RESTING-STATE FUNCTIONAL BRAIN NETWORKS IN BIPOLAR SPECTRUM DISORDER: A GRAPH THEORETICAL INVESTIGATION

A Dissertation
Submitted to
the Temple University Graduate Board

In Partial Fulfillment
of the Requirements for the Degree of
DOCTOR OF PHILOSOPHY

---

by
Chelsea L. Black, M.A.
July 2016

Examining Committee Members:

Lauren B. Alloy, Ph.D., Advisory Chair, Department of Psychology
Tania Giovannetti, Ph.D., Department of Psychology
Jason M. Chein, Ph.D., Department of Psychology
Eunice Y. Chen, Ph.D., Department of Psychology
Michael S. McCloskey, Ph.D., Department of Psychology
Thomas M. Olino, Ph.D., Department of Psychology
Ingrid R. Olson, Ph.D., External Member, Department of Psychology

ABSTRACT

Neurobiological theories of bipolar spectrum disorder (BSD) propose that the emotional dysregulation characteristic of BSD stems from disrupted prefrontal control over subcortical limbic structures (Strakowski et al., 2012; Depue & Iacono, 1989). However, existing neuroimaging research on functional connectivity between frontal and limbic brain regions remains inconclusive, and is unable to adequately characterize global functional network dynamics. Graph theoretical analysis provides a framework for understanding the local and global connections of the brain and comparing these connections between groups (Sporns et al., 2004). The purpose of this study was to investigate resting state functional connectivity in individuals at low and high risk for BSD based on moderate versus high reward sensitivity, both with and without a BSD diagnosis, using graph theoretical network analysis. Results demonstrated decreased connectivity in a cognitive control region (dorsolateral prefrontal cortex), but increased connectivity of a brain region involved in the detection and processing of reward (bilateral orbitofrontal cortex), among participants at high risk for BSD. Participants with BSD showed increased inter-module connectivity of the dorsal anterior cingulate cortex (ACC). Reward sensitivity was associated with decreased global and local efficiency, and interacted with BSD risk group status to predict inter-module connectivity. Findings are discussed in relation to neurobiological theories of BSD.

ACKNOWLEDGMENTS

I would like to thank my advisor, Dr. Lauren Alloy, for her incredible support, guidance, and mentorship throughout the course of my graduate training. I also thank Dr. Jason Chein and Dr. Tania Giovannetti, for their feedback and guidance, which was invaluable in the completion of my dissertation. For their dedication, support, and assistance in the management and preparation of the fMRI data, I also would like to acknowledge Katherine Damme and Christina Young. I also thank Dr. Robin Nusslock for his support, guidance, and advice in the development of this project. Finally, I would also like to express my gratitude for examining committee members, Dr. Thomas Olino, Dr. Eunice Chen, Dr. Michael McCloskey, and Dr. Ingrid Olson, for their valuable feedback

The research reported in this dissertation was supported by National Institute of Mental Health Grant MH77908 to Lauren B. Alloy.

TABLE OF CONTENTS

Page

LIST OF TABLES

CHAPTER 1

INTRODUCTION

Bipolar disorder (BD) is a serious, chronic mental illness characterized by the presence of discrete episodes of depression and (hypo)mania, separated by periods of euthymic mood (American Psychiatric Association, 2013). It has been estimated that bipolar disorder has a lifetime prevalence of 1% (for Bipolar I disorder) to 4% (for all bipolar spectrum disorders) worldwide and is associated with a number of serious individual and societal harms, such as increased suicidality (Judd & Akiskal, 2003), higher unemployment (Coryell et al., 1993), increased health care utilization and costs (Judd & Akiskal, 2003), and other psychosocial disability, which tends to fluctuate in accordance with the waxing and waning of symptoms (Judd et al., 2005).

The refinement and proliferation of neuroimaging techniques, particularly functional and structural magnetic resonance imaging (MRI), in the past two decades has begun to provide insight into the biological basis of BD, identifying both specific brain regions as well as distributed brain networks that may underlie the emotional, cognitive, and behavioral symptoms of this disorder. As mood dysregulation is the hallmark feature of BD, the majority of neurobiological theories of BD seek primarily to explain the oscillation between depressed and manic episodes in individuals with BD (Strakowski et al., 2012). However, it should be noted that the neural networks implicated in emotion regulation also play a role in a broad variety of functions that are known to be disturbed in BD, including neurovegetative functions (i.e.. sleep, arousal,

appetite, libido, energy), motivational and appetitive behaviors, and cognitive processes (Blond et al., 2012).

Neurobiological Theories of Bipolar Disorder

Mayberg (1997) proposed that the neurobiological basis of mood dysregulation in unipolar depression could be understood as abnormalities in the relationship between cortical and limbic structures. Within the context of major depressive disorder (MDD), it was proposed that a failure of the coordination between prefrontal cortical structures and subcortical limbic structures would result in the dysregulation of mood. According to this model, limbic overactivation, prefrontal underactivation, and failures in the reciprocal interaction of the two systems all play a role in the development of depressive episodes, while normalization of these activities results in disease remission (Mayberg, 1997). More recently, this model has been extended and adapted to bipolar spectrum disorders. The majority of current conceptualizations of the neurobiological basis of BD (Phillips, Ladouceur, & Drevets, 2008; Strakowski et al., 2012; Blond et al., 2012) generally propose that reduced prefrontal control over subcortical limbic structures may result in the emotional symptoms of BD.

Phillips, Drevets, Rauch, and Lane (2003) proposed a general model of emotion regulation, identifying dissociable prefrontal networks involved in emotion regulation. Within this model, identification of affectively-relevant stimuli is carried out by a ventral system comprised of the amygdala, insula, ventral striatum, ventral anterior cingulate cortex (ACC), and orbitofrontal cortex (OFC), which is also responsible for the mediation of autonomic responses to affective stimuli (e.g. automatic emotional processing). This is complimented by the dorsal neural system, comprised of the dorsal regions of the

prefrontal cortex (PFC), dorsal ACC, and hippocampus, which is responsible for the voluntary regulation of emotion. The ventral and dorsal systems may act with and on one another, possibly mediated by the OFC.

In an extension of this model, the authors proposed a dissociation between a lateral prefrontal network (including ventrolateral PFC (vlPFC) and dorsolateral PFC (dlPFC)) responsible for voluntary, effortful emotion regulation via feedback with subcortical structures, and a medial prefrontal network (including OFC, dorsomedial PFC (dmPFC) and ACC) responsible for automatic emotion regulation via a feedforward mechanism (Phillips et al., 2008). Both lateral and medial prefrontal networks may be simultaneously activated by emotional stimuli and work in concert to modulate emotional response.

When extended to BD, the authors proposed that observed left-sided structural and functional abnormalities within the OFC may reflect disrupted automatic emotion regulation processes responsible for mood instability (Phillips et al., 2008). Specifically, underactivation of ventromedial prefrontal structures (such as the OFC) may result in disruptions in automatic emotion regulation and attention modulation, particularly in response to affective cues. This may be further compounded by deficits in voluntary emotion regulation governed by the dorsal system. Dorsal prefrontal regions, including the dlPFC, dmPFC, and dorsal ACC have been consistently linked with voluntary, executive processes involved in emotional and cognitive regulation, including cognitive reappraisal, behavioral control, and effortful attentional redirection, and it has been suggested that these regions also may be abnormal in BD (Phillips et al., 2008). Specifically, increased dorsal and lateral prefrontal activity in BD is most consistently

observed during voluntary emotion regulation, whereas decreased dorsal and lateral activity is often observed during voluntary attentional control (Phillips et al., 2008). Ventromedial prefrontal structures (such as the OFC) also may mediate the activity of dorsal prefrontal regions, such that attenuated OFC efficiency not only results in automatic emotion processing deficits, but also may hinder (already compromised) dorsal prefrontal influence on subcortical structures (Phillips et al., 2008).

Strakowski and colleagues (2012) expanded the work of Phillips et al. (2008) and proposed an integrated neurobiological model of mood dysregulation in bipolar disorder involving abnormalities within and between neural networks governing emotion regulation. The first of these networks involves the vlPFC, with connections to the ventromedial striatum, globus pallidus, thalamus, amygdala, and ACC, and is thought to be involved in the processing of external emotionally salient cues (Strakowski et al., 2012). The second of these networks involves ventromedial PFC (vmPFC)/OFC and includes connections to the nucleus accumbens (NAcc), globus pallidus, thalamus, subgenual cingulate, and amygdala, and is involved in emotional processing of internal affective cues (e.g. internal emotional states). Additionally, as noted by Phillips et al. (2008), these networks modulate voluntary and automatic emotion processing, respectively.

According to this model, the emotional symptoms of bipolar spectrum disorders can arise in a number of different ways. One potential type of disruption may result from structural or functional abnormalities in one or more individual components of the system. As proposed by Strakowski and colleagues (2012), the amygdala is a critical region in the limbic networks underlying emotional responses to both internal and

external cues and its activity is likely disrupted in individuals with BD, although the exact nature of this disruption appears to be dependent on mood state and specific stimulus characteristics (Strakowski et al., 2012). Functional abnormalities also have been observed in the vlPFC and OFC, with observed underactivation of ventral prefrontal regions in BD patients relative to controls across a number of tasks (Strakowski et al., 2012).

Beyond abnormality in individual network components, overall system dysregulation also may arise via abnormality in the connections between components of the system. This can be investigated from both a structural standpoint by exploring white matter (WM) differences between brain regions within a given network, or functionally by exploring the time course of activation across different brain regions within the network, and identifying the degree of correlation between activation in different regions. Strakowski and colleagues (2012) noted decreased synchronization of activation between ventral prefrontal regions and the amygdala in individuals with BD, and suggested that this may reflect decreased within-network connectivity that again may contribute to decreased prefrontal regulation of limbic activity. Abnormality in integration across and between these relatively independent networks also must be considered as a potential source of overall system dysregulation. The model proposed by Strakowski and colleagues (2012) highlights the potential role of striatum, ACC, and thalamus as integrative regions that may serve to facilitate "cross-talk" between the ventrolateral and ventromedial networks; as such, disruption in the activity of these regions may result in decoupling of these networks and subsequent disruption of emotion regulation.

Strakowski and colleagues (2012) highlighted findings that suggest that impairment in network development may underlie subsequent changes in focal brain regions, and the development of bipolar disorder. Consistent with this proposal, WM abnormalities often precede first onset of BD in individuals at high familial risk of BD (Versace et al., 2010), and are observed in the early course of bipolar illness (Frazier et al., 2007). Conversely, gray matter changes in the amygdala and prefrontal regions are not observed prior to disease onset (Gogtay et al., 2007) and appear to progressively worsen over the course of illness (Lim et al., 2013). Strakowski et al. (2012) proposed that structural abnormalities in limbic-prefrontal networks, present premorbidly, lead to abnormal development of component brain regions (such as amygdala and prefrontal brain regions) during adolescence. The combined effect of abnormal connectivity and function within these networks is to destabilize mood regulation, leading to the onset and course of BD. Lacking healthy networks responsible for maintaining emotional homeostasis, individuals with BD experience drastic changes in mood in response to environmental cues and may have difficulty re-establishing euthymic mood (Strakowski et al., 2012).

Behavioral Approach System/Reward System Sensitivity Model

Beyond deficits in emotion processing, other models have been proposed to explain additional functional disruptions observed in BD. One such model is the Behavioral Approach System (BAS)/reward system hypersensitivity theory, proposed by Depue and Iacono (1989) and expanded by Urosevic, Abramson, Harmon-Jones, and Alloy (2008), which focuses on motivational dysregulation observed in BD. The BAS is a proposed neurobiological system whose functions and characteristics can be

conceptualized across psychosocial, behavioral, and neurobiological levels (Alloy & Abramson, 2010; Alloy, Nusslock, & Boland, 2015; Urosevic et al., 2008). From a behavioral standpoint, it has been proposed that the BAS serves to connect an organism with potentially rewarding stimuli by underlying detection and recognition of potentially rewarding stimuli, motivation for reward, initiation of action (whether locomotor or cognitive action) in response to incentive cues, and emotional and cognitive responses to reward-relevant stimuli and outcomes (Alloy & Abramson, 2010; Alloy et al., 2015; Depue & Iacono, 1989; Urosevic et al., 2008). Activation of the BAS may result in positively valenced emotions, such as happiness or excitement, if reward is obtained (Alloy & Abramson, 2010; Alloy et al., 2009). Conversely, if obtainment of the reward is thwarted, irritability or anger may result (Alloy & Abramson, 2010; Alloy et al., 2015; Carver, 2004; Urosevic et al., 2008). Definite failure to obtain rewards or significant losses may trigger an excessive down-regulation of the BAS, which, in turn, may result in a depressive episode (Alloy & Abramson, 2010; Alloy et al., 2009; 2015; Carver, 2004; Depue & Iacono, 1989; Urosevic et al., 2008).

Depue and Iacono (1989) highlighted the role of dopaminergic pathways, arising in the ventral tegmental area (VTA) and terminating in areas of the limbic system and neocortex, respectively, as potentially underlying the dysfunctions observed in BD. The mesolimbic dopamine pathways include those terminating in the NAcc, amygdala, ventral pallidum, septum, and hippocampus. Cortical dopaminergic pathways are particularly concentrated in the frontal lobes, with regions of dense DA receptor availability including areas involved in movement, including primary motor cortex, premotor area, and supplementary motor area (SMA). Dopaminergic projections from the

VTA also terminate in prefrontal regions including OFC, dmPFC, and ACC, which are regions known to be associated with the processing of risk and reward (Xue, Lu, Levin, Weller, Li, & Bechara, 2009). Depue and Iacono (1989) concluded that these DA pathways underlie two primary functions of the BAS; specifically, locomotor action and incentive/reward motivation. Accordingly, BAS hypersensitivity may result from disruptions in these dopaminergic pathways.

A substantial body of research has demonstrated the relationship between BAS sensitivity and BD; individuals with high BAS sensitivity are more likely to develop BD than individuals with moderate BAS sensitivity (Alloy et al., 2012a), and higher BAS sensitivity predicts progression along the bipolar spectrum from "softer" BD diagnoses (e.g. cyclothymia, BD-NOS) to more serious diagnoses (BD-II or BD-I) (Alloy et al., 2012b). More recently, neuroimaging has been utilized to investigate motivational/reward processing disruption in BD, with observed differences in vlPFC, ACC, OFC, and ventral striatum activation during reward tasks (Bermpohl et al., 2012; Chase et al., 2013; Nusslock et al., 2012). Notably, hyperactivity of ventral striatum and OFC in BD has been noted in anticipation of, but not receipt of, reward (Nusslock et al., 2012), suggesting that sensitivity to the possibility of future rewards, rather than positive affective experience alone, may be particularly relevant to BD.

There is substantial overlap in the emotion regulation and BAS sensitivity theories of BD presented above. First, both the emotion regulation model proposed by Phillips et al. (2008) and expanded by Strakowski et al. (2012) and the BAS sensitivity theory proposed by Depue and Iacono (1989) and expanded by Urosevic et al. (2008) propose that emotion dysregulation in BD results, at least in part, from abnormalities in

the activity of subcortical structures including the amygdala, ventral striatum, globus pallidus and ventral ACC. However, the proposed functional outcome of these disruptions differs between theories. Strakowski et al. (2012) propose that disruptions in this stream of processing among BD individuals result in disruptions of the automatic processing of affective cues, whereas Depue and Iacono (1989) suggest that reward processing is specifically disrupted. Additionally, Strakowski et al. (2012) propose that the primary deficit in BD is the result of the combined effect of limbic overactivity, particularly of the amygdala, underactivity of the ventral prefrontal cortex, and disruptions in the connectivity between ventral prefrontal brain regions and limbic structures. The BAS dysregulation model of BD also posits abnormalities in prefrontal cortical regions (OFC, dlPFC, and ACC; Schultz, 1997), but suggests that their involvement is related to detection of rewards rather than modulation of emotional reactions (Urosevic et al., 2008).

Functional Magnetic Resonance Imaging in Bipolar Disorder

Functional magnetic resonance imaging (fMRI) has been used to explore state and trait-related markers of brain activity among individuals with bipolar disorder. Traditional fMRI analyses have characterized activation by identifying specific voxels or brain regions that are more active during a given task than during rest. As with structural MRI, these analyses can be conducted across the entire brain to identify regions of activation that differ between groups, or can be conducted as region of interest (ROI) analyses specifically focusing on a few regions of a priori interest. A substantial body of work has investigated fMRI abnormalities in individuals with BD across a broad variety of tasks, including cognitive (i.e. N-back working memory;

Stroop task; Go-No Go task) and emotional (i.e. facial affect processing, emotion regulation, emotional prosody judgments), as well as tasks that encompass elements of both cognitive and emotional processing (i.e. emotional Stroop task, emotional Go-No Go task) (see Chen, Suckling, Lennox, Ooi, & Bullmore, 2011 for a review).

Although a substantial body of literature has provided insight about differences in magnitude of fMRI activation between BD patients and controls, there is also important information to be obtained by the investigation of relationships between activation in different brain regions. Functional connectivity refers to the temporal correlation of activation between anatomically distributed brain regions (Friston, Frith, Liddle, & Frackowiak, 1993). Exploring the brain as a collection of networks, rather than individual brain regions, may provide insight into how abnormal connectivity and network integration play roles in the etiology of BD. Further, functional connectivity provides additional information about brain networks beyond the information provided by structural connectivity analyses, such as diffusion tensor imaging (DTI). Functional connectivity analysis may provide information about both excitatory and inhibitory relationships between brain regions. Positive functional connectivity refers to relationships in which increased activity in one region is associated with increased activity in another region, whereas negative functional connectivity refers to relationships in which increased activity in one region is associated with decreased activity in another region, thought to reflect potential suppression of one region by another. Although the functional activity of the brain is necessarily linked to its structural organization, the exact relationship between structural and functional network organization remains unknown (Bullmore & Sporns, 2009; van den Heuvel & Pol, 2010). Thus, consideration

of both structural and functional connectivity is essential to understanding the neurobiological basis of BD.

Although activation-based studies are valuable in mapping regions that are active during various cognitive processes, there is additional important information to be gained by the evaluation of structural and functional brain networks. As noted by Sporns (2013), it is the interaction of various brain regions that enables cognition, rather than the activity of any one brain region alone. Consequently, there may be value in evaluating not only differences in the activation of individual brain regions, but also differences in the connectivity of brain regions in individuals with bipolar disorder.

Resting State Functional Connectivity

During the first fifteen years of functional neuroimaging research using fMRI, the patterns of brain activity observed during the resting state (when the participant is not engaged in any directed task) were widely considered unimportant and were even dismissed as "noise" (van den Heuvel & Pol, 2010). However, more recently it has been established that basal brain activity during rest conditions may at least in part reflect important underlying neuronal processes, including the recruitment of a number of organized neural networks (van den Heuvel & Pol, 2010). Resting state brain activity consistently has been shown across studies to reflect activity in a number of different networks, including the primary sensorimotor network, primary and extra-striate visual networks, and superior parietal and frontal attention networks (van den Heuvel & Pol, 2010). Additionally, a bilateral network involving the temporal/insular region and anterior cingulate cortex, and the default mode network consisting of posterior cingulate

cortex/precuneus, inferior parietal regions, and medial frontal regions, also all have been identified during rest (van den Heuvel & Pol, 2010).

The default mode network (DMN) bears particular relevance to the discussion of functional connectivity in the resting state, because unlike the other aforementioned networks, the default mode network is substantially more active during rest compared to active task engagement (Gusnard & Raichle, 2001; Gusnard, Akbudak, Shulman, & Raichle, 2001; Raichle et al., 2001). It has been proposed that the default mode network may contribute to self-referential processing activities such as theory of mind, thinking of the future, or remembering the past, which are engaged when an individual is not engaged in competing mental tasks (Buckner, Andrews-Hanna, & Schacter, 2008; Gusnard et al., 2001). As a result, the default mode network may have particular relevance for psychological disorders that involve impairment in these self-referent activities (Buckner et al., 2008), affective and cognitive processing (Ongur & Price, 2000).

Vargas and colleagues (2013) conducted a systematic review of the resting state MRI connectivity literature in BD. In the eight studies reviewed, they identified a number of regions of commonly identified activation differences during the resting state. Primarily, differences between BD patients and controls were observed in the patterns of connectivity of the PFC and ACC with mesolimbic structures, including amygdala, thalamus, and insula. However, the direction of these differences was inconsistent, as Vargas et al. identified studies with evidence of increased connectivity (e.g. Anticevic et al., 2013) as well as decreased connectivity (e.g. Anand et al., 2009). In two studies reviewed by Vargas and colleagues, DMN activity also was altered in

BD patients, with evidence for changes in the left parietal cortex and left frontal cortex. However, the authors noted that there is still limited research that has explored resting state activity in BD across mood states and there are a number of limitations, including medication effects, variable movement-related artifact between BD and controls, substance use history, and laterality, within the existing body of literature.

In summary, functional connectivity analyses of resting state data have provided evidence for disruption of connectivity within circumscribed regions of the frontal and prefrontal cortex (Anticevic et al., 2013; Liu et al., 2012; Ongur et al., 2010) and limbic regions (3et al., 2013) in bipolar disorder. Decreased connectivity has been observed within the mPFC (Anticevic et al., 2013; Liu et al., 2012; Ongur et al., 2010) and dlPFC (Ongur et al., 2010). Decreased connectivity within frontal lobe regions and increased connectivity within limbic regions may result in a weakening of frontal control over subcortical limbic structures, resulting in reduced cognitive control over emotional responding in individuals with BD.

There is also evidence for abnormal functional connectivity between regions of the frontal lobe. BD patients show a positive correlation between the mPFC (involved in emotion regulation) and vlPFC (involved in processing of emotional salience and motivation), whereas healthy controls show the reverse pattern, which may reflect excessive capture of processing and regulation resources by affectively salient stimuli (Chai et al., 2011). BD patients also do not show the expected inverse relationship between mPFC and dlPFC activation (Chai et al., 2011), which is consistent with the notion that individuals with BD may struggle to engage cognitive control particularly in the face of affectively salient stimuli.

Disrupted functional connectivity also has been observed between frontal and limbic structures in the resting state. BD patients show decreased corticolimbic functional connectivity between the amygdala and some prefrontal regions including the dlPFC (Anticevic et al., 2013), vPFC (Chepenik et al., 2010), and middle frontal gyrus (Torrisi et al., 2013), but increased connectivity between the amygdala and other prefrontal areas including the mPFC (Anticevic et al., 2013) and vlPFC (Torrisi et al., 2013). BD patients also have demonstrated decreased connectivity between the ACC and a number of subcortical structures, including the amygdala, thalamus, and pallidostriatum (Anand et al., 2009), but increased connectivity between the vPFC and the ventral striatum (Chepenik et al., 2010). BD patients show positive correlations between activity in the mPFC and the insula, as opposed to controls who evidence an inverse relationship between activity in these brain regions (Chai et al., 2011). Patients with BD and their affectively healthy first-degree relatives show increased connectivity between a mesolimbic network and a fronto-temporal/paralimbic network relative to healthy controls.

These findings are relevant to Strakowski and colleagues' (2012) theory of BD development. According to Strakowski et al., disruption in the early development of structural WM connections leads to decreased connectivity between prefrontal networks and the limbic system, particularly the amygdala. Inappropriate interaction between frontal and limbic regions results in mood instability, which over time may result in oscillations between depression and mania, as well as interepisode mood fluctuation. Although there is reasonably strong evidence for the existence of disruption in frontal and limbic brain regions, heterogeneous findings regarding the direction of disruption (e.g.,

increased vs. decreased connectivity) are common, and necessitate more research in order to determine the exact mechanisms of disorder in BD.

An important question that must be addressed is the optimal analysis method or methods for analyzing connectivity data. As previously described, a number of analysis methods exist for functional connectivity that vary with regards to their possible benefits and drawbacks as well as their appropriateness for specific data sets or research questions. It is probable that a sizeable proportion of the heterogeneity of structural and functional connectivity findings in BD is attributable to heterogeneity of analysis methodology, despite relatively consistent data acquisition techniques (Vargas et al., 2012). Consequently, it will be critically important to continue to refine methodologies and determine which method may be most optimal for the investigation of connectivity using neuroimaging data. Beyond the actual analytical methods used, selection of a metric or set of metrics with which to best characterize connectivity remains an open question (Bullmore, 2012; van den Heuvel & Pol, 2010). Further, questions remain as to the relationship between connectivity as measured by neuroimaging techniques including fMRI and diffusion tensor imaging, and connectivity at a neural level. The degree to which neuroimaging findings about connectivity in BD are scalable "down" to the synaptic level, or "up" to the behavioral level has direct relevance to their use as potential endophenotypes for disease (Bullmore, 2012).

Graph Theoretical Network Analysis

It has been proposed that a better understanding of the complex structure and organization of functional and anatomical brain networks may be accomplished through

the use of graph theoretical analysis (Sporns et al., 2004; van den Heuvel & Pol, 2010). A graph, within this context, refers to a mathematical description of a network, consisting of n nodes linked by k connections, which are called edges (Sporns et al., 2004; van den Heuvel & Pol, 2010). Although the nodes and edges are themselves simple on a local level, networks are highly complex as a result of the network's architecture (the spatial organization of nodes and edges), and dynamics (the behavior of nodes in interaction with one another) (Sporns et al., 2004; van den Heuvel & Pol, 2010). As such, the organization of the network (such as the brain) plays a role in its functional characteristics, including robustness against disruption, ability to integrate various inputs and outputs, and ability of nodes to communicate with one another (Sporns et al., 2004; van den Heuvel & Pol, 2010).

Graph theory provides a useful framework for understanding brain structure and function, as it is able to provide information about the overall topological organization of the brain, and may be able to provide insight into the relationship between anatomical characteristics and functional and effective connectivity patterns (Sporns et al., 2004). Understanding of the overarching organizational principles of cortical networks also may shed light on how a limited number of functionally segregated brain regions may give rise, through their interaction and integration, to the scope and complexity of human cognition (Sporns et al., 2004). Many networks, ranging from social to informational to biological networks, share common organizational principles, which are thought to underlie the networks' emergent behavior (Sporns et al., 2004). Small-world networks are defined by one such organizational principle; in these networks, nodes exist in tightly clustered "neighborhoods" with short node-to-node distances (Sporns et al., 2004; Watts

& Strogatz, 1998). Additionally, many networks demonstrate a scale-free architecture, such that the majority of nodes have a low number of connections (degree) but are connected indirectly with one another via a few highly connected nodes (hubs) (Sporns et al., 2004). Small-world attributes and scale-free architecture may be of particular relevance to the study of brain networks, as these types of organization permit rapid and efficient communication and integration of information, and are relatively robust to damage and disruption (Achard, Salvador, Whitcher, Suckling, & Bullmore, 2006; Latora & Marchiori, 2001; Mathias & Gopal, 2001; Sporns et al., 2004; Sporns & Zwi, 2004).

The local characteristics of nodes within the network, as well as the global network characteristics of a broader system, can be described using a limited number of metrics. On a local level, the connectivity of a node is described by its degree, which refers to the sum of its in-degree (the number of afferent) connections and out-degree (efferent) connections. A path refers to an ordered sequence of connections linking a source node to a target node; the length of the path refers to the number of distinct connections (edges) along the path (Sporns et al., 2004). The shortest path between a source node and a target node is referred to as the distance between those two nodes. Locally, the clustering coefficient, C, refers to the connectivity of a given node with its direct neighbors, and is determined by comparing the number of connections between a node and its neighbors relative to all possible connections between a node and its neighbors. A high local clustering coefficient indicates high connectivity of a given node; networks with a high average (global) clustering coefficient are considered to have small world properties (Watts & Strogatz, 1998). The betweenness centrality of a node, by

comparison, refers to how many of the shortest paths between all other node-node pairs within the network pass through the node (Bullmore & Sporns, 2009).

More globally, a connectivity distribution, P(k), (also referred to as a degree distribution; Bullmore & Sporns, 2009), characterizes the overall connectedness of a network and is defined as the probability distribution for nodes with k connections to other nodes within the network (Grigorov, 2005; van den Heuvel & Pol, 2010). The characteristic path length, L (also known simply as the path length), is defined as the average of all distances within the graph (e.g., the average of the shortest paths between each set of two nodes within the network); smaller values of L are thought to reflect globally increased connectivity within the network. Global efficiency refers to the average of the inverse of the shortest paths between each node-node pair; although similar to path length inasmuch as it reflects the functional integration of a network, global efficiency takes into account disconnected nodes (e.g. nodes that are not connected to any other nodes within the network) and is more heavily influenced by short paths (Rubinov & Sporns, 2010). As such, it has been proposed that global efficiency is superior to path length as a measure of the overall functional integration of the brain (Archard & Bullmore, 2007). Additionally, the modularity (which describes the level of functional segregation) of a network can be evaluated using hierarchical clustering, which identifies clusters of tightly interconnected nodes as "modules" (Girvan & Newman, 2002). With reference to their module, nodes can be described with regards to their role within the network, with provincial hubs being those that interact primarily with nodes within their own module, and connector hubs interacting across modules. The participation coefficient refers to the ratio of intramodular connectivity to intermodular

connectivity for a given node within the network, and can be the basis for distinguishing provincial and connector hubs.

Recently, there has been a substantial push to characterize the network characteristics of the human connectome, a term used to represent the complete set of all neural elements and structural connections within the brain (Sporns, Tononi, & Kotter, 2005). Principally, investigations of the human connectome have sought to explain the dynamic activity of the brain as a whole by identifying ways in which structural connections allow for the functional segregation of individual network communities, and simultaneously the functional integration of brain regions via communication of network communities (Sporns, 2013a). As such, particular attention has been paid to identifying the network characteristics that may give rise to this functional segregation and integration, such as small-worldness and participation coefficient (Bullmore & Sporns, 2012). There is evidence to suggest that human structural brain networks exhibit small world characteristics, including high clustering (Archard & Bullmore, 2007), short path lengths (Archard, Salvador, Whitcher, Suckling, & Bullmore, 2006; Eguiluz, Chialvo, Cecchi, Baliki, & Apkarian, 2005), and high efficiency (Latora & Marchioiri, 2001). Small-worldness is a critically important attribute of human brain networks, as this configuration is thought to be a near-optimal organizational structure that allows for both high functional specialization and integration while minimizing energy costs (He, Chen, & Evans, 2007; Sporns & Zwi, 2004).

The human connectome also shows strong evidence of modularity (Chen, He, Rosa-Neto, Germann, & Evans, 2008; He et al., 2009; Meunier, Lambiotte, Fornito, Ersche, & Bullmore, 2009) and it has been observed that the modular structure overlaps

significantly with functional systems in the cortex (Chen et al., 2008; Yu et al., 2011). Additionally, there is evidence that this modularity is hierarchical, with modules being nested within modules (Meunier et al., 2009). As noted by Sporns (2013b), nearly all studies of brain networks have identified modular architecture, with strong functional coupling within and between modules. Network hubs at each level of organizational hierarchy may serve to integrate information both by connecting various modules with one another, and being highly connected with other hubs (Sporns, 2013b). The precuneus, insula, superior parietal and superior frontal cortex, and anterior cingulate cortex all have been shown to have high centrality, high node degree, and high connection strength, which is suggestive of a role as network hubs (Gong et al., 2008; Hagmann et al., 2008; Iturria-Medina et al., 2007; Iturra-Medin, Sotero, Canales-Rodriguez, Aleman-Gomez, & Melle-Garcia, 2008; van den Heuvel & Sporns, 2011) and it has been proposed that these regions may form a "structural core" (also known as a "rich club") for the overall brain network (Hagmann et al., 2008; Sporns, 2013b; van den Heuvel & Sporns, 2011). Taken together, these studies are largely supportive of small-worldness of the human connectome, and fairly consistently identify hubs in parietal and prefrontal regions, and particularly the precuneus (Bullmore & Sporns, 2009; 2012).

Inasmuch as it is able to characterize both global and local network characteristics, graph theory provides a useful framework for understanding not only adaptive cognitive processes, but also the disruption of these processes in the context of psychopathology. It has been noted that the majority of neurological and psychological disorders involve the disruption of numerous cognitive and affective processes that are distributed across the brain; as such, comprehensive and accurate characterization of the

heterogeneous symptoms and presentations of psychiatric conditions requires a broad framework that is able to capture network-wide dysfunction (Menon, 2011). To date, graph theory has been applied to neuroimaging data in a number of clinical populations, and graph theoretical network attributes have been shown to discriminate between healthy controls and patient groups including schizophrenia (van den Heuvel & Fornito, 2014), attention deficit hyperactivity disorder (ADHD; e.g. Cao et al., 2013), Alzheimer's disease (e.g. Tijms et al., 2013), bipolar disorder (Leow et al., 2013), and major depression (Korgaonkar, Fornito, Williams, & Grieve, 2014). As noted by Menon (2011), the study of local and global network characteristics in clinical populations may be valuable in informing our understanding of the neurobiological basis of psychopathology by helping to identify circumscribed brain regions or large distributed networks that may be disrupted, identifying disrupted and compensatory neural processes, and predicting and monitoring disease onset and progression.

Graph Theory Analyses in Bipolar Disorder

To date, only one study has utilized graph theory in analyzing neuroimaging data with BD patients. Leow and colleagues (2013) utilized graph theory to investigate white matter network characteristics in conjunction with DTI among BD-I patients and healthy controls. Using a weighted approach (in which edges between a pair of nodes are weighted by the number of fibers connecting the nodes), the authors investigated white matter connectivity across the brain. Individuals with BD showed decreased white matter integrity in the genu, body, and splenium of the corpus callosum, but did not differ at any other white matter ROI. Global network analyses revealed that BD patients showed overall reduced global connectivity, with reduced global clustering, increased

characteristic path length, and lower global efficiency relative to healthy controls. Additionally, BD patients showed decreased clustering in the left hippocampus and right isthmus cingulate, and increased path length in the left hippocampus, left lateral OFC, and bilateral isthmus cingulate. Finally, BD patients showed decreased inter-hemispheric efficiency and longer inter-hemispheric path length relative to controls, predominantly in the frontal lobe, and decreased right-sided intra-hemispheric path length and efficiency. Taken together, these findings indicate the presence of white matter networks that are globally less efficient and locally less connected among individuals with BD; further, consistent with prevailing neurobiological models of BD, there is evidence for reduced node-level connectivity specifically in fronto-limbic regions. Additionally, this study found evidence for reduced inter-hemispheric integration in BD, which highlights the potential role of brain asymmetry in mood disorders (Leow et al., 2013).

The Current Study: Aims and Hypotheses

The purpose of the present study was to explore resting-state functional network connectivity in bipolar spectrum disorders (BSD) by characterizing the global and local network architecture across the brain using graph theoretical analysis with functional neuroimaging data. Specifically, this project sought to identify differences in network characteristics between individuals at low risk for BD (i.e., Moderate BAS [MBAS] sensitivity with no BSD), individuals at high risk for BD who have not developed a BSD (i.e., High BAS [HBAS] sensitivity with no BSD), and individuals at high risk who have developed a BSD (HBAS+BSD) to determine whether certain network attributes may reflect vulnerability to, rather than existing, BSD diagnosis. A second aim of this study was to evaluate relationships between functional network characteristics and behavioral

performance on a task assessing reward sensitivity, which is a key component of risk for BD (Alloy et al., 2008; 2012a,b).

Aim 1. To identify and compare resting functional network characteristics among individuals at varying levels of risk for BSD using graph theoretical analysis.

Given theories of BD risk that propose decreased prefrontal control over hypersensitive subcortical limbic structures (e.g. Strakowski et al., 2012), I hypothesized that the HBAS+BSD group would exhibit decreased nodal connectivity (local efficiency, betweenness centrality, and participation coefficient) of the mPFC, OFC, and dlPFC relative to the MBAS and HBAS groups, with the HBAS group falling intermediate to the MBAS and HBAS+BSD groups. Additionally, as it has been proposed that disruptions in the striatum, thalamus, and ACC may result in decoupling of frontal-limbic networks in BD (Strakowski et al., 2012), I proposed that decreased connectivity of the caudate, putamen, thalamus, and ACC would be observed only in the HBAS+BSD group.

The majority of literature examining global network architecture in clinical populations has found no differences in overall small world architecture between patients and controls, including work conducted with children with ADHD (Cao et al., 2014), adults with schizophrenia (Bassett et al., 2008), older adults with Alzheimer's disease (Lo, Wang, Chou, Wang, He, & Lin, 2010), and adults with bipolar disorder (Leow et al., 2013; van den Heuvel et al., 2010); as such, I hypothesized that all three groups would exhibit equal small-worldness. In contrast, previous work has shown decreased structural global efficiency and clustering in BD patients (Leow et al., 2013); as dysconnectivity is thought to be present prior to first onset in individuals with BD but to worsen over the

course of illness (Strakowski et al., 2012), I hypothesized that the MBAS group would evidence higher global efficiency and clustering than the HBAS group, who would evidence higher global efficiency and clustering than the HBAS+BSD group. Additionally, given findings of decreased callosal white matter integrity (see Heng, Song, & Sim, 2010, for a review), increased left intra-hemispheric integration and decreased inter-hemispheric integration in BD (Leow et al., 2013), but no evidence for degraded callosal WM in first degree relatives of BD patients (Linke et al., 2013), I hypothesized that the HBAS+BSD group would demonstrate increased left hemispheric functional integration relative to the other two groups, who would not differ from one another.

Aim 2. To evaluate relationships between global functional network characteristics (described above in Aim 1) and behavioral performance on a reward sensitivity task a) within the entire sample and b) moderated by Group status.

Among healthy adults, reward anticipation is associated with increased functional global efficiency, increased intra-cortical connectivity, and increased cortical-subcortical connectivity (Kinninson, Padmala, Choi, & Pessoa, 2012). Consequently, I hypothesized that increased sensitivity to reward would be associated with increased global efficiency, and that this relationship would be stronger for HBAS participants (with and without BSD) compared to MBAS participants. Given findings that reward sensitivity among healthy individuals is associated with decreased functional coherence within frontal and limbic regions (Hahn et al., 2012), I also hypothesized that increased reward sensitivity would be associated with decreased connectivity of the OFC, striatum, and amygdala. As BD is proposed to result from severe dysregulation of reward related regions, I hypothesized that the HBAS+BSD group would show lower connectivity of these regions

than the HBAS group, who would show lower connectivity than the MBAS group. Finally, as resting left frontal asymmetry is a well-known marker of approach motivation (Coan & Allen, 2004; Harmon-Jones et al., 2008; Nusslock et al., 2012), I hypothesized that increased left intra-hemispheric integration would be associated with increased reward sensitivity.

CHAPTER 2

METHODS

Participant Recruitment

Participants in the present study included 105 young adults (ages 18-27) recruited from a larger pool of adolescents and young adults currently participating in the Teen Emotion and Motivation (TEAM) project (Alloy et al., 2012a). Participants in Project TEAM were recruited via a two-step selection procedure. In the screening phase (Phase I), approximately 15,000 students (originally ages 14-19) were recruited from the greater Philadelphia region, including Philadelphia public high schools and universities. All participants in Phase I completed two measures of BAS sensitivity, the Carver and White Behavioral Inhibition System/Behavioral Activation System scales (BIS/BAS; Carver & White, 1994) and the Sensitivity to Punishment/ Sensitivity to Reward Questionnaire (SPSRQ; Torrubia, Ávila, Moltó, & Caseras, 2001). Those participants scoring in the 40th to 60th percentile on both the Total BAS subscale of the BIS/BAS scales and the Reward subscale of the SPSRQ were classified as moderate BAS sensitivity (MBAS, approximate n = 750), and those scoring in the 85th to 100th percentile on both measures were classified as high BAS sensitivity (HBAS, approximate n = 1,200). MBAS, rather than low BAS, participants were selected for several reasons. First, a MBAS group is more statistically "normal" as they are closer to the mean on BAS sensitivity. Further, comparing MBAS participants to HBAS participants provides a more conservative test of the BAS hypersensitivity theory, as only extremely elevated levels of BAS are thought to confer risk for BD, and low levels of BAS may be a protective factor against BD. Finally,

low BAS sensitivity may confer vulnerability to unipolar depression (e.g. Depue & Iacono, 1989; Depue, Krauss, & Spoont, 1987), suggesting that MBAS participants may be a more appropriate "healthy" comparison group.

Those individuals classified as MBAS and HBAS were invited to return for the second phase of screening (Phase II). Participants ages 18 and over provided written consent; participants under age 18 provided written assent and their parents provided written consent. Participants then completed a semi-structured diagnostic interview, conducted by extensively trained interviewers blind to participants' risk status, using the expanded Schedule for Affective Disorders and Schizophrenia- Lifetime interview (exp-SADS-L; Endicott & Spitzer, 1978; Alloy et al., 2012a), with 539 participants (334 high BAS and 205 moderate BAS) completing Phase II. Participants who met Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Text Revision (*DSM-IV-TR*; American Psychiatric Association, 2000) criteria for a primary psychotic disorder (e.g., schizophrenia or schizoaffective disorder, but not those with BD with psychotic features; n = 7) or those who were not fluent in English (n = 5) were excluded from further participation. Additionally, as Project TEAM was intended to prospectively predict first onset of BSDs, participants who had already met *DSM-IV-TR* criteria for a BSD at the time of Phase I were excluded from inclusion in the main project, and instead were followed as "extras." Participants who successfully completed Phase II were invited to complete additional baseline assessment measures as part of a Time 1 assessment that included questionnaires, behavioral tasks, and interviews. Time 1 was completed by 486 participants (300 high BAS and 176 moderate BAS). Participants enrolled in Project

TEAM also complete regular prospective assessments at approximately 6-month intervals over a period of up to five years.

A subset of Project TEAM participants ages 18 and over who completed a Time 1 assessment were invited to participate in the MRI component of the project as an additional study component, independent from their overall participation in Project TEAM. Exclusion criteria for the MRI study included the presence of ferrous metal in any part of the body, serious medical conditions, claustrophobia, attention deficit hyperactivity disorder (ADHD), left-handedness, and pregnancy. Additionally, participants were asked to report on history of head trauma or neurological insult or injury and medication usage (including prescribed psychoactive medications, non-psychoactive prescribed medications, and over-the-counter drugs). Participants provided informed written consent. Participants were compensated $100.00 for their participation in the MRI study, with the opportunity to win an additional, unspecified amount of money based on their performance on a behavioral task. Individuals who consented to MRI participation completed a set of trait-based self-report online questionnaires within the 48 hours prior to the MRI session utilizing an online survey presentation program. On the day of the MRI session, participants completed a set of state-based self-report questionnaires. Additionally, participants underwent a complete Society of Magnetic Resonance Imaging standardized MRI screening protocol conducted by a certified MRI technician, and completed practice rounds of two behavioral tasks outside of the scanner.

Current Study Participants

In all, 111 participants completed the MRI portion of the study. However, 4 participants were excluded due to technical issues with image acquisition, and 1 participant declined following completion of the localizer scan due to claustrophobia. One additional participant was excluded due to excessive head motion throughout scanning. Thus, participants in the current study sample included 105 adolescents and young adults, comprised of 36 participants from the MBAS group, 41 participants from the HBAS group, and 28 participants from the HBAS+BSD group. Of the participants in the HBAS+ BSD group, 6 participants were diagnosed with BD-NOS, 2 were diagnosed with cyclothymia, 16 were diagnosed with BD-II, and 4 were diagnosed with BD-I. Demographic and clinical characteristics of the study sample are presented in Table 1. One-way ANOVA and chi-square tests were conducted to assess potential differences between groups on demographic characteristics. The three groups did not significantly differ on age ($F(2, 102) = 1.31, p = 0.27$), gender ($\chi^2(2, N = 105) = 0.79, p = 0.67$), race ($\chi^2(10, N = 104) = 10.44, p = 0.40$), ethnicity ($\chi^2(2, N = 94) = 3.68, p = 0.16$) or usage of psychoactive medications ($\chi^2(2, N = 105) = 0.28, p = 0.90$).

Neuroimaging Data Acquisition

Neuroimaging data were collected using a 3.0T Siemens Verio MRI scanner, with a standard 12-channel head coil. Imaging sessions were conducted jointly by Temple University Hospital MRI technicians, responsible for MRI scanner operation, and trained Project TEAM research assistants, responsible for administering questionnaires, behavioral tasks, and diagnostic interviews to participants, as well as coordinating

stimulus presentation during scanning. Stimulus presentation during the resting state was conducted with Presentation software (Version 0.70, www.neurobs.com) using a rear-projection system.

After participants completed questionnaires, practice behavioral tasks, MRI safety screening, and were placed in the scanner, a 10 second localizer scan was run to ensure proper head position and gradient field mapping was conducted to enable offline correction of field heterogeneity. Participants then completed a single, 10-minute run of resting-state data acquisition. Participants were presented with a fixation cross, and were instructed to lay in the scanner with their eyes open, to look at the fixation cross and not to try to think of anything in particular. All BOLD scans utilized 4mm thick (no gap) steeply obliqued axial slices aligned 30 degrees above the anterior commissure-posterior commissure plane, collected in interleaved descending order for whole-brain coverage (TR = 2000 ms; TE = 20 ms; flip angle = 70°; FOV = 200 mm; matrix = 64 x 64). Structural 3D axial MPRAGE images also were acquired (1 mm thick; TR = 2200 ms; TE = 3.29 ms; FOV = 256; flip angle = 90°; 192 slices). In addition to the 10-minute resting-state scan, participants also completed a 64-direction, 2.5 mm isotropic resolution DTI scan, as well as two behavioral tasks. The first behavioral task, the Monetary Incentive Delay task (MID; Knutson, Fong, Adams, Varner, & Hommer, 2001), was completed in two runs of 9 minutes, 44 seconds each (separated by a rest break). This task was designed for use in neuroimaging to dissociate anticipation and receipt of rewards and punishments in a rapid event-related design. The second behavioral task, a response inhibition task (Go/No Go task) was completed over the course of a single, 8

minute, 36 second trial. This task was designed to measure participants' ability to inhibit prepotent response tendencies. Only resting state data were used in the current analyses.

Participants then were removed from the scanner, debriefed, and then completed an abbreviated structured diagnostic interview, consisting of the depression and mania/hypomania sections of the exp-SADS-L (Endicott & Spitzer, 1978; Alloy et al., 2012a). Participants who met diagnostic criteria for a current depressive, manic, or hypomanic episode (n = 4) were excluded from the current study in order to maximize the homogeneity of the HBAS+BSD group. One additional participant was excluded due to falling asleep during resting state data acquisition. A chi-square test indicated that excluded participants did not significantly differ on the basis of group, (χ^2 (2, N = 105)= 0.66, p = 0.72).

Measures

BIS/BAS Sensitivity

The Carver and White (1994) BIS/BAS scale is a widely used measure of trait BIS and BAS sensitivities, and consists of 20 four-point Likert-type items (1 = strongly disagree, 4 = strongly agree). The BIS/BAS scales are comprised of one BIS scale, indexing behavioral inhibition sensitivity, which also can be conceptualized as sensitivity to punishment (Carver & White, 1994; Torrubia et al., 2001), and three BAS subscales indexing different theoretically distinct facets of BAS sensitivity (Carver & White, 1994). The Drive (BAS-D) subscale includes items pertaining to the pursuit of appetitive goals (e.g. "When I want something, I usually go out of my way to get it,"); the Reward Responsiveness (BAS-R) subscale measures positive responses to anticipation or receipt

of reward (e.g. "When I get something I want, I feel excited and energized,"); and the Fun Seeking (BAS-F) subscale indexes both desire for rewarding experiences and the willingness to approach such experiences on the spur of the moment (e.g. "I will often do things for no other reason than they might be fun."). In Project TEAM, the BAS-D, BAS-R, and BAS-F subscales were summed to create a total BAS score (BAS-T), which had acceptable internal consistency (α = .80) in the Phase I sample. Research in other samples also has demonstrated acceptable test-retest reliability for BAS-T (Meyer, Johnson, & Winters, 2001) and each of the three BAS subscales (Carver & White, 1994).

The Sensitivity to Punishment/Sensitivity to Reward Questionnaire (SPSRQ; Torrubia et al., 2001) also was used to measure BIS and BAS sensitivities. The SPSRQ is comprised of 48 "yes" or "no" items organized into two subscales, the Sensitivity to Punishment (SPSRQ-P) subscale (e.g. "Generally, do you pay more attention to threats than to pleasant events?"), which measures BIS sensitivity, and the Sensitivity to Reward (SPSRQ-R) subscale (e.g. "Do you often do things to be praised?"), which measures BAS sensitivity. The Phase I sample of Project TEAM evidenced acceptable internal consistency for both the SPSRQ-P and SPSRQ-R subscales, α_{SP} = .84 and α_{SR} = .76, respectively.

Lifetime Psychopathology

The exp-SADS-L is a modification of the original SADS-L (Endicott & Spitzer, 1978), a structured diagnostic interview that aims to assess current and past psychopathology based on Research Diagnostic Criteria (RDC; Endicott & Spitzer, 1978) utilizing participant report of their most severe symptoms. The exp-SADS-L used in

Project TEAM was created in order to improve reliability and accuracy of diagnosing bipolar spectrum conditions (see Alloy et al., 2009) and included the addition of items and probes within the depression, (hypo)mania, and cyclothymia sections to assess the timing, frequency, and duration of mood symptoms; additional mood symptom probes based on the Behavioral Variability Interview (Depue, 1985), and additional probes to assess for *DSM-IV-TR* diagnostic criteria in all diagnostic categories also were added. The exp-SADS-L has demonstrated strong inter-rater reliability for both unipolar depression ($\varkappa \geq 0.96$) and BSDs ($\varkappa > .90$) (Alloy et al., 2008).

Handedness

Handedness was assessed with the Chapman and Chapman Handedness Questionnaire (Chapman & Chapman, 1987), a self-report questionnaire that consists of thirteen items asking the participant to identify which hand they use to complete daily tasks (such as writing, using a hammer, or stirring a can of paint). Participants are assigned a point value per their response on each item (left hand= 1 point, either hand = 2 points, right hand = 3 points), which are then summed to create a final score. Participants who reported left-handedness (total score < 32) were excluded from completing the MRI session due to potential neurological lateralization differences between right- and left-handers. In total, 28 participants were excluded due to being left-handed.

Reward Sensitivity

Reward sensitivity was assessed at baseline (Time 1) via the Card Arranging Reward Responsivity Objective Test (CARROT; Powell, Al-Adawi, Morgan, & Greenwood, 1996), a behavioral task designed to measure participants' responsivity to

external rewards. On the CARROT, participants receive a set of 60 cards printed with a series of 5 digits; each card includes either the digit 1, 2, or 3. Participants are asked to sort the cards into piles based on whether they have a 1, 2, or 3, over the course of three trials. In Trial 1, participants are instructed to sort the cards into piles as quickly as possible, thus establishing a baseline sorting speed. In Trial 2, participants are allotted 75% of their baseline sorting time (from Trial 1) to sort as many cards as possible. In Trial 3, participants are again allotted 75% of their baseline sorting time to sort as many cards as possible; however, participants are now told they will receive 25 cents per 5 cards sorted. An index of reward responsivity is derived by subtracting the number of cards sorted in the unrewarded condition (Trial 2) from the number of cards sorted in the rewarded condition (Trial 3). Previous work has shown that CARROT reward responsiveness is elevated among euthymic individuals with BD-I (Hayden et al., 2008), and predicts first-onset of bipolar spectrum disorders among individuals with high BAS sensitivity (Alloy et al., 2012a).

Medication Use

On the day of the MRI scan, participants are asked to complete a questionnaire assessing their use of prescription medications, over-the-counter medications, vitamins, and herbal substances. Participants report on the name, dosage, frequency, route of administration, and when they began taking each medication. Participants report current medications as well as all medications taken within the week prior to the scan. For the present study, medication use was defined as whether participants identified themselves as currently taking any medication(s) “for mood/emotional

problems/depression/anxiety/sleep," with 0 = not currently taking any psychoactive medications, and 1 = currently taking at least 1 psychoactive medication.

Depressive Symptoms.

Depressive symptoms on the day of the MRI scan are assessed using the Beck Depression Inventory (BDI; Beck, Rush, Shaw, & Emery, 1979), a self-report measure consisting of 21 items that assess the symptoms of depression. The BDI has shown good psychometric properties and validity in a number of clinical and non-clinical samples (Beck, Steer, & Garbin, 1988; Richter, Werner, Heerlein, Kraus, & Sauer, 1998). The BDI has acceptable internal consistency in the Project TEAM sample (α = .88).

(Hypo)manic Symptoms

Hypomanic symptoms on the day of the MRI scan are assessed using the Altman Self-Rating Mania Scale (ASRM; Altman, Hedeker, Peterson & Davis, 1997), a 5-item self-report measure assessing symptoms of (hypo)mania, including euphoria, grandiosity, reduced need for sleep, excessive activity, and talkativeness. The ASRM has been shown to have acceptable internal consistency in the Project TEAM sample (α = .75) and ASRM scores are significantly associated with self-reported manic symptomology, as well as semi-structured interview diagnoses of mania and hypomania (Altman, Hedeker, Peterson, & Davis, 2001).

Substance Use

Substance use is assessed using the Adolescent Alcohol and Drug Involvement Scale (AADIS; Moberg, 2000), a 13-item self-report questionnaire assessing frequency of substance use for 13 individual categories of substances (tobacco, alcohol, marijuana,

hallucinogens, amphetamines, powder cocaine, rock cocaine, barbiturates, PCP, opiates, inhalants, tranquilizers, and other). Participants are asked to rate their use of each substance (without a prescription) over the past 30 days on a scale of 0 (Never used) to 7 (Several times daily). Participants receive a total score, reflecting both the frequency and number of different substances used. Total scores on the AADIS have been shown to predict substance use disorders assessed via diagnostic interview (Winters, Botzet, Anderson, Bellehumeur, & Egan, 2001).

Graph Theory Analysis

fMRI Data Preprocessing Preprocessing of fMRI data was carried out via an automated pipeline designed for processing of resting-state functional MRI data (Song, Wang, Alpert, Wang, & Parrish, 2015a) on the Northwestern University Neuroimaging Data Archive (NUNDA; Alpert, Kogan, Parrish, Marcus, & Wang, 2016). Specific details of pipeline functions may be found at http://niacal.northwestern.edu/nunda_pipelines/10. Briefly, this pipeline was designed to prioritize minimization of motion artifact in the resting-state data, given evidence that head motion can introduce significant and systematic error in resting-state functional connectivity fMRI in general (Jo et al., 2013; Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Satterthwaite et al., 2012; Van Dijk, Sabuncu, & Buckner, 2012), and more specifically in studies utilizing graph theory (Yan, Craddock, He, & Milham, 2013).

Briefly, despiking was completed with AFNI's "3dDespike" program (Jo et al., 2013; Siegel et al., 2014), followed by a slice acquisition time correction to the middle slice. Images then were realigned to the middle volume in the time series to correct for

head motion, and then coregistered to the T1 image. White matter signal was regressed from EPI data using CompCor to remove physiological and motion-based artifacts (Behzadi, Restom, Liau, & Liu, 2007), and scrubbing was performed using a Friston 24-parameter model regression (Friston et al., 1996). Data then were linearly transformed into MNI space using FSL FLIRT (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001; Greve & Fischl, 2009) and were spatially smoothed using a 6mm FWHM filter (AFNI 3dBlurToFWHM). Finally, we performed intensity normalization to 10000 (rather than percent signal change) to best handle float point errors, as recommended by the Human Connectome Project (Glasser et al., 2013). Quality assurance for the data was carried out via an automated pipeline (Song et al., 2015b) accompanied by visual inspection carried out by trained post-baccalaureate research assistants supervised by a doctoral student. Temporal signal-to-noise ratio (tSNR) values were calculated as a measure of overall data quality, with a slice-weighted mean tSNR minimum of 120 applied to select cases with acceptable data quality (Song et al., 2015b). One participant (MBAS group) was excluded from the final sample due to excessive head motion that was not resolved adequately by these procedures and a slice-weighted mean tSNR of 110.63.

Network Construction. For each individual participant, network nodes were defined anatomically by parcellating the cortex into 90 cortical and subcortical regions based on the anatomical automatic labeling atlas (AAL; Tzourio-Mazoyer et al., 2002) using DPARSFA (Chao-Gan & Yu-Feng, 2010). A functional connectivity matrix was derived by computing the Pearson's correlation between the averaged regional time series for each pairwise set of nodes using GraphVar (Kruschwitz, List, Waller, Rubinov, &

Walter, 2015). For most graph theory analyses, a weighted approach was utilized in which the strength of the connection between each set of nodes was estimated by their correlation. For analysis of small worldness, a binary approach was utilized in which each pairwise connection was designated as either absent (0) or present (1) based on statistical significance ($p < .001$). For calculation of small worldness, 500 null-model networks for each individual participant were generated from which the participant's small worldness could be quantified (Humphries & Gurney, 2008). Given that the study hypotheses regarded undirected networks, negative correlations were transformed to their absolute value for all analyses.

Computation of Network Measures. Graph theory analyses were carried out using GraphVar (Kruschwitz et al., 2015), a graphical-user-interface (GUI)-based MATLAB toolbox that allows for network construction and graph-theoretical analyses of structural and functional MRI. In order to address the above hypotheses, both global and local measures of network connectivity were calculated. At the local level, the local efficiency, betweenness centrality, and participation coefficient were computed for the OFC, dlPFC, caudate, putamen, thalamus, and ACC ROIs. Global measures including the small worldness, global efficiency, and global clustering coefficient also were calculated. To investigate intrahemispheric integration, the mean participation coefficient for each hemisphere (45 AAL-defined nodes) was calculated, with higher mean participation coefficient taken to indicate increased integration (Leow et al., 2013). A measure of interhemispheric integration (II) was derived by subtracting right hemispheric integration (RHI) from left hemispheric integration (LHI), generating a metric whose absolute value reflects the magnitude of disparity between hemispheres. Positive values of II indicate

greater integration of the left hemisphere relative to the right, whereas negative values of II indicate more integration of the right hemisphere relative to the left.

CHAPTER 3

RESULTS

Clinical Characteristics of the Sample

One-way ANOVAs and chi-square tests were conducted to compare groups on their demographic and clinical characteristics (Table 1).

As might be expected, there was a significant main effect of group on hypomanic symptoms, $F(2, 95) = 7.23, p < .01$). A Tukey post-hoc test revealed that the HBAS+BSD group reported significantly higher hypomanic symptoms compared to the MBAS (mean difference = 3.35 ± .97, $p < .01$) and the HBAS (mean difference = 3.14 ± .95, $p < .01$) groups. There was no significant difference between the MBAS and HBAS groups (mean difference = 0.21 ± 0.64, $p = .97$). There also was a significant main effect of group on depressive symptoms, $F(2, 95) = 4.50$ $p = .01$. Tukey's post-hoc tests identified that the HBAS+BSD group reported significantly higher depression scores than the MBAS (mean difference = 4.39 ± 1.55, $p = .02$) and HBAS groups (mean difference = 3.78 ± 1.53, $p = .04$). Again, there was no significant difference between the MBAS and HBAS groups (mean difference = 0.61 ± 1.39, $p = .90$). There also was a significant main effect of group on substance use symptoms, $F(2, 95) = 4.85$ $p = .01$. Again, Tukey's post-hoc tests indicated that the HBAS+BSD group reported significantly higher substance use compared to the MBAS (mean difference = 3.33 ± 1.34, $p < .01$) and HBAS groups (mean difference = 3.96 ± 1.32, $p < .01$), who did not differ from one another (mean difference = 0.63 ± 1.20, $p = 0.86$). The groups did not significantly differ on medication usage, ($\chi^2 (2, N = 100) = 0.83, p = 0.66$).

Table 1. Demographic and Clinical Characteristics of the Sample

Characteristic	Overall Sample (n = 105)	MBAS (n = 36)	HBAS (n = 41)	HBAS + BSD (n = 28)
Female	52.4%	58.3%	51.2%	50.0%
Race				
White/Caucasian	63.8%	61.1%	65.9%	64.3%
African American	21.0%	27.8%	22.0%	10.7%
Asian American	6.7%	5.6%	2.4%	14.3%
Native American	1.0%	0.0%	0.0%	3.6%
Native Hawaiian/ Pacific Islander	0.0%	0.0%	0.0%	0.0%
Biracial/Multiracial	4.8%	2.8%	7.4%	3.6%
Other	1.9%	2.8%	2.4%	0.0%
Missing/Prefer not to say	1.0%	0.0%	0.0%	3.6%
Hispanic	4.8%	0.0%	5.3%	10.7%
Age, years (SD)	20.70 (1.89)	21.06 (2.01)	20.68 (1.89)	20.29 (1.72)
Medication	15.2%	13.9%	14.6%	17.9%
BDI (SD)	5.34 (6.60)	4.05 (5.14)	4.96 (7.07)	7.61 (7.46)
ASRM (SD)	3.97 (3.89)	3.06 (2.38)	3.33 (3.74)	6.13 (4.91)
AADIS (SD)	6.78 (5.25)	6.25 (5.37)	5.70 (4.17)	9.07 (5.98)

Note. MBAS = Moderate Behavioral Approach System Sensitivity (BAS) group, HBAS = High BAS group, HBAS+BSD = High BAS + Bipolar Spectrum Disorder (BSD) group, BDI = Beck Depression Inventory, ASRM = Altman Self-Rating Mania Scale, AADIS = Adolescent Alcohol and Drug Involvement Scale.

Relationships Among Study Variables

Bivariate correlations were conducted to evaluate relationships between demographic and clinical characteristics and primary study variables (Tables 2-4). Regarding local network characteristics, Pearson correlations between demographic/clinical characteristics and graph measures were conducted separately for each individual ROI in each hemisphere. For the present study, given the low number of participants in each group utilizing different classes of psychoactive medications, medication usage was defined as a dichotomous variable, with 1 = participant currently taking a psychoactive medication, or 0 = participant not currently taking any psychoactive medications. In addition, given the low number of participants in each individual non-white racial group, race was considered as a dichotomous variable (with 1 = non-white and 0 = white). In terms of betweenness centrality (Table 2), age was positively associated with connectivity of the right ACC, $r(98) = 0.23$, $p < .05$, such that older participants had higher betweenness centrality of the right ACC. Age was negatively associated with connectivity of the right amygdala at the trend level, $r(98) = -0.17$, $p < .10$, such that younger participants had higher connectivity of this region. Gender was significantly associated with betweenness centrality of the left mPFC, $r(98) = .22$, $p < .05$, such that males had higher connectivity than females. Race was associated with connectivity of the right OFC, $r(98)= .22$, $p < .05$, and the left caudate, $r(98) = 0.21$, $p < .05$, such that non-white participants showed higher betweenness centrality in these regions.

In terms of clinical variables, higher scores on the AADIS were associated at the trend level with decreased betweenness centrality in the right OFC, $r(98) = -0.18$, $p <. 10$

and the left mPFC, $r(98) = -0.17$, $p < .10$. Higher substance use as reported on the AADIS also was associated with significantly decreased betweenness centrality in the right putamen, $r(98) = -0.21$, $p < .05$ and increased betweenness centrality in the left thalamus, $r(98) = 0.21$, $p < .05$. Scores on the BDI were negatively correlated at the trend level with betweenness centrality of the right dlPFC $r(98) = -0.17$, $p < .10$. Medication status correlated with betweenness centrality of the left OFC at the trend level, $r(98) = 0.18$, $p < .10$, such that participants who were currently taking medication showed higher betweenness centrality in this region. CARROT scores positively correlated with betweenness centrality of the left mPFC, $r(79) = 0.31$, $p < .01$, and left putamen, $r(79) = .23$, $p < .05$.

CARROT scores were negatively correlated with local efficiency across all ROIs investigated (Table 3), such that increased reward sensitivity on the CARROT was associated with decreased local efficiency. In addition, gender was associated with local efficiency of the right OFC at the trend level, $r(98) = -0.18$, $p < .10$, such that females showed higher local efficiency of the right OFC than males.

Only race, hypomanic symptoms, and CARROT scores were significantly associated with participation coefficient (Table 4). Race significantly predicted the participation coefficient of the left dlPFC ($r(98) = -0.21$, $p < .05$), bilateral mPFC (left: $r(98) = -0.21$, $p < .05$; right: $r(98) = -0.21$, $p < .05$), right ACC ($r(98) = -0.21$, $p < .05$), left amygdala ($r(98) = -0.26$, $p < .01$), and predicted the participation coefficient of the left ACC at the trend level ($r(98) = -0.19$, $p < .10$). Across these regions, white participants showed higher participation coefficient than non-white participants. Hypomanic symptoms on the ASRM were associated with increased participation

Table 2. Correlations among Demographic and Clinical Characteristics and Betweenness Centrality

ROI	Age	Gender	Race	AADIS	ASRM	BDI	Med	CARROT
dlPFC (L)	-0.01	-0.01	-0.16	0.02	0.02	-0.06	0.03	0.18
dlPFC (R)	0.14	0.07	0.09	-0.07	0.01	-0.17†	0.08	0.14
OFC (L)	0.14	0.07	0.17	-0.04	-0.05	-0.02	0.18†	-0.07
OFC (R)	-0.02	-0.03	0.22*	-0.18†	-0.00	-.11	-0.05	0.12
mPFC (L)	0.05	0.22*	-0.00	-0.17†	-0.05	-0.03	-0.03	0.31**
mPFC(R)	0.00	0.13	0.19	-0.06	0.06	-0.01	0.05	-0.03
ACC (L)	0.05	0.08	-0.11	-0.14	-0.04	0.04	-0.02	0.19
ACC (R)	0.23*	0.05	-0.02	-0.10	-0.08	-0.02	-0.04	0.10
Amygdala (L)	0.10	0.03	-0.08	-0.02	-0.10	-0.16	-0.13	0.06
Amygdala (R)	-0.17†	0.16	-0.12	-0.09	-0.12	-0.09	-0.07	0.04
Caudate (L)	-0.01	0.16	0.21*	0.04	0.04	0.02	0.18	0.17
Caudate (R)	-0.06	0.12	0.01	0.08	0.00	-0.06	0.13	0.05
Putamen (L)	0.00	0.11	-0.11	-0.08	-0.08	0.11	0.02	0.23*
Putamen (R)	-0.02	-0.04	-0.05	-0.21*	0.05	-0.04	0.09	0.02
Thalamus (L)	-0.11	0.01	-0.03	0.21*	0.06	-0.05	-0.02	-0.02
Thalamus (R)	-0.07	0.12	0.09	0.14	-0.09	-0.05	0.05	-0.16

Note. ROI = Region of Interest, L = Left, R = Right, dlPFC = Dorsolateral Prefrontal Cortex, OFC = Orbitofrontal Cortex, mPFC = Medial Prefrontal Cortex, ACC = Anterior Cingulate Cortex, AADIS = Adolescent Alcohol and Drug Involvement Scale, ASRM = Altman Self-Rating Mania Scale, BDI = Beck Depression Inventory, Med = Medication status, CARROT = Card Arranging Reward Responsiveness Objective Test. †$p < .10$, *$p < .05$, **$p < .01$.

Table 3. Correlations among Demographic and Clinical Characteristics and Local Efficiency

ROI	Age	Gender	Race	AADIS	ASRM	BDI	Med	CARROT
dlPFC (L)	-0.02	-0.16	0.03	0.09	-0.08	-0.05	-0.12	-0.28*
dlPFC (R)	0.01	-0.15	0.07	0.07	-0.09	-0.02	-0.16	-0.26*
OFC (L)	-0.01	-0.14	0.04	0.10	-0.10	0.01	-0.08	-0.27*
OFC (R)	-0.05	-0.18†	0.04	0.05	-0.10	0.03	-0.12	-0.22†
mPFC (L)	-0.02	-0.13	0.04	0.07	-0.12	-0.02	-0.11	-0.23*
mPFC(R)	-0.03	-0.14	0.04	0.07	-0.09	-0.01	-0.13	-0.28*
ACC (L)	-0.03	-0.10	-0.03	0.10	-0.10	0.01	-0.13	-0.25*
ACC (R)	-0.01	-0.12	0.01	0.10	-0.10	0.02	-0.15	-0.27*
Amygdala (L)	-0.06	-0.07	0.01	0.06	-0.07	0.05	-0.12	-0.26*
Amygdala (R)	-0.04	-0.07	0.02	0.04	-0.12	0.04	-0.14	-0.24*
Caudate (L)	-0.06	-0.09	0.02	0.08	-0.01	0.08	-0.03	-0.27*
Caudate (R)	-0.07	-0.09	0.02	0.08	-0.03	0.07	-0.04	-0.26*
Putamen (L)	-0.06	-0.08	0.04	0.04	-0.05	0.09	-0.08	-0.27*
Putamen (R)	-0.08	-0.07	0.05	-0.02	-0.02	0.09	-0.07	-0.28*
Thalamus (L)	-0.06	-0.07	0.04	0.13	-0.02	0.10	-0.10	-0.27*
Thalamus (R)	-0.07	-0.07	0.06	0.13	-0.02	0.11	-0.09	-0.27*

Note. ROI = Region of Interest, L = Left, R = Right, dlPFC = Dorsolateral Prefrontal Cortex, OFC = Orbitofrontal Cortex, mPFC = Medial Prefrontal Cortex, ACC = Anterior Cingulate Cortex, AADIS = Adolescent Alcohol and Drug Involvement Scale, ASRM = Altman Self-Rating Mania Scale, BDI = Beck Depression Inventory, Med = Medication status, CARROT = Card Arranging Reward Responsiveness Objective Test. †$p < .10$, *$p < .05$, **$p < .01$.

Table 4. Correlations among Demographic and Clinical Characteristics and Participation Coefficient

ROI	Age	Gender	Race	AADIS	ASRM	BDI	Med	CARROT
dlPFC (L)	-0.10	-0.09	-0.21*	-0.01	0.28**	0.04	-0.15	-0.01
dlPFC (R)	-0.05	-0.11	-0.18	-0.04	0.26**	0.07	-0.07	-0.12
OFC (L)	-0.03	-0.03	-0.18	-0.04	0.20*	-0.01	-0.11	-0.13
OFC (R)	-0.08	-0.06	-0.16	-0.04	0.26*	0.03	-0.18	-0.10
mPFC (L)	-0.06	-0.00	-0.21*	-0.00	0.16	-0.03	-0.17	-0.15
mPFC(R)	-0.02	0.03	-0.21*	-0.00	0.14	-0.01	-0.12	-0.12
ACC (L)	0.02	0.05	-0.19†	0.06	0.12	-0.01	-0.93	-0.06
ACC (R)	0.01	-0.01	-0.21*	0.05	0.14	0.01	-0.15	-0.12
Amygdala (L)	-0.05	-0.05	-0.26**	0.07	0.18	0.08	-0.14	-0.09
Amygdala (R)	-0.05	-0.02	-0.18	0.06	0.21*	0.14	-0.09	-0.05
Caudate (L)	-0.02	-0.07	-0.18	0.04	0.22*	-0.02	-0.09	-0.19
Caudate (R)	0.00	-0.06	-0.17	0.03	0.19†	-0.01	-0.07	-0.14
Putamen (L)	-0.06	-0.06	-0.15	0.07	0.24*	0.03	-0.03	-0.19†
Putamen (R)	-0.09	-0.03	-0.11	0.04	0.24*	0.05	-0.07	-0.20†
Thalamus (L)	-0.01	-0.01	-0.19	0.04	0.22*	0.08	0.01	-0.12
Thalamus (R)	-0.02	-0.07	-0.17	0.05	0.20†	0.01	-0.03	-0.18

Note. ROI = Region of Interest, L = Left, R = Right, dlPFC = Dorsolateral Prefrontal Cortex, OFC = Orbitofrontal Cortex, mPFC = Medial Prefrontal Cortex, ACC = Anterior Cingulate Cortex, AADIS = Adolescent Alcohol and Drug Involvement Scale, ASRM = Altman Self-Rating Mania Scale, BDI = Beck Depression Inventory, Med = Medication status, CARROT = Card Arranging Reward Responsiveness Objective Test. †$p < .10$, *$p < .05$, **$p < .01$.

coefficient across the bilateral dlPFC (left: $r(98) = 0.28$; right: $r(98) = 0.26$; ps < .01), bilateral OFC (left: $r(98) = 0.20$; right: $r(98) = 0.26$; ps < .05), bilateral putamen (left: $r(98) = 0.24$; right: $r(98) = 0.24$; ps < .05), right amygdala ($r(98) = 0.21$, $p < .05$, left caudate ($r(98) = 0.21$, $p < .05$), and left thalamus ($r(98)= 0.22$, $p < .05$). ASRM scores also were associated at the trend level with the participation coefficient of the right caudate ($r(98) = 0.19$, $p < .10$) and right thalamus ($r(98) = 0.20$, $p < .10$). Across ROIs, higher hypomanic symptoms were associated with increased participation coefficient. CARROT scores were negatively associated at the trend level with the participation coefficient of the bilateral putamen (left: $r(79) = -0.19$; right: $r(79) = -0.20$; ps < .10), such that higher reward sensitivity on the CARROT was associated with decreased participation coefficient of the putamen.

Global network measures also were correlated with demographic and clinical variables (Table 5). Only CARROT scores were significantly correlated with global clustering, $r(98) = -0.27$, $p < .01$, global efficiency, $r(98) = -0.27$, $p < .05$, and small-worldness, $r(98) = 0.25$, $p < .05$. Higher CARROT scores were associated with decreased global clustering and global efficiency, but increased small-worldness.

Table 5. Correlations among Demographic and Clinical Characteristics and Global Graph Variables

Graph Metric	Age	Gender	Race	AADIS	ASRM	BDI	Med	CARROT
Global Clustering	-0.03	-0.14	0.05	0.09	-0.08	0.02	-0.11	-0.27*
Global Efficiency	-0.02	-0.15	0.05	0.11	-0.08	0.03	-0.12	-0.27*
Small-Worldness	0.17	-0.04	-0.03	-0.07	0.01	0.04	0.14	0.25*

Note. AADIS = Adolescent Alcohol and Drug Involvement Scale, ASRM = Altman Self-Rating Mania Scale, BDI = Beck Depression Inventory, Med = Medication status. CARROT = Card Arranging Reward Responsiveness Objective Test. *p < .05.

Finally, demographic and clinical variables were correlated with interhemispheric and intrahemispheric integration (Table 6). Race was significantly correlated with intrahemispheric integration of both the left hemisphere ($r(98) = -0.20, p < .05$), and the right hemisphere ($r(98) = -0.20, p < .05$), such that white participants showed higher intrahemispheric integration across hemispheres than nonwhite participants. Hypomanic symptoms were significantly positively associated with intrahemispheric integration of both the left hemisphere ($r(98) = 0.21, p < .05$), and the right hemisphere ($r(98) = 0.22, p < .05$), such that increased scores on the ASRM were associated with increased intrahemispheric integration bilaterally.

Table 6. Correlations among Demographic and Clinical Characteristics and Intra/Interhemispheric Integration Metrics

	Age	Gender	Race	AADIS	ASRM	BDI	Med	CARROT
Left Hemisphere Integration	-0.05	-0.04	-0.20*	-0.01	0.21*	0.03	-0.07	-0.16
Right Hemisphere Integration	-0.04	-0.05	-0.20*	-0.01	0.22*	0.04	-0.06	-0.15
Interhemispheric Integration	-0.05	0.08	0.01	0.05	-0.05	-0.05	-0.13	-0.10

Note. AADIS = Adolescent Alcohol and Drug Involvement Scale, ASRM = Altman Self-Rating Mania Scale, BDI = Beck Depression Inventory, Med = Medication status, CARROT = Card Arranging Reward Responsiveness Objective Test. *$p < .05$.

Test of Study Hypotheses: Aim 1

Differences in local network characteristics (local efficiency, betweenness centrality, and participation coefficient) between groups were evaluated using one-way analysis of covariance (ANCOVA). Given that each measured demographic and clinical variable was associated with at least one primary study outcome measure (described

above), age, gender, race, depressive and hypomanic symptoms, substance use, and medication use were included as covariates. A separate ANCOVA was conducted for each of the ROIs (OFC, mPFC, dlPFC, caudate, putamen, thalamus, and ACC) in each hemisphere for each individual network metric. Post-hoc tests were conducted using Tukey's Honest Significant Difference (HSD) procedure.

As shown in Table 7, there were no main effects of group on local efficiency at any of the 14 bilateral ROIs. However, there was a significant effect of group on betweenness centrality in the right dlPFC, $F(2, 97) = 4.52$, $p = .01$. Tukey's post-hoc tests revealed MBAS > HBAS (mean difference = 14.39 ± 4.81, $p = .01$), with HBAS+BSD falling intermediate. The HBAS+BSD group did not significantly differ from the MBAS (mean difference = -5.97 ± 6.04, $p = .98$) or HBAS (mean difference = 8.42 ± 5.97, $p = .49$) groups (see Table 8).

Table 7. Main Effect of Group on Local Efficiency

	Main Effect of Group*			Group Means (SE)*		
ROI	*F*	*p*	η^2	M_{MBAS}	M_{HBAS}	$M_{HBAS + BSD}$
mPFC (L)	0.55	0.58	0.01	0.44 (.03)	0.45 (.03)	0.40 (.03)
mPFC (R)	0.71	0.50	0.02	0.44 (.03)	0.43 (.03)	0.38 (.03)
dlPFC (L)	0.35	0.71	0.01	0.43 (.03)	0.43 (.03)	0.39 (.04)
dlPFC (R)	0.54	0.56	0.01	0.43 (.03)	0.42 (.03)	0.39 (.04)
OFC (L)	0.54	0.59	0.01	0.43 (.03)	0.44 (.03)	0.39 (.04)
OFC (R)	0.41	0.66	0.01	0.44 (.03)	0.45 (.03)	0.41 (.03)
Caudate (L)	0.90	0.41	0.02	0.41 (.03)	0.42 (.03)	0.36 (.04)
Caudate(R)	0.90	0.41	0.02	0.41 (.03)	0.43 (.03)	0.37 (.04)
Putamen (L)	1.09	0.34	0.02	0.40 (.03)	0.43 (.03)	0.36 (.04)
Putamen (R)	1.07	0.35	0.02	0.41 (.03)	0.43 (.03)	0.36 (.04)
Thalamus (L)	0.61	0.55	0.01	0.43 (.03)	0.43 (.03)	0.38 (.04)
Thalamus (R)	0.73	0.48	0.02	0.42 (.03)	0.43 (.03)	0.37 (.04)
ACC (L)	0.49	0.62	0.01	0.43 (.03)	0.42 (.03)	0.38 (.04)
ACC (R)	0.52	0.59	0.01	0.42 (.03)	0.41 (.03)	0.37 (.03)

Note. ROI = Region of Interest, SE = Standard Error, MBAS = Moderate Behavioral Approach System Sensitivity (BAS) group, HBAS = High BAS group, HBAS+BSD = High BAS + Bipolar Spectrum Disorder (BSD) group, L = Left, R = Right, mPFC = Medial Prefrontal Cortex, dlPFC = Dorsolateral Prefrontal Cortex, OFC = Orbitofrontal Cortex, ACC = Anterior Cingulate Cortex. *Controlling for age, gender, race, ASRM, BDI, AADIS, and medication status.

Table 8. Main Effect of Group on Betweenness Centrality

	Main Effect of Group*			Group Means (SE)*		
ROI	*F*	*p*	η^2	M_{MBAS}	M_{HBAS}	$M_{HBAS + BSD}$
mPFC (L)	1.46	0.24	0.03	37.12 (1.08)	6.19 (9.69)	54.31 (13.26)
mPFC (R)	0.10	0.91	0.00	29.36 (7.19)	25.18 (6.91)	25.98 (9.46)
dlPFC (L)	0.41	0.67	0.01	13.33 (3.72)	11.50 (3.57)	17.20 (4.89)
dlPFC (R)	4.52	0.01	0.09	21.05 (3.51)	6.66 (3.38)	15.08 (4.63)
OFC (L)	0.10	0.90	0.00	37.79 (7.70)	33.82 (7.40)	38.74 (1.13)
OFC (R)	0.21	0.81	0.01	44.74 (1.50)	47.50 (1.09)	56.38 (13.81)
Caudate (L)	0.31	0.74	0.01	21.92 (5.74)	18.89 (5.52)	26.45 (7.55)
Caudate(R)	1.79	0.17	0.04	14.43 (3.79)	12.78 (3.65)	24.64 (4.99)
Putamen (L)	0.12	0.29	0.00	2.49 (5.18)	22.66 (4.98)	24.67 (6.82)
Putamen (R)	0.26	0.77	0.01	22.43 (4.48)	21.72 (4.31)	17.08 (5.89)
Thalamus (L)	1.64	0.20	0.04	24.55 (9.12)	27.76 (8.77)	51.82 (11.99)
Thalamus (R)	0.49	0.62	0.01	16.7 (8.12)	25.86 (7.80)	28.37 (1.68)
ACC (L)	0.19	0.83	0.00	44.56 (12.02)	4.75 (11.55)	53.24 (15.81)
ACC (R)	0.28	0.76	0.01	17.20 (5.58)	16.85 (5.36)	23.49 (7.34)

Note. ROI = Region of Interest, SE = Standard Error, MBAS = Moderate Behavioral Approach System Sensitivity (BAS) group, HBAS = High BAS group, HBAS+BSD = High BAS + Bipolar Spectrum Disorder (BSD) group, L = Left, R = Right, mPFC = Medial Prefrontal Cortex, dlPFC = Dorsolateral Prefrontal Cortex, OFC = Orbitofrontal Cortex, ACC = Anterior Cingulate Cortex. *Controlling for age, gender, race, ASRM, BDI, AADIS, and medication status.

In addition, as shown in Table 9, there was a significant effect of group on participation coefficient in the bilateral OFC (left OFC: $F(2, 97) = 3.24, p = .04$; right OFC $F(2, 97) = 4.48, p = .01$). In both the left and right OFC, Tukey's post-hoc tests identified that the HBAS group showed a higher participation coefficient than the MBAS group at the trend level (left OFC: mean difference = .05 ± .02, $p = .08$; right OFC: mean difference = .04 ± .02, $p = .08$); the HBAS and HBAS+BSD groups did not differ (left OFC: mean difference = -0.01 ± 0.03; right OFC: mean difference = -0.02 ± .02, ps > .10).

There also was a significant effect of group on participation coefficient in the right ACC, $F(2, 97) = 3.67, p = .03$. Post-hoc tests revealed that the HBAS+BSD group showed a higher participation coefficient than the MBAS group at the trend level (mean difference = .06 ± .02, $p = .05$), with the HBAS group falling intermediate but not significantly differing from either the MBAS or HBAS+BSD groups (mean difference from MBAS = 0.04 ± 0.02; mean difference from HBAS + BSD = -0.02 ± .02, ps > .10).

Table 9. Main Effect of Group on Participation Coefficient

	Main Effect of Group*			Group Means (SE)*		
ROI	*F*	*p*	η^2	M_{MBAS}	M_{HBAS}	$M_{HBAS + BSD}$
mPFC (L)	2.96	0.06	0.06	0.50 (.02)	0.54 (.02)	0.55 (.02)
mPFC (R)	2.01	0.14	0.04	0.51 (.02)	0.54 (.02)	0.54 (.02)
dlPFC (L)	2.36	0.10	0.05	0.52 (.01)	0.55 (.01)	0.57 (.02)
dlPFC (R)	1.27	0.29	0.03	0.53 (.02)	0.55 (.01)	0.57 (.02)
OFC (L)	3.24	0.04	0.07	0.51 (.02)	0.56 (.01)	0.56 (.02)
OFC (R)	4.48	0.01	0.09	0.52 (.01)	0.56 (.01)	0.58 (.02)
Caudate (L)	1.39	0.25	0.03	0.53 (.02)	0.55 (.02)	0.57 (.02)
Caudate(R)	1.42	0.25	0.03	0.53 (.02)	0.56 (.02)	0.57 (.02)
Putamen (L)	1.25	0.29	0.03	0.53 (.02)	0.55 (.02)	0.57 (.02)
Putamen (R)	1.36	0.26	0.03	0.53 (.02)	0.55 (.02)	0.57 (.02)
Thalamus (L)	1.27	0.29	0.03	0.54 (.02)	0.55 (.01)	0.58 (.02)
Thalamus (R)	0.32	0.27	0.03	0.53 (.02)	0.55 (.02)	0.58 (.02)
ACC (L)	2.07	0.13	0.05	0.52 (.01)	0.55 (.01)	0.56 (.02)
ACC (R)	3.67	0.03	0.08	0.51 (.01)	0.55 (.01)	0.56 (.02)

Note. ROI = Region of Interest, SE = Standard Error, MBAS = Moderate Behavioral Approach System Sensitivity (BAS) group, HBAS = High BAS group, HBAS+BSD = High BAS + Bipolar Spectrum Disorder (BSD) group, L = Left, R = Right, mPFC = Medial Prefrontal Cortex, dlPFC = Dorsolateral Prefrontal Cortex, OFC = Orbitofrontal Cortex, ACC = Anterior Cingulate Cortex. *Controlling for age, gender, race, ASRM, BDI, AADIS, and medication status.

There also was a marginally significant effect of group on participation coefficient in the left mPFC, $F(2, 97) = 2.96$, $p = .06$. Post-hoc tests did not identify any significant differences between groups that survived adjustment for multiple comparisons. Contrary to hypotheses, there also was no evidence of local connectivity differences in the striatum (caudate or putamen) or thalamus.

Differences in global network characteristics (global efficiency, global clustering, and small-worldness) between groups were evaluated using one-way ANCOVA with age, gender, depressive and hypomanic symptoms, substance use, and medication use as covariates. A separate ANCOVA was conducted for each global network metric (Table 10). No significant group differences emerged with regard to global network measures.

Table 10. Main Effect of Group on Global Measures

	Main Effect of Group*			Group Means (SE)*		
Measure	*F*	*p*	η^2	M_{MBAS}	M_{HBAS}	$M_{HBAS + BSD}$
Global Efficiency	0.53	0.59	0.01	0.47 (.02)	0.47 (.02)	0.44 (.03)
Global Clustering	0.50	0.61	0.01	0.41 (.03)	0.42 (.03)	0.37 (.03)
Small-Worldness	0.05	0.95	0.00	1.03 (.01)	1.03 (.01)	1.03 (.01)

Note. MBAS = Moderate Behavioral Approach System Sensitivity (BAS) group, HBAS = High BAS group, HBAS+BSD = High BAS + Bipolar Spectrum Disorder (BSD) group. *Controlling for age, gender, race, ASRM, BDI, AADIS, and medication status.

RHI, LHI, and II were compared using one-way ANCOVAs with age, gender, depressive and hypomanic symptoms, substance use, and medication use as covariates.

No significant group differences emerged with regard to either intra-hemispheric or inter-hemispheric integration (Table 11).

Table 11. Main Effect of Group on Intrahemispheric/Interhemispheric Integration

	Main Effect of Group*			Group Means (SE)*		
Measure	*F*	*p*	η^2	M_{MBAS}	M_{HBAS}	$M_{HBAS + BSD}$
Left Hemisphere Integration	1.54	0.22	0.03	0.52 (0.01)	0.55 (0.01)	0.56 (0.02)
Right Hemisphere Integration	1.66	0.20	0.04	0.52 (0.01)	0.55 (0.01)	0.56 (0.02)
Interhemispheric Integration	0.84	0.44	0.02	-0.00 (0.00)	0.00 (0.00)	-0.00 (0.00)

Note. MBAS = Moderate Behavioral Approach System Sensitivity (BAS) group, HBAS = High BAS group, HBAS+BSD = High BAS + Bipolar Spectrum Disorder (BSD) group. *Controlling for age, gender, race, ASRM, BDI, AADIS, and medication status.

Test of Study Hypotheses: Aim 2

To investigate whether reward sensitivity predicts global and local network characteristics, hierarchical linear regressions were conducted controlling for age, gender, depressive and hypomanic symptoms, substance use, and medication use in the first step; CARROT score was entered in the second step.

Main effects of reward sensitivity on network characteristics are presented in Table 12. Hierarchical linear regressions demonstrated that reward sensitivity on the CARROT negatively predicted global efficiency, $\beta = -.28$, $t(69) = -2.47$, $p = .02$, such that increased reward sensitivity was associated with decreased global efficiency. Across all ROIs, reward sensitivity also significantly negatively predicted local efficiency, such that increased reward sensitivity was associated with decreased local efficiency (see Table 12). In addition, reward sensitivity significantly negatively predicted the

participation coefficient of the right putamen, $\beta = -.24$, $t(69) = -2.04$, $p = .045$, and marginally negatively predicted the participation coefficient of the left putamen, $\beta = -.22$, $t(69) = -1.89$, $p = .06$, and left caudate, $\beta = -.21$, $t(69) = -1.75$, $p = .08$.

Hierarchical linear regression was used to explore the interaction of reward sensitivity and group in predicting global efficiency, local efficiency, local participation coefficient, and interhemispheric and intrahemispheric integration. Utilizing the procedures outlined by the UCLA Statistics Consultation Group, first, group was dummy coded into three individual binary variables (Group 1 = MBAS, Group 2 = HBAS, Group 3 = HBAS+BSD). CARROT values then were centered around their mean. Next, Group by CARROT interaction terms were calculated as the product of each dummy-coded Group variable and the centered CARROT variable. Age, gender, race, depressive and hypomanic symptoms, substance use, and medication use were entered in the first step of the regression equation, and CARROT (centered) and dummy-coded Group 2 and Group 3 values were entered in the second step (with Group 1 serving as the comparison group). The interaction terms of CARROT by Group 2 and Group 3 were entered in the third step of the equation. Contrary to hypotheses, there were no significant interaction effects of group and reward sensitivity for global efficiency ($F2, 76) = 0.57$, $p = 0.57$, $\Delta R = 0.01$) or local efficiency (Table 13) at any of the ROIs.

Table 12. Main Effects of CARROT Reward Score Predicting Network Characteristics

Measure	β	*t*	Adjusted R^2			
Global Efficiency	-.28	-2.47*	.12			
	Left Hemisphere			Right Hemisphere		
Local Efficiency	β	*t*	Adjusted R^2	β	*t*	Adjusted R^2
OFC	-.29	-2.57*	.10	-.24	-2.07*	.09
Caudate	-.27	-2.25*	-.00	-.27	-2.24*	.03
Putamen	-.31	-2.63*	.07	-.32	-2.75**	.07
Amygdala	-.28	-2.39*	.07	-.28	-2.41*	.09
Participation Coefficient						
OFC	-.16	-1.32	.05	-.11	-.96	.04
Caudate	-.21	-1.75†	.04	-.17	-1.41	-.00
Putamen	-.22	-1.89†	.03	-.24	-2.04*	.04
Amygdala	-.15	-1.24	.06	-.13	-1.08	.04

Note. CARROT = Card Arranging Reward Responsiveness Objective Test, OFC = orbitofrontal cortex. †$p < .10$, *$p < .05$, **$p < .01$.

Table 13. Interaction of Group and CARROT Reward Score predicting Local Efficiency

	Left Hemisphere			Right Hemisphere		
	F	*p*	ΔR	F	*p*	ΔR
OFC						
Group x CARROT	0.84	0.44	0.02	0.41	0.67	0.01
Caudate						
Group x CARROT	0.99	0.38	0.03	1.08	0.35	0.03
Putamen						
Group x CARROT	0.80	0.45	0.02	0.33	0.72	0.01
Amygdala						
Group x CARROT	0.65	0.53	0.02	1.53	0.22	0.04

Note. CARROT = Card Arranging Reward Responsiveness Objective Test, OFC = orbitofrontal cortex.

However, at the left putamen ROI, Group and CARROT score interacted at the trend level to predict local participation coefficient (Table 14). A second regression model was conducted using Group 2 as the comparison group to obtain the remainder of pairwise comparisons between groups at this ROI. Regarding the participation coefficient of the left putamen, post-hoc analyses revealed that the HBAS+BSD group significantly differed from the HBAS group, and differed from the MBAS at the trend level. The HBAS and MBAS groups did not significantly differ from one another.

Table 14. Interaction of Group and CARROT Reward Score predicting Participation Coefficient

	Left Hemisphere			Right Hemisphere		
	F	*p*	ΔR	F	*p*	ΔR
OFC						
Group x CARROT	0.53	0.59	0.01	0.95	0.39	0.02
Caudate						
Group x CARROT	1.53	0.23	0.04	2.10	0.13	0.05
Putamen						
Group x CARROT	2.84	0.07	0.07	1.58	0.22	0.04
Amygdala						
Group x CARROT	0.85	0.43	0.02	0.53	0.59	0.01

Note. CARROT = Card Arranging Reward Responsiveness Objective Test, OFC = orbitofrontal cortex.

To investigate the form of this interaction, we followed the procedures outlined by Aiken and West (1991) and examined the simple effect of CARROT reward sensitivity for each group, controlling for age, gender, depressive and hypomanic symptoms, substance use, and medication use. Among individuals in the HBAS group, CARROT score significantly negatively predicted the participation coefficient of the left putamen (β = -0.44 $t(29)$ = -2.25, p = 0.03). Among individuals in the MBAS group, CARROT score did not significantly predict the participation coefficient of the left putamen (β = -0.3 $t(29)$ = -1.36, p = 0.19). Among individuals in the HBAS+BSD group, there was no significant effect of CARROT on participation coefficient (β = 3.52, $t(16)$ = 1.26, p = 0.24); however, visual inspection of the standardized regression coefficient suggests that this group significantly differed from the HBAS group and marginally differed from the MBAS group due to the direction of association (positive among

HBAS+BSD and negative in the other groups), although the association did not reach significance in the HBAS+BSD group.

Table 15. Post-hoc Comparisons for the Effect of CARROT on Participation Coefficient in the Left Putamen by Group

Group	Comparison Group	*t*	*p*
MBAS	HBAS	-0.56	0.58
	HBAS+BSD	1.87	0.06
HBAS	MBAS	0.56	0.58
	HBAS+BSD	2.35	0.02
HBAS+BSD	MBAS	-1.87	0.06
	HBAS	-2.35	0.02

Note. MBAS = Moderate Behavioral Approach System Sensitivity (BAS) group, HBAS = High BAS group, HBAS+BSD = High BAS + Bipolar Spectrum Disorder (BSD) group.

CHAPTER 4

DISCUSSION

The present study sought to characterize resting state functional brain network characteristics in individuals at low and high risk for BSD, both with and without a BSD diagnosis. Additionally, given the critical role of reward sensitivity in BSD, the current study sought to further elucidate the neurobiological underpinnings of reward responsiveness by examining the relationships between functional brain network connectivity and performance on a behavioral reward sensitivity task. Graph theoretical analysis was employed as a tool with which to characterize these network features, as this approach offers the ability to synthesize information about highly complex global and local network characteristics within a limited set of straightforward, easily interpretable metrics. Better understanding of neurobiological network characteristics in individuals with and at risk for BSD may allow for a more comprehensive understanding of the neurobiological mechanisms underlying the development and course of BSD, and may inform future interventions.

The first aim of this study was to compare local and global network characteristics among individuals from three groups: those at low risk for BSD without a BSD diagnosis (MBAS), those at high risk for BSD but without a diagnosis (HBAS), and those at high risk for BSD with a diagnosis (HBAS+BSD). Participants completed resting-state fMRI, from which functional connectivity data were derived; it has been suggested previously that resting-state brain activity may reflect the recruitment of organized neural networks (van den Heuvel & Pol, 2010), thus rendering it an ideal choice for exploration of brain networks.

Multiple theoretical models of BSD, including those of Strakowski and colleagues (2012) and the BAS Hypersensitivity theory proposed by Depue and Iacono (1989), and expanded by Urosevic and colleagues (2008; Alloy & Abramson, 2010; Alloy et al., 2015), posit that emotion dysregulation in BSD results from abnormalities in the structure or activity of prefrontal and limbic brain regions. Thus, analyses for the current study focused primarily on a set of prefrontal (including mPFC, dlPFC, OFC, and ACC) and subcortical (including caudate, putamen, amygdala, and thalamus) structures thought to be implicated in BD.

A specific set of graph measures was selected in order to tap various aspects of the functional network organization. At the local level, we investigated local efficiency, betweenness centrality, and participation coefficient. Given that both of the above theoretical models propose that individuals with BSD show decreased prefrontal control over subcortical structures (Strakowski et al., 2012; Urosevic et al., 2008), I hypothesized that individuals with BSD would show decreased efficiency, betweenness centrality, and participation in prefrontal nodes, including the mPFC, dlPFC, and OFC compared to the MBAS group, with the HBAS group falling intermediate. Support for this hypothesis was somewhat mixed. Consistent with this hypothesis, individuals from the MBAS group showed higher betweenness centrality than the HBAS group in the right dlPFC, a brain region that is involved in cognitive control and voluntary emotion regulation, suggesting that increased BAS sensitivity may be associated with lower connectivity of this region. This is consistent with neurobiological conceptualizations of approach motivation (Depue & Iacono, 1989), which suggest that decreased prefrontal control over subcortical regions may result in increased sensitivity to appetitive cues. These findings extend this

conceptualization, as it suggests that failures in prefrontal control may not merely result from decreased *activation* of prefrontal regions, but could also result from reduced functional coupling of prefrontal brain regions and their subcortical targets.

Contrary to hypotheses, the HBAS group showed a trend towards higher participation coefficient in the bilateral OFC compared to the MBAS group. Given that the participation coefficient of a node reflects how connected the node is to nodes within its own cluster, compared to how connected it is with nodes outside of its own cluster (Joyce, Laurienti, Burdette, & Hayasaka, 2010), this may suggest that for HBAS individuals, the OFC plays a more central role in communication with other regions. This may reflect the OFC's role in recognition and processing of reward cues (Xue et al., 2009; Nusslock et al., 2012); for those individuals with hypersensitivity to appetitive cues, the OFC may be more influential in communication with other brain regions than for those with lower BAS sensitivity.

Interestingly, the HBAS+BSD group consistently fell intermediate to the MBAS and HBAS groups across local network measures for prefrontal brain regions (OFC, dlPFC, mPFC), and did not significantly differ from either. Visual inspection of the estimated marginal means for each group identified that mean connectivity values for the HBAS+BSD group more closely resembled the HBAS group than the MBAS group across all of these comparisons, but the HBAS+BSD group showed significantly more variability. This variability could reflect the impact of additional factors associated with BSD onset and course. Whereas the MBAS and HBAS groups can be expected to differ primarily on the variable of BAS sensitivity, individuals with BSD also may have varied on a number of illness-related variables that were not assessed in the current study. For

example, although the present study controlled for current psychoactive medication use, individuals with BSD may have used medications in the past, which could have lasting implications for their structural and/or functional brain activity. Alternatively, the experience of having bipolar mood episodes may have lasting impacts on structural and functional brain characteristics, which, in turn, might be reflected in estimates of functional connectivity. Additional biobehavioral risk factors (such as impulsivity) that may contribute to the development of BSD among individuals at risk based on their BAS sensitivity also could be contributing to this increased variability in prefrontal functional connectivity.

It also has been proposed that disruptions in the striatum, thalamus, and ACC may result in reduced prefrontal control over limbic structures (Strakowski et al., 2012); thus, I hypothesized that individuals in the HBAS+BSD group would show decreased local connectivity of the caudate, putamen, thalamus, and ACC relative to both the MBAS and HBAS groups. Contrary to this hypothesis, individuals with BSD showed increased functional integration of the dorsal ACC, a brain region that (among its many functions) is thought to play a role in reward-based decision-making (Bush et al., 2002; Schultz, 1997). This finding suggests a higher centrality of the ACC among individuals with BSD, which is consistent with the BAS Hypersensitivity model that suggests that overactivation of brain regions involved in detection and anticipation of reward may result in overactivation of the BAS in response to reward cues, leading to bipolar mood episodes (Alloy & Abramson, 2010; Alloy et al., 2009; 2015; Urosevic et al., 2008). Again, the current findings also suggest BAS hypersensitivity could result from changes in the functional connectivity (such as increased centrality) of the ACC, rather than just

overactivity of this region. In contrast, this finding does not lend support to the model proposed by Strakowski and colleagues (2012), which suggests that decreased (rather than increased) dorsal ACC inter-modular communication should lead to reduced control of automatic emotion regulation mechanisms, and, in turn, be associated with BSD.

Given that previous research has demonstrated decreased structural global efficiency and global clustering among individuals with BSD (Leow et al., 2013), I also hypothesized that the MBAS group would evidence higher global efficiency and clustering than the HBAS+BSD group, with the HBAS group falling intermediate. Additionally, in light of prior work demonstrating increased left intra-hemispheric integration and decreased inter-hemispheric integration in BD (Leow et al., 2013), I also hypothesized increased left hemispheric functional integration and decreased inter-hemispheric integration among the HBAS+BSD group.

Contrary to these hypotheses, there was no evidence for group differences at the hemispheric or global level. The failure of the present study to identify group differences in global network characteristics or intra/interhemispheric integration like those observed by Leow and colleagues (2013) may reflect a number of factors. First, the study by Leow et al. (2013) was comprised solely of individuals with BD-I, whereas the current study was primarily comprised of individuals with "soft" bipolar spectrum diagnoses (e.g., cyclothymia, BD-II, and BD-NOS). Additionally, the current sample of BSD participants was substantially younger (mean age = 20.16 years) than the sample studied by Leow et al. (2013). Given these factors, participants in the current study likely have had a shorter and less severe illness course than the participants in the prior study, which may be reflected in relatively intact global connectivity and hemispheric integration. Moreover,

the current study explored functional rather than structural connectivity. Structural connectivity abnormalities may temporally (and even causally) precede disruption of functional connectivity (Frazier et al., 2007; Strakowski et al., 2012;Versace et al., 2010a), or structural network analysis may be more sensitive to small inter-group differences than functional network analysis.

Taken together, the findings relevant to Aim 1 of the current study do not support disruption of connectivity at a hemisphere-wide or global level among individuals with or at risk for BSD. However, they do support the notion of increased connectivity of brain regions involved in the detection of and response to reward (e.g. dorsal ACC, OFC) among individuals with high BAS sensitivity. Given the importance of reward sensitivity in risk for BSD, the second principal aim of this study was to evaluate the relationship between reward sensitivity, assessed via a behavioral task, and global and local network characteristics. Local network characteristics were evaluated for ROIs known to be involved in fronto-limbic circuits thought to be activated by reward cues, including the OFC, caudate, putamen, and amygdala.

Based on previous findings among healthy adults that reward anticipation is associated with a transient increase in global efficiency (Kinninson et al., 2012), I hypothesized that higher reward sensitivity would be associated with increased global efficiency. Contrary to this hypothesis, my findings suggested that reward sensitivity was associated with decreased global efficiency during the resting state. Similarly, on a local level, reward sensitivity also significantly negatively predicted local efficiency across all ROIs bilaterally, such that increased reward sensitivity was associated with decreased local efficiency. Our findings suggest that a tendency to respond strongly in the presence

of an external reward is associated with decreased resting-state efficiency of communication across the entire global network and more locally within reward-related brain regions.

Consistent with the above findings that reward sensitivity is negatively associated with functional connectivity in the resting state, an association also emerged between reward sensitivity and resting-state functional connectivity within the striatum. Specifically, reward sensitivity significantly negatively predicted the participation coefficient for the right putamen, and marginally negatively predicted the participation coefficient for the left putamen and left caudate. This may reflect either increasing intramodular communication or decreasing intermodular communication as reward sensitivity increases, which, in turn, points to more segregation of striatal activity among those high in reward sensitivity. Interestingly, the relationship between reward sensitivity and participation coefficient of the left putamen was moderated by group. Specifically, individuals with BSD significantly differed from those without BSD, while the MBAS and HBAS groups did not differ from one another. Prior work has demonstrated that the putamen may play a critical role in guiding reward-driven actions (Haruno & Kawato, 2006; Balleine, Delgado, & Hikosaka, 2007), which is thought to be one of the primary functions of the BAS (Depue et al., 1989); the current findings suggest that in individuals with BSD, there may be even more influence of the striatal components of the BAS, which could potentially contribute to BAS hypersensitivity.

Of note, these findings are somewhat in conflict with our findings from tests of Aim 1, which identified increased participation coefficient of brain regions involved in the detection of and response to reward (dorsal ACC, OFC) among individuals with high

BAS sensitivity and BSD. This can be understood in light of findings that in the current sample, we did not observe the expected relationship between group and CARROT. That is, we did not observe significant group differences in CARROT score ($F(2, 80) = 0.46$, $p = .63$), which may suggest that reward sensitivity as assessed by the CARROT measures a different construct than the self-report measures of BAS sensitivity upon which group status determinations were based. Whereas the CARROT measures one's behavioral responsivity to small monetary rewards, the measures used to determine BAS status in this study (e.g., the BIS/BAS Scales and the SPSRQ) index behavioral approach sensitivity more broadly, tapping one's sensitivity towards approach-related stimuli in general rather than monetary rewards specifically. This distinction may be theoretically important, as the BAS Hypersensitivity theory of BSD proposes that hypersensitivity to all approach-related stimuli, not just monetary rewards, may result in over-activation or excessive de-activation of the BAS in response to goal-related life events, resulting in mood episodes.

Taken together, the results of the current study suggest that increased reward sensitivity is associated with decreased efficiency of global functional networks and increased functional segregation of brain regions involved in the detection and processing of rewards. In contrast, when considering BAS sensitivity specifically, current findings point to increased functional integration of brain regions involved in the detection of and response to reward among individuals with high BAS sensitivity. Moreover, individuals with high BAS sensitivity showed reduced connectivity in cognitive control regions (dlPFC), but increased connectivity of brain regions involved in the detection and processing of reward (bilateral OFC). These findings were not specific to individuals

with BSD, but were observed in individuals with high BAS. In contrast, individuals with BSD, but not those at risk for BSD on the basis of high BAS sensitivity, also appear to show increased inter-modular integration of the ACC. This lends support to the BAS Hypersensitivity model of BSD, which suggests that overactivation of brain regions involved in detection and anticipation of reward may be a core feature of BSD (Alloy et al., 2015; Nusslock et al., 2012; Urosevic et al., 2008). The current findings also underscore the need to consider reward sensitivity and BAS sensitivity individually, as they appear to be associated with differential patterns of functional connectivity within the brain.

The current study has a number of strengths. First, by comparing individuals at low risk for BSD, at high risk for BSD, and with BSD, we were able to explore network characteristics that may be associated with risk for versus actual development of BSD. A better understanding of the factors that differentiate those at high risk for BSD from those who actually go on to develop the disorder may allow us to better identify an individual's risk for BSD, and may inform interventions targeting these underlying risk factors. The current study also excluded participants who were currently experiencing depressive or hypomanic mood episodes, and statistically controlled for current mood symptoms, which reduced the heterogeneity that may result from inclusion of participants in varying mood states. The current study also overcame limitations of prior research by statistically controlling for psychoactive medication usage and substance use, which may have significant impacts on brain activity as well as BOLD signal (Vargas et al., 2012).

The present study is also the first to utilize graph theoretical analysis to explore mechanisms of risk for bipolar disorder via functional connectivity analysis. This

approach offers complementary information to prior activation-based fMRI studies by allowing consideration of network characteristics of the brain used to explore functional segregation and integration, and may offer a more ecologically valid approach to exploring neurobiological correlates of risk for BSD. By better understanding the network characteristics of individuals with and at risk for BSD, we may be better able to understand how the interaction of different brain regions (rather than abnormal activity in any individual brain region) may give rise to the symptoms of BSD. This could allow for identification of new biomarkers for BSD, which, in turn, could lead to earlier identification of and intervention for individuals with BSD.

However, the current findings should be considered within the context of a number of limitations. First, within the current sample, we did not observe the expected relationship between group and CARROT reward responsivity. Although this highlights the notion that reward sensitivity and BAS sensitivity are indeed dissociable constructs, it is unclear whether the high BAS participants in the present study are truly representative of high BAS individuals in the larger TEAM project or in the general population, who would be expected to be high in reward sensitivity, or whether the CARROT task in the current study truly captured reward sensitivity. Thus, future research should seek to explore the relationship between reward sensitivity and functional network connectivity utilizing other behavioral measures of reward sensitivity. Given research that suggests that individuals with and at high risk for BSD may differ from those at low risk during reward anticipation (but not after receipt of reward) (Nusslock et al., 2012), utilization of a behavioral task that allows dissociation of the anticipatory and consummatory aspects of reward processing would be particularly interesting. Additionally, the current sample

did not include any participants identified as having low BAS sensitivity. Although this offers a conservative test of the role of BAS sensitivity in conferral of risk for BSD, it limits our ability to draw conclusions about the relationship between BAS sensitivity and resting state functional brain networks for those at the lower end of the BAS sensitivity spectrum.

From an analytical standpoint, there remain many controversies about how best to characterize network characteristics using graph theory. It is well known that the selection of parcellation scheme for node definition plays a large role in determination of functional and structural network characteristics (Shen et al., 2013; Sporns, 2013); thus, it is unclear the extent to which the findings of the current study would be replicated if a different parcellation scheme was used. Recent work has suggested that using functionally-defined ROIs may be particularly useful in construction of resting-state brain networks (Sohn, Yoo, Lee, Seo, Na, & Jeong, 2015), and future work should seek to explore network characteristics in individuals with and at risk for BSD using such a parcellation scheme. The results of the current study are also necessarily impacted by other decisions made regarding network construction, including the decision to explore weighted (as opposed to binary) undirected (as opposed to directed) networks and the decision not to apply a significance threshold to select which node-node pairs would be included in the overall networks. As there is currently not scientific consensus regarding these issues, these results should be interpreted with caution, particularly when comparing results to other studies in which different decisions regarding network construction were made.

Overall, the results from the current study suggest that risk for bipolar disorder (based on high BAS sensitivity) is associated with decreased connectivity in cognitive control regions (dlPFC), but increased connectivity of brain regions involved in the detection and processing of reward (bilateral OFC) and reward-based decision making (ACC). These findings suggest that it is not merely disruptions in the level of activity in these regions that underlies neurobiological risk for BSD, but rather, that differences in the functional connectivity of these regions with other areas of the brain also may contribute to development of BSD. Future research should seek to combine structural and functional measures of connectivity, as this would further help elucidate mechanisms of risk for BD, and potentially would allow identification of biomarkers for BSD risk. Additionally, it will be important for future work to examine the role of network characteristics in the development of BSD prospectively, as this might provide a more nuanced understanding of the developmental trajectory of BSD.

REFERENCES CITED

Achard, S., & Bullmore, E. (2007). Efficiency and cost of economical brain functional networks. *PLoS Computational Biology, 3*(2), e17. doi:06-PLCB-RA-0424R2 [pii]

Achard, S., Salvador, R., Whitcher, B., Suckling, J., & Bullmore, E. (2006). A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 26*(1), 63-72. doi:26/1/63 [pii]

Alloy, L. B., Abramson, L. Y., Walshaw, P. D., Cogswell, A., Grandin, L. D., Hughes, M. E., . . . Hogan, M. E. (2008). Behavioral approach system and behavioral inhibition system sensitivities and bipolar spectrum disorders: Prospective prediction of bipolar mood episodes. *Bipolar Disorders, 10*, 310-322.

Alloy, L. B., & Abramson, L. Y. (2010). The role of the behavioral approach system (BAS) in bipolar spectrum disorders. *Current Directions in Psychological Science, 19*(3), 189-194. doi:10.1177/0963721410370292

Alloy, L. B., Abramson, L. Y., Walshaw, P. D., Gerstein, R. K., Keyser, J. D., Whitehouse, W. G., . . . Harmon-Jones, E. (2009). Behavioral approach system (BAS)–relevant cognitive styles and bipolar spectrum disorders: Concurrent and prospective associations. *Journal of Abnormal Psychology, 118*(3), 459-471. doi:10.1037/a0016604

Alloy, L. B., Bender, R. E., Whitehouse, W. G., Wagner, C. A., Liu, R. T., Grant, D. A., . . . Abramson, L. Y. (2012a). High behavioral approach system (BAS) sensitivity, reward responsiveness, and goal-striving predict first onset of bipolar spectrum disorders: A prospective behavioral high-risk design. *Journal of Abnormal Psychology, 121*(2), 339-351.

Alloy, L. B., Nusslock, R., & Boland, E. M. (2015). The development and course of bipolar spectrum disorders: An integrated reward and circadian rhythm dysregulation model. *Annual Review of Clinical Psychology, 11*, 213-250. doi:10.1146/annurev-clinpsy-032814-112902

Alloy, L. B., Urošević, S., Abramson, L. Y., Jager-Hyman, S., Nusslock, R., Whitehouse, W. G., & Hogan, M. (2012b). Progression along the bipolar spectrum: A longitudinal study of predictors of conversion from bipolar spectrum conditions to bipolar I and II disorders. *Journal of Abnormal Psychology, 121*(1), 16-27. doi:10.1037/a0023973; 10.1037/a0023973.supp (Supplemental)

Alpert, K., Kogan, A., Parrish, T., Marcus, D., & Wang, L. (2016). The northwestern university neuroimaging data archive (NUNDA). *Neuroimage, 124*(Pt B), 1131-1136. doi:10.1016/j.neuroimage.2015.05.060 [doi]

Altman, E., Hedeker, D., Peterson, J. L., & Davis, J. M. (2001). A comparative evaluation of three self-rating scales for acute mania. *Biological Psychiatry, 50*(6), 468-471. doi:S0006322301010654 [pii]

Altman, E. G., Hedeker, D., Peterson, J. L., & Davis, J. M. (1997). The Altman self-rating mania scale. *Biological Psychiatry, 42*(10), 948-955. doi:10.1016/S0006-3223(96)00548-3

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed, text rev. ed.). Washington, DC: Author.

Anand, A., Li, Y., Wang, Y., Lowe, M. J., & Dzemidzic, M. (2009). Resting state corticolimbic connectivity abnormalities in unmedicated bipolar disorder and unipolar depression. *Psychiatry Research: Neuroimaging, 171*(3), 189-198. doi:10.1016/j.pscychresns.2008.03.012

Anticevic, A., Brumbaugh, M. S., Winkler, A. M., Lombardo, L. E., Barrett, J., Corlett, P. R., . . . Glahn, D. C. (2013). Global prefrontal and fronto-amygdala dysconnectivity in bipolar I disorder with psychosis history. *Biological Psychiatry, 73*(6), 565-573. doi:10.1016/j.biopsych.2012.07.031

Balleine, B. W., Delgado, M. R., & Hikosaka, O. (2007). The role of the dorsal striatum in reward and decision-making. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 27*(31), 8161-8165. doi:27/31/8161 [pii]

Bassett, D. S., Bullmore, E., Verchinski, B. A., Mattay, V. S., Weinberger, D. R., & Meyer-Lindenberg, A. (2008). Hierarchical organization of human cortical networks in health and schizophrenia. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 28*(37), 9239-9248. doi:10.1523/JNEUROSCI.1929-08.2008 [doi]

Beck, A. T., Rush, A. J., Shaw, B. F., & Emery, G. (1979). *Cognitive therapy of depression*. New York: Guilford Press.

Beck, A. T., Steer, R. A., & Garbin, M. G. (1988). Psychometric properties of the beck depression inventory: Twenty-five years of evaluation. *Clinical Psychology Review, 8*(1), 77-100. doi:10.1016/0272-7358(88)90050-5

Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage, 37*(1), 90-101. doi:S1053-8119(07)00383-7 [pii]

Bermpohl, F., Kahnt, T., Dalanay, U., Hägele, C., Sajonz, B., Wegner, T., . . . Heinz, A. (2010). Altered representation of expected value in the orbitofrontal cortex in mania. *Human Brain Mapping, 31*(7), 958-969. doi:10.1002/hbm.20909

Blond, B. N., Fredericks, C. A., & Blumberg, H. P. (2012). Functional neuroanatomy of bipolar disorder: Structure, function, and connectivity in an amygdala–anterior paralimbic neural system. *Bipolar Disorders, 14*(4), 340-355. doi:10.1111/j.1399-5618.2012.01015.x

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network. *Annals of the New York Academy of Sciences, 1124*(1), 1-38. doi:10.1196/annals.1440.011

Bullmore, E., & Sporns, O. (2009). Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nature Reviews Neuroscience, 10*(3), 186-198. doi:10.1038/nrn2575

Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. *Nature Reviews.Neuroscience, 13*(5), 336-349. doi:10.1038/nrn3214 [doi]

Bullmore, E. (2012). Functional network endophenotypes of psychotic disorders. *Biological Psychiatry, 71*(10), 844-845. doi:10.1016/j.biopsych.2012.03.019

Bush, G., Vogt, B. A., Holmes, J., Dale, A. M., Greve, D., Jenike, M. A., & Rosen, B. R. (2002). Dorsal anterior cingulate cortex: A role in reward-based decision making. *Proceedings of the National Academy of Sciences of the United States of America, 99*(1), 523-528. doi:10.1073/pnas.012470999 [doi]

Cao, M., Shu, N., Cao, Q., Wang, Y., & He, Y. (2014). Imaging functional and structural brain connectomics in attention-deficit/hyperactivity disorder. *Molecular Neurobiology,* doi:10.1007/s12035-014-8685-x [doi]

Cao, Q., Shu, N., An, L., Wang, P., Sun, L., Xia, M. R., . . . He, Y. (2013). Probabilistic diffusion tractography and graph theory analysis reveal abnormal white matter structural connectivity networks in drug-naive boys with attention deficit/hyperactivity disorder. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 33*(26), 10676-10687. doi:10.1523/JNEUROSCI.4793-12.2013 [doi]

Carver, C. S., & White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS scales. *Journal of Personality and Social Psychology, 67*, 319-333.

Carver, C. S. (2004). Negative affects deriving from the behavioral approach system. *Emotion, 4*(1), 3-22. doi:10.1037/1528-3542.4.1.3

Chai, X. J., Whitfield-Gabrieli, S., Shinn, A. K., Gabrieli, J. D. E., Castañón, A. N., McCarthy, J. M., . . . Öngür, D. (2011). Abnormal medial prefrontal cortex resting-state connectivity in bipolar disorder and schizophrenia. *Neuropsychopharmacology, 36*(10), 2009-2017. doi:10.1038/npp.2011.88

Chao-Gan, Y., & Yu-Feng, Z. (2010). DPARSF: A MATLAB toolbox for "pipeline" data analysis of resting-state fMRI. *Frontiers in Systems Neuroscience, 4*, 13. doi:10.3389/fnsys.2010.00013 [doi]

Chapman, L. J., & Chapman, J. P. (1987). The measurement of handedness. *Brain and Cognition, 6*(2), 175-183. doi:10.1016/0278-2626(87)90118-7

Chase, H. W., Nusslock, R., Almeida, J. R. C., Forbes, E. E., LaBarbara, E. J., & Phillips, M. L. (2013). Dissociable patterns of abnormal frontal cortical activation during anticipation of an uncertain reward or loss in bipolar versus major depression. *Bipolar Disorders, 15*(8), 839-854. doi:10.1111/bdi.12132

Chen, C., Suckling, J., Lennox, B. R., Ooi, C., & Bullmore, E. T. (2011). A quantitative meta-analysis of fMRI studies in bipolar disorder. *Bipolar Disorders, 13*(1), 1-15. doi:10.1111/j.1399-5618.2011.00893.x

Chepenik, L. G., Raffo, M., Hampson, M., Lacadie, C., Wang, F., Jones, M. M., . . . Blumberg, H. P. (2010). Functional connectivity between ventral prefrontal cortex and amygdala at low frequency in the resting state in bipolar disorder. *Psychiatry Research: Neuroimaging, 182*(3), 207-210. doi:10.1016/j.pscychresns.2010.04.002

Coan, J. A., & Allen, J. J. B. (2004). Frontal EEG asymmetry as a moderator and mediator of emotion. *Biological Psychology, 67*(1-2), 7-49. doi:10.1016/j.biopsycho.2004.03.002

Coryell, W., Scheftner, W., Keller, M., & Endicott, J. (1993). The enduring psychosocial consequences of mania and depression. *The American Journal of Psychiatry, 150*(5), 720-727.

Depue, R. A. (1985). *The behavioral variability interview* University of Minnesota.

Depue, R. A., & Iacono, W. G. (1989). Neurobehavioral aspects of affective disorders. In L. W. Porter (Ed.), *Annual review of psychology, vol. 40*. (pp. 457-492). Palo Alto, CA US: Annual Reviews.

Depue, R. A., Krauss, S. P., & Spoont, M. R. (1987). A two-dimensional threshold model of seasonal bipolar affective disorder. In A. Öhman (Ed.), *Psychopathology: An interactional perspective*. (pp. 95-123). San Diego, CA US: Academic Press.

Eguiluz, V. M., Chialvo, D. R., Cecchi, G. A., Baliki, M., & Apkarian, A. V. (2005). Scale-free brain functional networks. *Physical Review Letters, 94*(1), 018102.

Endicott, J., & Spitzer, R. L. (1978). A diagnostic interview: The schedule for affective disorders and schizophrenia. *Archives of General Psychiatry, 35*(7), 837-844.

Frazier, J. A., Breeze, J. L., Papadimitriou, G., Kennedy, D. N., Hodge, S. M., Moore, C. M., . . . Makris, N. (2007). White matter abnormalities in children with and at risk for bipolar disorder. *Bipolar Disorders, 9*(8), 799-809. doi:10.1111/j.1399-5618.2007.00482.x

Friston, K. J., Frith, C. D., Liddle, P. F., & Frackowiak, R. S. J. (1993). Functional connectivity: The principal-component analysis of large (PET) data sets. *Journal of Cerebral Blood Flow and Metabolism, 13*(1), 5-14. doi:10.1038/jcbfm.1993.4

Friston, K. J., Williams, S., Howard, R., Frackowiak, R. S., & Turner, R. (1996). Movement-related effects in fMRI time-series. *Magnetic Resonance in Medicine, 35*(3), 346-355.

Girvan, M., & Newman, M. E. (2002). Community structure in social and biological networks. *Proceedings of the National Academy of Sciences of the United States of America, 99*(12), 7821-7826. doi:10.1073/pnas.122653799 [doi]

Glasser, M. F., Sotiropoulos, S. N., Wilson, J. A., Coalson, T. S., Fischl, B., Andersson, J. L., . . . WU-Minn HCP Consortium. (2013). The minimal preprocessing pipelines

for the human connectome project. *Neuroimage, 80*, 105-124. doi:10.1016/j.neuroimage.2013.04.127 [doi]

Gogtay, N., Ordonez, A., Herman, D. H., Hayashi, K. M., Greenstein, D., Vaituzis, C., . . . Rapoport, J. L. (2007). Dynamic mapping of cortical development before and after the onset of pediatric bipolar illness. *Journal of Child Psychology and Psychiatry, 48*(9), 852-862. doi:10.1111/j.1469-7610.2007.01747.x

Gong, G., He, Y., Concha, L., Lebel, C., Gross, D. W., Evans, A. C., & Beaulieu, C. (2009). Mapping anatomical connectivity patterns of human cerebral cortex using in vivo diffusion tensor imaging tractography. *Cerebral Cortex (New York, N.Y.: 1991), 19*(3), 524-536. doi:10.1093/cercor/bhn102 [doi]

Grigorov, M. G. (2005). Global properties of biological networks. *Drug Discovery Today, 10*(5), 365-372. doi:S1359644605033696 [pii]

Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: Functional imaging and the resting human brain. *Nature Reviews Neuroscience, 2*(10), 685-694. doi:10.1038/35094500

Gusnard, D. A., Akbudak, E., Shulman, G. L., & Raichle, M. E. (2001). Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. *Proceedings of the National Academy of Sciences, 98*(7), 4259-4264. doi:10.1073/pnas.071043098

Hahn, T., Dresler, T., Ehlis, A. C., Pyka, M., Dieler, A. C., Saathoff, C., . . . Fallgatter, A. J. (2012). Randomness of resting-state brain oscillations encodes gray's personality trait. *Neuroimage, 59*(2), 1842-1845. doi:10.1016/j.neuroimage.2011.08.042 [doi]

Hahn, T., Dresler, T., Ehlis, A., Plichta, M. M., Heinzel, S., Polak, T., . . . Fallgatter, A. J. (2009). Neural response to reward anticipation is modulated by gray's impulsivity. *Neuroimage, 46*(4), 1148-1153.

Harmon-Jones, E., Abramson, L. Y., Nusslock, R., Sigelman, J. D., Urosevic, S., Turonie, L. D., . . . Fearn, M. (2008). Effect of bipolar disorder on left frontal cortical responses to goals differing in valence and task difficulty. *Biological Psychiatry, 63*(7), 693-698. doi:10.1016/j.biopsych.2007.08.004

Haruno, M., & Kawato, M. (2006). Heterarchical reinforcement-learning model for integration of multiple cortico-striatal loops: FMRI examination in stimulus-action-reward association learning. *Neural Networks : The Official Journal of the International Neural Network Society, 19*(8), 1242-1254. doi:S0893-6080(06)00161-4 [pii]

Hayden, E. P., Bodkins, M., Brenner, C., Shekhar, A., Nurnberger, J. I., Jr., O'Donnell, B., & Hetrick, W. P. (2008). A multimethod investigation of the behavioral activation system in bipolar disorder. *Journal of Abnormal Psychology, 117*(1), 164-170. doi:10.1037/0021-843X.117.1.164

He, Y., Chen, Z. J., & Evans, A. C. (2007). Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. *Cerebral Cortex (New York, N.Y.: 1991), 17*(10), 2407-2419. doi:bhl149 [pii]

Heng, S., Song, A. W., & Sim, K. (2010). White matter abnormalities in bipolar disorder: Insights from diffusion tensor imaging studies. *Journal of Neural Transmission, 117*(5), 639-654. doi:10.1007/s00702-010-0368-9

Humphries, M. D., & Gurney, K. (2008). Network 'small-world-ness': A quantitative method for determining canonical network equivalence. *PloS One, 3*(4), e0002051. doi:10.1371/journal.pone.0002051 [doi]

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage, 17*(2), 825-841. doi:S1053811902911328 [pii]

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis, 5*(2), 143-156. doi:S1361841501000366 [pii]

Jo, H. J., Gotts, S. J., Reynolds, R. C., Bandettini, P. A., Martin, A., Cox, R. W., & Saad, Z. S. (2013). Effective preprocessing procedures virtually eliminate distance-dependent motion artifacts in resting state fMRI. *Journal of Applied Mathematics, 2013*, 10.1155/2013/935154. doi:10.1155/2013/935154 [doi]

Joyce, K. E., Laurienti, P. J., Burdette, J. H., & Hayasaka, S. (2010). A new measure of centrality for brain networks. *PloS One, 5*(8), e12200. doi:10.1371/journal.pone.0012200 [doi]

Judd, L. L., & Akiskal, H. S. (2003). The prevalence and disability of bipolar spectrum disorders in the US population: Re-analysis of the ECA database taking into account subthreshold cases. *Journal of Affective Disorders, 73*(1-2), 123-131. doi:10.1016/S0165-0327(02)00332-4

Judd, L. L., Akiskal, H. S., Schettler, P. J., Endicott, J., Leon, A. C., Solomon, D. A., . . . Keller, M. B. (2005). Psychosocial disability in the course of bipolar I and II disorders. *Archives of General Psychiatry, 62*(12), 1322-1330. doi:10.1001/archpsyc.62.12.1322

Khadka, S., Meda, S. A., Stevens, M. C., Glahn, D. C., Calhoun, V. D., Sweeney, J. A., . . . Pearlson, G. D. (2013). Is aberrant functional connectivity a psychosis endophenotype? A resting state functional magnetic resonance imaging study. *Biological Psychiatry, 74*(6), 458-466. doi:10.1016/j.biopsych.2013.04.024

Kinnison, J., Padmala, S., Choi, J. M., & Pessoa, L. (2012). Network analysis reveals increased integration during emotional and motivational processing. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 32*(24), 8361-8372. doi:10.1523/JNEUROSCI.0821-12.2012 [doi]

Knutson, B., Fong, G. W., Adams, C. M., Varner, J. L., & Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI.

NeuroReport: For Rapid Communication of Neuroscience Research, 12(17), 3683-3687. doi:10.1097/00001756-200112040-00016

Korgaonkar, M. S., Fornito, A., Williams, L. M., & Grieve, S. M. (2014). Abnormal structural networks characterize major depressive disorder: A connectome analysis. *Biological Psychiatry,* doi:S0006-3223(14)00134-6 [pii]

Kruschwitz, J. D., List, D., Waller, L., Rubinov, M., & Walter, H. (2015). GraphVar: A user-friendly toolbox for comprehensive graph analyses of functional brain connectivity. *Journal of Neuroscience Methods, 245*, 107-115. doi:10.1016/j.jneumeth.2015.02.021 [doi]

Latora, V., & Marchiori, M. (2001). Efficient behavior of small-world networks. *Physical Review Letters, 87*(19), 198701.

Leow, A., Ajilore, O., Zhan, L., Arienzo, D., GadElkarim, J., Zhang, A., . . . Altshuler, L. (2013). Impaired inter-hemispheric integration in bipolar disorder revealed with brain network analyses. *Biological Psychiatry, 73*(2), 183-193. doi:10.1016/j.biopsych.2012.09.014 [doi]

Lim, C. S., Baldessarini, R. J., Vieta, E., Yucel, M., Bora, E., & Sim, K. (2013). Longitudinal neuroimaging and neuropsychological changes in bipolar disorder patients: Review of the evidence. *Neuroscience and Biobehavioral Reviews, 37*(3), 418-435. doi:10.1016/j.neubiorev.2013.01.003

Liu, C., Li, F., Li, S., Wang, Y., Tie, C., Wu, H., . . . Wang, C. (2012). Abnormal baseline brain activity in bipolar depression: A resting state functional magnetic resonance imaging study. *Psychiatry Research: Neuroimaging, 203*(2-3), 175-179. doi:10.1016/j.pscychresns.2012.02.007

Lo, C. Y., Wang, P. N., Chou, K. H., Wang, J., He, Y., & Lin, C. P. (2010). Diffusion tensor tractography reveals abnormal topological organization in structural cortical networks in Alzheimer's disease. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 30*(50), 16876-16885. doi:10.1523/JNEUROSCI.4136-10.2010 [doi]

Mathias, N., & Gopal, V. (2001). Small worlds: How and why. *Physical Review.E, Statistical, Nonlinear, and Soft Matter Physics, 63*(2 Pt 1), 021117.

Mayberg, H. S. (1997). Limbic-cortical dysregulation: A proposed model of depression. *The Journal of Neuropsychiatry and Clinical Neurosciences, 9*(3), 471-481.

Menon, V. (2011). Large-scale brain networks and psychopathology: A unifying triple network model. *Trends in Cognitive Sciences, 15*(10), 483-506. doi:10.1016/j.tics.2011.08.003 [doi]

Meyer, B., Johnson, S. L., & Winters, R. (2001). Responsiveness to threat and incentive in bipolar disorder: Relations of the BIS/BAS scales with symptoms. *Journal of Psychopathology and Behavioral Assessment, 23*(3), 133-143. doi:10.1023/A:1010929402770

Moberg, D. P. (2000). *The adolescent alcohol and drug involvement scale*. Madison, WI: University of Wisconsin, Center for Health Policy and Program Evaluation.

Nusslock, R. R., Almeida, J. R. C., Forbes, E. E., Versace, A., Frank, E., LaBarbara, E. J., . . . Phillips, M. L. (2012). Waiting to win: Elevated striatal and orbitofrontal cortical activity during reward anticipation in euthymic bipolar disorder adults. *Bipolar Disorders, 14*(3), 249-260. doi:10.1111/j.1399-5618.2012.01012.x

Öngür, D., Lundy, M., Greenhouse, I., Shinn, A. K., Menon, V., Cohen, B. M., & Renshaw, P. F. (2010). Default mode network abnormalities in bipolar disorder and schizophrenia. *Psychiatry Research: Neuroimaging, 183*(1), 59-68. doi:10.1016/j.pscychresns.2010.04.008

Öngür, D., & Price, J. L. (2000). The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral Cortex, 10*(3), 206-219. doi:10.1093/cercor/10.3.206

Phillips, M. L., Ladouceur, C. D., & Drevets, W. C. (2008). A neural model of voluntary and automatic emotion regulation: Implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Molecular Psychiatry, 13*(9), 833-857. doi:10.1038/mp.2008.65

Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003). Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biological Psychiatry, 54*(5), 515-528. doi:10.1016/S0006-3223(03)00171-9

Powell, J. H., Al-Adawi, S., Morgan, J., & Greenwood, R. J. (1996). Motivational deficits after brain injury: Effects of bromocriptine in 11 patients. *Journal of Neurology, Neurosurgery & Psychiatry, 60*(4), 416-421. doi:10.1136/jnnp.60.4.416

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage, 59*(3), 2142-2154. doi:10.1016/j.neuroimage.2011.10.018 [doi]

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences, 98*(2), 676-682. doi:10.1073/pnas.98.2.676

Richter, P., Werner, J., Heerlein, A., Kraus, A., & Sauer, H. (1998). On the validity of the beck depression inventory. A review. *Psychopathology, 31*(3), 160-168. doi:psp31160 [pii]

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *Neuroimage, 52*(3), 1059-1069. doi:10.1016/j.neuroimage.2009.10.003 [doi]

Satterthwaite, T. D., Wolf, D. H., Loughead, J., Ruparel, K., Elliott, M. A., Hakonarson, H., . . . Gur, R. E. (2012). Impact of in-scanner head motion on multiple measures of functional connectivity: Relevance for studies of neurodevelopment in youth. *Neuroimage, 60*(1), 623-632. doi:10.1016/j.neuroimage.2011.12.063 [doi]

Schultz, W. (1997). Dopamine neurons and their role in reward mechanisms. *Current Opinion in Neurobiology, 7*(2), 191-197. doi:10.1016/S0959-4388(97)80007-4

Shen, X., Tokoglu, F., Papademetris, X., & Constable, R. T. (2013). Groupwise whole-brain parcellation from resting-state fMRI data for network node identification. *Neuroimage, 82*, 403-415. doi:10.1016/j.neuroimage.2013.05.081

Siegel, J. S., Power, J. D., Dubis, J. W., Vogel, A. C., Church, J. A., Schlaggar, B. L., & Petersen, S. E. (2014). Statistical improvements in functional magnetic resonance imaging analyses produced by censoring high-motion data points. *Human Brain Mapping, 35*(5), 1981-1996. doi:10.1002/hbm.22307 [doi]

Sohn, W. S., Yoo, K., Lee, Y. B., Seo, S. W., Na, D. L., & Jeong, Y. (2015). Influence of ROI selection on resting state functional connectivity: An individualized approach for resting state fMRI analysis. *Frontiers in Neuroscience, 9*, 280. doi:10.3389/fnins.2015.00280 [doi]

Song, X., Wang, X., Alpert, K., Chen, Y., Huang, K., Wang, L., & Parrish, T. (2015b). Rapid automatic comprehensive quality assurance metrics evaluation for neuroimaging studies. *Organization for Human Brain Mapping Annual Meeting,* Honolulu, HI, USA.

Song, X., Wang, X., Alpert, K., Wang, L., & Parrish, T. (2015a). Robust web-based parallel-optimized minimal pre-processing and analyzing pipeline for fMRI big data. *Organization for Human Brain Mapping Annual Meeting,* Honolulu, HI, USA.

Sporns, O. (2013). The human connectome: Origins and challenges. *Neuroimage, 80*, 53-61. doi:10.1016/j.neuroimage.2013.03.023 [doi]

Sporns, O., Tononi, G., & Kotter, R. (2005). The human connectome: A structural description of the human brain. *PLoS Computational Biology, 1*(4), e42. doi:10.1371/journal.pcbi.0010042 [doi]

Sporns, O., & Zwi, J. D. (2004). The small world of the cerebral cortex. *Neuroinformatics, 2*(2), 145-162. doi:NI:2:2:145 [pii]

Sporns, O., Chialvo, D. R., Kaiser, M., & Hilgetag, C. C. (2004). Organization, development and function of complex brain networks. *Trends in Cognitive Sciences, 8*(9), 418-426.

Strakowski, S. M., Adler, C. M., Almeida, J., Altshuler, L. L., Blumberg, H. P., Chang, K. D., . . . Townsend, J. D. (2012). The functional neuroanatomy of bipolar disorder: A consensus model. *Bipolar Disorders, 14*(4), 313-325. doi:10.1111/j.1399-5618.2012.01022.x

Tijms, B. M., Wink, A. M., de Haan, W., van der Flier, W. M., Stam, C. J., Scheltens, P., & Barkhof, F. (2013). Alzheimer's disease: Connecting findings from graph theoretical studies of brain networks. *Neurobiology of Aging, 34*(8), 2023-2036. doi:10.1016/j.neurobiolaging.2013.02.020 [doi]

Torrisi, S., Moody, T. D., Vizueta, N., Thomason, M. E., Monti, M. M., Townsend, J. D., . . . Altshuler, L. L. (2013). Differences in resting corticolimbic functional

connectivity in bipolar I euthymia. *Bipolar Disorders, 15*(2), 156-166. doi:10.1111/bdi.12047

Torrubia, R., Ávila, C., Moltó, J., & Caseras, X. (2001). The sensitivity to punishment and sensitivity to reward questionnaire (SPSRQ) as a measure of gray's anxiety and impulsivity dimensions. *Personality and Individual Differences, 31*(6), 837-862. doi:10.1016/S0191-8869(00)00183-5

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., . . . Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage, 15*(1), 273-289. doi:10.1006/nimg.2001.0978 [doi]

Urošević, S., Abramson, L. Y., Harmon-Jones, E., & Alloy, L. B. (2008). Dysregulation of the behavioral approach system (BAS) in bipolar spectrum disorders: Review of theory and evidence. *Clinical Psychology Review, 28*(7), 1188-1205. doi:10.1016/j.cpr.2008.04.004

van den Heuvel, M. P., Mandl, R. C. W., Stam, C. J., Kahn, R. S., & Hulshoff Pol, H. E. (2010). Aberrant frontal and temporal complex network structure in schizophrenia: A graph theoretical analysis. *The Journal of Neuroscience, 30*(47), 15915-15926.

van den Heuvel, M. P., & Fornito, A. (2014). Brain networks in schizophrenia. *Neuropsychology Review, 24*(1), 32-48. doi:10.1007/s11065-014-9248-7 [doi]

van den Heuvel, M. P., & Pol, H. E. H. (2010). Exploring the brain network: A review on resting-state fMRI functional connectivity. *European Neuropsychopharmacology, 20*(8), 519-534. doi:10.1016/j.euroneuro.2010.03.008

Van Dijk, K. R., Sabuncu, M. R., & Buckner, R. L. (2012). The influence of head motion on intrinsic functional connectivity MRI. *Neuroimage, 59*(1), 431-438. doi:10.1016/j.neuroimage.2011.07.044 [doi]

Vargas, C., López-Jaramillo, C., & Vieta, E. (2013). A systematic literature review of resting state network—Functional MRI in bipolar disorder. *Journal of Affective Disorders, 150*(3), 727-735. doi:10.1016/j.jad.2013.05.083

Versace, A., Ladouceur, C. D., Romero, S., Birmaher, B., Axelson, D. A., Kupfer, D. J., & Phillips, M. L. (2010). Altered development of white matter in youth at high familial risk for bipolar disorder: A diffusion tensor imaging study. *Journal of the American Academy of Child & Adolescent Psychiatry, 49*(12), 1249-1259.

Watts, D. J., & Strogatz, S. H. (1998). Collective dynamics of 'small-world' networks. *Nature, 393*(6684), 440-442. doi:10.1038/30918 [doi]

Winters, K. C., Botzet, A., Anderson, N., Bellehumeur, T., & Egan, B. (2001). *Screening and assessment study, Wisconsin division of juvenile corrections, alcohol and other drug abuse*. Minneapolis, MI: University of Minnesota- Minneapolis Center for Adolescent Substance Abuse Research.

Xue, G., Lu, Z., Levin, I. P., Weller, J. A., Li, X., & Bechara, A. (2009). Functional dissociations of risk and reward processing in the medial prefrontal cortex. *Cerebral Cortex, 19*(5), 1019-1027. doi:10.1093/cercor/bhn147

Yan, C. G., Craddock, R. C., He, Y., & Milham, M. P. (2013). Addressing head motion dependencies for small-world topologies in functional connectomics. *Frontiers in Human Neuroscience, 7*, 910. doi:10.3389/fnhum.2013.00910 [doi]