example, we can use whole brain voxel-wise approaches to go beyond *a priori* ROI approaches and determine if other neural regions are additionally important to the abnormal processing and regulation of emotions and reward in youth at risk for BD. Such approaches may also identify abnormalities in regions, such as the medial prefrontal cortex, that are important to emotion or reward circuitry but that have not yet been identified in OBP. We can also use different modeling approaches to construct a normative model of emotion and reward neural circuitries. We can perform developmental studies to help determine exactly when differences between groups emerge and to help discern the contributing effects of environmental factors on our results. Additionally, we can run risk prediction tests in order to be determine whether the neural abnormalities identified throughout these analyses are risk factors for the development of BD. Furthermore, we can run mediation analyses to better understand relationships between some of our findings, such as the potential role of the connectivity

between the rACC and the amygdala in affective lability severity. Such future directions may help us better understand the implications of the findings presented here and further contribute to our comprehensive understanding of the pathophysiology that underlies the development of BD in at-risk youth.

6.6 FINAL REMARKS

In this dissertation, we examined activity, FC, and WMT structure in emotion processing, emotion regulation, and reward processing neural circuitries in youth at risk for BD. Our primary goals were to better understand the pathophysiology underlying BD risk and potentially identify neural markers that confer risk for the development of BD. Our findings primarily implicated the ACC as a key region involved in all three circuitries that helps distinguish youth at risk for BD from youth at risk for other psychiatric disorders and healthy controls. We also found that symptoms of affective lability, and relationships between this symptom measure and the ACC, additionally aid in the distinction between OBP and control groups. The results from our analyses additionally have potential implications for both the diagnosis and treatment of BD. Together, these findings offer insights into the underlying pathophysiology of BD risk and will hopefully contribute to improved outcomes for youth at risk for BD.

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