

Cognitive Functioning in Bipolar Disorder

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ABSTRACT

To align the neuropsychological functioning of our adult euthymic patient group with that reported in previous studies on euthymic bipolar disorder (BD), we used a neuropsychological battery that examined sustained attention (Rapid Visual Information Processing Task), verbal memory (California Verbal Learning Task), executive functioning (Intradimensional-Extradimensional Shift Task, Barrett Impulsivity Task, and Framing Task), and emotion responsiveness/regulation (Positive Affect/Negative Affect Scales, Behavioral Inhibition/Behavioral Activation Scale, and Affective Lability/Affective Intensity Scales) in patients versus healthy volunteers (HV). Our results corroborated existing evidence of reduced sustained attention, impaired verbal memory and executive functioning, and abnormal emotional responsiveness and regulation in euthymic BD relative to healthy controls (Chapter 2).

To investigate how abnormal development of brain function in BD leads to deficits in decision-making, motor inhibition, and response flexibility, we examined child and adult BD using a novel risky decision-making task, and used cross-sectional (age x diagnosis) functional magnetic resonance (fMRI) designs to examine neural activation associated with motor inhibition and response flexibility in BD relative to HV. During the risky decision-making task, adult euthymic BD patients were no different from healthy controls in their proportion of risky lottery choices over a range of competing lotteries. This matched behavioral performance was associated with similar prefrontal and striatal brain activation between the patient and control groups during response, anticipation, and outcome phases of decision-making (Chapter 3). These results are different from previous studies that have shown increased risk taking during decision-making in euthymic BD. Similarly, young BD patients were no different from age-matched healthy and patient controls in their pattern of decision making during the risky choice task. This was evidenced by a similar number of risky lottery selections over the range of changing expected values between the young BD group and control groups (Chapter 4).

Using a cross-sectional, fMRI analytic design during the stop signal task, we found that child and adult BD showed similar behavioral performance to child and adult HV during motor inhibition. However, this matched behavioral performance was associated with abnormal neural activation in patients relative to controls. Specifically, during unsuccessful motor inhibition, there was an age group x diagnosis interaction, with BD youth showing reduced activity in left and right ACC compared to both age-matched HV and adult BD, and adult BD showing increased activation in left ACC compared to healthy adults. During successful motor inhibition there was a main effect of diagnosis, with HV showing greater activity in left VPFC and right NAc compared to BD (Chapter 5). These neuroimaging data support existing laboratory-based evidence of motor inhibition impairments in BD relative to HV, and indicate brain dysregulation during motor control is important to BD pathophysiology.

A previous behavioral study showed impaired response flexibility in young BD patients relative to age-matched controls when using the change task. Here, we used the change task during fMRI to examine response flexibility in child and adult BD compared to child and adult HV. We found that patient and control groups showed similar change signal reaction times in response to change cues. However, this matched behavioral performance was associated with abnormal age group x diagnosis activations in brain regions important in signal detection, response conflict, response inhibition, and sustained attention. Specifically, during successful change trials, child BD participants showed frontal, parietal, and temporal hyperactivation relative to healthy children and adult BD, while adult BD showed hypoactivation in these regions relative to healthy adults. These novel fMRI findings during the change task indicate impaired neural activation during response flexibility may be important to the pathophysiology of BD development.

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Chapter 1: Introduction to the thesis

1.1 General Introduction:

Research in Bipolar disorder (BD) has revealed important associations between diminished psychosocial functioning during acute episodes, and neuropsychological impairments in decision-making (Adida et al., 2011), motor inhibition (Swann et al., 2003), and response flexibility (Dickstein et al., 2007), compared to healthy volunteers (HV). However, only limited knowledge exists on how these neuropsychological impairments are related to abnormal brain development in BD relative to HV. A brain dysfunction perspective of BD is important since it can help researchers develop medicines targeted at reversing abnormal neural functioning, thereby improving psychosocial outcomes for patients. Additionally, a neurodevelopmental perspective of BD is important since it can help researchers understand how the pathophysiology of child BD is similar or different from adult BD, as well as enable psychiatrists to follow disease progression by monitoring a patient's brain development from childhood into adulthood.

1.2 Aligning the neuropsychological function of euthymic bipolar patients to examine the existence of a cognitive endophenotype

There is increased interest in researching the cognitive deficits that persist during euthymic phases of BD illness, since these impairments can help better understand the pathophysiology of the illness, as well as how the disease is inherited. For example, by examining neuropsychological functioning of patients outside of acute episodes, and comparing that to

unaffected first-degree relatives, researchers can begin to understand what cognitive impairments are inherited in the disorder (Gottesman and Gould, 2003). More specifically, the presence of specific cognitive deficits existing similarly in both remitted patients and unaffected relatives, compared to healthy controls, adds to a growing literature on a 'cognitive endophenotype' in BD (Bora et al., 2009). According to Bora (Bora et al., 2009) and Gottesman (Gottesman and Gould, 2003) a cognitive endophenotype in BD should be (1) associated with the illness, (2) should be heritable, (3) should co-segregate within families with the illness, (4) must be mood state-independent (present in remitted patients), and (5) the cognitive phenotype should be demonstrable at a higher prevalence in unaffected relatives of patients compared to the general population. It should also be identifiable in young people at risk or with the disorder, illustrating the need for studies examining neuropsychological functioning in at risk youth compared to the normal population.

While a number of meta-analyses have shown impairments in remitted BD patients (Bora et al., 2009, Arts et al., 2008, Torres et al., 2007, Robinson et al., 2006), few have addressed impairments present in unaffected family members of BD patients. Arts (Arts et al., 2008) reviewed literature on cognitive functioning in first-degree relatives of BD patients, and found unaffected relatives had worse neuropsychological performance in all cognitive domains studied. While effect sizes were generally small, first-degree relatives could still be distinguished from healthy controls in executive function and verbal memory. A separate study in twins discordant for BD diagnosis, showed that the unaffected sibling showed lower performance on tests measuring declarative and working memory, compared to control twins (Kieseppa, 2004).

Nevertheless, studies have shown that unaffected relatives of patients may also show cognitive deficits compared to healthy controls, indicate these impairments are inherited in BD families.

By examining the cognitive functioning of euthymic BD patients, we can elucidate what neuropsychological impairments should also be examined in unaffected relatives. For example, recent studies indicate that adult BD show increased numbers of risky choices during laboratory-based decision-making tasks compared to HV, and this may be related to the increased risky behaviors commonly observed during acute episodes in patients (Adida et al., 2011). Importantly, increased risky decision-making has been shown to persist in patients during euthymia (Adida et al., 2011, Yechiam et al., 2008, Christodoulou et al., 2006), which suggests it is an important deficit to understand in BD. While a previous study reported this increased risky decision-making may be due to an inability to update response patterns to reinforcement history (Adida et al., 2011), no study has examined whether this behavior is due to altered sensitivity to changes in risk associated with choices compared to HV. Evidence that decision making is different in euthymic BD compared to HV when the risk associated with dilemmas is changed would suggest this impairment should be studied as a potential cognitive endophenotype of the disorder.

In order to elucidate how changes in risk guide decision-making in euthymic BD, we examined the decision-making of a group of adult euthymic BD patients, aligned in neuropsychological functioning to euthymic groups reported in previous studies (Torres et al., 2007, Robinson et al., 2006) during an fMRI lottery-based decision-making task. The task was developed so that the risks associated with lottery choices changed on a trial-by-trial basis, allowing us to disentangle whether BD is associated with an insensitivity to changes in risk associated with choices (chapter

3). Evidence of decision-making impairments in euthymic BD during this task would suggest future studies examining this function in unaffected relatives can help our understanding of how this disease is transmitted.

1.3 Examining the development of BD

While longitudinal analytic designs are ideal for making developmental comparisons in BD versus HV, two important research techniques can help investigators reach preliminary conclusions on BD development. First, by examining the neuropsychological functioning of young patients in cognitive domains that have been shown to be impaired in adult BD, we can gain a better understanding on what cognitive dysfunction emerges early versus late in the illness. Using this approach, we examined whether child BD showed a similar pattern as adult BD in increased risky choices during decision-making, compared to controls. Decision-making performance in child BD was examined using the same decision-making task we utilized in our adult patients (chapter 3). Evidence of increased risky choices during decision-making in child BD would suggest impaired decision-making emerges early in BD development, and is important in understanding the pathophysiology of pediatric BD.

A second research technique that can be used to investigate the development of abnormal brain activation in BD is using cross-sectional age (child vs. adult) x diagnosis (healthy vs. bipolar) fMRI designs. Significant age x diagnosis interaction effects in cross-sectional designs can indicate one of two possibilities. First, that brain activation abnormalities change during the course of BD illness, with young patients having one direction, or pattern, of brain dysfunction

compared to healthy youth, which later in life turns into another direction, or pattern, of brain dysfunction in adult BD compared to age-matched controls. Alternatively, age x diagnosis interactions may indicate that the pathophysiologic mechanisms associated with child versus adult forms of illness are all together different. Here, we used this research method during fMRI to investigate how child and adult BD differ from their age matched controls in neural activation during motor inhibition (chapter 5) and response flexibility (chapter 6) tasks.

Below is a brief overview of historical and diagnostic considerations in BD. This is important given the strict inclusion and exclusion criteria that must be used when studying BD. This introduction will conclude with important predictions, based on this literature, of the cognitive and neural functioning outcomes we expected in our patients during our neuropsychological and fMRI examinations, relative to controls.

1.4 Diagnosis of BD

Since these first descriptions of manic-depression, later to be referred to as bipolar disorder (BD) (Goodwin et al., 2007), psychiatrists have continually developed the diagnostic criteria of this condition to better capture the signs, symptoms, and clinical outcomes unique to BD. The diagnostic criteria for BD were first described in 1952 in the American Psychiatric Association Diagnostic Manual (Grob, 1991). Numerous changes were made to these original BD criteria for it to result in its current form (American Psychiatric Association, 2000). These changes took into consideration the improved recognition of emotional and behavioral symptoms seen specifically in BD and not other disorders (e.g. distinct episodes of mood elevation lasting a certain period of

time, and increased risk-taking during mania), as well as the recognition that varying levels of BD severity exists (i.e. the bipolar spectrum). For example, with an estimated lifetime prevalence of approximately 2% (Soldani et al., 2005), BD-I is the most debilitating form of illness, and is characterized by mania lasting for at least seven days (American Psychiatric and American Psychiatric Association. Task Force on, 2000). Mania in these patients is characterized by an elevated and/or expansive mood, markedly different from baseline. This mood episode can sometimes be predominantly irritability. Behavioral symptoms may include decreased need for sleep, poor judgment, increased reckless behaviors, and increased distractibility. The BD-II diagnosis, on the other hand, is reserved for persons that suffer from a less severe form of illness (i.e. hypomania), due to shorter duration of manic symptoms (i.e. 4-7 days) and symptoms causing less psychosocial difficulties than that seen in classic mania. Hypomanic patients may present with increased optimism, pressured speech and activity, and decreased need for sleep. But, the symptoms of BD-II are not impairing enough to prevent completion of important tasks, like work or family duties. Importantly, an episode of major depression must be accounted for in BD-II. Finally, BP-NOS (not otherwise specified) is a catch all subtype of BD reserved for patients who do not meet criteria for BP subtypes I or II, but still show bipolar characteristics that affect the quality of life for the patient.

Two important factors complicate the diagnosis of BD in adolescence. First, research on the normal development of impulse regulation (Williams et al., 1999), cognitive control (Bunge et al., 2002), emotional regulation (McRae et al., 2012), indicate that these functions continue to improve from childhood into adulthood. This means that increased impulsivity or decreased emotion regulation detected in young patients may be due to an interaction of underlying disease

with normal neuropsychological development. Nevertheless, the role of normal cognitive development underling between-group differences in BD relative to controls can be reduced in research paradigms by using age-matched comparisons. Secondly, BD diagnosis in youth can be complicated by high rates of co-occurring behavioral and mood disorders. For example, in the largest prospective, naturalistic study of pediatric BD, Birmaher (Birmaher et al., 2006) reported that, in a sample of BP-I, BP-II, and BP-NOS children, rates of co-occurring attention deficit hyperactive disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD) and anxiety disorders were 58.6%, 39.2%, 12.5%, and 38.4%, respectively. This means it is not uncommon for a child with BD to have an additional psychiatric disorder. This also means that, because there is considerable overlap in the symptoms of BD and, for instance, the symptoms of ADHD (e.g. decreased need for sleep, distractability, talkativeness, increased goal-directed activity), it is particularly important in to distinguish when these behavioral symptoms are the result of episodic mood changes in child BD, versus chronic mood disturbances seen in other disorders (Leibenluft and Rich, 2008). This distinction is crucial, since there is increasing evidence that children often mischaracterized as BD have a different psychiatric trajectory than children with true BD. For example, in the first longitudinal, epidemiological study to evaluate the outcomes of young patients with SMD, a disorder characterized by disabling, chronic irritable mood and behavioral disturbances (Leibenluft et al., 2003b), versus children with DSM-IV-R criteria of BD, patients with SMD were more likely to develop depression later in life than BD (Brotman et al., 2006). This difference in long-term psychiatric outcome in SMD versus BD illustrates the importance of (1) adhering to standardized evaluations for BD diagnosis in youth, by expert clinical staff, (2) investigating the distinct pathophysiologic mechanisms that likely

exists in child BD versus SMD, and (3) and the importance of using strict inclusion and exclusion criteria in research paradigms examining child BD.

For the purpose of making comparisons between children and adults with classic descriptions of BD, all BD participants in this thesis met diagnostic criteria for mania or hypomania based on DSM-IV-TR guidelines.

1.5 Thesis aims

This thesis aims to address three important research questions on the pathophysiology of BD using both brain functioning and neurodevelopmental perspectives. First, previous studies indicated that euthymic BD patients suffer from a deficit in decision-making, evidence by increased risky choices compared to HV (Adida et al., 2011; Christodolou, 2006). However, no study has examined whether this pattern of decision-making in euthymic BD may be related to altered behavioral or neural responses to changes in risk during decision-making, relative to HV. Evidence of a decision-making impairment in euthymic BD compared to HV when the risk associated with dilemmas changes would lay the foundations for future studies in unaffected relatives. Using a group of adult euthymic BD patients, aligned in neuropsychological functioning to groups reported in previous studies (Torres et al., 2007, Robinson et al., 2006), we used fMRI to examine brain activation in BD during a decision-making task where levels of risk changed on a trial-by-trial basis, compared to HV. Based on previous cognitive studies in euthymic BD, we expected our neuropsychological examination would reveal a pattern of decreased sustained attention and verbal memory, and impaired executive and emotion

regulation function, in BD relative to age-matched controls. Further, based on data that euthymic BD show increased risky choices during a card selection task (Adida et al., 2011, Yechiam et al., 2008, Christodoulou et al., 2006), and evidence of abnormal anterior cingulate cortex (ACC) and ventral prefrontal cortex (VPFC) activation during risk taking in mania (Rubinsztein et al., 2001), we expected our patients would show increased risky choices during decision-making, relative to HV, and this would be associated with abnormal ACC, VLPFC, and dorsolateral prefrontal cortex (DLPFC) activation relative to controls (Chapter 3).

Second, using a development perspective, we investigated BD performance during decision-making, motor inhibition, and response flexibility using two different research methods. We first examined whether young BD patients show a similar pattern of increased risky choices as adult BD during decision-making. Specifically, utilizing the same decision-making task we used in our adult euthymic patients, we measured whether child BD show increased risky selections compared to age-matched controls (Chapter 4). Evidence of increased risky decision-making in young BD would suggest decision-making impairments emerge early in BD development. Also, using cross-sectional (age x diagnosis) fMRI designs, we examined neural activation associated with motor inhibition (chapter 5) and response flexibility (chapter 6) in child and adult BD. Results from these studies can provide clues on whether child and adult forms of illness share common pathophysiological mechanisms, or if the pattern of brain dysregulation during motor inhibition and response flexibility changes from childhood into adulthood in BD. Based on existing evidence of the roles of ACC, VLPFC, and DLPFC activation during motor inhibition and response flexibility, we expected BD would show abnormal activation in these regions during performance relative to HV.

This thesis will conclude (Chapter 7) with a review of the important neuropsychological and fMRI findings from these experiments, and how these results can inform future studies examining the pathophysiology of BD.

Chapter 2: Neuropsychological Impairment in Recovered Adult Bipolar Patients

2.1 Introduction

Bipolar Disorder (BD) is characterized by periods of polarized moods of mania or depression, and intermittent periods of remission. Manic and depressive phases of the illness have each been associated with certain cognitive deficits measured by neuropsychological tests (Sole et al., 2012, Goldberg et al., 1993). Until recently, euthymia was assumed to be associated with full recovery of neuropsychological function. However, this understanding has been challenged by studies demonstrating persistent deficits in verbal memory, sustained attention, and executive function in euthymia (Bora et al., 2009, Martinez-Aran et al., 2008). Cognitive impairment during euthymia is important to understand because it may provide clues to the neurobiology of mood disorder, what neuropsychological deficits persist during euthymia that may relate to relapse, as well as help understand what prevents return of full functioning in remitted patients. Also, since one of the aims of this thesis is to examine impaired decision-making in euthymic BD, and euthymic BD has already been associated with a pattern of neuropsychological dysfunction in verbal memory, sustained attention, and executive function (Torres et al., 2007, Robinson et al., 2006), we wanted to align the neuropsychological functioning of our patient sample with that of previous studies.

2.1.1 Neuropsychological examination: cognitive performance differences from healthy volunteers

Several studies have shown an association between neuropsychological performance in euthymia and functional recovery in work, school, or home. For example, a recent longitudinal study of euthymic BD patients showed that performance on executive function tasks (e.g. digits backwards) was highly predictive of occupational functioning in patients (Bonnín et al., 2010). Martinez-Aran (Martínez-Arán et al., 2004) demonstrated that verbal memory scores were worse in euthymic BD compared to HV, and this was highly correlated with global assessment of function scores. Additionally, Zubieta (Zubieta et al., 2001) showed that measures of social and occupational functioning were strongly correlated with verbal learning and executive function performance in BD. These studies corroborated other studies that demonstrated a relationship between minor, but persistent, cognitive deficits in subgroups of BD with poor social outcomes or responses to treatment in during euthymia (Carlson et al., 1974, Johnstone et al., 1985, Gitlin et al., 1995). Taken together, minor impairment in neuropsychological function persists in euthymia, may be related to poor response to pharmacological intervention, and can contribute to continued psychosocial impairment during recovery.

The comparison of neuropsychological performance between euthymic BD patients and healthy volunteers has yielded important preliminary results. Some have shown relatively large effect sizes when comparing the cognitive function of BD versus HV (Altshuler et al., 2004, Balanzá-Martínez et al., 2005), while others have only detected mild impairments (Zubieta et al., 2001, van Gorp et al., 1999, Martínez-Arán et al., 2004). For example, a recent meta-analysis that examined neuropsychological functioning in euthymic BD patients reported medium to large effect sizes in domains of attention/processing speed, episodic memory, and executive functioning (Torres et al., 2007). In a different meta-analysis, euthymic patients were most

impaired in executive function and verbal learning, whereas attention, psychomotor speed and immediate memory were less affected (Robinson et al., 2006). In a different study, focused on executive functioning and verbal memory in BD, patients were significantly impaired in 10 out of the 15 neuropsychological tasks employed, including the Wisconsin Card Sorting Task (WCST) (executive function, rule learning), the Trail-Making Task (TMT) (executive function, response flexibility), backward digit span (executive function), and verbal memory tasks, compared to controls (Martínez-Arán et al., 2004). Importantly, verbal memory performance in BD was significantly correlated with disease chronicity, number of previous manic episodes, number of previous hospitalizations, and psychosocial functioning in that study.

These studies demonstrate that impairments in executive functioning, verbal memory, and attention persist in euthymic BD patients, and may be related to disease course. Since an important objective of the present study is to align the neuropsychology of patients to that found in patients from previous studies, we focused our neuropsychological examination on sustained attention, verbal memory, and executive functioning. Below is a review of findings that guided our hypothesis that our current sample of euthymic BD patients would also be impaired in domains in executive functioning, verbal memory, and attention, compared to healthy controls.

2.1.2 Sustained Attention

Sustained attention is defined as the “ability to direct and focus cognitive activity on specific stimuli” (DeGangi, 1990). This ability is important in any task where diminished focus leads to performance deficits, such as maintaining attention during a teacher’s lecture or important

instructions at work. Therefore, decreased sustained attention in BD has been related to decreased psychosocial functioning in at work, school, and home (Godard et al., 2011, Fleck et al., 2012), since many activities in these domains require lengthy attention spans. For this reason, most neuropsychological examinations of BD have included a measure in sustained attention.

Continuous performance tasks (CPTs) are neuropsychological measures that test sustained attention, and rely on intact performance monitoring, signal detection, motor inhibition, and cognitive control. Meta-analysis of studies using CPTs in BD showed medium to large effect sizes in sustained attention deficits (Bora et al., 2009, Arts et al., 2008, Torres et al., 2007). In one meta-analysis, an effect size of $d=.83$ was found for omission errors during CPT performance (Bora et al., 2009). This means BD patients were impaired in their ability to detect visual targets among distractor targets, compared to controls. An effect size of $d=.60$ was reported in a different meta-analysis for response latency during CPT in BD (Robinson et al., 2006). This means that BD patients showed slower psychomotor responses to attention targets, possibly due to increased conflict when making responses, compared to controls. Finally, in a study of neuropsychological impairment in euthymic BD, sustained attention deficits, measured using the rapid visual information-processing (RVIP) task, were the only differences that remained significant after controlling for mild affective symptoms (Clark et al., 2002). Importantly, the severity of these deficits in sustained attention was previously related to disease course, with manic patients, or patients with repeated acute episodes, showing the worst performance (Clark and Goodwin, 2004).

Continuous performance tasks rely on healthy functioning of performance monitoring, motor inhibition, and cognitive control. Importantly, fMRI studies have highlighted the role of the ACC for performance monitoring, motor selection, and error detection (Chevrier et al., 2007, Botvinick et al., 2004), the ventrolateral prefrontal cortex (VLPFC) for motor inhibition (Aron et al., 2003), and the DLPFC for signal detection and cognitive control (Fleck et al., 2012, Tana et al., 2010). Additionally, a study that examined distractibility during sustained attention showed that the DLPFC was active when detecting behaviorally relevant stimuli embedded in sequences of distractor stimuli (Yamasaki et al., 2002). These studies illustrate the importance of healthy ACC, DLPFC, and VLPC functioning during CPT tasks since performance on these tasks rely on detecting behaviorally relevant visual signals, motor inhibition/selection, and cognitive control.

Sustained attention deficits have been linked to abnormal neural activation when examining CPT performance adult BD compared to HV. Specifically, a study in manic BD showed decreased DLPFC activation during CPT performance compared to HV, and this was associated with a greater decreasing sensitivity to targets versus non-targets (Fleck et al., 2012). In a study using a CPT in euthymic unmedicated BD, patients differed from HV by showing increased activation in the inferior frontal cortex, insula, VPFC, and subcortical regions during fMRI (Strakowski et al., 2004). Finally, during a positron emission tomography (PET) study using a CPT in euthymic BD, patients showed an increased number of omission errors compared to HV, and this was associated decreased DLPFC metabolism (Brooks et al., 2010). These studies show that DLPFC dysfunction exists in BD during sustained attention tasks, irrespective of mood state. Since the DLPFC is important in signal detection and cognitive control (Fleck et al., 2012, Tana et al.,

2010), dysfunction of this region in BD may underlie existing evidence of target detection impairments during neuropsychological examination (Torres et al., 2007).

The studies reviewed here demonstrate that sustained attention deficits persist during recovery in BD. In order to align the neuropsychological functioning in sustained attention of the present euthymic sample with that of previous studies, we included a measure of sustained attention (rapid visual information processing task (RVIP) (Robbins et al., 1994)) here. We expected our patients would show decreased target detection and increased response latency when compared to the performance of HV. Additionally, given evidence of more severe performance deficits in patients with repeated episodes of mood disturbance, we expected deficits during sustained attention would be worse in patients with more manic episodes.

2.1.3 Verbal Memory

The decreased ability to organize and recall verbal information in BD may relate to decreased functioning at school (Vonk et al., 2012), work, and home (Depp et al., 2012), since the retention of newly learned verbal material is important to functioning in these domains. A recent longitudinal study in euthymic BD patients found that free delayed recall scores during verbal memory testing was one of the strongest predictors of overall psychosocial functioning (Bonnín et al., 2010). Additionally, patients with multi-episode manic histories have been showed to have the worst verbal memory functioning compared to other BD patients (Martínez-Arán et al., 2004). Importantly, relatively consistent memory deficits have been found in euthymic BD. Torres (Torres et al., 2007) recently published a meta-analysis on verbal memory in euthymic BD.

Studies included evaluated patient performance during short-delay memory of words, long-delay memory of words, and recognition of previously learned words. Large effect sizes were found short-delay memory of words (Altshuler et al., 2004, Martínez-Arán et al., 2004, van Gorp et al., 1999), and long-delay memory of words (Thompson, 2005; Altshuler, 2004), but not recognition of words, where effect sizes were medium to small (Thompson, 2005, Fleck et al., 2003).

Verbal memory function is dependent on the encoding, storage, and retrieval of learned words (Andreasen et al., 1995). Studies using fMRI to examine the encoding and retrieval phases of verbal memory in HV showed task related increases in medial temporal lobe (Cabeza and Nyberg, 2000, Lepage et al., 1998), as well as prefrontal, supplementary motor, parietal (Jansen et al., 2009) regions. In a structural MRI study examining the relationship between white matter tract disruptions and verbal memory performance, participants with lesions near the hippocampus, amygdala, and the anterior temporal stem showed reduced verbal memory storage compared to non-lesion controls (Sepulcre et al., 2009), suggesting these tracts are important in the transfer of information about stored memoranda. Finally, in an fMRI study using the California Verbal Learning Task (CVLT), HV showed increased activation in the right DLPFC during delayed word recognition, and increased right anterior hippocampus activation during recognition of novel words (Johnson et al., 2001). This literature illustrates the importance of healthy functioning of the DLPFC and medial temporal lobe structures, including the hippocampus and amygdala, during verbal memory encoding, storage, and retrieval.

Neuroimaging studies in BD suggest that poor performance by during memory tasks is due to abnormal DLPFC and medial temporal lobe functioning compare to healthy control. Specifically,

using PET in euthymic adult BD during a verbal learning task, patients showed decreased ability learning lists of words, and this was associated with decreased DLPFC and hippocampus activity relative to HV (Deckersbach et al., 2006). In an fMRI study where participants memorized lists of words presented visually, euthymic BD adults showed decreased parahippocampal activity during delay periods compared to HV (Lagopoulos and Malhi, 2007). Further, using an N-back memory task in depressed, manic, and euthymic BD patients, patients showed decreased bilateral DLPFC across mood states, relative to controls (Townsend et al., 2010). These data implicate a general pattern of DLPFC and hippocampus hypoactivation in BD compared to controls during tasks requiring the short-term retention of memoranda. Since the DLPFC and hippocampus are important in delayed word recognition and encoding newly learned words (Sepulcre et al., 2009, Johnson et al., 2001), dysfunction of these regions in BD may underlie existing evidence of reduced short and long-delay recall of words during neuropsychological testing, compared to HV (Torres et al., 2007).

These studies show the importance of examining verbal memory function in euthymia. For this reason, we included the California Verbal Learning Test (CVLT) (Delis et al., 1988) to examine verbal learning, short-delayed memory, long-delayed memory, and long-delayed recognition memory functioning. Based on previous results, we expected our patients would be impaired in all of these subtests of the CVLT, and this would be worse in patients with more episodes of mania.

2.1.4 Executive Functioning

Executive functioning (EF) is a catchall phrase to describe any cognitive processes that controls or manages other cognitive processes, such as shifting between tasks or mental states, or the inhibition of dominant, or 'prepotent', response (Miyake et al., 2000). Therefore, EF underlies a range of important cognitive abilities, from flexibly responding to changing environmental stimuli, to response inhibition and decision-making.

Cognitive flexibility is an executive function needed to adapt one's behavior to changing environmental demands, and is important in decision-making, problem solving, and emotion regulation (Kim et al., 2012). This is highly relevant to BD, since patients with BD show difficulty adjusting behavioral responses to changing reward contingencies (Dickstein et al., 2007). Cognitive flexibility deficits have been found in both children (Dickstein et al., 2004, McClure et al., 2005) and adults with BD (Arts et al., 2008). During the change task, young BD patients showed slower response flexibility to changing environmental demands, compared to age-matched controls (McClure et al., 2005). Finally, in adult BD, the Wisconsin Card Sorting task (WCST) has been used to measure cognitive flexibility. In a meta-analysis of WCST results in euthymic BD, there was a large effect size of concept shifting (i.e. WCST perseverative errors) in patients, indicating cognitive flexibility impairments exist in euthymia (Arts et al., 2008).

The intradimensional-extradimensional shift task (ID-ED) is another task that has been used to examine cognitive flexibility in BD. Briefly, the ID-ED has nine stages of stimulus-response matching based on visual discrimination, rule generation, and attention shifting. When using the ID-ED in early-onset BD, patients showed deficits on intradimensional and extradimensional shifts compared to controls (Dickstein et al., 2007). This finding suggested that young BD

patients were impaired in learning what stimulus dimension was rewarded, as well as switching attention to a newly rewarded stimulus dimension. Using this task in euthymic BD adults and unaffected relatives, both groups showed increased errors during the extra-dimensional shift stage compared to controls (Clark et al., 2005). This finding meant patients were impaired at switching their attention from a previously rewarded stimulus dimension to a newly rewarded stimulus dimension, and thus showed perseveration in their attention.

Taken together, both child and adult BD show deficits in switching attention between behaviorally salient cues based on changing reward contingencies. In order to align the attention flexibility of our patient sample to that of Clark (Clark et al., 2005), we included the ID/ED task in our neuropsychological investigation. Based on previous findings, we expected our patients would show increased errors during intradimensional and extradimensional shifts, and increased attempts at extradimensional shifting, compared to controls.

Decision-making is an important executive function that has been shown to be impaired in BD (Adida et al., 2011), and may be related to the increased risk-taking found during acute episodes of the disorder. One way to examine decision-making is by way of the framing task (Chandler et al., 2009). During this task, participants are instructed try and earn points from a ‘stake’ by choosing one of two visually presented dilemmas on each trial. In positively framed trials, participants tried to win some or all of the stake, and in negatively framed dilemmas participants tried avoiding losing some or all of the stake. In the healthy population, people tend to make more risky choices during negatively framed dilemmas than in positively framed dilemmas (Shafir, 1994). Chandler (Chandler et al., 2009) used this task in BD-II, and showed that patients

were less influenced in the number of risky choices they made in response to framing the dilemmas. Specifically, patients compared to HV, made fewer risky choices in the negatively framed dilemmas and took longer to make safe choices in the positively framed dilemmas compared to healthy controls. This means BD patients showed an altered susceptibility to framing, and may be influenced by different psychological variables during decision-making, and this may lead to increased risk-taking. However, no study has investigated whether similar framing effect exists in BD-I as in BD-II patients.

To investigate whether BD-I patients show similar framing effects to BD-II and BD-NOS patients, we used the framing task in the present study. Given evidence of decreased risky choices during negatively-framed dilemmas in BD-II patients, we expected our patients would also show decreased susceptibility to framing by showing decreased risky choices during negatively-framed dilemmas.

Finally, decreased ability to inhibit motor responses is an executive function that has been shown to be impaired in BD, and may be related to the impulsivity that leads drug-taking and suicide in patients (Swann et al., 2004). While impulsivity encompasses a variety of component processes such as cognitive impulsivity and motor impulsivity (Evenden, 1999), a recent meta-analysis suggested that impaired response inhibition (i.e. impaired motor inhibition) was the most consistent finding seen in BD (Bora et al., 2009). Importantly response inhibition is referred to as “the suppression of actions that are inappropriate in a given context”. The ability to exert response inhibition in hypothetical contexts can be measured by using the Barrett Impulsivity Scale (Carver and White, 1994) . Indeed, adult BD patients showed increased self-reported

impulsivity during BIS, and this was associated with response inhibition deficits compared to controls during a motor inhibition task (Swann et al., 2003). A later study showed that increased self-reported impulsivity also exists in BD patients during periods of remission (Ekinici et al., 2011).

Since a previous study in euthymic BD showed elevated BIS scores compared to HV, it is important to include a measure for impulsivity in the present study. Given existing evidence of elevated impulsivity when using the BIS in euthymia (Ekinici et al., 2011, Swann et al., 2003), we expected our sample of patients would also show increased impulsivity during BIS examination.

2.1.5 Emotional Regulation

Emotion regulation refers to the conscious and unconscious appraisal of emotional stimuli, and the strategies we use to increase, maintain, or decrease components of the emotional response (Gross, 2002). Several neuropsychological models have been developed to account for different strategies used during emotion regulation (Ochsner and Gross, 2005). One prominent model proposed by Gross (Gross, 1998) states that emotion regulation is stratified as ‘antecedent-focused’ or ‘response-focus’ strategies. Antecedent-focused strategies refer to things that one does to regulate emotional responses before exposure to emotionally provocative stimuli, such as preparing for a stressful interview. Response-focused strategies for emotion regulation refer to things and individual does once an emotional response is already underway, such as arguing in response to a stressful event.

Affect dysregulation is a core feature of BD diagnosis. Indeed, during a self-report measure of affect, depressed BD patients reported experiencing anhedonia and decreased incentive drive, while manic patients reported experiencing high enjoyment, increased satisfaction, and increased drive (Ahearn et al., 2001). According to Gray (1981), the cognitive underpinning of affect dysregulation is dysfunction of the behavioral inhibition/activation system (BIS/BAS). The BAS is an important motivational system that is responsive to expected reinforcements, and is closely related to positive affect. An overactive BAS is related to increased drive, positive affect, and increased engagement with the environment. The BIS is responsible for stopping appetitive behaviors and reallocation of attention in response to aversive or novel stimuli. An individual with an overactive BIS is more likely to inhibit appetitive responses when confronted with an aversive stimulus in comparison to a person with underactive BIS. According to this model, BD can be characterized as a poorly regulated BAS, being more “perturbed by stimuli of positive and negative valence” than healthy controls. In a study evaluating BIS/BAS in remitted BD-I, patients were shown to have higher scores on the reactivity to non-reward and BIS subscales of the BIS/BAS, compared to healthy volunteers (Wright et al., 2008). Further, results indicated that, history of mania in remitted patients related to slower recovery after behavioral engagement with rewards, while history of mania and depression in patients related to slower recovery following frustration.

This data reviewed here indicate that differences in the motivational system of patients may be important in affective responses to rewarding and frustrating events, even in euthymia. For this reason, we have included the BIS/BAS measure in this investigation. Based on existing evidence

of BAS/BIS abnormalities in remitted patients, we expected our patients would show increased BAS scores relative to HV.

Elevated affective intensity in BD predisposes patients to a state of persistent emotional arousal and susceptibility to overly reactive emotional responses to provocative stimuli. This increased affective intensity may predispose patients to acute relapse (Henry et al., 2008). The Affective Intensity/Lability Scales (AIS/ALS) are self-report measures that have been used to measure affective intensity (i.e. intensity at which one experiences emotional responses) and affective lability (i.e. the rate in which patients shift between emotional states). According to Larsen (Larsen et al., 1987), all things being equal, the magnitude of an emotional response should be strongly related to the magnitude of the emotional stimulus.

Early-onset BD patients have been shown to be more responsive to both positive and negative emotional stimuli than age-matched controls (Leibenluft et al., 2003a). A previous study in adult, euthymic BD patients using the AIS and ALS scales indicated that affective intensity, as well as the rate at which affective states change (i.e. affective lability), are higher in euthymic BD patients compared to healthy volunteers (Henry et al., 2008). Further, age of onset of BD was highly correlated with ALS scores, suggesting earlier-onset BD patients show higher affective lability compared to later-onset BD. Taken together, affect intensity and affective lability is higher in euthymic BD patients, and may be related to acute relapse.

In order to extend the existing literature on increased affective intensity and reactivity in euthymic BD, we included the AIS/ALS measures in the present study. Based on the

investigations presented above, we expected our patients would show increased positive and negative affective intensity and reactivity compared to HV.

The positive and negative affect scale (PANAS (-S: State; -T: Trait)) is another important measure that assesses the two primary dimensions of positive and negative affect (Watson et al., 1988). In a study in remitted BD patients using the PANAS, mean positive and negative affect scores were not different from healthy controls over the span of the study week (Knowles et al., 2007). However, BD patients showed significantly more positive and negative affect fluctuation, compared to controls, over the study period. This indicated that euthymic BD may be associated with more frequent mood fluctuations, detected on self-report affective scales, even during periods of remission. In a study that included persons at risk for developing BD, according to the hypomanic personality scale (Eckblad and Chapman, 1986), persons with high levels of manic symptoms reported increased positive and negative affect during PANAS, compared to controls (Hofmann and Meyer, 2006). The authors concluded that the increased affective responding, reported during PANAS in at-risk populations, was representative of vulnerability to BD.

In order to examine whether positive and negative affective intensity is elevated in our patient group, we examined trait (i.e. past 6 months) and state (i.e. current) positive and negative affect using the PANAS-S and PANAS-T. Based on the studies reviewed above, we expected that PANAS-S scores would be similar in euthymic BD and controls, but PANAS-T scores would differ from HV due to increased fluctuating mood in the previous 6 months.

Functional imaging studies have highlighted the importance of prefrontal-limbic activation during emotion regulation. For example, numerous fMRI studies have shown that the amygdala is important in generating and experiencing negative emotions (Phillips et al., 2001, Phan et al., 2005, Phan et al., 2002, Zald, 2003), while positive emotional experiences has been associated with nucleus accumbens (Knutson et al., 2008, Meseguer et al., 2007) and medial OFC (Berridge and Kringelbach, 2008) activation . Prefrontal cortex activation, on the other hand, has been implicated in the *regulation* of both positive and negative emotional experiences. Specifically, increased ACC (Beauregard et al., 2006) and lateral PFC (Ochsner and Gross, 2005) has been shown to modulate amygdala activation when processing negative emotions, while increased VLPFC activation has been shown to modulate positive emotions (Cooney et al., 2007).

Several recent fMRI studies have shown dysfunctional prefrontal-limbic activation during emotion processing and regulation in BD. For example, in a study investigating emotional face labeling deficits in child BD, patients showed increased activation of the amygdala, VMPFC, and DLPFC when viewing happy faces, and decreased DLPFC activity when viewing fearful faces, in comparison to age-matched controls (Ladouceur et al., 2011). Abnormal brain activation has also been found in adult BD during emotional processing. For example, a meta-analysis of emotion processing tasks revealed a general pattern of increased amygdala activation when responding to both positive and negative affective stimuli in adult BD compared to HV, and amygdala dysregulation persisted in euthymia (Houenou et al., 2011). Finally, during an emotional go/no-go task in euthymic BD versus HV, adult patients were shown to have increased OFC, insula, caudate, and cingulate cortex activation when inhibiting responses to fearful and happy faces in comparison to neutral faces (Roiser et al., 2009). These studies suggest that

existing evidence of impaired emotion regulation in BD may be due abnormal functioning in prefrontal regions important in emotion regulation, such as the ACC, and subcortical regions important in processing positive and negative emotional stimuli, such as the amygdala and nucleus accumbens.

Taken together, these studies demonstrate that sustained attention, verbal memory, executive functioning, and emotional regulation impairments in euthymic BD. Additionally, these may be related to decreased psychosocial functioning in recovered patients, and predispose patients to relapse. Here, we used tests to evaluate sustained attention, verbal memory, executive functioning, and emotional regulation to align the cognitive functioning of our sample with that of previous neuropsychological examinations in euthymic BD. Based on previous results (Torres et al., 2007, Robinson et al., 2006), we expected patients will show deficits in sustained attention, verbal memory, executive functioning, and emotion regulation compared to HV.

2.2 Methods

2.2.1 Subjects

This study was approved by the Oxfordshire Psychiatric Research Ethics Committee. Patients provided informed consent prior to diagnostic interview on study day 1.

Patients (N = 24) with bipolar disorder were recruited from outpatient services at the Warneford Hospital, Oxford per referral of consultant psychiatrist. Patients who were referred were

informally described by the consultant psychiatrist as meeting criteria for euthymia prior to participation in the study. Healthy volunteers (N=21) were recruited by way of advertisement in the community and had no lifetime history of psychiatric diagnosis, or first-degree relatives with psychiatric illness. Exclusion criteria for both patients and healthy controls were: IQ < 80, major medical illness, neurological damage/disorder, claustrophobia, or medical history that would preclude a person's ability to enter an MRI scanner. All participants were aged 18-65.

All interviews were completed by the thesis author (JW). On the first study day, patients were assessed using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) and the Young Mania Rating Scale (YMRS) (Young et al., 1978). HAM-D responses were assessed at both the time of neuropsychological testing and on the day of neuroimaging. A patient met criteria for 'euthymia' if they (1) currently denied depressive or manic symptoms (cutoff score of 8 on both the HAM-D and YMRS) and (2) demonstrated an absence of these symptoms for at least 8 weeks prior to the study. Inclusion criteria for patients was a diagnosis of bipolar disorder (BD) type 1 according to DSM-IV-TR criteria. One patient (1/24) was excluded because of endorsing current symptoms of mania. Seven (7/23) patients endorsed a remote history of substance abuse (1/23 cocaine; 6/23 marijuana), but did not meet criteria for previous history substance abuse disorder.

All patients were on medication at the time of testing. Nineteen (19/23) patients were receiving anti-epileptic drugs, twelve (12/23) were receiving anti-psychotic drugs, two (2/23) were receiving anti-depressant drugs, and nine (9/23) were receiving lithium. However, sixteen patients (16/23) were receiving more than one medication type.

2.2.2 Procedure

The study lasted for two days, with each study day separated by no more than two weeks. The first study day will be discussed in this chapter. The second study day, which consisted of a one-hour session of neuroimaging, is discussed in chapter 2.

Study day 1 lasted for approximately 2 hours and consisted of initial diagnostic screening using the MINI, mood measurements using the HAM-D and YMRS, and neuropsychological testing using the following battery of instruments:

- 1) **I.Q:** Weschler Abbreviated Intelligence Scale (WAIS) (matrix reasoning and vocabulary subscales) (Wechsler, 1955).

- 2) **Verbal memory:** California Verbal Learning Test (CVLT) (Delis et al., 1988):

The CVLT consists of two lists (lists A & B) of 16 words, each composed of four different word categories (e.g. tools, fruits, etc). Words from each list are read aloud in a pseudo-randomized order. List A is presented five times, followed by a single presentation of list B to induce interference for short and delayed recall of list A.

After each list presentation, participants are asked to repeat the words they remember from the list. For list A, number of correctly recalled words is summed across the five presentations (Trials 1-5 ('words recalled')). Following the presentation of list B, participants are asked to recall words from list A ('short delay free recall'). Twenty minutes after the short delay free recall, participants are again asked to recall words

from list A ('long delay free recall'). Finally, participants are read a list of words out loud, and asked to indicate which words they recognized from list A ('Recognition').

- 3) **Emotion regulation:** Affective Lability Scale (ALS; (Harvey et al., 1989)) and Affective Intensity Scale (AIS; (Larsen et al., 1987)):

The ALS is a self-report scale used to assess changes in affect. Participants rate the descriptive accuracy, using a four-point scale ('1' = very undescriptive; '4' = very descriptive), of comments that describe changes between anxious and depressed moods (Affective Lability: Anxiety/Depression), depressed and elated moods (Affective Lability: Depression/Elation), and normal ('euthymic) and anxious moods.

The AIS is a self-report scale used to assess individual differences in the intensity of responses to emotion-provoking stimuli. Based on responses to this six-point scale ('1' = strongly disagree; '6' = strongly agree), a measure of (1) response intensity to positive stimuli ('Positive Affective Intensity'), (2) response intensity to negative stimuli ('Negative Affective Intensity'), (3) reactivity to positive stimuli ('Positive Affective Reactivity'), and (4) reactivity to negative stimuli ('Negative Affective Reactivity') is calculated for each participant.

- 4) **Emotion regulation/reward responsiveness:** Behavioural Inhibition/Activation Scales (BIS/BAS) (Carver and White, 1994):

The BIS/BAS is a self-report measure composed of 20 items with four-point scales ('1' = strongly disagree; '4' = strongly agree) to measure individual sensitivity levels of the behavioral activation system and behavioral inhibition system. Responses to seven of these items are summed for the BIS score ('BAS: Behavioral Inhibition'), five items for reward responsiveness ('BAS: Reward Responsiveness'), four items for drive ('BAS: Drive'), and four for fun-seeking ('BAS: Fun Seeking').

- 5) **Executive functioning-Impulsivity:** Barrett Impulsivity Scale (BIS) (Patton et al., 1995):

This 44-item self-report scale is composed of comments describing instances of inattention, cognitive instability, motor impulsivity, lack of perseverance, lack of self-control, and intolerance of cognitive complexity. Participants were asked to think of how they would typically respond in these situations, and rate comments as true or false. For the purpose of this study, composite scores for each individual was calculated as the number of 'true' responses made during the BIS.

- 6) **Emotion regulation:** Positive Affect Negative Affect Scales (PANAS) (Watson et al., 1988):

The PANAS is a brief measure of mood state. PANAS-state (PANAS-S) is used to measure current affect, PANAS-trait (PANAS-T) is used to measure affect over the past 3-month period. Both measures are composed of 10 adjectives describing

positive emotional states (e.g. enthusiastic, alert, active), and 10 adjective describing negative emotional states (e.g. distressed, upset, guilty). Participants are asked to rate how descriptive each adjective is, based on a five-point scale ('1' = very slightly or not at all; '5' = extremely), to their current mood (PANAS-S) and mood over the past 3 months (PANAS-T). The 'PANAS Trait: Positive Affect' score is the summed score of responses to positive adjectives in the PANAS-T, the 'PANAS Trait: Negative Affect' score is the summed score of responses to negative adjectives in the PANAS-T. PANAS State scores are calculated similarly.

7) Executive Functioning-Cognitive flexibility/attention-shifting:

Intradimensional/Extradimensional Set Shift Task (ID-ED) (CANTAB; (Robbins et al., 1994)):

This task measures a person's ability to pay attention to specific attributes about compound stimuli, and shift attention between these attributes based on reinforcement history. Specifically, participants are instructed to make responses to a touch screen where various visual stimuli are presented simultaneously. The stimuli consist of shapes and fractals of various colors. Participants are instructed to touch the stimuli they think is 'correct'. In order to learn which stimulus to respond to, subjects are given feedback from the computer after each response. In this way subjects can learn rules based on the appearance of the stimulus to sort out which stimulus is the correct stimulus on each go. A persons' tendency to perseverate in responses can be measured by the number of responses they continue to make to the previously

rewarded stimulus. The complexity at which these visual stimuli represent correct responses gradually increases through the duration of the game. The dependent measures in the task are (1) total number of errors during the task (2) total number of errors during reversal stages (3) total number of attempts at extradimensional shift, and (4) total number of errors during extradimensional shift.

- 8) **Sustained attention:** Rapid Visual Information Processing Task (RVIP) (CANTAB; (Robbins et al., 1994)):

The RVIP is a continuous performance task (CPT) that measures a person's sustained attention and motor control. Participants are asked to concentrate on detecting signals (a string of 3 numbers) that are visually presented intermittently between sequences of distracting signals (strings of randomized numbers, strings of numbers where the first digit in a sequence matches target signals, and strings of numbers where the first two digits in a sequence match a target sequence). Subjects are instructed to attend to the sequence of numbers presented on the computer screen and response with a button press whenever they see a target sequence appears. Dependent measures on this task are the number of targets detected correctly with a button response (hits), latency ('Response Latency') to make these responses, and false alarms (i.e. making inappropriate button responses). Calculations based on signal detection theory (McNicol, 2005, Sahgal, 1987) are used to compute a target sensitivity ('Target Detection %') and response bias (Response Bias (β)) scores. (N.B. β measures the

tendency to respond to a stimulus regardless of whether it is a target, or not. Higher β reflects making fewer false alarms).

9) **Executive functioning-Decision-making:** Framing Task (Chandler et al., 2009):

The framing task is a computerized decision-making task that measures risk-taking behavior when changing the saliency of gain and loss outcome information within a dilemma. Dilemmas were composed of two gambles to secure all, or some portion, of a monetary reward (i.e. 'stake'). Importantly, the two gambles of each dilemma had the same expected value. During positively framed dilemmas, participants made decisions in order to win all or some of the stake. During negatively framed dilemmas, participants made decisions in order to avoid losing all or some of the stake. Each dilemma contained a safe and risky option. The safe option could have a high probability (e.g. $p = 1.00$ or $p = 0.90$) of winning (or losing) some of the stake. The risky option could have lower probabilities (e.g. $p = 0.33$ or $p = 0.67$) of winning (or losing) some of the stake. Participants were presented with 16 positively-framed dilemmas and 16 negatively-framed dilemmas, in a random order. The dependent measures for this task were (1) proportion of risky choices in response to positively compared to negatively-framed dilemmas, and (2) mean reaction time for safe and risky decisions during these frame conditions.

All tasks were administered in this order for each subject individually. A 15-minute break was given to each participant between the PANASS/PANAST. Because the delayed free-recall

section of the CVLT required a twenty-minute delay, participants were asked to complete the ALS/AIS during this period of twenty minutes. Upon conclusion of this study, participants were debriefed and scheduled for a neuroimaging scan (Study day 2).

2.3 Statistical Analysis

Most dependent measures collected from self-report measures, age, intelligence, and neuropsychological tasks listed above conformed to a normal distribution (Kolmogorov-Smirnov test $p > .05$), and were therefore tested using independent-samples t-tests. ID-ED measures were not normally distributed and were therefore analyzed using Mann-Whitney U tests. To test the effect of clinical course on neuropsychological performance, partial correlations controlling for number of medication, duration of illness, number of manic episodes, number of depressive episodes, and current depressive symptoms was performed on key neuropsychological measures (Keppel and Zedeck, 1989). With a sample size of 20 per group, this design has a power of .70 to detect an effect size of approximately 1.0 with an alpha of 0.05.

Target sensitivity during the RVIP can decrease over time (Clark et al., 2002). Therefore, in order to assess whether patients versus healthy volunteers showed a different decrement in target sensitivity (i.e. vigilance decrement) a repeated-measures ANOVA was performed the target detection scores of patients versus controls, with a within-subject factor of time (7 levels representing each minute block of the task) and a single between-subject factor of diagnosis (HV versus BD).

2.4 Results

2.4.1 Group characteristics

Group characteristics for patients and healthy volunteers are depicted in Table 2.1. Groups were matched for I.Q., gender and age. Note subsyndromal mood symptoms, especially depressive, in patients.

Table 2.1. Characteristics of euthymic bipolar patients and healthy volunteers

Characteristic	Healthy Volunteers (N=21)	Bipolar (N=23)
	Mean (S.D.)	Mean ($\pm$ S.D.)
Age	43.96 $\pm$ 10.56	40.67 $\pm$ 8.00
WAIS Full-scale IQ ^a	111.62 $\pm$ 10.68	110.32 $\pm$ 10.11
YMRS ^b		.25 $\pm$ 0.57
HAMD-S ^{c,a}		7.43 $\pm$ 4.77
HAMD-N		6.96 $\pm$ 4.85
Number of medications ^d		1.91 (range=1-3)
Duration of Illness ^{a,e}		22.13 (range=4-45)
Manic Episodes ^a		9.04 (range=1-30)
Depressive Episodes ^a		7.69 (range=2-17)
	N (%)	N (%)
Male	14 (56)	11 (47.8)
Atypical Antipsychotic		12 (50.0)
Lithium		9 (37.5)
Antiepileptic		19 (79.2)
Antidepressant		2 (8.3)

^aMissing data from 1 bipolar patient

^bYoung Mania Rating Score

^cHamilton Rating Scale for Depression (*-S (at time of Scan), *-N (at time of neuropsychological testing))

^dMissing data from 2 bipolar patients

^e years

2.4.2 Neuropsychological performance

Outcomes of self-reports are displayed in Table 2.2. Patients differed from healthy volunteers on every measure except positive affective reactivity ($p = .527$), affective lability (anger) ($p = .213$),

PANASS positive affect ($p = .242$), BAS reward ($p = .743$), drive ($p = .268$), and fun-seeking ($p = .823$), and BIS ($p = .692$).

Table 2.2. Self-report measures of affective intensity, lability, positive and negative affect, impulsivity, and behavioral activation

Variable	Controls (S.D.) N=21	Bipolar (S.D.) N=23	Group Comparison df(1,42)
Positive Affective Intensity ^a	21.38 (5.2)	27.35 (7.2)	$t=3.12, p<..003$
Negative Affective Intensity	17.62 (5.0)	24.70 (6.2)	$t=4.18, p< .000$
Positive Affective Reactivity	30.81 (6.3)	32.22 (8.1)	$t=0.64, p = .527$
Negative Affective Reactivity	20.05 (4.2)	22.96 (4.0)	$t=2.34, p<.023$
Affective Lability: Anxiety/Depression ^b	7.05 (2.6)	11.04 (4.3)	$t=3.70, p<.001$
Affective Lability: Depression/Elation	12.90 (4.0)	16.35 (6.6)	$t=2.05, p<.047$
Affective Lability: Anger	6.23 (2.1)	7.52 (4.0)	$t=1.23, p=.213$
PANAS_Trait: Positive Affect	32.38 (6.6)	29.09 (8.3)	$t=1.45, p<.002$
PANAS_Trait: Negative Affect	15.00 (4.6)	21.13 (9.3)	$t=2.73, p<.009$
PANAS_State: Positive Affect	31.43 (7.8)	28.73 (7.3)	$t=1.19, p=.242$
PANAS_State: Negative Affect	11.33 (2.8)	14.95 (7.6)	$t=2.06, p<.046$
BAS: Reward Responsiveness ^c	14.81 (2.1)	15.04 (2.6)	$t=0.33, p=.743$
BAS: Drive	9.62 (2.2)	8.74 (2.9)	$t=1.12, p=.268$
BAS: Fun Seeking	10.33 (2.1)	10.18 (2.5)	$t=0.23, p=.823$
BAS: Behavioral Inhibition	17.71 (2.6)	20.35 (2.2)	$t=3.58, p<.001$
Barrett Impulsivity Scale	20.29 (4.3)	21.00 (6.9)	$t=0.40, p=.692$

Dependent measures from neuropsychological tasks are displayed in Table 2.3. Graphical depiction of performance on RVIP, ID-ED, and framing tasks are shown in Figures 2.1-2.4. Significant differences emerged between patients and controls during neuropsychological testing, with patients showing impairments in sustained attention, cognitive flexibility, and verbal memory, compared to HV. Specifically, patients showed decreased target detection ($p < .002$), a decreased response bias ($p < .005$), and increased response latency ($p < .025$), during the RVIP relative to HV (Figure 2.1). The decrement for vigilance was seen under conditions of practice and test demands: so equally present under low or high target complexity equally. Also, during the CVLT, patients showed reduced short delay free recall ($p < .015$) and decreased delayed

recognition ($p < .038$), relative to HV. During the ID-ED task, patients showed increased total errors on the ID-ED ($p < .020$) (Figure 2.2), and increased number of attempts at extradimensional shift ($p < .004$) compared to HV (Figure 2.2 B). Finally, while there was no difference in susceptibility to framing in decision-making measured during the framing task between patients and controls (Figure 2.3), patients did show increased mean deliberation times during positively-framed safe ($p < .006$) and risky ($p < .001$) decision-making, and during negatively-framed safe ($p < .045$) and risky ($p < .002$) decision-making (Figure 2.4)

Table 2.3. Neuropsychological performance on attention, verbal learning, and memory tasks

Variable	Controls (S.D.)	Bipolar (S.D.)	Group Comparison
<i>RVIP</i> ^a			
Target Detection %	87.1 (5.8)	77.0 (9.0)	$t=3.47, p<.002$
Response Bias (β) ^b	0.9 (0.1)	0.8 (0.1)	$t=3.81, p<.005$
Response Latency (msec)	430.9 (105.2)	513.1 (50.9)	$t=2.39, p<.025$
<i>ID/ED Shift</i> ^c			
Total Errors	10.4 (7.2)	16.4 (11.5)	$z= 2.32, p<.020$
Errors at Reversal	4.1 (3.0)	2.8 (1.7)	$z= 1.16, p=.242$
Attempts at EDS	11.1 (2.1)	16.7 (5.7)	$z=2.88, p<.004$
Errors at EDS	3.1 (5.4)	6.6 (11.0)	$z= 0.02, p=.982$
<i>CVLT</i> ^d			
Trials 1-5(words recalled)	57.1 (10.1)	54.3 (11.4)	$t=0.82, p=.420$
Short Delay Free Recall	13.5 (1.4)	11.6 (2.9)	$t=2.54, p<.015$
Long Delay Free Recall	12.8 (1.6)	12.1 (3.1)	$t=0.81, p=.421$
Recognition	15.9 (0.3)	15.3 (1.0)	$t=2.15, p=.038$

^a Missing data from 6 healthy volunteers and 11 bipolar patients. Degrees of freedom = 25.

^b Response bias calculated by: $\beta=y(1-y)-x(1-x)/y(1-y)+x(1-x)$, where x = the probability of false alarm (number of false alarm/number of correct rejections).

^c Missing data from 7 healthy volunteers and 5 bipolar patients. Degrees of freedom = 30.

^d Missing data from 3 controls. Degrees of freedom = 39.

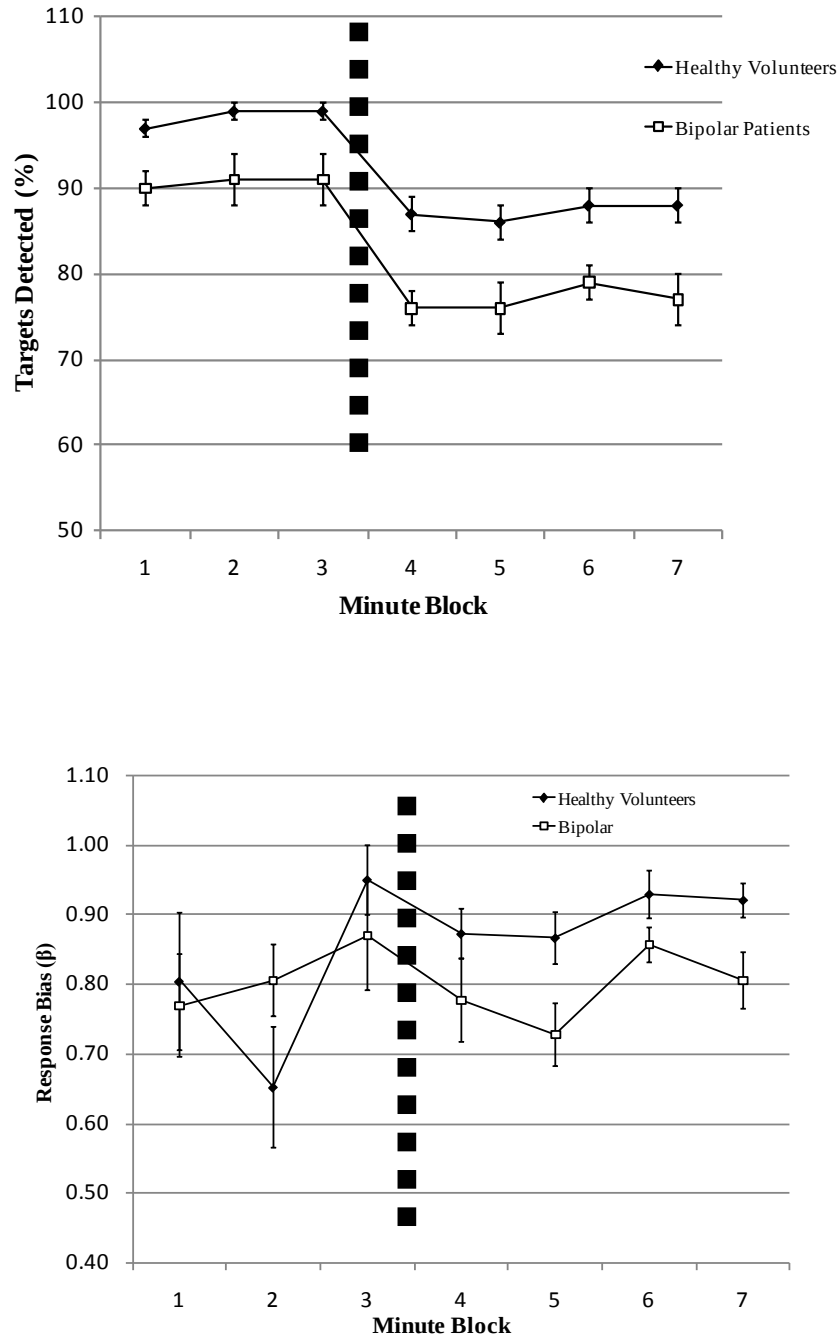


Figure 2.1 Target detection (A) and response bias (B) versus minute block in RVIP task. Vertical dashed line (- - -) demarcates the change from practice blocks (minutes 1-3) to test blocks (minutes 4-7). During practice blocks persons needed to detect 1 target sequence. During test blocks persons needed to detect 4 target sequences. (A) Percent targets detected. (B) Response bias. Open symbols BD, closed symbols controls.

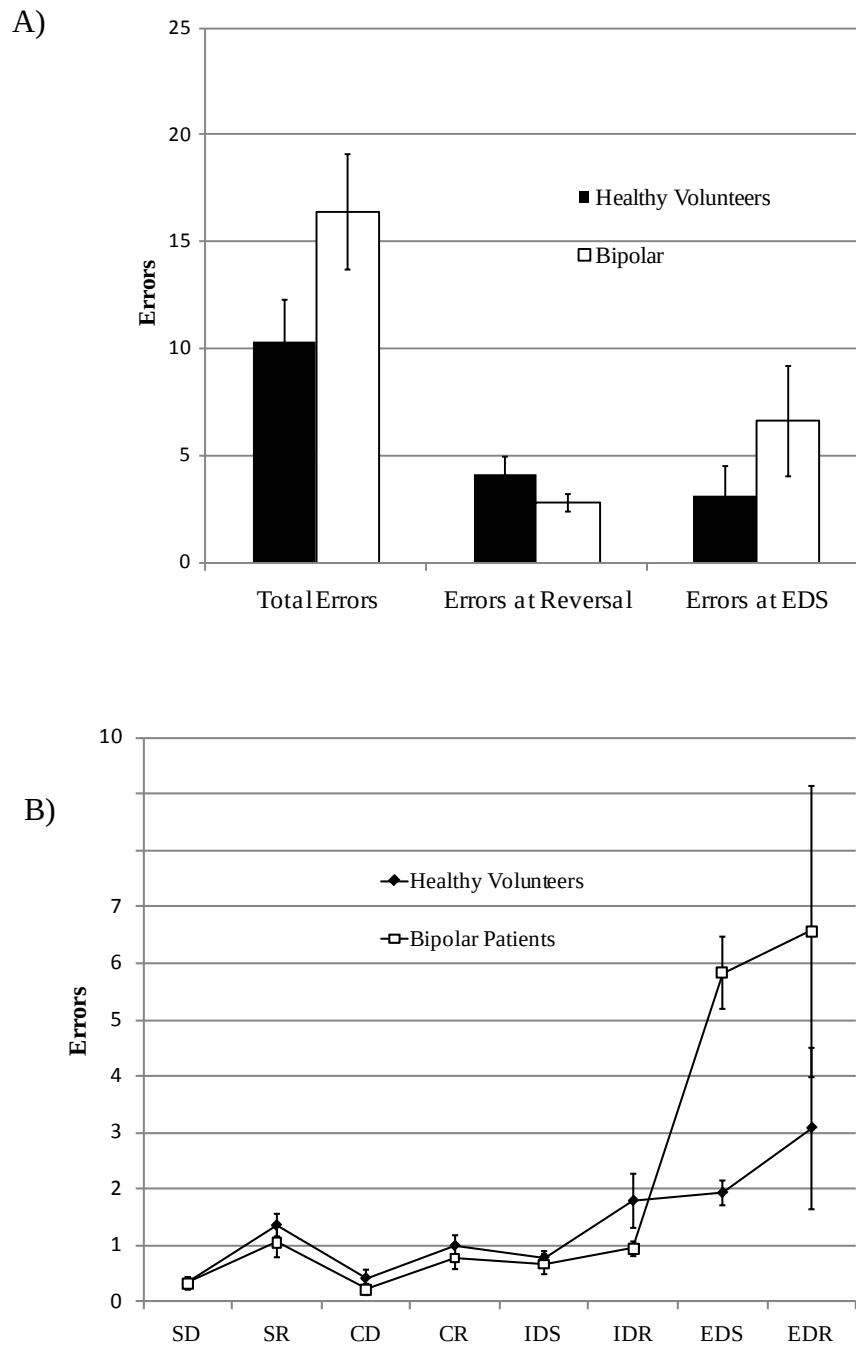


Figure 2.2 ID-ED performance. (A) Total errors, errors during reversal, and error at extradimensional shift. (B). Errors at each stage of ID-ED. SD=simple discrimination, SR=simple reversal, CD=compound discrimination, CR=compound reversal, IDS=intradimensional-shift, IDR= intradimensional-reversal, EDS=extradimensional-shift, EDR=extradimensional reversal.

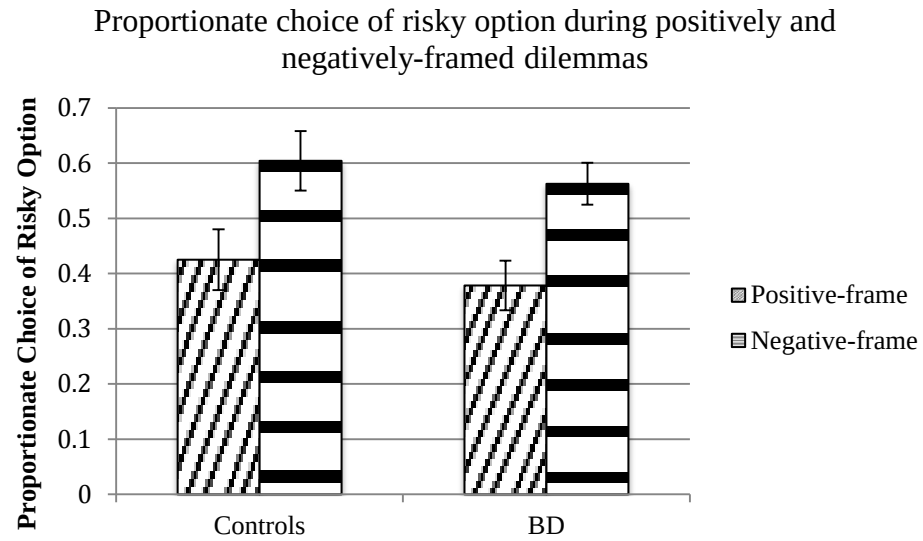


Figure 2.3. Proportionate choice of risky option during positively and negatively-framed dilemmas. BD = Bipolar Disorder.

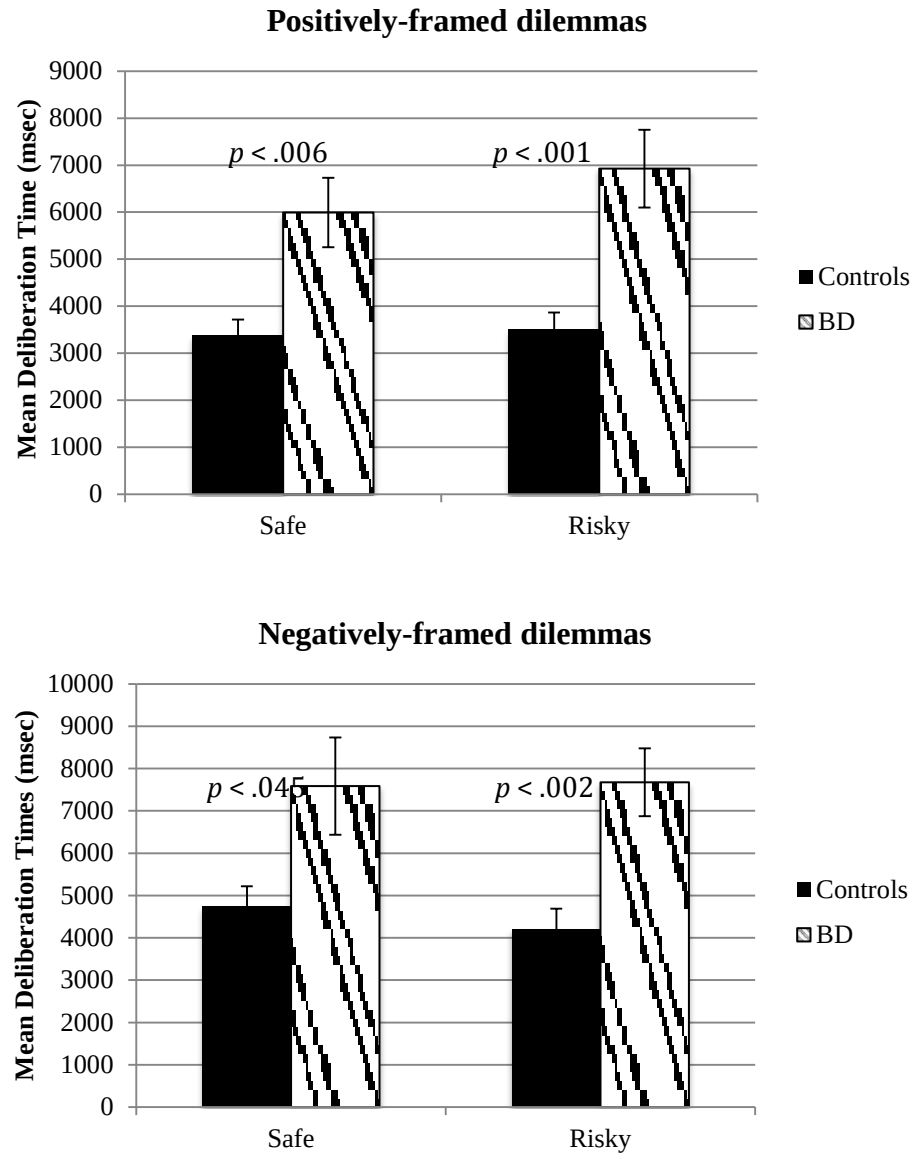


Figure 2.4 Framing task performance. Mean deliberation time (seconds) during safe and risky decision in positively and negatively-framed dilemmas. Data missing from 6 healthy volunteers and 5 bipolar patients.

2.4.3 Effect of clinical variables on neuropsychological performance

In attempt to quantify the effect of clinical course on neuropsychological performance, partial correlation analysis was performed on total number of words recalled on CVLT, number of

attempts at all ID-ED reversals, number of attempts at extradimensional shift on ID-ED, mean RVIP accuracy, and number of risky decisions made during positive and negatively framed dilemmas during the framing task. Partial correlations, controlling for age, are represented in Table 2.4. While most tests appeared to be unaffected by clinical course in BD, there was a highly significant negative correlation between number of medications and number of attempts at extradimensional shift on the ID-ED (*partial correlation* = $-.61$, $p < .01$). Importantly, neither verbal learning nor RVIP accuracy was affected by number of medications, duration of illness, number of manic episodes, number depressive episodes, or current depressive symptoms.

Table 2.4. Partial correlations of neuropsychological measures against clinical variables, controlling for age. Total number of medications is negatively correlated with attempts at extradimensional shift.

	CVLT Total Words	ID-ED Reversal	ID-ED: ED Shift	RVIP Accuracy	RVIP (β)
Number medications	-.10	-.13	-.61**	-.17	-.32
Duration Illness	.06	-.29	.09	.06	.15
Number manic episodes	.05	-.24	.08	.22	.50
Number depressive episodes	.04	-.32	.12	.29	.30
HAM-D (Neuro)	-.09	-.31	-.29	-.09	-.45

2.5 Discussion

During the RVIP sustained attention task, our patients showed decreased signal detection, decreased response bias, and increased response latency in comparison to HV. During the CVLT verbal memory test, patients showed decreased short-delay free recall and delayed recognition.

Sustained attention and verbal memory deficits were unrelated to the number of manic or depressive episodes in this patient group (Table 2.4), in contrast with previous reports that verbal memory and sustained attention impairments are worse in patients with more episodes of mania ((Martínez-Arán et al., 2004, Clark and Goodwin, 2004). During the ID-ED, which examines cognitive flexibility, patients showed increased total errors across all blocks of the task, and increased number of attempts to extradimensional shift, compared to HV. Finally, when using self-report measures of affective intensity and reactivity, patients showed increased responsiveness to both positive and negative emotional stimuli, and a decreased threshold of switching between ‘normal’ (i.e. euthymic) mood and anxiety, and depressed mood and elation, compared to HV. The present study therefore showed that our patients were broadly aligned in verbal memory, sustained attention, and cognitive flexibility impairments to euthymic BD patients reported in previous studies ((Bora et al., 2009, Torres et al., 2007, Robinson et al., 2006), and adds to a growing literature that important neuropsychological deficits persist in remission.

2.5.1 Sustained attention deficits during RVIP

Impairments in sustained attention in BD have been associated with poor functioning, during work and school in particular, because the activities require lengthy attention spans (Godard et al., 2011, Fleck et al., 2012). Here, we found that euthymic BD patients had decreased target accuracy, a decrease response bias, and increased response latency, during the RVIP task compared to HV (Table 2.3; Figure 2.1). Decreased target accuracy in BD means detection of fewer target sequences embedded in distracter sequences. Decreased response bias in BD

indicated that patients were less conservative than controls in making responses, so BD were more likely to make responses to all sequences, regardless of whether they were target or distracter sequences. Finally, increased response latency in BD compared to controls suggests they experienced increased response conflict when target sequences were presented.

Decreased sustained attention has been shown in manic (Bora et al., 2009) and depressed (Brooks et al., 2010) BD patients. Two recent meta-analyses in euthymic patients revealed medium to large effect sizes in sustained attention (Torres et al., 2007, Robinson et al., 2006), indicating this impairment persists in recovery. In those studies, patients showed slower responses to targets, and increased errors at detecting targets. Therefore, the present findings in sustained attention in BD are similar those found in previous meta-analyses. This indicates that the sustained attention functioning of our patients was similar to that of previous studies in euthymic BD.

Performance during a CPT is reliant on healthy functioning of the ACC for performance monitoring, motor selection, and error detection (Chevrier et al., 2007, Botvinick et al., 2004), the VLPFC for motor inhibition (Aron et al., 2003), and the DLPFC for detecting familiar stimuli and cognitive control (Yamasaki et al., 2002, Fleck et al., 2012, Tana et al., 2010). Importantly, these regions have been shown to be dysfunctional in acute and remitted BD during sustained attention. For example, in PET study of depressed BD patients, PFC metabolic activity correlated to impaired CPT performance in patients (Brooks et al., 2010). Specifically, slower hit rate during sustained attention was associated with decreased subgenual PFC activity (encompassing the ACC), while increased commission errors was associated with decreased DLPFC activity in

patients. Using a CPT during fMRI in manic patients, presence of distracters was associated with decreased bilateral VLPFC activity in patients relative to controls (Strakowski et al., 2008). Finally, in an fMRI study examining euthymic, unmedicated BD performance during the CPT-Identical Pairs task, patients showed increased VLPFC activation relative to controls (Strakowski et al., 2004). The difference in VLPFC activation (hypo- versus hyper-) during CPT performance between euthymic and manic BD patients may be related to mood state, or the fact that different versions of CPT tasks used in these studies. Nevertheless, these studies indicate that a PFC network, encompassing the ACC, VLPFC, and DLPFC is dysfunctional across mood states in BD, and may underlie the decreased sustained attention we find here.

Since decreased sustained attention exists in both recovered BD patients and their unaffected relatives (Bora et al., 2009), this impairment may be transmitted genetically. This means decreased target accuracy, response bias, and increased response latency during CPT may be a useful marker for the inheritance of BD. Future cross-sectional studies examining euthymic BD patients, their unaffected relatives, and healthy controls could help reveal whether sustained attention deficits are inherited.

2.5.2 Verbal memory deficits during CVLT

Memory impairments are important in BD, since patients with decreased memory functioning may show difficulties remembering to complete important daily tasks, their work responsibilities, or comply with daily medicine schedule. Here, we found that BD patients had decreased short-delayed verbal memory, and decreased recognition of words at long-delay (20 minutes),

compared to HV (Table 2.3). The finding of decreased short-delayed recall of words in BD means patients have diminished ability in retention of learned verbal material over short intervals, compared to controls. Decrease word recognition at long delay in BD indicates patients were more susceptible than controls to forgetting learned words, or more susceptible than controls to memory interference.

Verbal memory deficits have been shown in manic (Fleck et al., 2003, Clark et al., 2002), and depressed patients (Wolfe et al., 1987). In a meta-analysis, examination of verbal memory impairment during CVLT in euthymic BD revealed an effect size of $d = .81$ for verbal learning, $d = .74$ for short-delay recall, $d = .72$ for long-delay recall, and $d = .43$ for word recognition (Torres et al., 2007). This means the present study extends existing evidence of short-delay free recall and word recognition deficits in recovered BD, but failed to replicate long-delay recall and verbal learning findings. Importantly, however, three of our control patients did not complete CVLT, potentially limiting our ability to detect differences in long-delay recall or learning in the present study. Nevertheless, our verbal memory deficit findings are in partial accordance with previous studies examining verbal memory in recovered BD.

Few studies have used the CVLT during neuroimaging in healthy volunteers, so the brain functioning underlying performance during this task is poorly understood. In an investigation using the CVLT during fMRI in healthy participants, subjects showed increased activation in the right DLPFC during delayed word recognition, and increased right anterior hippocampus activation during recognition of novel words (Johnson et al., 2001). No investigation has used fMRI during CVLT in BD patients. However, in a PET study in euthymic BD using a verbal

learning task related to the CVLT, patients had increased difficulty learning lists of words, compared to HV, and this was associated with decreased DLPFC and hippocampus blood flow (Deckersbach et al., 2006). The N-back task is another measure related to the CVLT that has been used to examine memory in BD. Briefly, participants are instructed to make a button press when they recognize a stimulus shown 'N-back' (N = predetermined number) stimuli before. While this task doesn't require participants to remember stimuli for much longer than 10 seconds, it does engage brain regions important in retaining recent events in memory. Using this task in depressed, manic, and euthymic BD patients, patients, across mood states, showed decreased bilateral DLPFC relative to controls. This means DLPFC hypoactivation in BD, across mood states, may be important during tasks that require maintenance of recent events in memory, similar to the CVLT.

Here, we extend existing evidence that short-delayed recall deficits are important in euthymic BD cognitive functioning. Since this verbal memory deficit is found across mood states in BD, as well as in unaffected relatives (Bora et al., 2009), this too may be an inherited impairment and thus a useful diagnostic marker for BD.

2.5.3 Executive functioning deficits during ID-ED, BIS-measured impulsivity, and the framing task

Executive functioning is pertinent to BD, since impairments in motor inhibition, cognitive flexibility, and decision-making can lead to symptoms of increased impulsivity, increased perseveration/decreased attention flexibility, and increased risk-taking, respectively, in patients.

Here, we used the BIS scale to measure impulsivity, ID-ED to measure cognitive flexibility, and the framing task to measure decision-making in the context of framed dilemmas. Each of these measures of executive functioning will be discussed separately.

2.5.3.1 ID-ED deficits in cognitive/attention flexibility

Patients made more total errors summed across all stages of the task, and more attempts at extradimensional shift, than controls (Figure 2.4). While patients showed increased errors during intradimensional-reversal stage compared to HV, this stage does not measure cognitive flexibility per-se since participants are responding to the same rule (i.e ‘set’) as the previous trials. Nevertheless, the finding of increased attempts at extradimensional-shift in BD, relative to controls, indicates patients had diminished cognitive flexibility required to shift their attention to the new, behaviorally salient attributes of the visual stimuli. As would be expected, patients were no different from controls in the number of stages completed during the ID-ED task.

This extradimensional-shift finding extends results from a previous study using the ID-ED in euthymic BD patients and their unaffected relatives (Clark et al., 2005). In that study, both patients and relatives showed increased extradimensional shift errors in comparison to HV. This means the cognitive flexibility impairment in the present sample aligns with that of a previous group of euthymic patients. However, in a study using the ID-ED in mania, ID-ED performance failed to distinguish patients from HV (Clark et al., 2002).

The ID-ED task is reliant on brain regions involved in attention shifting, visuospatial function, concept formation, and rule learning. Recent neuroanatomical investigations have shown that distinct areas of the PFC are responsible for concept formation versus attentional-set shifting. In nonhuman primates, lesions of the lateral orbitofrontal cortex lead to impaired concept learning while lesions of the DLPFC lead to impaired extradimensional-shifting (Dias et al., 1996). Similarly, in a positron emission tomography study (PET) Rogers (Rogers et al., 2000) reported separable activation for reversal learning versus EDS learning versus IDS learning. Relative to IDS learning, EDS learning caused increased activation in the left anterior PFC and right DLPFC, while reversal learning relative to IDS learning caused increased activation in the left caudate nucleus. No study has used the ID-ED during fMRI in BD. But, since the present study showed patients had increased number of attempts at extradimensional shifts, and this ability relies on DLPFC functioning in primates and humans, the impaired performance in recovered patients we show here may be due to dysfunctional DLPFC.

Future studies should (1) examine ID-ED performance in acute BD (2) examine the relationship between ID-ED impairments in during euthymia and other cognitive dysfunction in acute episodes, (3) the relationship between ID-ED performance during euthymia and long-term prognosis, and (4) brain function during fMRI using ID-ED across mood states in BD.

2.5.3.2 Impulsivity in BIS

Using the BIS, we found no significant difference on self-reported impulsivity between patients and healthy volunteers (Table 2.2). This negative finding is different from previous studies using

this measure in euthymic BD patients (Ekinici et al., 2011, Swann et al., 2003), suggesting our patients' performance during BIS does not align with previous euthymic samples. Using the BIS in euthymic BD, Ekinici (Ekinici et al., 2011) showed patients scored significantly higher on total BIS scores compared to controls. However, authors in that study did not report percentage of patients receiving medication, nor type of medications used, at the time of testing. Similarly, while Swann (Swann et al., 2003) also report increased impulsivity during BIS in euthymia, authors do not report association between medication status and performance. The effect of medication in BIS reporting is important given evidence that drugs commonly used in BD, such as lithium, reduces impulsive behaviors in BD, such as problem gambling (Hollander et al., 2005), and in animal models reduces impulsive responding during motor tasks (Ohmura et al., 2012). Since all patients in the present study were receiving medication at time of testing, this may have reduced self-reported impulsivity during BIS. Future studies examining impulsivity using the BIS in BD should test for associations between main outcome measures and medication status.

The neural underpinnings of impulsivity have also been examined by using motor inhibition tasks. Chapter four of this thesis reviews findings from brain lesion patients, as well as from the use of fMRI, during motor inhibition tasks. It also presents the results of an fMRI study examining impulsivity in child and adult BD using a motor inhibition task.

2.5.3.3 Framing task

Here, we do not show a difference in the proportion of risky choices taken in positive or negative frames between BD and healthy volunteers (Figure 2.3). This means our BD patients were no different in risk-seeking or risk-aversion, when dilemmas were couched in terms of gains or losses, compared to HV. This is different from data collected in young unmedicated euthymic patients with a history of hypomania, who differed from HV during this task by not showing the same increase in number of risky choices made during negatively framed compared to positively framed dilemmas as HV. However, consistent with previous findings in BD-II patients (Chandler et al., 2009), our patients spent a longer period of time, compared to controls, when deciding which lottery to select during both positive and negative frames (Figure 2.4). This latter finding may indicate that patients experience increased conflict when deliberating between competing dilemmas, compared to HV. Importantly, our negative finding in the proportion of risky choices made during negatively framed dilemmas may be due to methodological differences between the present study and Chandler (Chandler et al., 2009). Specifically, the present study included fewer participants, potentially limiting our power to detect between group differences. Also, participants in Chandler (Chandler et al., 2009) had a lower mean age, and patients were unmedicated at time of testing.

There has been increased interest in examining the neural underpinning of choice behavior in BD. Chapter three of this thesis reviews the current literature on this topic, and presents data on brain activation during choices in a lottery-based decision-making task in euthymic BD adults.

2.5.4 Emotional regulation in euthymic BD

Affective reactivity to emotionally salient environmental stimuli is thought to underlie mood cycling in BD (Ellicott et al., 1990), and this can be assessed using self-report measures like the AIS, ALS, and PANAS. Here, euthymic patients showed higher scores on emotional intensity (both positive and negative) and negative emotional reactivity during the AIS, and increased depressive, anxious, and elated emotional lability during the ALS comparison to healthy volunteers (Table 2.2). This means that, even during periods of recovery, BD patients show a heightened sensitivity to responding to emotionally salient stimuli (AIS findings), and this can lead to increased fluctuations in mood (ALS findings), compared to controls. This supports previous findings in euthymic BD where patients scored higher on all affective intensity and lability measures in comparison to age-matched controls, and this effect was stronger in patients with earlier onset disease (Henry et al., 2008). Therefore, the present findings add to existing literature demonstrating emotion dysregulation exist in recovered adult patients, and may cause significant problems for patients during remission.

During the PANAS, patients reported elevated levels of trait positive and negative affect, and state negative affect (Table 2.2). This indicated that our clinically recovered patients continued to have abnormally elevated positive and negative affective responses in the past 3 months, and increased negative affective response currently, compared to healthy controls. Similar increases in responsiveness to both positive and negative stimuli have been reported in child BD (Leibenluft et al., 2003a). Our findings are in contrast, however, to a study that showed euthymic BDs were no different from healthy controls in responses during the PANAS (Knowles et al., 2007). However, when evaluating the stability of PANAS responses over the two-week study period, patients showed increased fluctuation in responses (i.e. increased variability) than

controls, suggesting increased affective instability in that group. Our findings of increased trait positive negative affect, and increased state negative affect, may differ from Knowles (Knowles et al., 2007) due to differences in gender (Knowles: 4 males, 14 females) and/or methodological differences (Knowles: patients completed surveys at home, not in the laboratory). Nevertheless, the present PANAS findings demonstrate that euthymic adult patients continue to suffer from heightened expressions of positive and negative emotions, relative to controls, and this may lead to continued difficulties in emotion regulation for patients during recovery.

During BAS/BIS self-reporting, we found that euthymic BD patients showed no difference from healthy comparisons on BAS scores (reward responsiveness, drive, and fun seeking subscales) (Table 3.2), but did show elevated levels of BIS scores. This means our patients are more likely to inhibit appetitive responses to aversive environmental cues than HV. This is different from a recent investigation in euthymic BD using the BAS/BIS, where patients showed elevated BAS scores, across all three domains, but were no different from controls in BIS score (Salavert et al., 2007). Importantly, however, a larger proportion of patients in that study were receiving lithium maintenance therapy compared to the current study. This is important since recent investigations in animals models of reward learning has shown that lithium decreased reward valuation in comparison to control animals (Hernandez et al., 2011), suggesting patients on chronic lithium treatment may show diminished responsiveness to rewarding stimuli. Additionally, mean HAM-D measures of depressive symptoms in that study was considerably lower (mean = 1 (range 0-5) in comparison to the present study (mean = 7 (3-11)). This is important since a previous study using the BAS/BIS in depressed BD found that patients were no different from controls in BAS, but did have increased BIS. This means our present findings of increased BIS in may be

explained by increased subsyndromal depressive symptoms in patients, and since increased BIS has been associated with decreased appetitive response to rewarding stimuli, may explain the findings of normal BAS ratings in relation to controls. Future studies should collect longitudinal BAS/BIS data in BD to track correlations between individual differences in mood and response on BAS/BIS.

The present data showing increased affective intensity, reactivity, and lability in patients may be due to impaired functioning of emotional brain networks in BD. Specifically, studies have shown a general pattern of increased fronto-striatal activity in euthymia relative to HV, and may explain the heightened affective responses that persist in euthymia. For example, in a study comparing euthymic adults to HV during an emotional go/no go task, patients showed increased OFC, ACC, insula, and caudate nucleus activity when inhibition emotional stimuli compared to neutral stimuli (Wessa et al., 2007). Using a word-based mood induction task in euthymia, patients showed reduced activation of the ACC, medial PFC, and hippocampal gyri, compared to HV, during both positive and negative affect induction (Malhi et al., 2007). In a study that examined neural activation in euthymia when happy, fearful, and neutral faces, patients showed increased left striatal activation when viewing happy faces, and decreased DLPFC activation when viewing neutral, happy, and fearful faces, relative to HV (Hassel et al., 2008). When viewing neutral, happy, and angry faces in pediatric BD, patients showed decreased ventrolateral PFC and increased ACC, amygdala, and paralimbic cortex activity during both angry and happy faces, relative to neutral faces, compared to HV (Pavuluri et al., 2007). Therefore, while no study has used fMRI during AIS, ALS, PANAS, or BIS/BAS specifically, these fMRI studies reviewed

here suggest increased affective intensity and reactivity in euthymic patients may be based on dysfunctional activity in fronto-striatal circuitry when processing emotional stimuli.

2.6 Summary

Our results extend existing evidence that verbal memory, sustained attention, and executive function deficits persist in euthymic BD patients. In addition, we showed that affective regulation impairments continue in clinically recovered patients, and this is evidence by increased self-reported affective sensitivity, intensity, and reactivity compared to HV. Numerous reviews have illustrated the importance enduring neuropsychological impairments in clinically recovered patients, as these deficits have been correlated with decrease psychosocial functioning, and may increase the risk for relapse (Gitlin et al., 1995, Johnstone et al., 1985, Carlson et al., 1974). Future studies should use longitudinal designs to monitor the changes in neuropsychological function when patients cycle from euthymia to acute episodes. Ideally, these studies would also use fMRI measures to examine whether brain activation abnormalities are the same during acute episodes and euthymic. If patients continue to show the same pattern of brain dysregulation in euthymia and acute episodes, and this can be associated with trait neuropsychological impairments, then medications should be developed to improve this abnormal brain function in order to prevent relapse or decrease psychosocial functioning.

Chapter 3: An fMRI Investigation of Decision-Making in Euthymic BD Adults

3.1 Introduction

Decision-making is a neuropsychological process of increasing interest to researchers in bipolar disorder (BD), since deficits in this domain may underlie the poor life choices patients make during acute episodes. Indeed, during mania, patients may show a pattern of risky decision-making that shows a diminished regard for long-term consequences. This trait can manifest in various ways during mania or depression. For instance, family members of manic BD report patients making poor investment decisions, or engaging in risky behaviors such as drug-taking or sexual promiscuity. Indeed, over 50% of BD patients reported a lifetime substance use disorder (SUD) in an epidemiological survey (Regier et al., 1990). In one study, 40% of BD with a co-occurring SUD reported having sex with multiple sex partners at the time of testing, while recent manic episode independently predicted total HIV infection risk (Meade et al., 2011). In depression, poor decision-making can lead to suicide. Sadly, upwards of 50% of BD patients attempt suicide at least once (Jamison, 1986). These increased risky behaviors in BD may be due to their decreased ability to calculate risk associated with choices, a decreased ability to incorporate risk assessments into decision-making, or increased risk-seeking during dilemmas associated with unknown outcomes, compared to controls. An understanding on how changes in risk guide decision-making in BD can provide important clues on the neuropsychological underpinnings of increase risky behaviors in acute patients, as well as guide future studies in the cognitive functioning of unaffected relatives.

While the cognitive mechanisms of decision-making impairments in BD remains elusive, recent research suggests increased risk taking on laboratory-based tasks in BD may result from an interaction of increased impulsivity (Swann et al., 2003), and a decreased ability to change choice behavior in response to long-term negative outcomes (Adida et al., 2011, Yechiam et al., 2008, Christodoulou et al., 2006) . In a study that used self-reports to measure impulsivity in BD, euthymic, manic, and depressed patients were found to have increased attention, motor, and non-planning impulsivity, compared to HV (Swann et al., 2003). During CPT performance, however, manic, but not euthymic, patients showed behavioral evidence of increased motor impulsivity. This means self-report measures of impulsivity in euthymia may not correlate well with behavioral task performance. Using the Iowa Gambling Task (IGT), Adida (Adida et al., 2011) showed that euthymic, manic, and depressed patients made increased selections from the risky card decks, compared to HV. Importantly, however, patients showed a similar preference as HV for card decks that had a low versus high loss outcome frequencies. This means that the increased risky choices found in BD during the IGT was not due to a decreased sensitivity to loss outcomes, but instead was due to subtle differences in reinforcement mechanisms that operate during decision-making in BD (Adida et al., 2011). These findings corroborated previous evidence of decision-making abnormalities in euthymia using the IGT (Yechiam et al., 2008), but differed from results reported in Martino (Martino et al., 2011), which showed patients were no different from controls in the number of card selected from the risky deck. Nevertheless, these data indicate that increased self-reported impulsivity, as well as a diminished ability to respond to increased risk during a reinforcement task, may persist in patients who have recovered from acute episodes of mania or depression. These impairments may, in part, underlie the increased risk taking that has been shown during decision-making tasks in euthymic patients.

The WOF task is a decision-making task related to the risky choice task (RCT) used in the present investigation, since it requires participants to choose between competing lotteries over a range of expected values (EVs). Using this task during fMRI, healthy adults showed increased decision-RT activation of the insula, amygdala, cingulate cortex, and basal ganglia when choosing high, relative to low, reward magnitude lotteries (Smith et al., 2009). This means these regions are important in incorporating reward magnitude information into choices about competing lotteries. When choosing high probability of winning relative to low probability of winning, and high risk relative to safe lotteries, participants showed increased activation of the anterior cingulate cortex (ACC). This means the ACC is important in incorporating probability and risk information into choices about competing lotteries. Additionally, recent fMRI studies in healthy adults have emphasized the role of prefrontal and ventral striatal activation during both the anticipation and experience of decision outcomes. Specifically, during a decision-making task, subjects showed increased ventral tegmental and nucleus accumbens activation during anticipation to reward and loss outcomes (Carter et al., 2009, McClure et al., 2004), increased ventromedial prefrontal cortex (VMPFC) activation while experiencing reward outcomes (Smith et al., 2009), and increased insula activation to both rewards and punishments (Knutson et al., 2000). Finally, a study in HV during an action selection task showed that the dorsolateral prefrontal cortex (DLPFC) was important in using reward outcome representations to guide future value-based choices (Kahnt et al., 2011).

Few studies have examined decision-making during neuroimaging in BD. Using PET to examine Cambridge Gambling task (CGT) performance in mania, patients showed task-related increases in ACC and right frontal polar activation, and decreased activation in the inferior

frontal gyrus, compared to controls (Rubinsztein et al., 2001). To our knowledge, no functional neuroimaging study has examined risky decision-making in BD depressed or euthymic patients. However, euthymic patients show similar pattern of performance during the IGT as patients with lesions to the VMPFC (Adida et al., 2011, Bechara, 1994). Specifically, similar to euthymic BD patients, VMPFC lesion patients made significantly more selections from the risky card deck compared to non-lesion participants (Bechara, 1994). This indicates that the decision-making deficits found between euthymic BD and controls during the IGT may be due to abnormal functioning of the VMPFC (Jogia et al.). Based on the neuroimaging data in HV and BD reviewed here we expected that, when using fMRI during decision-making, euthymic BD patients would show abnormal ACC, VMPFC, insula, and basal ganglia activation relative to controls.

An emerging method used by neuropsychologists to examine decision-making is the use of lottery-based choice tasks. Lotteries provide a means to study how changing the probability and magnitudes of gain and loss outcomes impacts choice behavior between competing lotteries. Within a lottery, expected value (EV; $((\text{probability of win}) \times \text{magnitude of win}) + ((\text{probability of loss}) \times \text{magnitude of loss}) = \text{EV}$) can be manipulated in order to make a competing lottery appear more, less, or equivocally attractive. Based on Prospect Theory (PT) (Kahneman and Tversky, 1982), individuals can be described as ‘risk-seeking’ when selecting lotteries where the probability of winning a large amount is small relative to the probability of a loss, and ‘risk-averse’ when selecting lotteries with a high probability of small gains relative to the probability of a loss. The Advantage Model (AM) (Shafir et al., 1993) is an extension of PT, and is used to describe choice behavior when neither of the competing lotteries have a guaranteed outcome (i.e.

two ‘mixed lotteries’). According to this model, decision-makers evaluate competing lotteries separately on the dimension of gains (probability of gain (p) x magnitude of gain (g)) and on the dimension of losses (probability of loss (p') x magnitude of loss (l)) (where $p + p' = 1$). This means mixed lotteries are effectively reduced to two simple lotteries, where the decision-maker first forms a preference by comparing the $p \times g$ value of the two lotteries, and then forms a preference by comparing the $p' \times l$ values between the lotteries. Finally, the ‘attractiveness’ of each lottery is made up of the sum of its evaluations, in the dimension of gains versus losses. Indeed, the advantage model was a better predictor of choice behavior when deciding between mixed lotteries over a range of different EVs, than PT alone (Shafir et al., 1993).

Here, we utilized mixed lottery dilemmas to examine the effect of EV manipulation on lottery choices, in BD versus HV. In this design, one mixed lottery was considered a ‘risky’ lottery, with an EV that changed on a trial-by-trial basis. The other mixed lottery was considered a ‘safe’ lottery, with an EV = 0 on all trials. Based on preliminary evidence that patients have a diminished ability to respond to increased risk during a reinforcement task, we expected the lottery selections of our patients would be less influenced by increases in risk relative to HV, and this would be evident by an increased proportion of risky lottery selections (i.e. risk-seeking), per EV, in BD compared to HV.

Previous behavioral investigations on decision-making in euthymic BD have yielded inconsistent results, with some studies reporting increased risky choices during laboratory testing (Adida et al., 2011, Yechiam et al., 2008), and others failing to find this difference (Martino et al., 2011, Clark et al., 2002). A better understanding of decision-making impairments in euthymic BD will

provide clues to why patients continue to show diminished psychosocial functioning in recovery (Gitlin et al., 1995), as well as be a useful diagnostic tool for patients out of acute phases. Importantly, no study has examined whether this increased risk taking during decision-making in BD is due to an alteration in how patients respond to *changing* levels of risk associated with choices, compared to HV. Additionally, only one neuroimaging study has examined risky decision-making in BD, and this was limited to patients in mania (Rubinsztein et al., 2001). Here, we utilized a novel, mixed lottery-based decision-making task during fMRI to examine whether euthymic patients respond differently from HV to changing levels of risk in competing lotteries. Based on preliminary evidence of increased risky choices during decision-making in euthymic BD (Adida et al., 2011), and the importance of ACC, VMPFC, insula and basal ganglia activation during lottery selections (Smith et al., 2009), we expected our patients would choose more risky lotteries across a range of EVs, and this would be associated with ACC, VMPFC, insula and basal ganglia dysfunction during fMRI.

3.2 Methods

3.2.1 Subjects

This study was approved by the Oxfordshire Psychiatric Research Ethics Committee. Patients provided informed consent prior to diagnostic interview on study day 1. This consent was applicable to study day 2.

Twenty-four right-handed, euthymic BD-I patients were recruited from outpatient services at the Warneford Psychiatric Hospital, Oxford University as described previously (see chapter 2, ‘Methods’ for complete review). Twenty-one HV were recruited from the community. Of the twenty-three BD who met inclusion and exclusion criteria (see chapter 2 ‘Methods’) and scanned for this study, 21 (91.3%) (11 males; 10 females) data sets were used. The remaining 2 (8.7%) sets were discarded due to intolerable amounts of motion artifact. Of the twenty-one HV recruited, 20 (95.2%) (13 males; 7 females) data sets were used. The remaining data set (4.8%) was discarded due to excessive motion.

3.2.2. Procedure

Study day 2 took place at the Functional Magnetic Resonance Imaging Brain Centre (FMRIB), the experimental neuroimaging suite of Oxford University. Based on FMRIB scanning procedures, all participants were screened for history of seizure disorders, claustrophobia, implantation of ferromagnetic materials, or other medical history that would preclude participation in a fMRI research protocol. After screening, participants were asked to complete the Hamilton Depression Inventory (HAMD) (Hamilton, 1960) questionnaire to assess current level of depressive symptoms prior to scanning. Participants were then asked to play a short out-of-scanner practice version of the RCT (described below), in order to become acquainted with the instructions and aims of the game. This lasted approximately 3 minutes. Upon completion of the practice trials, participants began the scanning portion of the experiment, which last approximately 30 minutes.

3.2.2.1 Risky Choice Task neuroimaging data acquisition

Participants were scanned using the Siemens Magnetum Trio Scanner (Siemens Medical Solutions, Erlanger, Germany) at 3 Teslas. Following manual shim and sagittal localization procedures, functional imaging data was collected by means of T2-weighted echo planar images (EPI) (Deichmann et al., 1995) (TE: 30 ms, TR: 3 s, 45 slices angled at 30° in A-P axis, voxel size: 3x3x3). A high-resolution T1-weighted anatomical image, with a slice thickness of 1mm, was then collected for co-registration with EPI data.

To see the visual displays generated from the central computer, a reflective mirror was positioned above the participant's eyes and approximately 1 meter away from the screen. Visual stimuli were generated by Presentation Neurobehavioral Systems software (San Pablo, CA, USA) on a central computer.

We used an fMRI-adapted version of the risky choice task from Rogers (Rogers et al., 2003). Specifically, participants were asked to choose one of 2 competing, mixed lotteries (see Figure 3.1). The independent variables of the lotteries were 1) the probability of win versus loss outcomes, 2) the magnitude of win outcomes, and 3) the magnitude of loss outcomes. On each trial, one lottery ('safe' lottery) was always the same, with a 50% chance of winning 10 points and a 50% chance of losing 10 points ($EV = 0$). The other lottery presented during each trial ('risky' lottery) had an EV that varied from trial-to-trial. The EV of the risky lottery was based on a parametric modulation of the probability of winning, magnitude of wins, and magnitude of losses within the lottery. Using eight different trial types (i.e. 'conditions'), a spread of eight EV

values was established the risky lottery, ranging from -55 to 55 points. Each trial was randomly presented six times, for a total number of 48 trials. Participants were instructed to earn as many points possible in their lottery selections, as these points would be exchanged for real cash earnings at the completion of the experiment.

Each trial of the RCT was structured as follows (Figure 3.1): at the start of each trial a white fixation-cross appeared at the center of the screen for approximately 4.5 seconds (min 3 seconds, max 12 seconds) (Figure 3.1, ‘fixation’). Immediately after the fixation display, the risky and safe lotteries appeared on the screen (‘decision-RT’). Each lottery had a probability associated with winning, depicted by the number of green balls (P-green) present in the box over the total number of balls (P-total) in the box (i.e. win probability = $P\text{-green}/P\text{-total}$), and an associated probability of losing, depicted by the number of red balls (P-red) present over the total number of balls in the box (i.e. loss probability = $P\text{-red}/P\text{-total}$). Each ball also had a ‘point value’ associated with it, depicted as a number on each ball. Participants were instructed to use the button-box provided to make their lottery selection. If the person wanted the lottery presented on the left side of the screen they indicated this by pressing the left button, and vice versa for the lottery on the right side of the screen. The participant’s lottery choice was highlighted in yellow after their button response. After the button response (Figure 3.1, ‘anticipation-phase’), a selection algorithm would randomly select one of the balls in the lottery of their choice. The anticipation phase lasted approximately 4.5 seconds (min 3 seconds; max 12 seconds). The ball that the computer selected from the chosen lottery was highlighted in yellow, and was the outcome for that trial. If the computer selected a green ball then the person gained the points displayed on that ball, and this was summed to their total earnings. If the computer selected a

red ball, the person lost those points from their total sum of earnings. The outcome for the trial (Figure 3.1.) was displayed for a fixed 3 seconds ('outcome-phase'), before the next trial started.

3.3 Statistical Analysis

3.3.1 Behavior

We tested for diagnosis (BD vs. HV) x condition interactions, with each condition representing the different EVs of the risky lottery (see above). In this way, we could examine how changes in probability of winning, magnitude of gains, and magnitude of losses affected decision-making. For this analysis, we first calculated the proportion of risky lottery choices made by each participant in each condition. The mean proportionate choice of risky lottery per condition was then arcsine transformed for each participant in order to normalize the distribution of scores. These values were then analyzed using a repeated-measures ANOVA in SPSS 16.0 software, with the within-subject variable being the risky lottery condition, and the between subject variable being group (BD vs. HV). Similar to Rogers, 2003, statistical analysis was performed on transformed values, but untransformed results are displayed in our tables.

3.3.2 Neuroimaging Data

FMRI Expert Analysis Tool (FEAT) version 5.98 was used for preprocessing and statistical analysis of imaging data (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) software library, www.fmrib.ox.ac.uk/fsl). Preprocessing included removal of

non brain matter from all images, slice timing correction (interleaved), motion correction via high-pass filter, spatial normalization to Montreal Neurological Institute (MNI) space, and smoothing with a Gaussian filter (kernel FWHM = 5). To compensate for magnetic field inhomogeneities at bone-tissue interfaces, a fieldmap sequence was generated for each participant and used to unwarp individual EPI images to ignore areas of signal loss in analysis (Jenkinson, 2003).

At the subject level, event-related response amplitudes were estimated using the General Linear Model. Main effect analysis examined the effect of decision response time ('decision-RT') (i.e. comparison 1), anticipation of outcome ('anticipation-phase') (i.e. comparison 2), and outcomes ('outcome-phase') (i.e. comparison 3) on BOLD-dependent brain activity. Given the evidence of phasic neural responses (1 second duration) due to dopamine activity in the prediction of reward outcomes (McClure et al., 2004) and the processing of loss and reward outcomes, we analyzed brain activation during the first second of comparison 3 (contrasts 6-8, see summary below), and brain activation during the first second of comparison 2 (contrast 3). Additionally, to examine the effect of the changes in EV of the RT and anticipation phases, comparisons 1 was also analyzed using the EV of the risky lottery as a covariate (contrast 2), while comparison 2 was analyzed using the EV of the selected lottery as a covariate (contrast 5). We examined how the different values of lottery outcomes affected main outcome phase neural activity by examining comparison 3 using the value of the lottery outcome (de-meaned) as a covariate (contrast 7). Finally, in order to examine neural activation associated with differences in the expected value of the risky lottery, and the outcome of the lottery selected, comparison 3 was examined using: ('risky lottery EV' – 'lottery outcome value' (de-meaned)) as a covariate (contrast 8).

Events were then convolved with a gamma hemodynamic response function (HRF). Individual contrast images were created using pair-wise comparisons of event-related response amplitudes, which were then entered into second-level random-effects group analyses using FMRIB's Local Analysis of Mixed Effects (Woolrich et al., 2004). High-pass temporal filtering was applied to the model. These analyses produced statistical maps of Z scores (Gaussianized T/F) across all images. These images were thresholded using clusters determined by $Z > 2.3$, and a corrected cluster significance threshold of $p < .05$ (Worsley, 2003).

3.3.2.1 Summary of contrasts used

Contrast 1: main effect of decision-RT.

Contrast 2: main effect of decision-RT (EV of risky lottery use as a covariate)

Contrast 3: main effect of anticipation-phase during phasic response.

Contrast 4: main effect of anticipation-phase using full duration

Contrast 5: main effect of anticipation-phase using full duration (EV of lottery selected used as a covariate)

Contrast 6: main effect of outcome-phase during phasic response

Contrast 7: main effect of outcome-phase during phasic response (demeaned value of lottery outcome used as a covariate)

Contrast 8: main effect of outcome-phase during phasic response (demeaned value of ('risky lottery EV' - 'lottery outcome value') used as a covariate)

3.4 Results

3.4.1 Demographics and clinical characteristics

Patient and controls were matched in age, I.Q., gender (Table 3.1). Atypical anti-psychotics were been used in 11 (52.4%), lithium in 9 (42.9%), anti-epileptics in 16 (76.2%), and anti-depressants in 2 (9.5%) of patients at time of scan.

3.4.2 Behavioral findings

All participants made more risky lottery choices when the probability of winning was high compared to low ($F(1,39) = 20.80, p < .000$). However, this pattern of risky lottery selection was no different between BD or HV ($F(1,39) = 2.24, p = .143$) (Table 3.2). Also, all participants selected the risky lottery when the magnitude of possible gain outcomes were high compare to low ($F(1,39) = 32.86, p < .000$), as well as when the magnitude of possible loss outcomes were low compare to high ($F(1,39) = 72.29, p < .000$). But, this pattern of risky lottery selection was no different in BD versus HV in gains ($F(1,39) = 0.01, p = .934$) or losses ($F(1,39) = 0.75, p = .391$).

Response times to make a lottery selection was significantly shorter for all participants when the probability of winning was high compared to when it was low ($F(1,39) = 20.80, p < .000$), however was no different in this pattern from the BD group ($F(1,39) = 0.00, p = .957$) (Table 3.2). Similarly, response times to make a lottery selection were significantly shorter in all participants when the magnitude of possible gain outcomes was high compared to low ($F(1,39) =$

17.99, $p < .000$), as well as when the magnitude of possible loss outcomes was low compared to high ($F(1,39) = 5.89$, $p < .020$). However, this pattern of response times was not different between BD and HV in gains ($F(1,39) = 1.95$, $p < .170$) or losses ($F(1,39) = 0.59$, $p < .448$).

3.4.3 Neuroimaging findings

Contrast 1: main effect of decision-RT

BD and HV showed increased task-related activity in bilateral dorsal and rostral ACC, dorsolateral prefrontal cortex (DLPFC), VMPFC, basal ganglia (encompassing the caudate, putamen, and ventral striatum), and insula, during the main effect of decision-RT contrast (Figure 3.2). However, none of these regions were differently activated in BD versus HV.

Contrast 2: main effect of decision-RT (EV of risky lottery used as a covariate)

BD and HV showed increased task-related activity in bilateral dorsal ACC and caudate during this contrast (Figure 3.3). However, this activation was no different in BD versus HV.

Contrast 3: main effect of anticipation-phase during phasic response

Participants showed increased task-related activity in bilateral insula, DLPFC, VMPFC, and ventral striatum during this contrast (Figure 3.4). There were no differences between BD and HV in this activation.

Contrast 4: main effect of anticipation-phase using full duration

Participants showed increased task-related activity in the bilateral insula and DLPFC during this contrast (Figure 3.5). There were no differences between BD and HV in this activation.

Contrast 5: main effect of anticipation-phase using full duration (EV of lottery selected used as a covariate)

No significant mean BOLD-dependent task-related activity was detected during this contrast.

Contrast 6: main effect of outcome-phase during phasic response

Participants showed increased task-related activity in bilateral insula and right DLPFC activity during this contrast (Figure 3.6). However, this activation was no different between patients and controls.

Contrast 7: main effect of outcome-phase during phasic response (demeaned value of lottery outcome used as a covariate)

No significant mean BOLD-dependent task-related activity was detected during this contrast.

Contrast 8: main effect of outcome-phase during phasic response (demeaned value of ('risky lottery EV' - 'lottery outcome value') used as a covariate)

No significant mean BOLD-dependent task-related activity was detected during this contrast.

3.5 Discussion

Patients with bipolar disorder engage in increased risky behavior during periods of mania and depression, and this is evidenced by decision-making with an apparent disregard for long-term consequences. Recent neuropsychological studies suggest this pattern of decision-making may be due to increased impulsivity (Swann et al., 2003) and increased risky choices in the laboratory with the Iowa gambling task (IGT) (Adida et al., 2011). Impulsivity is often used in clinical descriptions simply to characterize wrong decisions made in haste and the IGT has a strong learning component. Here, we used an fMRI-adapted lottery decision-making task, where trial-by-trial changes in the EV of a risky lottery allowed us to examine how patients respond to changing levels of risk during decision-making relative to HV. Results indicated that BD was no different from HV in their lottery choices. Specifically, patients chose risky versus safe lotteries at the same frequency as HV across a range of positive and negative EVs. Additionally, fMRI results indicated that patients and HV similarly activated prefrontal areas, encompassing the ACC, VMPFC, and DLPFC, insula, and subcortical regions, including caudate and ventral striatal, during decision-RT, anticipation-phase, and outcome-phase periods of lottery selections (Figures 3.2-6). These behavioral and neuroimaging data suggest that euthymic BD are no different from HV in incorporating risk calculations in decisions, or in anticipating or experiencing outcomes of those decisions, between competing lotteries.

The IGT is a highly utilized measure of decision-making in patient populations (Adida et al., 2011, Yechiam et al., 2008, Christodoulou et al., 2006). Healthy performance on this task depends on the ability to integrate cumulative reinforcement histories into card-selection choices. Patients with lesions to the VMPFC showed an inability to integrate long-term loss outcome information, evidenced by an increased number of choices from the high-risk versus to low-risk

card decks during IGT, compared to non-lesion patients. Importantly, this same pattern of increased risky card selection during IGT was demonstrated in BD across mood states (Adida et al., 2011). Since this deficit was found across mood states in BD, the authors of that study suggested decision-making deficits may be a trait in BD. However, a similar study in a different group of clinically recovered patients failed to show this pattern of impairment during IGT compared to controls (Martino et al., 2011), challenging the notion that this pattern of decision-making is a trait in BD.

Here, we showed that, when euthymic BD are confronted with competing lotteries, where one lottery is more or less ‘riskier’ than the other, patients selected the risky lottery at the same frequency as HV over a range of positive and negative EVs (Table 3.2A). This result means that, when the relative risk of the experimental lottery was changed in relation to the control lottery, patients were no more risk-seeking in their choices compared healthy comparisons. We also found that patients and HV took a similar amount of time deciding between competing lotteries (‘RT’) across the range of EVs used (Table 3.2B). This finding suggests that BD did not experience any more conflict when choosing between competing lotteries compared to HV (Carter, 1998). These findings may differ from the increased risk taking found in Adida (Adida et al., 2011), Yechiam (Yechiam et al., 2008), and Christodoulou (Christodoulou et al., 2006) because of differences in task demands between the IGT and RCT. Specifically, performance on the IGT requires participants to integrate the accumulated reinforcement history of each of the card decks when making a choice. Retention of reinforcement history during decision-making is highly dependent on healthy functioning of sustained attention and working memory. Decisions during the RCT, on the other hand, can be made independent from one another, since the

probability of winning or losing during each lottery is unrelated to any previous trial. This means the RCT has less processing demands during decision-making compared to the IGT. Since numerous studies have shown decreased working memory in euthymic BD (Yates, 2011, Bearden et al., 2001, Ferrier et al., 1999), the increased risky decision-making during IGT, but not RCT, may be due to the IGT's reliance on dysfunctional working memory in euthymic BD.

A recent functional magnetic resonance (fMRI) study in HV showed choosing risky versus safe options during the Wheel of Fortune task (WOF) was associated with increased ACC activation, while choosing high versus low reward options was associated with increased insula, amygdala, middle and posterior cingulate, and basal ganglia activity (Smith et al., 2009). Additionally, using PET to examine CGT performance in manic BD, patients showed increased task-related metabolic activity in the ACC and right frontal pole, and decreased activity in the inferior frontal gyrus, compared to HV (Rubinsztein et al., 2001). Here, we found that both patients and HV showed increased task-related activity in prefrontal areas, encompassing the ACC, VMPFC, and DLPFC, insula, and in the basal ganglia, encompassing the caudate and ventral striatum, during response, anticipation, and outcome phases of lottery selection. These ACC, insula, and basal ganglia findings support existing evidence that their activation is important when assessing risk and outcomes associated with lottery selections (Smith et al., 2009). However, in contrast to Rubinsztein (Rubinsztein et al., 2001), our analysis failed to reveal between-group differences in brain activation, including in the ACC, between BD and HV. These negative fMRI findings may indicate one of two possibilities: (1) clinical recovery in BD is associated with a return of normal brain functioning during laboratory-based decision-making tasks, or (2) the neuropsychological

task used in this study did not sufficiently engage decision-making neural networks to detect between-group differences.

Specifically, during the decision-RT phase of lottery selections, we found that both BD and HV showed similar task-related activity in bilateral dorsal and rostral ACC, dorsolateral prefrontal cortex (DLPFC), VMPFC, basal ganglia (encompassing the caudate, putamen, and ventral striatum), and insula (Figure 3.2), irrespective of the EV of the risky lottery. Importantly however, this activation was no different between BD and HV, indicating that BD show healthy prefrontal, insula, and subcortical functioning when confronted with choices between competing mixed lotteries. Further, when the EV of the risky lottery was added as a covariate in the decision-RT contrast, patients and controls showed similar task-related activity in the bilateral dorsal ACC and caudate (Figure 3.3). This pattern of activation, however, was no different in BD compared to HV, indicating that BD responded to changes in the relative risk of lotteries in a similar fashion as HV. Since the ACC and insula were previously shown to be important when assessing the riskiness of lotteries (Smith et al., 2009), the present decision-RT fMRI results suggest that euthymic BD are no different from HV in neural activation during risk assessments of competing lotteries.

Our analysis of phasic neural activity during the anticipation of outcomes in this task revealed a similar pattern of activation in BD and HV. Specifically, activity in the bilateral insula, DLPFC, VMPFC, and ventral striatum was increased in the first-second during the anticipation of lottery outcomes (Figure 3.4). However, BD was not different from HV in this activation. This means that one-second, phasic neural activity, which has previously been associated with dopamine

sensitive reward predictions (McClure et al., 2004), was similar in patients and controls while waiting for outcomes. When analyzing the main effect of anticipation, using the full duration of the anticipation-phase, BD and HV showed task-related activity in the bilateral insula and DLPFC, irrespective of the lottery choices made (Figure 3.5). Again, however, this activation was no different in patients versus controls. While no study has examined neural activation in euthymic BD when anticipating the outcomes of lottery choices, our findings indicate clinically recovery (and associated medication in most cases) in BD is associated with normal functioning of brain regions involved in reward anticipation during decision-making, such as the VMPFC, ventral striatum, and insula activation (Carter et al., 2009, McClure et al., 2004), relative to HV.

Finally, analysis of the BOLD-dependent activity associated with phasic neural responses during outcome-phases of lottery choices was no different in BD compared to HV. Specifically, both BD and HV showed task-related activity in the bilateral insula and right DLPFC during the outcome-phase of lottery selections (Figure 3.6), irrespective of lottery selection. This increase in DLPFC and insula activation during the processing of outcomes supports existing evidence for the DLPFC's role in using outcome information to guide future value-based choices (McClure et al., 2004), and the insula's role in processing both rewards and punishments (Knutson et al., 2000). Importantly, we failed to show task-related increases in VMPFC activity during outcome processing in this task. Our negative VMPFC finding may be due to differences in the outcome stimuli presentation used in our task compared to previous decision-making studies. Specifically, our outcome stimulus depicted both actual (e.g. 'you win 20 points') and counterfactual (e.g. 80 point loss ball) information within the same lottery, possibly diminishing the VMPFC activation shown when processing actual reward outcomes alone (Smith et al., 2009). Nevertheless, since

phasic neural responses have previously been shown to be important in processing of reward and loss outcomes (McClure et al., 2004), the present insula and DLPFC findings indicate that patients not only respond to rewards and losses in a similar fashion to HV in this task, but also show similar activation of a prefrontal regions (i.e. the DLPFC) important in using this outcome information to guide future value-based decisions.

An important limitation in this study was the small number of trials ($n = 6$) used for each EV condition during scanning. A recent slow-event fMRI study using a lottery selection task similar to the one used here showed between-group differences in brain activation when using 20 trials of each condition, in 18 at-risk and 13 HV participants (Cservenka and Nagel, 2012). Nevertheless, while it is important to collect sufficient enough fMRI data to examine between-group activations, this must be balanced with limiting the length of in-scanner time for participants. One possible solution to this problem when using the RCT is analyzing the data using three, versus eight, independent variables. These independent variables could be high versus low probability, magnitude of gain, and magnitude of loss, over the range of 8 EVs. In doing so, the number of trials for each of these three conditions can be increased to 24, thereby increasing the RCTs power to detect between group differences.

Recent investigations have made an association between increased risk taking on laboratory measures of decision-making in BD, and the increased risk taking observed during acute periods of mania and depression (Adida et al., 2011). Yet, no previous studies have examined whether this decision-making deficit is due to differences in how patients respond to changes in risk associated with choices, relative to HV. This is the first fMRI study to examine risk taking

during decision-making, by way of competing lotteries, in clinically recovered BD. Our results indicate the euthymic patients are no are no different from HV in responding to changes in risk during lottery selections, evidenced by similar numbers of risky lottery choices over a range of positive and negative EVs. Further, our patients were no different from HV in ACC, VMPFC, DLPFC, insula, ventral striatum, and caudate activation when choosing a lottery (i.e. decision-RT), anticipating its outcome (i.e. anticipation-phase), or experiencing the outcome (i.e. outcome-phase). These results suggest that existing evidence of increased risky decision-making in euthymic BD during IGT is not due to differences in how patients assess or incorporate changes in risk into decisions, but instead due to differences in the reinforcement mechanisms that operate during decision-making in BD. Future studies should examine whether mania or depression is associated with a different pattern of decision-making when using the RCT during fMRI, compared to euthymia.

Table 3.1 Demographics

Characteristic	Healthy Volunteers (N=20)	Bipolar (N=21)
	Mean (S.D.)	Mean ($\pm$ S.D.)
Age	42.33 $\pm$ 10.01	41.89 $\pm$ 6.27
WASI Full-scale IQ	111.33 $\pm$ 9.98	109.37 $\pm$ 9.56
YMRS		.25 $\pm$ 0.42
HAMD-S		7.43 $\pm$ 4.77
Number of medications		1.97 (range=1-3)
Duration of Illness		19.13 (range=4-35)
Manic Episodes		9.30 (range=1-30)
Depressive Episodes		7.83 (range=2-14)
	N (%)	N (%)
Male	13 (65)	11 (52.4)
Atypical Antipsychotic		11 (52.4)
Lithium		9 (42.9)
Antiepileptic		16 (76.2)
Antidepressant		2 (9.5)

Table 3.2 Behavioral performance on Risky Choice Task. (A) Proportionate choice of risky lottery in each group (B) Response times to lottery in each group.

A)				
	<i>Risky Choice Task ^a:</i>	HV (S.E.)	BD (S.E.)	<i>Between-group tests</i>
	Proportionate Choice of Risky Gamble: <i>Effect of Probability</i>	High: 0.91(.03)	High: 0.86(.03)	$F(1,39)=2.24, p=.143$
		Low: 0.16 (.04)	Low: 0.20(.04)	
	Proportionate Choice of Risky Gamble: <i>Effect of Magnitude of Gains</i>	High: 0.61(.03)	High: 0.60(.02)	$F(1,39)=0.01, p=.934$
		Low: 0.47(.03)	Low: 0.46(.03)	
	Proportionate Choice of Risky Gamble: <i>Effect of Magnitude of Losses</i>	High: 0.46(.03)	High: 0.42(.03)	$F(1,39)=0.75, p=.391$
		Low: 0.62(.03)	Low: 0.63(.02)	
B)				
	<i>Risky Choice Task ^a:</i>	HV (S.E.)	BD (S.E.)	<i>Between-group tests</i>
	Response time (ms): <i>Effect of Probability</i>	High: 2478 (314)	High: 2750 (287)	$F(1,39)=0.00, p=.957$
		Low: 3042 (221)	Low: 3301(298)	
	Response time (ms): <i>Effect of Magnitude of Gains</i>	High: 2535 (281)	High: 2912 (257)	$F(1,39)=1.95, p=.170$
		Low: 2985 (342)	Low: 3138 (313)	
	Response time (ms): <i>Effect of Magnitude of Losses</i>	High: 2961 (383)	High: 3130 (349)	$F(1,39)=0.59, p=.448$
		Low: 2558 (246)	Low: 2920 (224)	

BD = bipolar disorder; HV = healthy volunteer

Figure 3.1 Trial design for risky choice task (RCT). $\bar{X}$ = mean jitter duration

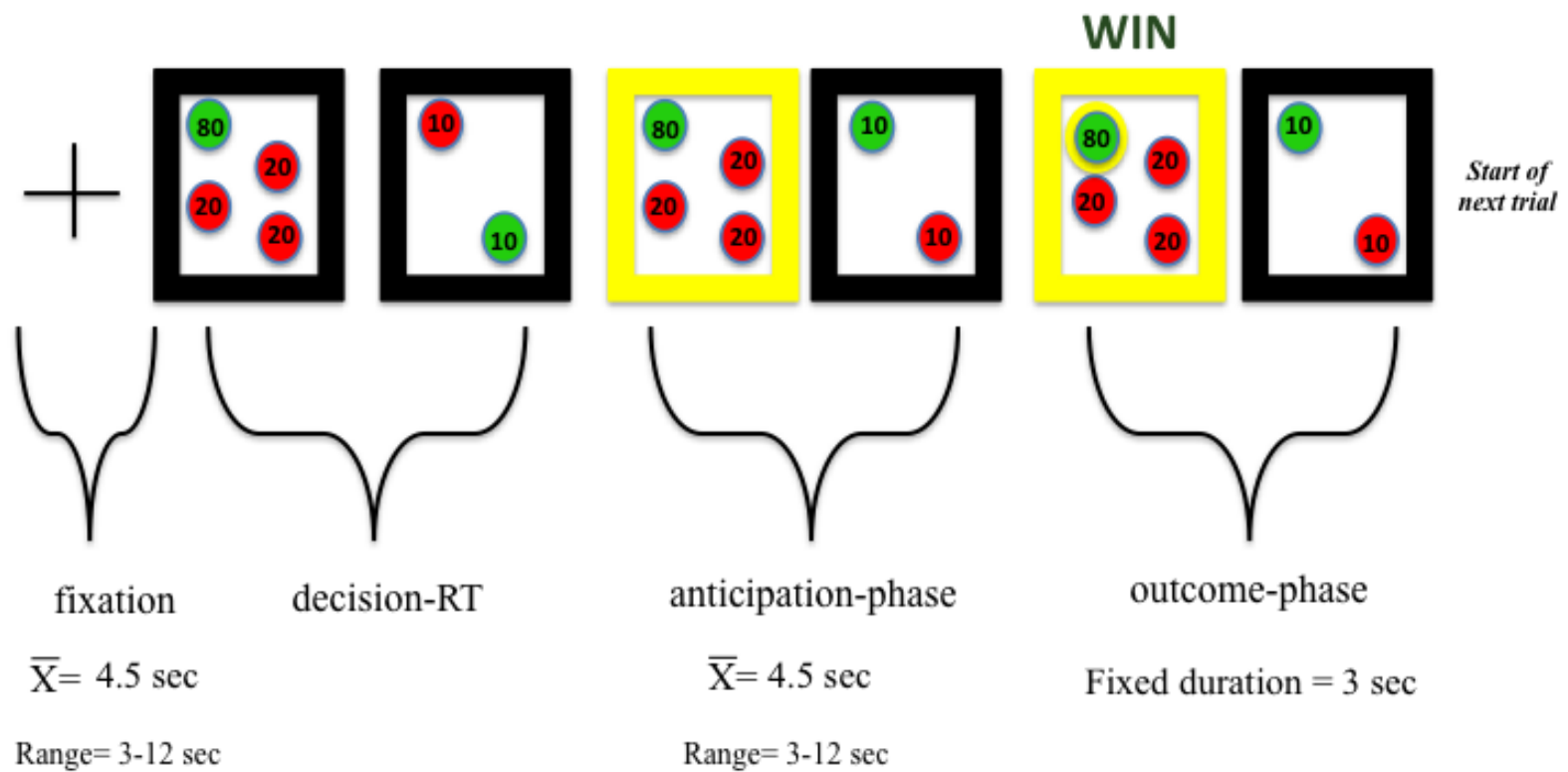


Figure 3.2 Mean activation in bilateral dorsal and rostral ACC, dorsolateral prefrontal cortex (DLPFC), VMPFC, basal ganglia (encompassing the caudate, putamen, and ventral striatum), and insula during decision-RT

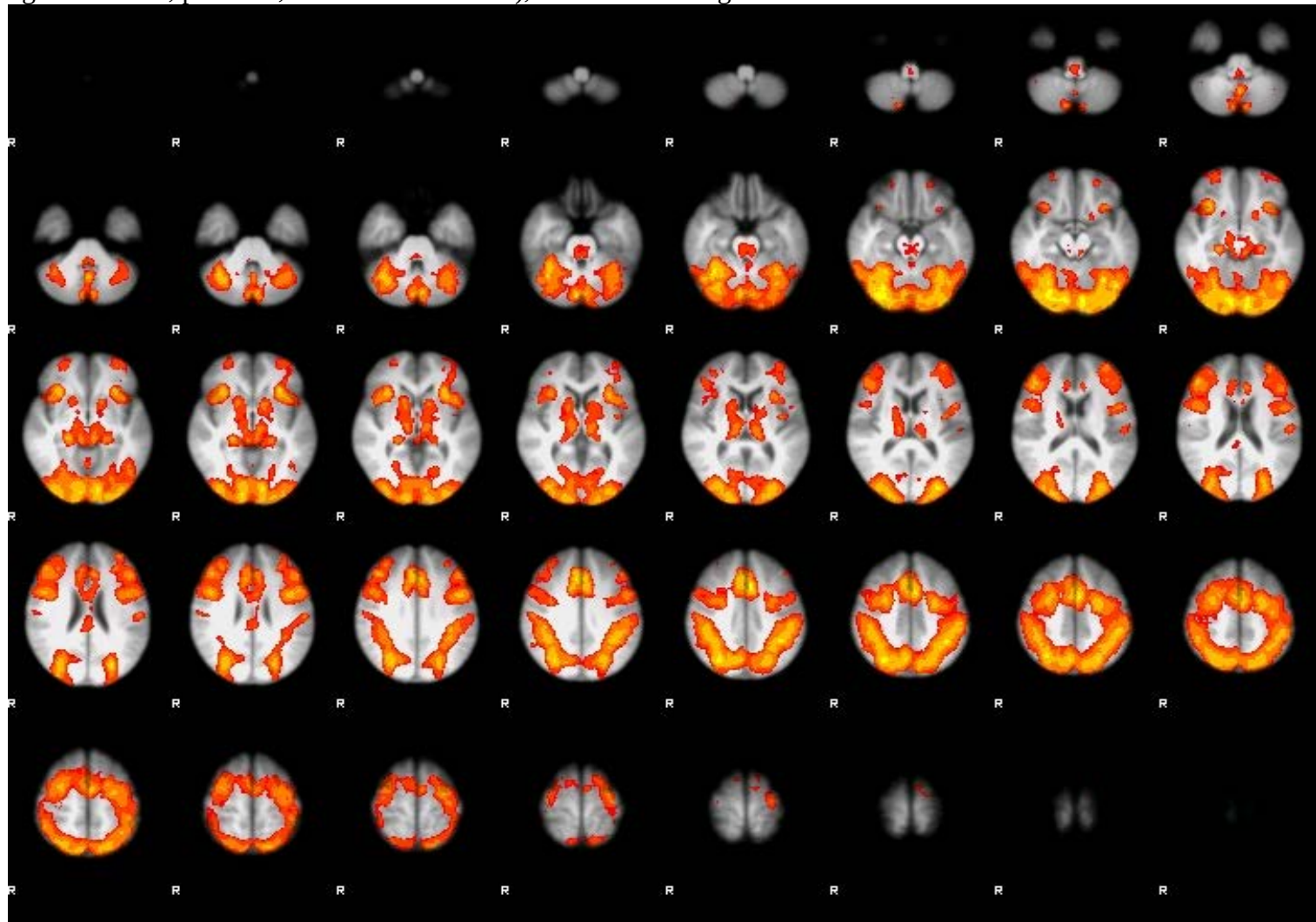


Figure 3.3 Mean activation in bilateral dorsal ACC and caudate during decision-RT (EV of risky lottery used as a covariate)

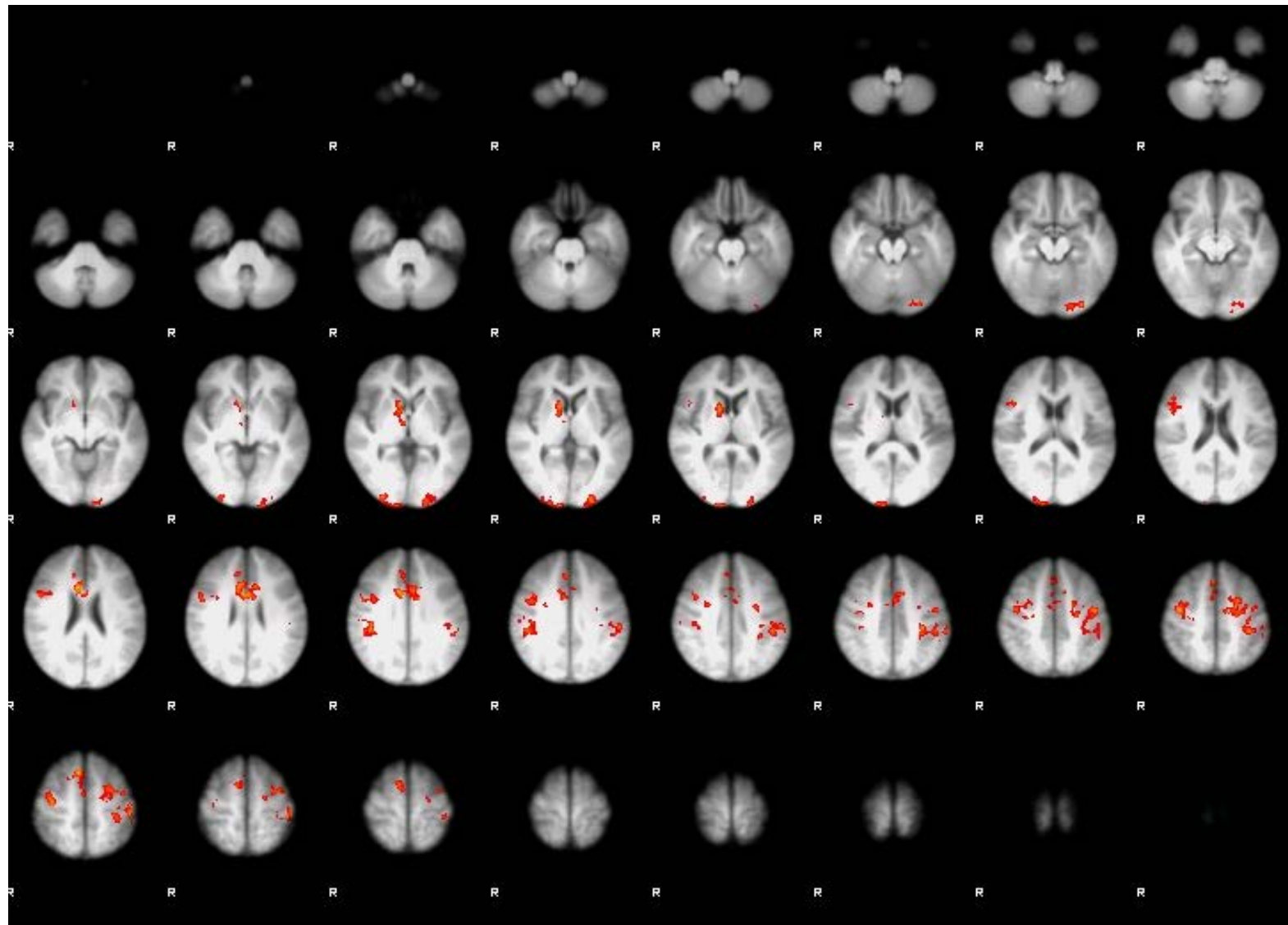


Figure 3.4 Mean activation in bilateral insula, DLPFC, VMPFC, and ventral striatum during anticipation-phase (phasic response).

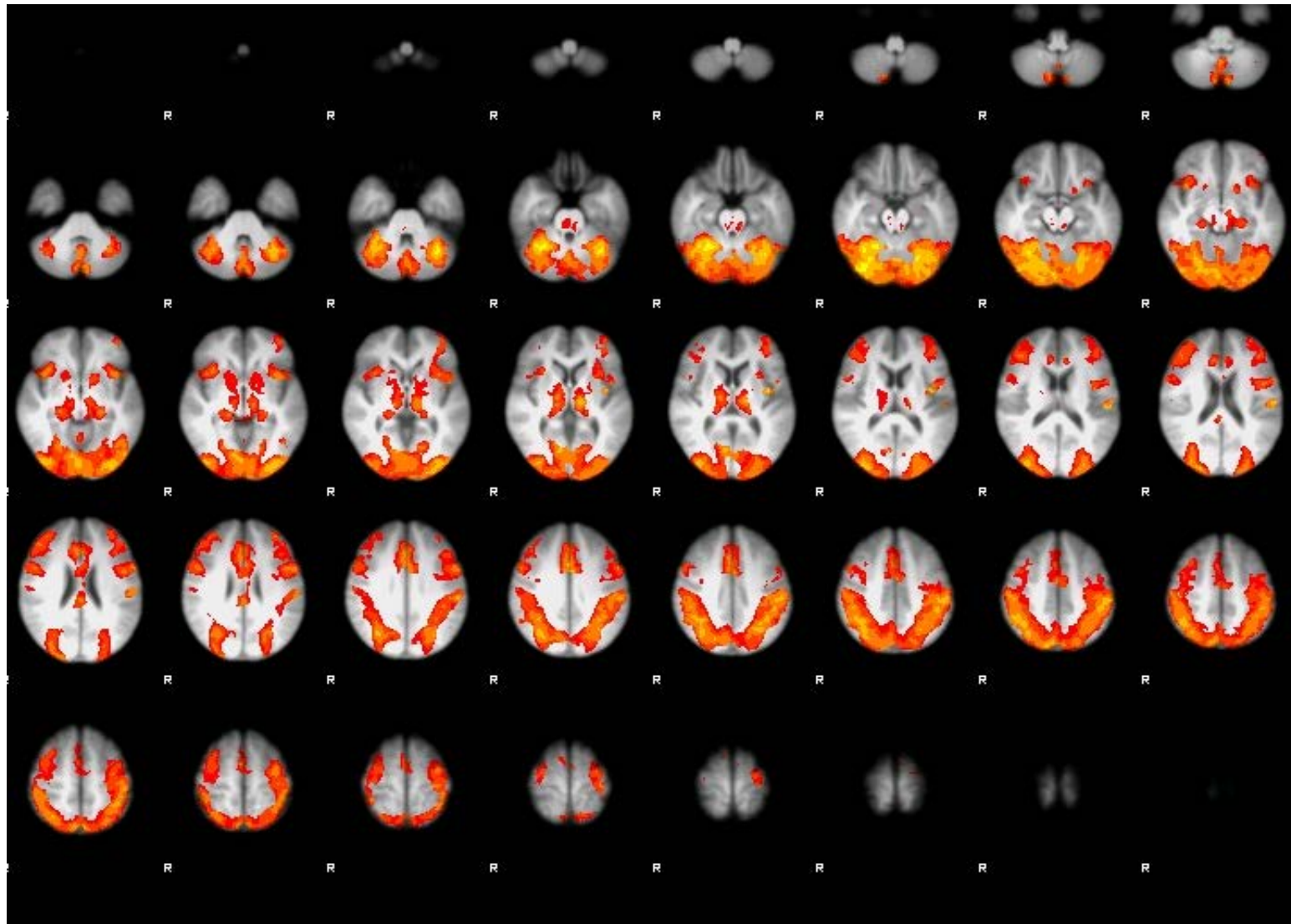


Figure 3.5 Mean activation in bilateral insula and DLPFC during anticipation-phase (using full duration).

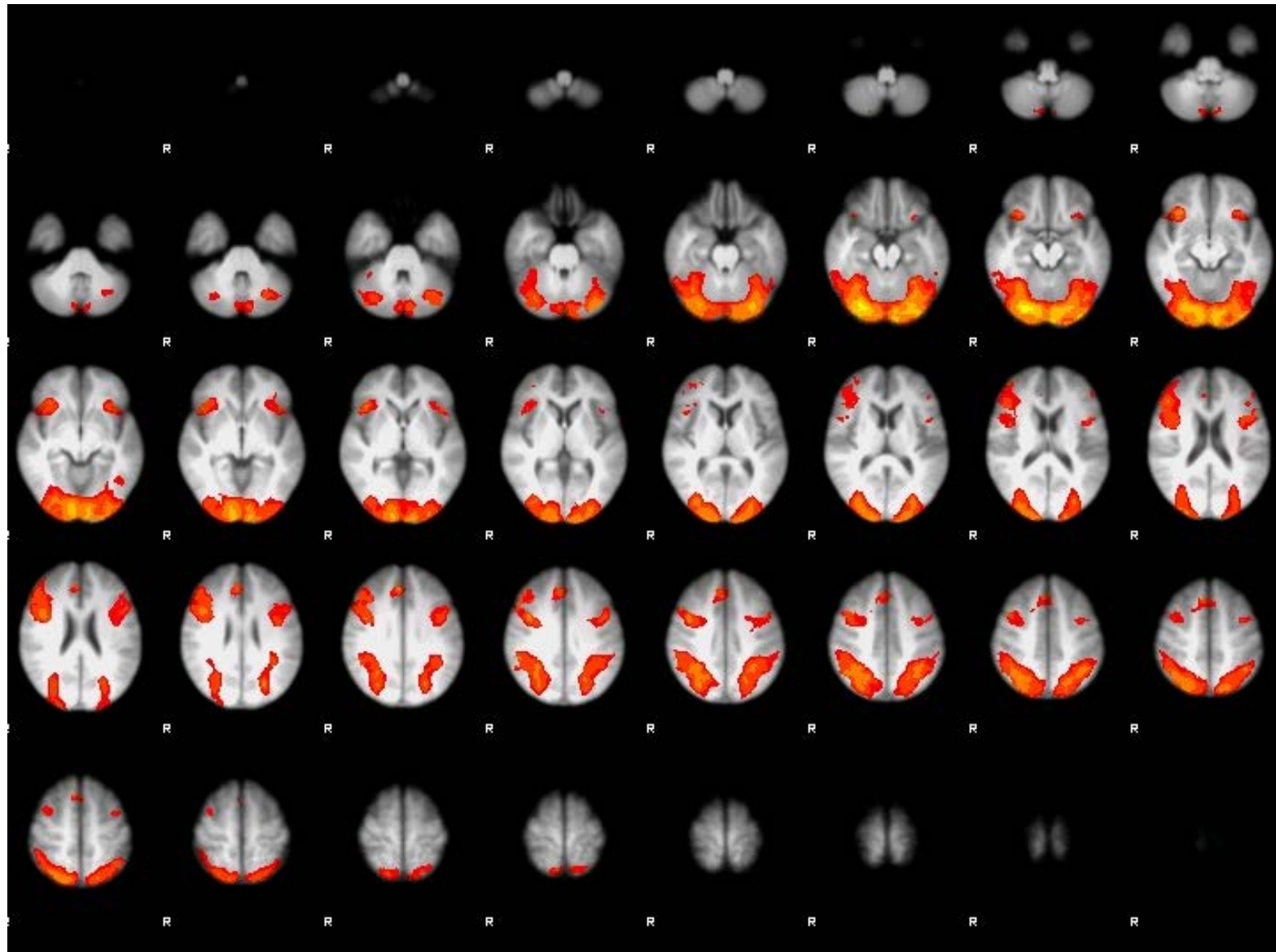
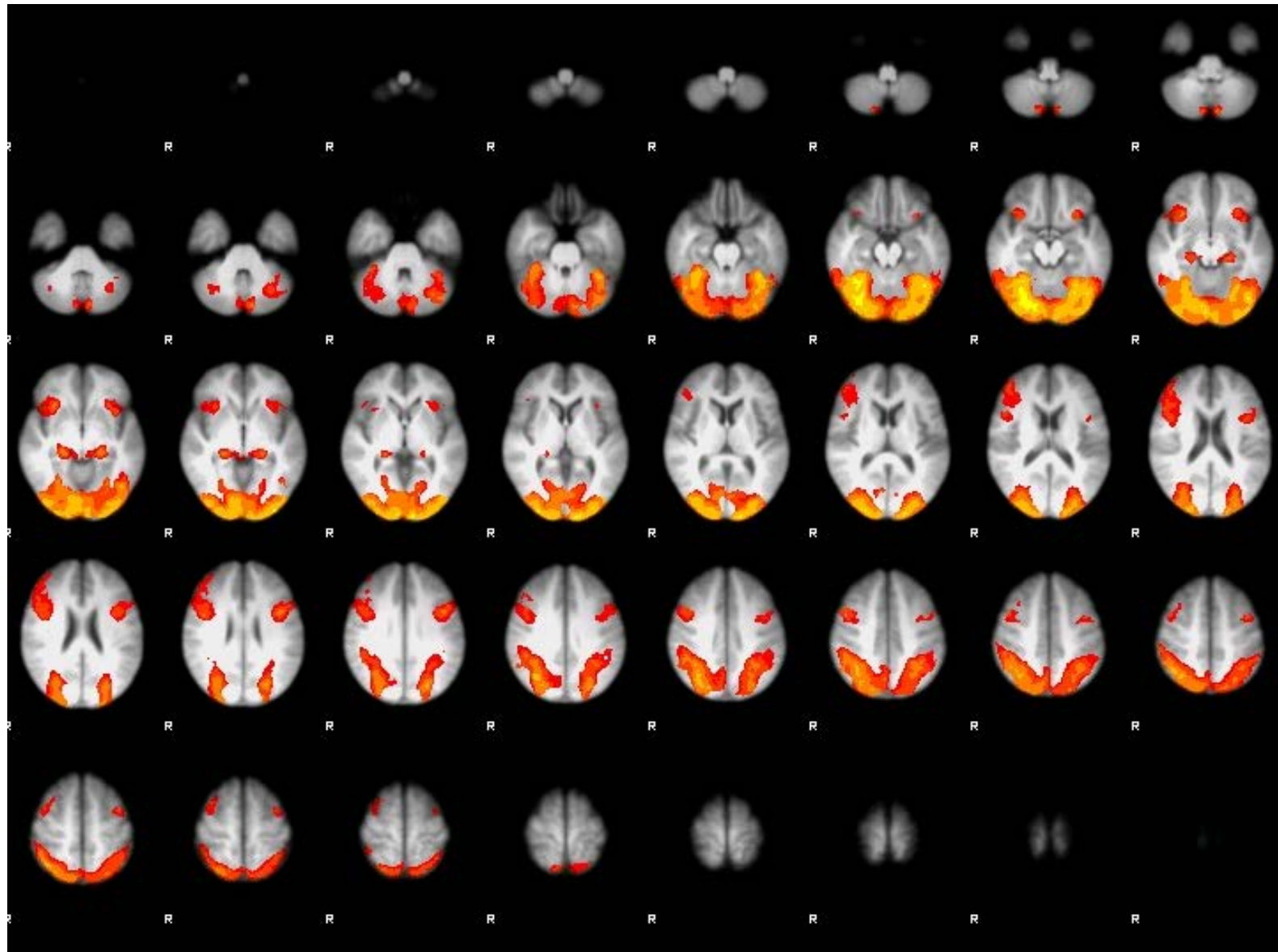


Figure 3.6 Mean activation in bilateral insula and right DLPFC during outcome-phase (using phasic response)



Chapter 4: Decision Making in Early-Onset Bipolar Disorder

4.1 Introduction

This chapter examines decision-making in children with BD, compared to healthy volunteers (HV) and children with severe mood dysregulation (SMD), using a novel, child-friendly, lottery-based decision-making task. The results of using this task in adult BD are presented in chapter 3 of this thesis. Neuropsychological evidence of abnormally risky decision-making in young BD patients could help elucidate the neural mechanisms of pediatric BD, map the developmental trajectory of cognitive dysfunction in BD, and provide targets for interventions to improve cognitive functioning.

Reckless behavior, or behaviors where precautions against known risks are not taken, is an important diagnostic criterion for a manic episode (DSM-IV-R). Persons with BD engage in risky behaviors during mania, with high potential for negative consequences (Holmes et al., 2008). As discussed in Chapter 1, risk-taking in manic adults can manifest in a number of ways, including reckless financial decisions, sexual indiscretions, and drug taking. However, increased risk-taking may manifest differently in youth with BD vs. adults with the illness (McClellan and Werry, 1997). For instance, financial dependence on caretakers, immature sexual development, and reduced access to illicit drugs make the aforementioned symptoms of adult mania uncommon in pediatric mania. Instead, mania in children may manifest as jeopardizing physical safety (e.g. jumping out of a moving vehicle), rule-breaking, theft, or lying. An abnormal sensitivity to reward and punishment is thought to promote reckless behavior in child BD (Ernst and Paulus, 2005). Nevertheless, while a recent behavioral study reported increased risky choices in adult BD, and suggested this may be related to symptoms

of increased risk-taking in adults (Adida et al., 2011), no study has examined whether young BD patients also show increased risky choices in the laboratory.

Real-world reckless behaviors have been associated with increased risky decisions during experimental tests. For instance, using the Balloon Analogue Risk Task (BART) in healthy adolescents and adults, Lejuez (Lejuez et al., 2002) demonstrated that risky behaviors, such as cigarette smoking, interpersonal aggression, and alcohol consumption, were correlated with number of risky decisions during BART. However, since risk-taking is common in both mania and normal developing adolescents (Steinberg, 2010, Boyer et al., 2006, Arnett et al., 1997), it is important to consider what the development of risky behaviors is in healthy, growing youth. Research on the development of risk taking indicates that reckless behaviors, like heavy drinking, cigarette smoking, and sexual promiscuity, emerge and increase in non-clinical, adolescent populations (Broidy et al., 2003, Arnett et al., 1997). The fact that these behaviors increase in prevalence from early childhood into adolescence suggests that increased risk taking is part of normal adolescent development (Boyer et al., 2006). Factors thought to promote reckless behavior in healthy adolescents include sensation seeking, immature psychosocial development, and the decreased ability to remember prior decisions and the consequences of those decisions (Steinberg, 2004, Klaczynski, 2001, Arnett et al., 1997). These data indicate that, while child BD is associated with increased risk taking in relation to age-matched healthy youth, these symptoms should be contextualized within the normal developmental trajectory of risky behaviors in adolescence.

Risky decision-making occurs when an individual must decide between competing options with known probabilities of gain and loss outcomes. One method used to study this in our lab is the Risky Choice Task (RCT) (see Chapter 3 for review). For the purpose of this thesis, the

RCT was adapted to a child-friendly format, which was used in both youth and adults. Based on existing literature in adult BD (Adida et al., 2011), we expected young BD patients would be more risk-seeking than controls, and this would be evidenced by an increased number of risky lotteries choices, across a range of EVs, during the RCT.

Decision-making during the RCT is reliant on mature computational reasoning, or the integrating of probability and outcome information in a single lottery. On the other hand, performance during the IGT is dependent on learning to anticipate future outcomes and make advantageous decisions over the long-term, and not on the integration of probability and outcome information in a single choice (Bechara, 1994). It is therefore important to consider the development of computational reasoning when using the RCT to measure decision-making in adolescents, specifically. Traditional theories on the development of this ability (e.g. Piaget) indicate an early reliance on intuition for probability estimation (Davidson, 1987). Later in childhood, around the ages of 12-13, youth grow to use base (i.e. probability) estimations in computing the value of a decision (Jacobs and Klaczynski, 2002). A recent study showed that the integration of base estimations with outcome information to compute the value of a decision continues to develop through adolescence and adulthood. Specifically, Eshel (Eshel et al., 2007) administered a task closely related to the RCT, the WOF, during functional magnetic resonance (fMRI) scanning to healthy adolescents and adults. When analyzing choice behavior in adolescents and adults combined, risky choice selection during this task was negatively correlated with age (Eshel et al., 2007). Taken together, adolescents mature to use base estimation when making decisions, compared to young children, but the ability to use integrated probability and outcome information when making decisions using the WOF continues to develop into adulthood.

Decision-making during the RCT may also be strongly influenced by the development of ‘simplifying heuristics’ (Jacobs and Klaczynski, 2002). Simplifying heuristics are seen in decision-making using lotteries when subjects make a choice based on a single variable in a lottery (e.g. magnitude of outcomes) (Jacobs and Potenza, 1991). This is in contrast to basing decisions on the integrated value of outcome *and* probability information (i.e. expected value) within the lottery (Kahneman and Tversky, 1982). The use of simplifying heuristics in youth may be due to limits in information processing and working memory (Jacobs and Klaczynski, 2002). Indeed, previous research showed that a child’s ability to reason about the inter-relationship of the multiple components of a problem (e.g. probability of an outcome, magnitude of outcome gains, and magnitude outcome losses) continues to develop through adolescence (Schlottmann, 2001). Further, research indicates that youth becoming increasingly reliant on simplifying heuristics in decision-making, and that this peaks in adolescence (Steinberg, 2004). This means that the use of simplifying heuristics matures in adolescents before the ability to integrate the multiple components of a problem. A recent study by Levin (Levin et al., 2007) supports this view. Using a decision-making task where participants decided between a sure outcome and a lottery with varying probability of gains and losses, a developmental pattern of decision-making emerged. Specifically, adults chose lotteries based on changing EV, whereas young children chose lotteries based solely on how many points could possibly be won. This indicated that children used a simplifying heuristic by ignoring probability information and based their decisions only on salient gain outcome information, making their cumulative choices in the task more ‘risky’ compared to adults.

Previous investigations using the IGT in bipolar adults has yielded inconsistent results, with some studies showing increased risk taking during decision-making (Adida et al., 2011, Rubinsztein et al., 2001), and others failing to find these differences (Martino et al., 2011). To

our knowledge, only one study has used a task related to the IGT to examine decision-making in child BD (Ernst et al., 2004). In that study, BD children were no different from healthy children in their number of risky choices. However, unlike the IGT, which measures decision making when the outcome of a decision trial can be either a win or a loss (Bechara, 1994), the Wheel of Fortune (WOF) task measures decision-making when the outcome of a decision trial is either a win vs. no win, or loss vs. no loss (Ernst et al., 2004). In this thesis, the decision-making performance of child and adult BD is measured in a similar fashion in both groups, by using a novel, lottery-based choice task. Since risky decision-making is mediated by brain regions implicated in BD, including the ventrolateral prefrontal cortex (VLPFC) (Chen et al., 2011), we hypothesized that young BD patients would show increased risk-taking during decision-making when compared to age-matched controls.

Mania is associated with increased reckless behavior and risk-taking, and this may be due to differences in decision-making abilities in BD patients. As noted above, laboratory data on decision-making in adult BD is inconsistent, with some studies showing increased risky choices in patients compared to healthy volunteers, and others failing to find these differences. A study that used an IGT-related task in child BD failed to find differences between patients and age-matched controls in risky decisions (Ernst et al., 2004). However, studies measuring decision-making in a similar fashion, in both adult and child BD, are lacking. Here we utilize a novel risky choice task to examine how decision-making varies in child BD when the EV of a lottery changes from trial-to-trial. Our comparison groups were healthy children (HV) and children with severe, chronic irritability (SMD). We chose the latter group as a patient control group since they shared symptoms of hyperarousal with BD patients, but lacked the episodes of expansive mood, irritability or euphoria that are central elements of the diagnosis of mania. Given clinical reports of increased risk-taking in child and adult BD, and preliminary

laboratory evidence of increased risky decision-making in adult BD (Adida et al., 2011), we hypothesized that, when confronted with a risky lottery and a safe lottery, young BD patients would be more likely to choose risky lotteries across different EVs, compared to HV and SMD children.

4.2 Methods

4.2.1 Subjects

Participants were part of an ongoing institutional review board (IRB) approved study at the National Institute of Mental Health, Health and Human Services, Bethesda, Maryland, USA. Parents/guardians of children provided informed consent, while children provided informed assent.

Patient recruitment was through advertisements to support groups and clinicians (22 BD children and 40 SMD children). Sixteen HV were recruited from the community through advertisements; they had no lifetime psychiatric diagnoses or first-degree relatives with a mood or anxiety disorder. Exclusions for all participants included: IQ<80, substance abuse within the past three months, major medical illnesses, neurological damage/disorder, and pervasive developmental disorders.

Children were assessed for Axis-I disorders with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) (Kaufman et al., 1997), and for SMD using a supplementary assessment module (Leibenluft et al., 2003b). Child BD participants ($n = 23$) met criteria for “narrow phenotype” BD, with at

least one hypomanic (≥ 4 days) or manic (≥ 7 days) episode with abnormally elevated mood or grandiosity and at least three criterion “B” mania symptoms (Leibenluft et al., 2003b).

Nineteen children (82.6%) were BD-I and 4 (17.4%) BD-II. SMD participants ($n = 40$) were characterized by chronic irritability and hyperarousal symptoms, meeting predefined criteria (Leibenluft et al., 2003b). Interviewers were masters or doctoral level clinicians with excellent interrater reliability ($\kappa > 0.9$ for all diagnoses).

In patients, mood was assessed within 48 hours of scanning using the Children’s Depression Rating Scale (CDRS) (Poznanski et al., 1984) and the Young Mania Rating Scale (YMRS) (Young et al., 1978).

4.2.2 Risky Choice Task Behavioral Data Acquisition

The structure of this task was described in Chapter 3. Briefly, participants were asked to choose one of two competing, mixed lotteries. One lottery was ‘safe’, having a .5 chance of winning 10 points and a .5 change of losing 10 points ($EV = 0$). The other lottery was ‘risky’, having a high (.75) or low (.25) probability of winning ($p(\text{win})$). The probability of losing on a risky lottery was always $1 - p(\text{win})$. The expected value (EV) of the risky lottery varied from trial-to-trial, based on a parametric modulation of the probability of winning, magnitude of wins, and magnitude of losses. Using eight different trial types (i.e. ‘conditions’), a spread of eight EV values was established, ranging from -55 to 55 points. Each trial was randomly presented six times, for a total number of 48 trials.

Participants completed a five minute practice session before beginning the task. Upon completion of the task, participants were debriefed using a Likert-scaled questionnaire asking

A) how easy it was to understand how to play the game; B) how easy it was to decide which button to press; and how important each of the following were in their decisions: C) the number of ‘win’ balls in the risky lottery (probability of winning); D) the number of ‘lose’ balls in the risky lottery (probability of losing); E) the number of win points possible in the risky lottery (magnitude of win outcome); and F) the number of lose points possible in the risky lottery (magnitude of loss outcome) (Supplement 1). The scale was designed so that ‘1’ represented ‘very easy’ for questions A and B and ‘no importance’ for questions C-F, while ‘5’ represented ‘very difficult’ for questions A and B and ‘very important’ for questions C-F.

4.2.3 Statistical Analysis

We tested for diagnosis (BD vs. HV vs. SMD) x condition interactions, with each condition representing the different EVs of the risky lottery (see above). In this way, we could examine how changes in probability of winning, magnitude of gains, and magnitude of losses affected decision-making. For this analysis, we first calculated the proportion of risky lottery choices made by each participant in each condition. The mean proportionate choice of risky lottery per condition was then arcsine transformed for each participant in order to normalize the distribution of scores. These values were then analyzed using a repeated-measures ANOVA in SPSS 16.0 software, with the within-subject variable being the risky lottery condition, and the between-subject variable being group (BD vs. HV vs. SMD). Similar to Rogers (Rogers et al., 2003), statistical analysis was performed on transformed values, but untransformed results are displayed in our tables.

A previous study that detected decision-making deficits in BD using a related task included significantly higher numbers of BD (N = 167) and HV (N = 150) participants (Adida et al.,

2011). Since our group sizes were considerably smaller than this (BD = 23, SMD = 40, HV = 16), and possibly under powered to detect between-group differences, we also tested for the effect size of probability, magnitude of gain, and magnitude of loss manipulations on choices between-groups. Effect size was measured using a partial eta-squared calculation in SPSS. This calculated the total variance (SS) in choices attributable to change in probability, magnitude of gain, or magnitude of loss manipulations between-groups, over total variance plus an error term ($SS_{\text{between}} / SS_{\text{total}} + SS_{\text{error}}$). Finally, since mean age was greater in BD patients than in SMD ($p < .002$), and trended higher in BD compared to HV ($p = .052$), we added age as a covariate in our analysis.

We tested for diagnosis x condition interactions on response time (RT) by taking the mean RT for each condition in each participant, and performing a repeated-measures ANOVA on these data in a similar fashion to the analysis above.

We conducted separate exploratory post-hoc analyses examining the impact of mood state, medication status, and comorbid illnesses (anxiety disorders and oppositional defiant disorder (ODD)) on patient performance. Analysis for effect of ADHD on performance was not done due to the low number of non-ADHD patients in our samples. To test whether our behavioral data changed when controlling for these differences, we stratified the BD sample into euthymic vs. non-euthymic and hypomanic vs. non-hypomanic. We also stratified both patient groups into medication vs. no medication, anxiety disorders vs. no anxiety disorder, and ODD vs. no ODD.

For the debriefing questionnaire, scores were tabulated for each individual and analyzed using a between-groups ANOVA, with the between group variable being diagnosis (BD vs. HV vs. SMD).

4.3 Results

4.3.1 Demographics and clinical characteristics

There was no difference in gender or I.Q. between the three groups. Bipolar participants were significantly older than SMD ($p < .002$), and, at a trend level, than HV ($p = .052$) (Table 4.1).

Sixteen (69.6%) child BD were euthymic ($YMRS \leq 12$ and $CDRS \leq 40$), six (26.1%) were hypomanic ($YMRS = 12-24$ and $CDRS \leq 40$), and one (4.3%) was depressed ($YMRS \leq 12$ and $CDRS \geq 40$). All SMD patients were euthymic. More SMD children met criteria for ODD than BD children ($p < .014$). There was no difference in the number of patients medicated in the BD group versus the SMD group ($p = .069$). Yet, the number of medications used in the BD group was higher compared to the SMD group ($p < .002$), with more BD than SMD patients were receiving lithium treatment ($p < .000$) and atypical antipsychotics ($p < .017$) (Table 4.1).

4.3.2 Behavioral findings

There were no between group differences in proportionate choice of the risky lottery when the probability of winning, magnitude of gains, or magnitude of losses was changed between trials (Table 4.2A). In all groups, selection of the risky lottery had a very strong association with

probability of winning ($p < .000$). But, this association did not differ between groups ($p = .675$). No between-group differences emerged on the proportion of risky lottery choices when the magnitude of win outcome changed ($p = .432$). Similarly, in all groups, changes in magnitude of win outcome had no effect on choice of risky lottery ($p = .732$). Finally, there were no between-group differences on the proportion of risky lottery choices when the magnitude of loss outcome changed ($p = .614$). However, all groups showed a trend decrease in the selection of risky lottery when the magnitude of loss outcome was high ($p = .086$).

Since our samples sizes were considerably smaller than a previous decision-making study in BD (Adida et al., 2011), we examined the effect sizes of probability of winning, magnitude of win outcome, and magnitude of loss outcome manipulation on decision-making between groups. Partial eta-squared values for probability, win outcome magnitude, and loss outcome magnitude ($\eta^2 = .01, .02, \text{ and } .01$, respectively) were small (Table 4.3).

When subjects were playing the risky lottery, there were no group differences in response time based on changes in the probability of winning, magnitude of gains, or magnitude of losses (Table 4.2B). Also, there was no effect of probability of winning ($p = .937$), magnitude of gains ($p = .719$), or magnitude of loss ($p = .706$) on response time across all subjects.

4.3.3 Effect of mood, medication status, and comorbid illness on performance

When only euthymic BD patients were included in the analysis, the results replicated those in the primary analysis. That is, when only euthymic patients were examined, there was no between-group difference in proportionate choice of risky lottery based on changes in the probability of winning ($p = .744$), magnitude of gains ($p = .418$), or magnitude of losses (p

= .634) in the risky lottery. Also, there were no group differences in response time to lottery based on the probability of winning ($p = .622$), magnitude of gains ($p = .309$), or magnitude of losses ($p = .502$) in the risky lottery. Similarly, when only including hypomanic BD patients, no group differences in proportionate choice of risky lottery emerged based on the probability ($p = .435$), magnitude of gains ($p = .512$), or magnitude of losses ($p = .610$) of the risky lottery.

When only medicated BD and SMD patients were included in the analysis, there were no between group differences in proportionate choice of risky lottery based on probability, magnitude of gains, or magnitude of losses in the risky lottery. This was also true of the mean response times in each group. No between group differences in risky choice performance, or response times, were found when excluding patients with comorbid ODD.

4.3.4 Debriefing questionnaire

There were no group differences in ratings on our debriefing questionnaire (Table 4.4). On average, participants described the task instructions as ‘very easy’ (Question A). Responses to this question did not differ between diagnostic groups ($p = .461$). Similarly, participants rated the difficulty at making decisions as ‘easy’, with no between group differences ($p = .204$) (Question B). Participants rated the importance of the probability of winning on the risky lottery as ‘important’, and this did not differ between groups ($p = .602$) (Question C). There was a trend difference in the importance of the probability of losing the risky lottery ($p = .099$), with HV participants rating this as ‘important’ and SMD participants rating it as ‘medium importance’ ($p = .086$) (Question D). No difference was found between groups ($p = .244$) on the importance of magnitude of win points possible in the risky lottery, with all groups rating this variable as ‘important’ (Question E). Finally, no between group difference was found in

the importance of magnitude of loss points possible in the risky lottery ($p = .486$), will all groups rating this as ‘important’ (Question F).

4.4 Discussion

A previous study in adult BD found increased risky decision-making on the IGT, and this was related to lack of insight measured by the YMRS and Hamilton Depression Scale (Adida et al., 2011). No study has examined whether early onset BD patients also show increased risky decision-making in the laboratory. Based on tentative evidence of impaired decision-making in adult BD patients (Adida et al., 2011, Yechiam et al., 2008, Minassian et al., 2004), we hypothesized that BD youth would show increased risky choices when compared to HV and SMD. We used a novel risky choice task requiring participants to choose between a risky lottery, with changing EVs, versus a safe lottery ($EV = 0$). As expected, youth used a simplifying strategy when making lottery choices. Specifically, decision-making by young participants was overwhelming guided by changes in probability within the lottery, and not on changes in gain or loss outcome information (Table 4.2A). This differs from the results in adults on this task, which showed decision-making was guided by changes in probability, gain, and loss outcome information (chapter 3). Additionally, young BD patients did not differ from HV or SMD in proportion of risky choices during the RCT. Specifically, BD youth chose the risky lottery at similar rates as HV and SMD when the probability of winning was high, when the probability of winning was low, as well as when the magnitude of wins and loss within the risky lottery were either high or low (Table 4.2A). Also, the between-group effect of changes in probability, gain outcome, and loss outcome in decision-making were small in our effect size analysis (Table 4.3). There were no between-group differences in response time to decision-making (Table 4.2B). There were also no group differences in the self-reported use

of probability or magnitude information when making a decision (Table 4.4). Finally, there was no association between decision-making and baseline mood, medication status, or comorbid psychiatric diagnosis in patient populations. Therefore, young BD patients do not differ from healthy peers or children with chronic irritability in behavior on a task that measures the risk assumed when making decisions to win or lose money.

Here, BD youth did not differ from HV or SMD participants in proportion of risky choices or response times to decision-making. Our failure to detect between-group differences in this study may be due to a variety of causes. First, laboratory evidence of increased risky decision-making in adult BD is tentative, with some studies showing increased risky decisions in BD patients in mania, depression, and euthymia (Adida et al., 2011, Jollant et al., 2007), and other failing to find behavioral differences from controls (Clark et al., 2002, Martino et al., 2011). Indeed, in Chapter 3 we reported that the same task failed to show differences in risky decision-making between euthymic BD and HV adults. Our finding that youth with BD do not differ from HV and SMD in the riskiness of their decision-making is thus in agreement with our own and other studies that failed to show consistent performance differences between adult BD and HV. Second, previous research suggests that adolescents show difficulty integrating the variables within in a lottery, such as probability and magnitudes (Schlottmann, 2001). Further, adolescents have been shown to use simplifying heuristics when confronted with competing lotteries, basing their decision on a single variable like magnitude of gain outcomes (Levin et al., 2007). This means that, while our young participants performed as expected for developmental age by choosing lotteries based on a single variable (i.e. probability of winning), they were unable to base their decisions on calculated risk assessments of the lotteries, thereby making the current paradigm weak at detecting risky decision-making differences between our BD youth and control groups.

Preliminary findings of risky decision-making in adult BD are inconsistent, with certain studies showing increased risk taking during decision-making compared to healthy controls (Adida et al., 2011, Jollant et al., 2007) and others failing to find this difference (Yechiam et al., 2008, Martino et al., 2011). Importantly, however, the studies with negative findings when comparing decision-making BD and controls were under powered in comparison to studies that detect differences. For instance, patient sample sizes in Adida (Adida et al., 2011) and Jollant (Jollant et al., 2007) were $N = 167$ and $N = 545$, respectively, while sample sizes in Martino (Martino et al., 2011), Yechiam (Yechiam et al., 2008), and Clark (Clark et al., 2002) were $N = 88$, $N = 24$, and $N = 15$, respectively. The lower power in the latter studies may account for the failure to find between-group differences. Nonetheless, the inconsistent findings regarding risky decision-making in manic and euthymic BD patients generates two possible conclusions; (1) risky decision-making measured by decision-making tasks is not a central neuropsychological feature of BD, or (2) decision-making deficits are limited to certain subsamples of BD patients that differ from other BD patients in some undefined diagnostic way.

Our behavioral findings differ from the qualitative responses made by participants to the debriefing questionnaire. Specifically, respondents indicated that, with respects to choosing the risky lottery, the probability of winning was as important as the magnitude of the win or loss outcomes, and this was no different between groups (Table 4.3). This is in contrast, however, with participants behavioral performance (Table 4.2A), which showed no effect of changes in win or loss outcome information on lottery choices. The difference we find between behavioral performance and debriefing measures on the RCT may indicate that abstract reasoning about the multiple variables of a decision matures earlier than the ability to

execute behaviors informed by this reasoning. Since youth appeared unable to apply a computational strategy to assess risk in the present study, and this is possibly due to limits in information processing or working memory, this RCT may be insensitive at detecting between-group differences risky decision-making in clinical samples.

The present study has four important limitations. First, this is the first clinical study to use the RCT in young participants. Given that decision-making ability continues to develop through adolescence, it is possible that the task demands of the RCT are too complex to detect between-group differences younger populations. Specifically, in order to properly incorporate risk assessments into decisions during the RCT, participants need to be able to integrate both probability and magnitude information into their choices. However, similar to previous studies on decision-making in young subjects, our participants used a simplifying strategy when making choices, and this was evident by choices in youth being guided only by changes in the probability of outcomes. This means the task demands for calculating risk during the RCT may be too great for youth, and is therefore a poor measure of risky decision-making in adolescents. Nevertheless, the current findings should be replicated in larger groups to ensure the present findings are not Type II errors. Second, our inability to detect a difference in the pattern of decision-making in child BD vs. controls may be due to our rather narrow range of risky lottery EVs used. In other words, it may be that youth are more influenced by *larger* variations in EVs during decision-making than adults are. Negative findings in this context may reflect ceiling effects for the narrow EV range we used, instead of a true lack of between-group differences. Future studies using the RCT should examine whether child performance approximates that of adult performance (see chapter 3) when a wider range of positive and negative EVs are used. Thirdly, all of the child BD were medicated at the time of this study. Medication in our patient groups may have diminished between-group differences in decision-

making. Future studies using the RCT should include medicated and unmedicated patient populations. Finally, our sample sizes were much smaller than those used in previous decision-making studies that found differences between BD and healthy comparisons (Adida et al., 2011, Jollant et al., 2007). Therefore, our study may have been under powered to detect decision-making impairments in child BD using the RCT.

Mania is associated with increased reckless behavior, and this may be due to impairments in decision-making in BD. Using a novel, risky choice task we found that young BD patients did not differ from HV or SMD in proportionate choice of risky lotteries or in response time to decision making. We also found that decision-making was overwhelmingly influenced by the probability of winning points from the risky lottery, and this did not differ between groups. Additionally, there were no group differences in the self-reported importance of probability or magnitude information in choosing lotteries. These findings reflect youth's inability to employ computational strategies during decision-making, making it impossible to detect between-group differences in performance on this task. Indeed, abstract reasoning about the multiple variables in a decision may mature in adolescence before the ability to make decisions based on this reasoning. Finally, our data, coupled with inconsistent findings of decision-making impairments in adults with BD, indicate that laboratory-based decision-making impairments may not be central neuropsychological feature of BD. Future decision-making studies, sensitive to developmental differences between youth and adults in calculating risk, will help decipher whether increased risky decision-making will aid in understanding the neural mechanisms of child and adult BD.

Table 4.1. Subject Characteristics

Characteristic	HV (N = 16)	BD (N = 23)	SMD (N = 40)
	Mean ± SD	Mean ± SD	Mean ± SD
** Age ^a	13.44 ± 1.88	15.43 ± 2.18	13.16 ± 2.54
WASI Full-scale IQ	107.23 ± 17.87	103.78 ± 13.59	108.20 ± 13.98
YMRS		9.13 ± 5.97	
CDRS		25.26 ± 9.75	26.55 ± 6.51
Age of onset: Mania		9.26 ± 3.13	
**Number of medications		4.0 ± 1.98	2.40 ± 1.79
	N (%)	N (%)	N (%)
Male	9 (58.8)	14 (60.7)	27 (67.5)
Euthymic		16 (69.6)	40 (100)
Depressed		1 (4.3)	0 (0.0)
Hypomanic		6 (26.1)	
Bipolar I		19 (82.6)	
Bipolar II		4 (17.4)	
Any Comorbidity		23 (100.0)	37 (92.5)
ADHD		20 (87.0)	30 (80.0)
Any Anxiety Disorder		16 (70.0)	22 (55.0)
*ODD		7 (30.4)	25 (62.5)
CD		1 (4.3)	0 (0.0)
Unmedicated		2 (8.7)	11 (27.5)
*Atypical Antipsychotic		18 (78.3)	19 (47.5)
***Lithium		15 (65.2)	4 (10.0)
Antiepileptic		11 (47.2)	11 (27.5)
Antidepressant		6 (26.1)	14 (35.0)
Stimulants		11 (47.8)	22 (55.0)

^a BD > SMD ($p < .002$); BD > HV ($p = .052$)

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for between group differences in patients

Table 4.2. Behavioral performance on Risky Choice Task. (A) Proportionate choice of risky lottery in each group
(B) Response times to lottery in each group.

(A)

<i>Risky Choice Task :</i>	HV (S.E.)	BD (S.E.)	SMD (S.E.)	<i>Between-group Tests</i>
Proportion of risky choices: <i>Effect of Probability</i>	High: 0.93(.03)	High: 0.95(.03)	High: 0.91(.02)	$F(2,69)=0.46, p=.675$
	Low: 0.11 (.05)	Low: 0.12 (.04)	Low: 0.13(.03)	
Proportion of risky choices: <i>Effect of Magnitude of Gains</i>	High: 0.57(.03)	High: 0.57(.03)	High: 0.55(.02)	$F(2,69)=0.78, p=.462$
	Low: 0.47(.03)	Low: 0.50(.03)	Low: 0.49(.02)	
Proportion of risky choices: <i>Effect of Magnitude of Losses</i>	High: 0.45(.03)	High: 0.48(.03)	High: 0.47(.02)	$F(2,69)=0.49, p=.614$
	Low: 0.59(.03)	Low: 0.58(.02)	Low: 0.57(.02)	

(B)

<i>Risky Choice Task :</i>	HV (S.E.)	BD (S.E.)	SMD (S.E.)	<i>Between-group Tests</i>
Response time (ms): <i>Effect of Probability</i>	High: 3276 (58)	High: 3271 (48)	High: 3374 (34)	$F(2,69)=1.18, p=.313$
	Low: 3278 (49)	Low: 3392 (41)	Low: 3384 (29)	
Response time (ms): <i>Effect of Magnitude of Gains</i>	High: 3382 (64)	High: 3333 (53)	High: 3402 (38)	$F(2,69)=1.37, p=.262$
	Low: 3172 (63)	Low: 3329 (53)	Low: 3355 (37)	
Response time (ms): <i>Effect of Magnitude of Losses</i>	High: 3274 (63)	High: 3352 (53)	High: 3365 (37)	$F(2,69)=0.32, p=.727$
	Low: 3280 (49)	Low: 3311 (41)	Low: 3393 (29)	

HV = healthy volunteers; BD = bipolar disorder; SMD = severe mood dysregulation

Table 4.3. Effect size of association between diagnosis (bipolar disorder vs. severe mood dysregulation vs. healthy volunteers) and changes in probability, magnitude of gain, and magnitude of loss on decision-making

	Partial η^2 (95% C.I.)
<i>Effect of Probability</i>	.011
<i>Effect of Magnitude of Gains</i>	.022
<i>Effect of Magnitude of Losses</i>	.014

C.I. = confidence interval

Table 4.4. Mean (S.D.) likert-scale responses on debriefing questionnaire.

	<u>HV (S.D.)</u>	<u>BD (S.D.)</u>	<u>SMD (S.D.)</u>	<i>Between-group test F(2,69)</i>
A) How easy was it to understand how to play this game? (‘1’ is very easy, ‘5’ is very difficult)	1.3 (.63)	1.1 (.30)	1.3 (.86)	$F = 0.78, p = .461$
B) How easy was it deciding which button to press? (‘1’ is very easy, ‘5’ is very difficult)	2.4 (.29)	2.0 (.18)	1.8 (.18)	$F = 1.63, p = .204$
C) When making your decision about which bet to choose, how important was the number of GREEN ball in the lottery? (‘1’ is not important at all, ‘5’ is very important)	4.5 (.22)	4.1 (.18)	4.2 (.21)	$F = 0.51, p = .602$
D) When making your decision about which bet to choose, how important was the number of RED balls in the lottery? (‘1’ is not important at all, ‘5’ is very important)	4.5 (.24)	3.6 (.31)	3.4 (.28)	$F = 2.40, p = .099$
E) When making your decision about which bet to choose, how important was the number of points you could WIN ? (‘1’ is not important at all, ‘5’ is very important)	3.5 (.29)	3.7 (.25)	4.1 (.22)	$F = 1.44, p = .244$
F) When making your decision about which bet to choose, how important was the number of points you could LOSE ? (‘1’ is not important at all, ‘5’ is very important)	3.6 (.27)	4.0 (.26)	3.6 (.25)	$F = 0.73, p = .486$

HV = healthy volunteers; BD = bipolar disorder; SMD = severe mood dysregulation

Chapter 5: A Developmental Study of the Neural Circuitry Mediating Motor Inhibition in Bipolar Disorder

5.1 Introduction

There is increased interest in the developmental trajectory of bipolar disorder (BD), since the developmental perspective can lead to prevention and appropriate treatment interventions. While considerable research on development uses family-history or longitudinal designs, few studies utilize neuroscience approaches. To compare neural correlates of pediatric and adult BD, the current study uses functional magnetic resonance imaging (fMRI) and the stop-signal task to map the neural correlates of motor inhibition.

Motor inhibition impairments have been demonstrated in both adult and pediatric BD. Studies clearly implicate deficient motor inhibition in adult BD (Swann et al., 2003), whereas data in pediatric BD are suggestive though less definitive (McClure et al., 2005). In adult BD, motor-inhibition deficits (Swann et al., 2003) have been linked to impulsivity during mania (Swann et al., 2004). In healthy adults, successful motor-inhibition requires intact functioning of the anterior cingulate cortex (ACC), ventral prefrontal cortex (VPFC), and striatum (Hester, 2004, Rubia et al., 2001). These regions enable conflict monitoring, error detection, and response inhibition (Chevrier et al., 2007, Botvinick et al., 2004, Aron et al., 2003). Data comparing neural correlates of motor inhibition in healthy youth and adults generate inconsistent conclusions, with some studies reporting increased PFC involvement in youth (Luna et al., 2001, Casey et al., 1997), and others reporting the reverse (Rubia et al., 2007b).

We recently found that unsuccessful response inhibition in pediatric BD was associated with decreased striatal, VPFC, and ACC activation compared to healthy volunteers (HV) (Leibenluft et al., 2007). Interpretation of these findings was complicated by comorbid ADHD in BD, as both diagnoses are characterized by impulsivity. Similarly, differences in VPFC and ACC activation were seen in manic BP vs. HV youth during a task requiring motor inhibition (Passarotti et al., 2010), differences that were reversed with lamotrigine therapy (Pavuluri et al., 2010). Finally, data indicate that adults with mania show decreased VPFC (Mazzola-Pomietto et al., 2009) and ACC (Fields and Fristad, 2009) activation compared to controls during response inhibition.

Overall, this literature generates three conclusions: motor inhibition deficits exist in BD and may be related to impulsivity; motor inhibition is mediated by frontostriatal circuitry that is dysfunctional during inhibition in BD; and functional circuitry mediating inhibition may vary developmentally. However, neurodevelopment in adult and pediatric BD remains poorly understood, and no study directly contrasts the neural correlates of motor inhibition in adult and pediatric BD. Using event-related fMRI, we tested for age-group-by-BD interactions during successful and unsuccessful inhibition on the stop-signal task. We excluded patients with ADHD given evidence it complicates the interpretation of neuroimaging findings (Leibenluft et al., 2007). Available data reviewed above generates three, clear regions of interest (ROI): ACC, VPFC, and striatum. Based on this literature, we hypothesized that BD patients, compared to HV, would exhibit reduced levels of activity in these regions during failed inhibition (Passarotti et al., 2010, Mazzola-Pomietto et al., 2009, Leibenluft et al., 2007) and, given evidence of increasing inhibitory ability through adolescence (Rubia et al., 2007b), that this effect would be most pronounced in youth.

5.2 Methods

5.2.1 Subjects

Participants were part of an ongoing IRB approved study at the National Institute of Mental Health. Adult subjects and parents/guardians of child subjects provided informed consent, while children provided informed assent.

Patient recruitment was through advertisements to support groups and clinicians. Comparison subjects, (21 healthy children, 29 healthy adults) were recruited from the community through advertisements; they had no lifetime psychiatric diagnoses or first-degree relatives with a mood or anxiety disorder. Exclusions for both comparison subjects and patients included: IQ < 80, substance abuse within the past three months, major medical illnesses, neurological damage/disorder, comorbid ADHD, and pervasive developmental disorders. No participants were related.

Children were assessed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) (Kaufman et al., 1997).

Child BD participants ($n = 16$) met criteria for “narrow phenotype” BD, with at least one hypomanic (≥ 4 days) or manic (≥ 7 days) episode with abnormally elevated mood or grandiosity and at least three criterion “B” mania symptoms (Leibenluft et al., 2003b).

Thirteen children (81.3%) met criteria for BD-I and three (18.8%) for BD-II. Inclusion criteria for adult patients was a diagnosis of BD-I or BD-II using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition (SCID-I/P) (First MB, 2002) or the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994). The adult BD group ($n = 23$) consisted of fourteen (60.9%) BD-I and nine (39.1%) BD-II patients. All interviewers were

masters or doctoral level clinicians with excellent interrater reliability ($\kappa > 0.9$ for all diagnoses).

Mood was assessed within 48 hours of scanning using the Children's Depression Rating Scale (CDRS) (Poznanski et al., 1984) and the Young Mania Rating Scale (YMRS) (Young et al., 1978) for children, and the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (SIGH-SAD) (Williams, 1988) and YMRS for adults (YMRS and SIGH-SAD; data missing for two adult patients).

Of the 153 individuals scanned, data were excluded for 80 (52.2 %) for excessive movement, poor performance, equipment failure, or abnormal clinical findings. The final sample ($n = 89$) includes 16 child BD and 21 healthy children reported previously (Leibenluft et al., 2007).

5.2.2 Stop Signal Task (Logan et al., 1997)

A white fixation cross appeared at the screen center for 500 ms at the start of each trial. This was replaced by an "X" or "O" "go-signal" for 1000 ms. Using a button-box, subjects were instructed to press "1" for "X" and "2" for "O". Participants were told to respond within 1000 ms, unless the stop signal appeared (i.e., background changed to red). This occurred on 25% of trials i.e., "stop" trials. Subjects were instructed to refrain from button pressing if the stop signal appeared.

On the first stop trial, the stop signal appeared 250 ms after the go-signal. Subsequent stop-signal timing was adjusted on a trial-by-trial basis based on subject performance. If the subject inhibited successfully, the next stop signal appeared 50 ms later than on the last stop trial; if

the subject failed, the signal appeared 50 ms earlier than on the last stop trial. Trials were separated by 750 ms.

Before scanning, subjects were trained to a mean reaction time (RT) less than 1000 ms on “go” trials. During scanning, trial types were presented randomly: 32 go, 16 stop, and 16 fixation trials.

5.2.3 Neuroimaging data acquisition

Scans were conducted in a General Electric Signal 3T magnet. Participants viewed stimuli through Avotec Silent Vision Glasses (Stuart, FL) positioned in the head coil above the eyes. A high-resolution T1 weighted anatomical image following standardized magnetization prepared gradient echo sequence was collected (180 1 mm sagittal slices; FOV = 256; NEX = 1; TR = 11.4 ms; TE = 4.4 ms; matrix = 256 x 256; TI = 300 ms; bandwidth = 130 Hz/pixel, 33kHz/256 pixels). Gradient echo planar images (23 contiguous 5 mm axial slices/brain volume; parallel to anterior commissure posterior line; single shot gradient echo T2* weighting [matrix 64x64; TR = 2000 ms; TE = 40ms; FOV = 240mm; voxels were 3.75 x 3.75 x 5mm]) were collected following manual shim and sagittal localization procedures.

5.2.4 Analyses

5.2.4.1 Behavior

For each group, we computed means for accuracy on go and stop trials; response time (RT) on go trials (GoRT); and, on stop trials, the time between the go signal onset and the stop signal onset, or ‘inhibit delay’. Stop signal reaction time (SSRT) was calculated by subtracting mean

GoRT minus mean inhibit delay at the point when the participant's accuracy on stop trials was 50% (Logan et al., 1997) (if accuracy rate was not 50%, interpolation was performed by subtracting the mean inhibit delay from the RT at the X^{th} percentile of go trials, where X was the participant's stop trial accuracy).

Differences in mean stop and go accuracy, RT, inhibit delay, and SSRT were independently tested using a 2 (Age group: children and adult) x 2 (Diagnosis: BD and HV) factorial univariate analysis of variance (ANOVA). Post-hoc contrasts between groups were done using the Tukey's test.

5.2.4.2 Imaging data

SPM8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) and Matlab 7 (The MathWorks, Natick, MA) were used. Preprocessing included slice timing correction, motion correction, spatial normalization to Montreal Neurological Institute (MNI) space, and smoothing (kernel FWHM = 8). At the subject level, event-related response amplitudes were estimated using the General Linear Model (GLM). Event types included unsuccessful stop ("stop incorrect"), go ("go correct"; only *correct* go trials included) and successful stop ("stop correct") trials. Three contrasts were used in the primary analysis: stop correct versus go; stop correct versus stop incorrect; and stop incorrect versus go. These contrasts controlled for response accuracy, task demand, and presence of a motor response, respectively. Individual contrast images were created using pair-wise comparisons of event-related response amplitudes, which were then entered into second-level random-effects group analyses. A high pass filter (0.0078 Hz) was used.

Motivated by previous findings (Leibenluft et al., 2007, Mazzola-Pomietto et al., 2009, Passarotti et al., 2010, Fields and Fristad, 2009), we used small volume corrected (SVC) ROI analyses to test our hypotheses. Since adult groups differed in age, we used age as a covariate of adult data in our analysis. We used a factorial design to test for a 2 (age group: children and adult) x 2 (diagnosis: BD and HV) interaction in each ROI (bilateral putamen, caudate, nucleus accumbens, ACC, and VPMC) using anatomical templates applied to individual participant's data. For each contrast, we: (1) identified clusters whose peak surpassed the $p < .05$ threshold, using the SVC procedure in SPM8; (2) averaged the estimated contrast values across these clusters for each participant; (3) conducted univariate ANOVAs and Tukey post-hoc tests in SPSS to clarify group activation differences in the identified clusters.

To decompose the complex interactions represented by the primary contrasts, we compared group differences on stop incorrect vs. fixation, stop correct vs. fixation, and go vs. fixation, separately, in the clusters identified by the primary analysis. Guided by previous work, an exploratory whole-brain analysis was conducted for each primary contrast using a statistical threshold of $p=.005$ with a spatial extent of 20 contiguous voxels (Blumberg et al., 2003).

We conducted separate exploratory post-hoc analyses examining the impact of mood state, medication status, and comorbid oppositional defiant disorder (ODD) as child and adult BD differed on these. To test whether primary effects remained significant when controlling for these differences, we stratified the BD sample into euthymic vs. non-euthymic, and + medication vs. –medication groups. Similar techniques were used to test the effect of ODD.

5.3 Results

5.3.1 Demographic and clinical characteristics

The prevalence of BD subtype (I vs. II) did not differ between child and adult BD (Table 5.1). There were no between-group differences in I.Q. or gender across any group, however, adult BD's ($M = 40.85$, $SD = 11.81$) were older than healthy adults ($M = 35.18$, $SD = 8.06$), $t(50) = -2.05$, $p < .05$.

Twelve (75.0%) child BD were euthymic ($YMRS \leq 12$ and $CDRS \leq 40$), and four (25.0%) hypomanic ($YMRS = 12-24$ and $CDRS \leq 40$) (Table 1). Eleven (47.8%) adult BD were euthymic ($YMRS \leq 12$ and $SIGH-SAD < 20$), eight depressed (34.8%) ($YMRS \leq 12$ and $SIGH-SAD \geq 20$), one (4.3%) hypomanic ($YMRS = 12-24$ and $SIGH-SAD < 20$), and one (4.3%) was in a mixed state ($YMRS > 12$ and $SIGH-SAD \geq 20$). BD groups did not differ in the percentage of euthymic patients (Table 5.1). Mean YMRS was higher in child BD ($M = 7.75 \pm 5.98$) than adult BD ($M = 3.90 \pm 4.90$), $t(35) = 2.15$, $p < .04$, and more adult BD than child BD were depressed ($p < .01$, Fisher's Exact Test). Child BD were more likely than adult BD to meet criteria for ODD, and more child BD than adult BD were unmedicated ($N=22$ (95.7%) adult BD vs. $N=19$ (56.2%) child BD were medicated; $p < .00$, Fisher's Exact Test) (Table 5.1). As expected, mean age (in years) at mania onset differed between patient groups (children: $M = 11.7 \pm 3.64$; adults: $M = 21.8 \pm 10.7$; $t(34) = 3.41$, $p < .00$).

5.3.2 Behavioral findings

No age group x diagnosis interactions emerged on any measure. There was a main effect of diagnosis on stop accuracy, with HV having higher accuracy than BD ($F(1,85)=4.30$, $p < .042$). There was also a main effect of age on stop accuracy ($F(1,85)=13.41$, $p < .001$), GoRT ($F(1,85)=17.83$, $p < .001$), and mean inhibit delay ($F(1,85)=14.60$, $p < .001$), indicating

adults performed the task better than children across diagnostic groups. No group differences emerged for SSRT (Table 5.2).

5.3.3 Imaging Data

ROI Analysis

Stop-incorrect versus go:

On stop-incorrect versus go (Figure 5.1), there was an age group x diagnosis interaction in a cluster spanning the left ACC ($F(3,85)=12.98, p < .001$) and right ACC ($F(3,85)=13.80, p < .001$) (Table 5.3A). In both left and right ACC, child BD had decreased activation relative to both healthy children (L: $p < .008$; R: $p < .001$) and adult BD (L: $p < .001$; R: $p < .002$). Activation in left ACC was higher in adult BD than that in healthy adults ($F(2,49)=4.71, p < .013$). In right ACC, activation in healthy children was higher than in healthy adults ($p < .037$).

Post-hoc analyses of the stop incorrect vs. fix contrast revealed decreased activation in left and right ACC in child BD compared to both healthy children (L: $t(35) = 2.08, p < .05$; R: $t(35) = 2.42, p < .02$) and adult BD (L: $t(37) = 2.63, p < .01$; R: $t(37) = 2.91, p < .01$). No group differences emerged on go vs. fix.

Stop-correct versus go:

There was a main effect of diagnosis in the right nucleus accumbens (NAc), with healthy subjects having greater activation than BD ($F(3,85)=7.77, p < .01$) (Figure 5.2). Post-hoc

analysis of the stop-correct vs. fix contrast showed that this was driven by increased activity in the right NAc in HV vs. BD during stop-correct trials ($t(87) = 2.58, p < .01$).

There was also a main effect of diagnosis in the left ventral prefrontal cortex (VPFC), again with HV showing increased activation vs. BD ($F(3,85)=12.97, p < .00$) (Figure 5.2). Post-hoc analysis of the stop-correct vs. fix contrast showed that this was driven by increased activity in HV vs. BD during stop-correct trials ($t(87) = 3.00, p < .00$).

Stop-correct versus stop-incorrect:

There were no age group x diagnosis, age group, or diagnosis effects.

Whole-Brain Analysis

No effects were found on the three primary contrasts.

5.3.3.1 Associations of Clinical Variables with Brain Activation

Mood:

The age group x diagnosis interaction for the stop incorrect versus go contrast remained significant when only euthymic BD participants (child BD (N=12, 75.0%); adult BD (N=11, 47.8%)) were included (L ACC: $F(3,69)=6.40, p < .014$; R ACC: $F(3,69)=7.22, p < .009$). The main effect of diagnosis (BD vs. HV) in the stop correct versus go contrast, in both right NAc and left VPFC, also remained significant when only euthymic patients were included ($t(71) = 2.11, p < .04$) and ($t(71) = 2.87, p < .01$), respectively).

Medication status:

The age group x diagnosis interaction for the stop incorrect versus go contrast remained significant when only medicated patients were included (child BD (N = 9, 56.2%); adult BD (N= 22, 95.7%); right ACC ($t(27) = 2.14, p < .04$, left ACC ($t(27) = 2.63, p < .01$).

Comorbid ODD:

The age group x diagnosis interaction for the stop incorrect versus go contrast remained significant when child BD with comorbid ODD (N=4) were excluded (left ACC ($F(3,80)=10.21, p < .002$); right ACC ($F(3,80)=8.25, p < .005$). Also, on the stop-correct versus go contrast, the main effects of diagnosis in the right NAc ($t(82) = 2.66, p < .01$) and left VPFC ($t(82) = 2.84, p < .01$) remained significant.

5.4 Discussion

Recent reports emphasize the importance of studying neurodevelopment in BD (Health, 2010, Blumberg et al., 2004). Here, we used an event-related design to examine the neural correlates of response inhibition in adults and children with BD and age-matched comparison subjects. We confirmed our hypothesis that BD participants show frontostriatal dysregulation during response inhibition, and this is most pronounced in youth. Specifically, during unsuccessful inhibition, there was an age group x diagnosis interaction, with BD youth showing reduced activity in left and right ACC compared to both age-matched HV and adult BD, and adult BD showing increased activation in left ACC compared to healthy adults. During successful inhibition there was a main effect of diagnosis, with HV showing greater

activity in left VPFC and right NAc compared to BD. These findings are particularly compelling, as we excluded participants with comorbid ADHD and further analyses ruled out the contributions of other potential clinical factors including mood, comorbid ODD, and medication status.

The ACC mediates conflict monitoring and error detection during choice tasks (Botvinick et al., 2004), but it is unclear how this activity changes with age (Rubia et al., 2007b, Luna et al., 2001, Casey et al., 1997). Few investigations in BD have focused on ACC activation during motor inhibition; none directly compare adult and pediatric BD. Data comparing motor inhibition in children with mania vs. healthy comparisons found decreased ACC activity (Passarotti et al., 2010), while a study in adults with BD failed to find differences with healthy comparisons (Welander-Vatn et al., 2009). We found that, while ACC dysfunction is present across the age spectrum in BD, the nature of that dysfunction varied developmentally i.e., youth with BD had *decreased* activation during failed motor inhibition relative to both age-matched HV and adults with BD, whereas adults with BD had *increased* activation relative to adult HV. Thus, our data suggest that cortical dysfunction is already present in youth with BD and does not necessarily arise first in adulthood (Blumberg et al., 2004). The current ACC finding is supported by literature showing that behavioral impairments differ between child and adult BD, with BD youth showing decreased accuracy to go and stop signals (Pavuluri et al., 2010, Leibenluft et al., 2007) and adult BD showing increased response times to such signals (Gruber et al., 2007, Strakowski et al., 2010).

Here, youth with BD do not engage the ACC appropriately during cognitive conflict induced by an error, which could diminish their ability to inhibit stimulus-incongruent responses to external cues as they manifest in real-world environments, such as when children interact with

teachers, parents, and friends. Also, while adults with BD activate the ACC during failed motor inhibition, their neural function may be inefficient, requiring hyper-activation relative to adult HV to produce comparable performance. This, combined with data showing early onset BD may have a unique mode of inheritance (Somanath et al., 2002, Grigoriu-Serbanescu et al., 2001) and increased genetic loading (Bellivier et al., 1998) compared to adult onset BD, demonstrates the need for longitudinal studies that combine neuroimaging with repeated clinical assessments to see if brain activity changes with time in BD youth, or if pediatric BD represents a separable form of illness.

During successful inhibition, HV subjects showed an increase in BOLD-related signal in the left VPFC and NAc compared to patients. The VPFC supports inhibition by suppressing basal ganglia output (Aron, 2004), while the NAc receives input from the brainstem important in conditioned learning (O'Doherty et al., 2003, Gottfried et al., 2002). Our findings are consistent with considerable published literature showing abnormalities in these regions, particularly in adults with BD (Altshuler et al., 2005, Elliott, 2004, Blumberg et al., 2003). The demonstration that the VPFC and NAc are dysfunctional in BD across the developmental spectrum suggests that impaired inhibitory signals to the basal ganglia and aberrant associative learning mechanisms arise early in BD and persist throughout its course. However, longitudinal studies are necessary to confirm this hypothesis.

This is the first study to compare behavioral performance on a motor inhibition task between pediatric and adult BD patients. While we found between-group differences in neural activity, patients and HVs did not differ on stop signal reaction time (SSRT) or other behavioral measures, consistent with the observation that fMRI measures can be more sensitive than behavioral measures in detecting between-group differences. It is not uncommon for in-

scanner studies to fail to find between-group differences, even in instances where such differences have been found consistently in clinic-based studies. This relatively common observation may be due to differing sample sizes in clinic vs. scanning studies or to the unique testing environment in the scanner (Beesdo et al., 2009).

Our findings must be viewed in light of two important limitations. The first is small sample sizes. This limitation is particularly germane to our negative findings in the exploratory whole-brain analysis; it impacts less significantly on the significant group-differences that we found. Additionally, the effect of medication on the imaging results could not be investigated thoroughly, since only one adult BD patient was unmedicated. However, ethical considerations complicate the recruitment of medication-free patients, and data, including some from the youth in this study, suggest that medication increases the probability of Type II, but not Type I, errors (Leibenluft et al., 2007).

Finally, cross-sectional comparisons represent only a first step in a truly informed developmental-imaging approach, which ultimately should involve prospective collection of imaging data alongside clinical data. Nevertheless, in many areas of medicine, history suggests that cross-sectional comparisons of pathophysiology among children and adults with similar clinical presentations represents a vital “first step” when developing developmentally informed models. No prior fMRI study has compared pediatric and adult BD using any cognitive task; the current report examines motor inhibition, one of the few psychological constructs implicated with some consistency in both pediatric and adult BD. Hence, these results might initiate a new phase of developmentally-informed longitudinal imaging.

In summary, this study provides evidence of developmental differences in frontostriatal activation between patients with BD and healthy subjects. Understanding how brain activation and behavior progresses in BD can only be addressed with longitudinal fMRI studies. Doing so would help with accurate diagnosis of BD in youth, understanding age-specific deficits in BD, and applying intervention strategies appropriate for developmental stage in BD.

Table 5.1. Subject Characteristics

Characteristic	Child BD (N = 16)	Adult BD (N = 23)	Child HV (N = 21)	Adult HV (N = 29)
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Age ^a	14.65 $\pm$ 2.19	40.85 $\pm$ 11.81	13.79 $\pm$ 1.97	35.18 $\pm$ 8.06
WASI Full-scale IQ ^b	107.81 $\pm$ 11.88	114.80 $\pm$ 10.35	114.00 $\pm$ 13.95	115.57 $\pm$ 9.37
*YMRS ^c	7.75 $\pm$ 5.98	3.90 $\pm$ 4.90		
CDRS ^d	24.81 $\pm$ 5.43	NA		
SIGH-SAD ^e	NA	16.62 $\pm$ 11.40		
*Age of onset: Mania ^f	11.71 $\pm$ 3.65	21.82 $\pm$ 10.66		
Number of medications	1.57 $\pm$ 1.65	2.48 $\pm$ 1.53		
	N (%)	N (%)	N (%)	N (%)
Male	8 (50.0)	7 (30.4)	12 (57.1)	11 (37.9)
Euthymic	12 (75.0)	11 (47.8)		
**Depressed	0 (0)	8 (34.8)		
Hypomanic	4 (25.0)	1 (4.3)		
Mixed State	0 (0)	1 (4.3)		
Bipolar I	13 (81.3)	14 (60.9)		
Bipolar II	3 (18.7)	9 (39.1)		
Any Comorbidity	13 (81.3)	15 (60.0)		
Any Anxiety Disorder	7 (43.8)	6 (26.1)		
*ODD	4 (25.0)	0 (0)		
CD	1 (6.25)	0 (0)		
Any Substance Abuse/Dependence	0 (0)	2 (8.7)		
**Unmedicated	7 (43.8)	1 (4.3)		
Atypical Antipsychotic	4 (25.0)	10 (43.8)		
Lithium	3 (18.8)	5 (21.7)		
Antiepileptic	6 (37.5)	15 (65.2)		
Antidepressant	5 (31.3)	9 (39.1)		
Stimulants	2 (12.5)	1 (4.3)		

^a Note, significant difference between adult groups ($t=2.05^*$), but not pediatric groups ($t=1.26$).

^bMissing data from 2 adults with BD and 1 adult control.

^cYoung Mania Rating Score; Missing data from 2 adults with BD.

^dChildren's Depression Rating Scale.

^eThe Structured Clinical Interview Guide for the Hamilton Rating Scale, Seasonal Affective Disorders Version. Missing data from 2 adult BD patients.

^fData missing from 2 children with BD and 1 adult with BD.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ for between group differences in patients

HV= healthy volunteers; BD= bipolar disorder

Table 5.2. Performance of subjects on the stop signal task during scanning, presented by group.

Variable	Child Healthy volunteer N=21	Children with Bipolar Disorder N=16	Adult Healthy volunteer N=29	Adults with Bipolar Disorder N=23	Age by Diagnosis Factorial <i>F</i> statistic			Planned post hoc's (Tukey's test)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Interaction	Diagnosis	Age	
Accuracy Go (%)	83.9 (11.4)	83.0 (12.5)	85.8 (10.5)	82.2 (11.1)	0.3	0.8	0.0	
Accuracy Stop (%)	53.4 (10.8)	48.4 (8.5)	59.0 (7.7)	56.3 (7.2)	0.4	4.3*	13.4***	Adult BD>Child BD**; Adult HV>Child BD***
Go ReactionTime (msec)	696.8 (109.4)	656.3 (80.7)	763.9 (94.9)	757.0 (75.1)	0.7	1.4	17.8***	Adult BD>Child BD**; Adult HV>Child BD***
Inhibit Delay ^a (msec)	504.6 (127.6)	431.8 (110.5)	562.1 (119.0)	558.9 (82.7)	2.0	2.5	14.6***	Adult BD>Child BD**; Adult HV>Child BD***
Stop signal reaction time ^b (msec)	198.6 (41.3)	210.3 (39.3)	235.3 (84.2)	218.4 (43.4)	1.2	0.04	3.0	

^a Inhibit Delay=interval between onset of go and onset of stop signals.

^b See text for method of calculation.

*p<0.05, **p<0.01, ***p<0.001

HV= healthy volunteers; BD = bipolar disorder

Table 5.3. Between group differences in brain activation

Table A

Primary Contrast	Effect	Area of Activation (secondary contrast)	Side	cluster size†	MNI coordinates			F	p <	Between-group differences
					x	y	z			
Stop Incorrect vs Go Correct	Interaction of Diagnosis and Age	ACC	R	777	4	42	6	$F_{(3,85)}=13.80$	.00	Child HV>Child BD***; Child HV>Adult HV**; Adult BD>Child BD**
		(stop incorrect vs. fixation)								Adult BD>Child BD**; Child HV>Child BD**
		ACC	L	869	4	42	6	$F_{(3,85)}=12.98$	.00	Adult BD>Child BD***; Adult BD>Adult HV** Adult BD> Child BD**; Child HV>Child BD**
		(stop incorrect vs. fixation)								

Table B

Primary Contrast	Effect	Area of Activation (secondary contrast)	Side	cluster size†	MNI coordinates			F	p	Between-group differences	
					x	y	z				
Stop Correct vs Go Correct	Main Effect of Diagnosis	NAC	R	24	16	4	-6	$F_{(3,88)}=7.77$	.01	HV>BD**	
		(stop correct vs. fixation)									HV>BD**
		VPFC	L	405	-26	26	-8	$F_{(3,85)}=12.97$	.00	HV>BD**	
		(stop correct vs. fixation)									HV>BD**

* $p < .10$, ** $p < .05$, *** $p < .001$. BD = bipolar disorder, HV= healthy volunteers, ACC= anterior cingulate cortex, VPFC= ventral prefrontal cortex, NAC= nucleus accumbens. x,y, and z coordinates refer to the voxel with maximum signal intensity. † determined using a significance threshold of $p < .05$ and corrected for the number of voxels in each region. Secondary contrasts were conducted in regions identified by the primary contrasts (e.g., stop incorrect vs. go correct) to be significantly different between groups

Figure 5.1. Mean activation in left and right anterior cingulate cortex (ACC) during stop-incorrect vs. go contrast

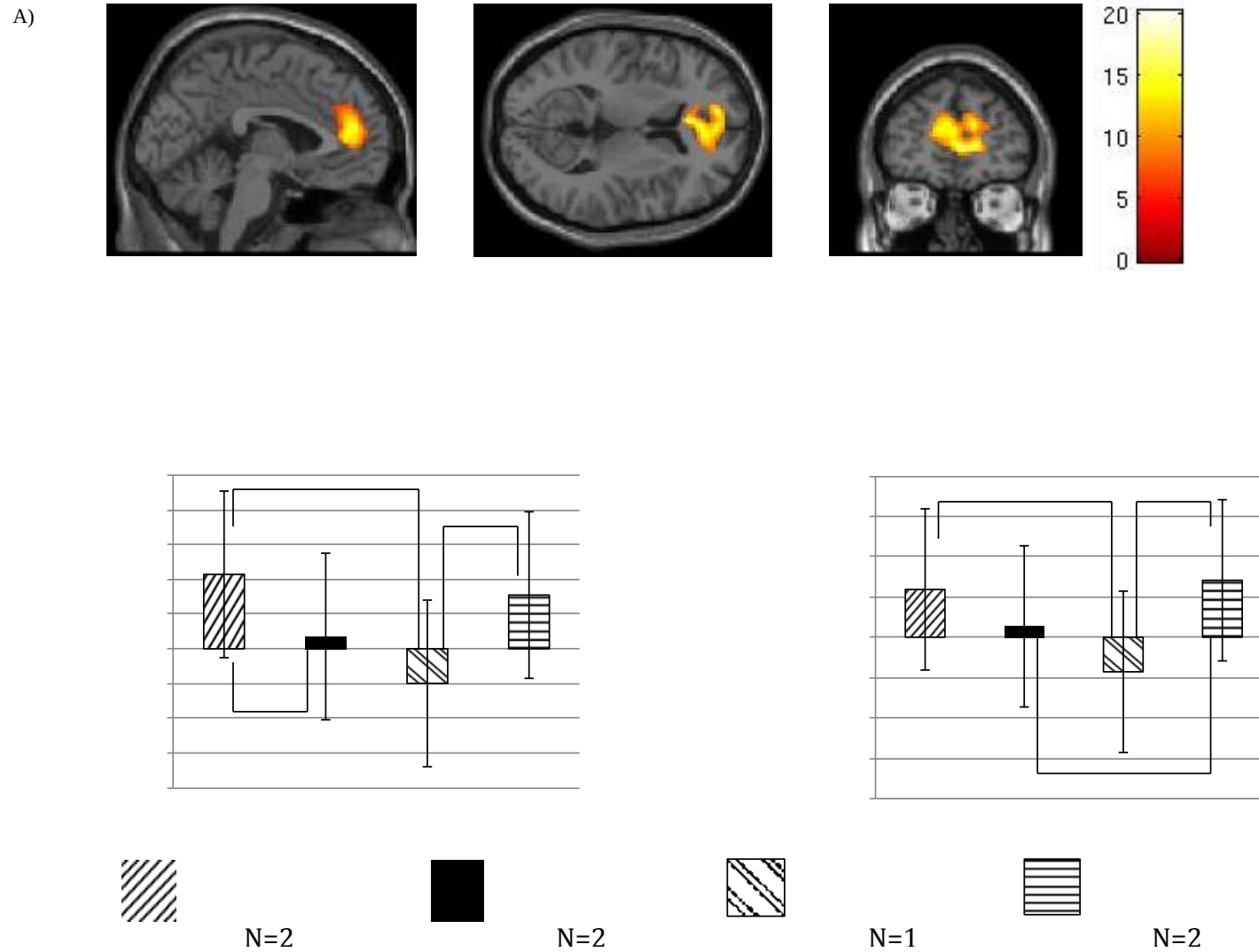
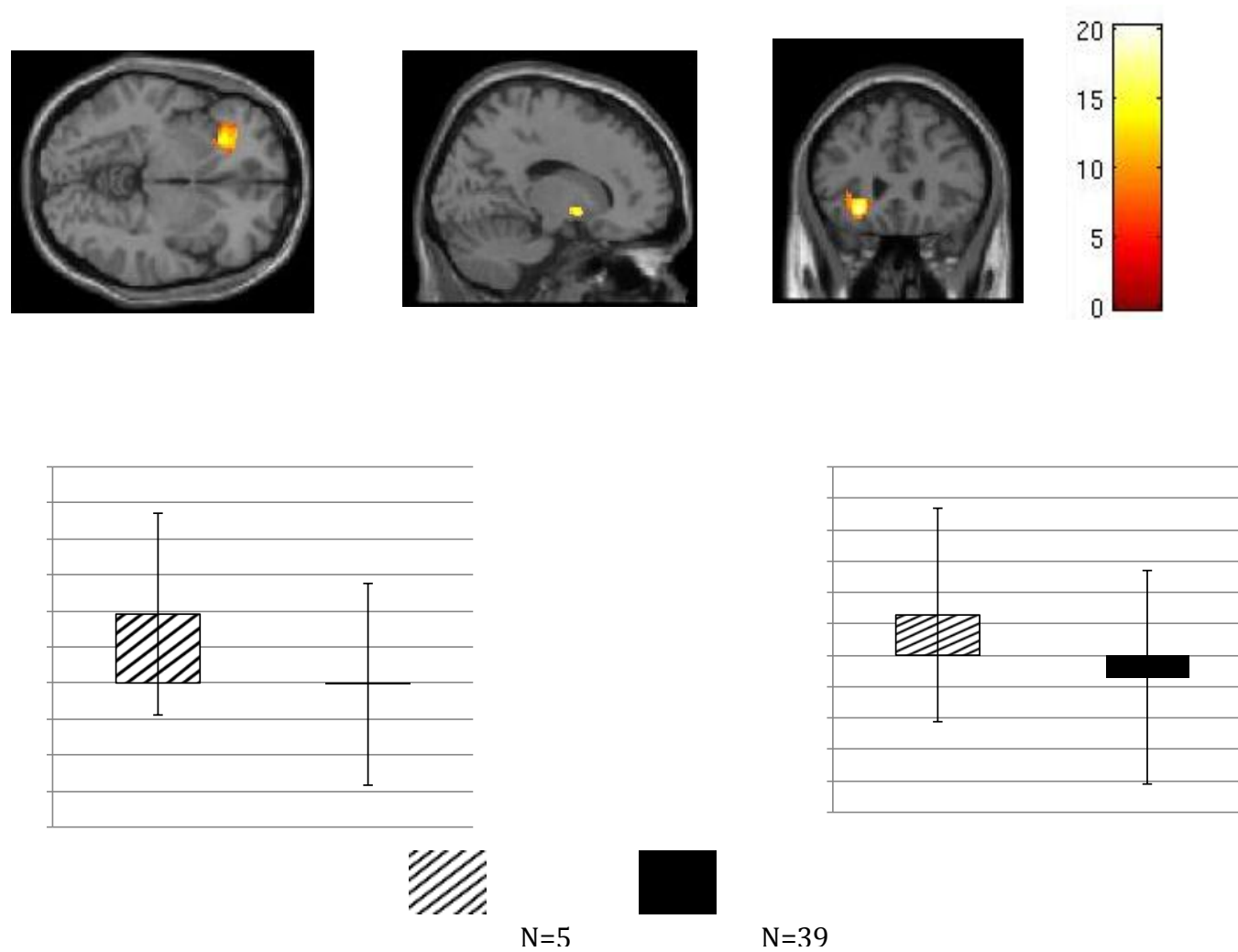


Figure 5.2 . Mean activation in left ventral prefrontal cortex (VPFC) and right nucleus accumbens (NAc) during stop-correct vs. go contrast



Chapter 6: A Developmental Study on the Neural Circuitry Mediating Response Flexibility in Bipolar Disorder

6.1 Introduction:

Developmental studies in bipolar disorder (BD) can inform future treatment and prevention efforts (National Institute of Mental Health Strategic Plan, 2010). Specifically, cross-sectional comparisons of neural activity in youths vs. adults with and without BD lay the groundwork for more definitive longitudinal studies designed to determine the extent of shared pathophysiology in early- and later-onset BD. For example, a previous functional magnetic resonance (fMRI) study found evidence of age- and BD-related frontal dysfunction during unsuccessful motor inhibition. Specifically, compared with age-matched comparison subjects, children with BD showed anterior cingulate cortex (ACC) hypoactivation, while adults with BD showed ACC hyperactivation (Weathers, in press). However, no study has compared neural activity in adults and youth with BD during response flexibility. Here, we used a response flexibility task to compare brain activation in child and adult BD, versus age-matched controls, when subjects were confronted with changing behavioral demands (McClure et al., 2005). Response flexibility is important to study in BD because BD patients show reduced ability to modify behavior deployed toward emotional stimuli, such as when fixating inappropriately on pleasurable activities while in a manic episode (DSM-IV-R; B Criteria).

Response flexibility can be examined using many paradigms, including the change and visual oddball tasks, which both require subjects to inhibit a prepotent response and substitute an alternative one. Data from the change task indicate that BD youth are slower at substituting a prepotent response (“go”) with an alternate response (“change”) (McClure et al., 2005), and thus have impaired response flexibility. While no study uses the change task in adults with

BD, data indicate that adults with BD are impaired in psychological domains related to response flexibility, such as attention shifting (Iverson et al., 2009) and motor inhibition (Bora et al., 2009).

In healthy volunteers (HV), successfully making the alternate response during both the change and oddball tasks engages brain regions mediating inhibition, response conflict, sustained attention, and signal detection (Thomas et al., 2011, Rubia et al., 2007a). Studies suggest that response flexibility improves with age, with healthy adults showing faster response times to change signals than healthy children (Thomas et al., 2011). In addition, regions mediating processes involved in response flexibility all show greater engagement in healthy adults than healthy youths, including 1) inferior frontal cortex (IFC) during motor inhibition; 2) anterior cingulate cortex (ACC) during response conflict and error monitoring 3) precuneus and inferior parietal cortex activation during sustained attention; and 4) middle frontal gyrus and temporal cortex activation during signal detection (Rubia et al., 2007a, Thomas et al., 2011, Carp et al., 2012).

In child BD compared to child HV, we reported previously that successful change trials in the change task, compared to go trials, were associated with middle frontal gyrus and precuneus hyperactivation (Nelson et al., 2007). While no fMRI study has tested response flexibility in adult BD patients, middle temporal gyrus, precuneus, and inferior frontal gyrus hypoactivation occurs during prepotent response inhibition in adult BD compared to adult HV (Mazzola-Pomietto et al., 2009, Strakowski et al., 2008). Since inhibition of prepotent responses is a core component of response flexibility (Kenner et al., 2010), these data suggest that adults with BD may also exhibit neural dysfunction during response flexibility. Finally, during motor inhibition errors, a cross-sectional fMRI comparison showed ACC hypoactivation in

child BD relative to child HV and adult BD, and ACC hyperactivation in adult BD relative to adult HV (Weathers, in press).

Using event-related fMRI and the change task, the current study compares adults and youths with BD and age-matched healthy volunteers on neural function during successful and unsuccessful change trials. As noted above, existing literature shows 1) improved response flexibility to change signals in adult vs. child HV (Thomas et al., 2011); 2) increased activation of precuneus, middle frontal gyrus, and IFC cortex during successful change trials in adult vs. child HV (Thomas et al., 2011); 3) middle frontal gyrus and precuneus hyperactivation in child BD vs. child HV during successful change trials (Nelson et al., 2007); 4) IFC hypoactivation in adult BD vs. adult HV during response inhibition (Mazzola-Pomietto et al., 2009); and 5) ACC hypoactivation in child BD and hyperactivation in adult BD during errors in response inhibition (Weathers, in press). Based on these prior findings, we hypothesize that, compared to age-matched healthy subjects, BD patients show hyperactivation of middle frontal, precuneus, IFC, and ACC cortex during successful change versus go trials, and that this dysfunction will be more pronounced in BD youth than BD adults.

6.2 Methods

6.2.1 Subjects

Participants were part of an ongoing IRB approved study at the National Institute of Mental Health. Adult subjects and parents/guardians of child subjects provided informed consent, while children provided informed assent.

Patients were recruited via advertisements to support groups and clinicians. Twenty healthy children and 27 healthy adults were recruited as comparison subjects from the community through advertisements. They had no lifetime psychiatric diagnoses or first-degree relatives with a mood or anxiety disorder. All subjects were excluded for: I.Q. < 80, substance abuse within the past three months, major medical illnesses, neurological damage/disorder, comorbid ADHD, and pervasive developmental disorders. No participants were related.

Children were assessed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) (Kaufman et al., 1997) by masters or doctoral level clinicians with excellent interrater reliability ($\kappa > 0.9$ for all diagnoses). Child BD participants ($n = 15$) met criteria for “narrow phenotype” BD, with at least one hypomanic (≥ 4 days) or manic (≥ 7 days) episode with abnormally elevated mood or grandiosity and at least three criterion “B” mania symptoms (Leibenluft et al., 2003b). The final sample included 12 children (80.0%) whom met criteria for BD-I and three (20.0%) for BD-II (Table 1). Inclusion criteria for adult patients was a diagnosis of BD-I or BD-II using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition (SCID-I/P) (First MB, 2002) or the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994). The adult BD group ($n = 23$) consisted of fourteen (60.9%) BD-I and nine (39.1%) BD-II patients (Table 1).

Within 48 hours of scanning, mood was assessed using the Children’s Depression Rating Scale (CDRS) (Poznanski et al., 1984) and the Young Mania Rating Scale (YMRS) (Young et al., 1978) for children, and the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (SIGH-SAD) (Williams, 1988) and YMRS for adults (YMRS and SIGH-SAD; data missing for two adult patients).

Of the 153 individuals scanned, data were excluded for 68 (44.4%) for excessive movement (19.6%), poor performance (15.7%), equipment failure (7.1%), or abnormal clinical findings (2.0%). The final sample ($n = 85$) includes 15 child BD (CBD), 20 healthy children (CHV), and 27 healthy adults (AHV) reported previously (Nelson et al., 2007, Thomas et al., 2011, Kim et al., 2012), and 23 adult BD (ABD). None of the adult patients have been reported previously.

6.2.2 Change Task

The paradigm used in this study has been described in detail elsewhere (Nelson et al., 2007, Thomas et al., 2011, McClure et al., 2005), and is a adaptation of the stop-signal paradigm (Logan et al., 1997). Briefly, at the start of each trial a white fixation cross appeared at the screen center for 500 ms. This was replaced by an “X” or “O” “go-signal” for 1000 ms. Using a button-box, subjects were instructed to press “1” for “X” and “2” for “O”. Participants were told to respond within 1000 ms, unless the change signal appeared (i.e., background changed to blue) when they were instructed to press “3”.

On the first change trial, the change signal appeared 250 ms after the go-signal. Subsequent change-signal timing was adjusted on a trial-by-trial basis based on subject performance. If the subject changed successfully, the next change signal appeared 50 ms later than on the last change trial; if the subject failed, the signal appeared 50 ms earlier than on the last change trial leading to an approximate change accuracy rate of 50%. Trials were separated by 750 ms.

Before scanning, subjects were trained to a mean reaction time (RT) less than 1000 ms on “go”. To ensure the prepotency of the go response, there were more go trials ($n = 176$) than

change trials (n = 80) while scanning. Therefore the less common “3” button press to the change stimulus acts as a measure of response flexibility versus prepotent responding. Eighty-eight fixation trials were presented to measure baseline neural functioning. During scanning, four 3.5 minute runs of randomly presented go (n = 44), change (n = 20), and fixation trials (n = 22) were completed by each participant, for a total of 176 go trials, 80 change trials, and 88 baseline fixation trials.

6.2.3 Neuroimaging data acquisition

Scans were conducted in a General Electric Signal 3T magnet where participants viewed stimuli through Avotec Silent Vision Glasses (Stuart, FL) positioned in the head coil above the eyes. Following manual shim and sagittal localization procedures, gradient echo planar images (23 contiguous 5 mm axial slices/brain volume; parallel to anterior commissure posterior line; single shot gradient echo T2* weighting [matrix 64x64; TR = 2000 ms; TE = 40ms; FOV = 240mm; voxels were 3.75 x 3.75 x 5mm]) were obtained. A high-resolution T1 weighted anatomical image, following standardized magnetization prepared gradient echo sequence, was collected for spatial registration (180 1 mm sagittal slices; FOV = 256; NEX = 1; TR = 11.4 ms; TE = 4.4 ms; matrix = 256 x 256; TI = 300 ms; bandwidth = 130 Hz/pixel, 33kHz/256 pixels).

6.2.4 Analyses

6.2.4.1 Behavior

For each group, we computed means for accuracy on go and change trials; response time (RT) on go trials (GoRT); and, on change trials, the time between the go signal onset and the

change signal onset, or ‘inhibit delay’. Change signal reaction time (CSRT) was calculated by subtracting mean GoRT minus mean inhibit delay at the point when the participant’s accuracy on change trials was 50% (if accuracy rate was not 50%, interpolation was performed by subtracting the mean inhibit delay from the RT at the X^{th} percentile of go trials, where X was the participant’s change trial accuracy) (Nelson et al., 2007).

Using a 2 (Age group: children and adult) x 2 (Diagnosis: BD and HV) factorial univariate analysis of variance (ANOVA), differences in mean change and go accuracy, RT, inhibit delay, and CSRT were tested. Post-hoc contrasts between groups were done using the Tukey’s test.

6.2.4.2 Imaging

Functional imaging data was analyzed using SPM8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) and Matlab 7 (The MathWorks, Natick, MA). Preprocessing included slice timing correction, motion correction, spatial normalization to Montreal Neurological Institute (MNI) space, and smoothing (kernel FWHM = 8). At the subject level, event-related response amplitudes were estimated using the General Linear Model (GLM). Event types included unsuccessful change (“unsuccessful change”), go (“go correct”; only *correct* go trials included) and successful change (“successful change”) trials. Two contrasts were used in the primary analysis: successful change versus go and successful change versus unsuccessful change. These contrasts controlled for task demand and response accuracy, respectively. Individual contrast images were created using pair-wise comparisons of event-related response amplitudes, which

were then entered into second-level random-effects group analyses. A high pass filter (0.0078 Hz) was used.

A whole-brain analysis was conducted for each of the two primary contrasts using a statistical threshold of $p=.005$ with a spatial extent of 20 contiguous voxels (Lieberman and Cunningham, 2009). We used a factorial design to test for a 2 (age group: children and adult) x 2 (diagnosis: BD and HV) interaction across the whole-brain. Our age groups differed in mean GoRT (Table 2). Additionally, a previous study suggested that the ‘RT-BOLD’ relationship may be stronger in adults than in children (Carp et al., 2012). To control for these differences, we used GoRT x age group (children and adult) as a covariate in our analysis. Clusters of significant activation were identified in SPM8 and then spatially located by converting MNI coordinates to Talairach space (Talairach and Tournoux, 1988). Percent signal change averaged across suprathreshold clusters on each contrast was extracted from each participant using MarsBaR (Marseille boîte à région d’intérêt; Brett et al., 2002). These data were then entered into SPSS (SPSS, Inc., Chicago, Ill) for between-group post-hoc testing.

The interactions represented by the two primary contrasts are complex. However, they can be further studied by comparing percent signal change, using a univariate ANOVA, associated with individual trial types versus baseline fixation (e.g. successful change versus fixation). Specifically, using the regions found in the primary analysis, we tested group differences in successful change vs. fixation, go vs. fixation, and unsuccessful change vs. fixation in the regions that showed significant between-group differences on the primary contrasts.

Finally, given differences between our child and adult patient groups on a number of clinical variables (e.g., number currently in a depressed mood state, medication status, and comorbid

ODD), we conducted exploratory post-hoc analyses to examine the impact of these variables on our findings. To test whether primary effects remained significant when controlling for these differences, we stratified the BD sample into depressed vs. non-depressed, and + medication vs. –medication groups. Similar techniques were used to test the effect of ODD.

6.3 Results

6.3.1 Demographic and clinical characteristics

There were no between-group differences in I.Q. or gender across any group, or in age between HV's or patients within the child or adult groups (Table 6.1). The prevalence of BD subtype (I vs. II) did not differ between child and adult BD.

Twelve (80.0%) child BD were euthymic ($YMRS \leq 12$ and $CDRS \leq 40$), and three (20.0%) hypomanic ($YMRS = 12-24$ and $CDRS \leq 40$) (Table 1). Eleven (52.3%) adult BD were euthymic ($YMRS \leq 12$ and $SIGH-SAD < 20$), eight depressed (38.1%) ($YMRS \leq 12$ and $SIGH-SAD \geq 20$), one (4.8%) hypomanic ($YMRS = 12-24$ and $SIGH-SAD < 20$), and one (4.8%) was in a mixed state ($YMRS > 12$ and $SIGH-SAD \geq 20$). Differences emerged between patient groups in percentage euthymic; more adult BD than child BD were depressed ($p < .01$, Fisher's Exact Test). Child BD were more likely than adult BD to meet criteria for ODD, and more child BD than adult BD were unmedicated ($N=22$ (95.7%) adult BD vs. $N= 9$ (60.0%) child BD were medicated; $p < .01$, Fisher's Exact Test) (Table 6.1). As expected, mean age (in years) at mania onset differed between patient groups (children: $M = 11.7 \pm 3.79$; adults: $M = 21.8 \pm 10.7$; $t(33) = 3.29$, $p < .01$).

6.3.2 Behavioral findings

No age group x diagnosis interactions emerged on any measure (Table 6.2). There was a main effect of diagnosis on change accuracy and mean inhibit delay, with HV having higher accuracy ($F(1,81)=8.43, p < .005$) and shorter delay ($F(1,81)=7.12, p < .01$) than BD. There was also a main effect of age group on GoRT and mean inhibit delay, with adults having longer GoRT ($F(1,81)=20.62, p < .001$) and longer mean inhibit delay ($F(1,81)=10.56, p < .005$) than children. No diagnosis- or age-related group differences emerged for CSRT (Table 2).

6.3.3 Imaging Data

Successful Change versus go:

Significant between-groups differences were seen in a number of frontal, temporal, and parietal regions, with a similar pattern across clusters i.e., increased activation in CBD versus CHV and ABD, and increased activation in AHV versus ABD (Figure 6.1_(A-C)). Specifically, age x diagnosis interactions were detected in the right middle frontal gyrus (BA 6) (Figure 6.1_A), left precentral gyrus (BA 6), right cingulate gyrus (BA 24), left middle temporal gyrus (BA 22) (Figure 6.1_B), bilateral superior temporal gyri (BA 21 and 22), left inferior temporal gyrus (BA 37), left superior parietal lobule (BA 7) (Figure 6.1_C), left paracentral lobule (BA 5), right supramarginal gyrus (BA 40), and left postcentral gyrus (BA 4) (Table 6.3).

Comparison of successful change versus fixation activation between groups revealed a general pattern of increased activation in CBD compared to ABD and CHV, and in AHV compared to ABD. Yet, many of these differences failed to reach significance in the different clusters. For

instance, while activation in the left superior temporal gyrus was greater in AHV versus ABD ($p < .02$) during successful change versus fixation, this effect was not significant in the left middle temporal gyrus. Similarly, activation in the left paracentral lobule in CBD versus CHV trended higher ($p = .06$) during successful change versus fixation, but this trend was not seen in the left superior temporal gyrus, left middle temporal gyrus, or left postcentral gyrus.

Comparison of go versus fixation activation between groups yielded a common pattern across clusters, with AHV showing hyperactivation compared to other groups. However, most of these differences failed to reach significance. In the left superior parietal lobule, AHV showed greater activation than CBD ($p < .001$), while ABD showed a trend toward hyperactivation compared to CBD ($p = .09$).

Successful change versus unsuccessful change:

The findings on this contrast were similar to those on the successful change vs. go contrast. That is, there were significant between-groups differences in a number of frontal, temporal, and parietal regions, with the general pattern of increased activation in CBD versus CHV and ABD, and increased activation in AHV versus ABD (Figure 6.2_(A-C)). Specifically, significant age x diagnosis interaction effects were detected in left cingulate gyrus (BA 24) (Figure 6.2 A), left inferior frontal gyrus (BA 45) (Figure 6.2 B), right middle frontal gyrus (BA 8), right medial frontal gyrus (BA 8), left middle frontal gyrus (BA 6), left and right middle temporal gyrus (BA 37, 39, and 22), the right superior parietal lobule (BA 7) (Figure 6.2 C), and the right supramarginal gyrus (BA 40) (Table 6.3).

Consistent with the results reported above, post-hoc analyses of the successful change versus fixation contrast indicated hyperactivation in CBD compared to ABD and CHV, and hyperactivation in AHV compared to ABD. However, only two of these post-hoc comparisons reached significance. In the right superior parietal lobule (Figure 6.2), AHV showed hyperactivation vs. CHV ($p < .01$). In the right supramarginal gyrus, CBD showed hyperactivation compared to ABD ($p < .05$).

In comparing unsuccessful change versus fixation across groups, we found hyperactivation in AHV compared to CBD in the right superior parietal lobule ($p < .03$).

6.3.4 Association of Clinical Variables with Brain Activation:

Depressed Mood:

The age group x diagnosis interactions on the two primary contrasts remained significant when only euthymic patients ($YMRS \leq 12$ and $SIGH-SAD < 20$ or $CDRS \leq 40$) were included.

Medication:

The age group x diagnosis interactions on the two primary contrasts remained significant when only medicated patients were included.

Comorbid ODD:

The age group x diagnosis on the two primary contrasts remained significant when patients with comorbid ODD were excluded.

6.4 Discussion

Developmentally informed fMRI studies inform diagnostic, therapeutic, and prevention strategies in BD (National Institute of Mental Health Strategic Plan, 2007). Tests of age x diagnosis effects evaluate the nature of brain dysfunction central to BD pathophysiology, and how this dysfunction varies with age. Using fMRI and a response flexibility task in child and adult BD versus healthy volunteers, we confirmed our hypotheses that, across age groups, BD is associated with impaired frontal and parietal activation during response flexibility.

Moreover, we also found that dysfunction is more marked in youth with BD than in adults with the illness. In addition, we found marked dysfunction in temporal regions in BD patients. Relative to the three other groups in the study (i.e., HV youth, adults with BD, and HV adults), youth with BD showed hyperactivation in MFG, IFG, ACC, precuneus, and middle and superior temporal gyri. Relative to HV adults, adults with BD showed hypoactivation in a more limited number of frontal, temporal, and parietal regions. Thus, while all BD patients show brain dysfunction during successful signal detection and response switching, BD children showed increased engagement in regions mediating inhibition, response conflict, sustained attention, and signal detection, while BD adults showed decreased engagement in a subset of these regions.

In a prior study using the stop task, we found that neural activity in both adults and children with BD differed from age-matched healthy subjects, with the direction of the difference varying developmentally. That is, during unsuccessful motor inhibition, we found ACC hypoactivation in youths with BD but ACC hyperactivation in adults with the illness (Weathers, in press). Here, during response flexibility, youths with BD showed

hyperactivation in frontal, temporal, and parietal regions, while adults with BD showed hypoactivation in these regions. Neural hyperactivation in BD patients relative to controls may represent cortical inefficiency (Gruber et al., 2010), while hypoactivation in BD may represent difficulty engaging a particular brain region during a specific task (Pompei et al., 2011). Therefore, there is evidence for cortical inefficiency in child BD patients when replacing one motor response with another (present study), while there is evidence for such inefficiency in adult BD patients when failing to inhibit a prepotent motor response (Weathers, in press). There is also evidence that adult BD patients have difficulty engaging widespread cortical regions when replacing one motor response with another (present study), while child BD patients have difficulty engaging the ACC when failing to inhibit a prepotent motor response (Weathers, in press). These differences in hyperactivation versus hypoactivation in adult versus child BD may exist either because (1) early onset BD is a different disorder from adult BD, in terms of brain activation, genetics (Grigoriu-Serbanescu et al., 2001), and symptom expression (Birmaher et al., 2006), or (2) the brain dysregulation in child BD changes over time as the underlying disease interacts with brain development, eventually coming to resemble the dysregulation that we observed in adults. Only longitudinal fMRI studies can answer this question definitively.

We found that successful change trials were associated with precuneus and inferior parietal cortex hyperactivation in young BD patients, and hypoactivation in adult BD. The parietal cortex mediates sustained attention and attention switching, which are central psychological processes in response flexibility tasks (Rubia et al., 2007a, Tamm et al., 2004, Downar et al., 2001). Previous behavioral studies demonstrate that both adult and pediatric BD patients have deficits in sustained attention and attention flexibility (Iverson et al., 2009, Dickstein et al., 2004) compared with healthy subjects. This is the first study to examine parietal cortex

activation in adult BD during attention switching and response flexibility. Yet, the present parietal cortex findings in BD youth support existing evidence that young patients have parietal hyperactivation in tasks requiring attention switching (Dickstein et al., 2010).

A similar pattern was seen in the frontal cortex during successful change trials, with pediatric patients showing hyperactivation relative to healthy youth (and adult BD) and adult patients showing hypoactivation relative to healthy adults (and pediatric BD). When successful change trials were contrasted with go trials, this pattern was evident in the MFG and left cingulate gyrus, whereas when successful change trials were contrasted with unsuccessful change trials, this pattern was present in MFG, left cingulate gyrus, and IFG. The MFG is activated when detecting a target that guides a motor response (Downar et al., 2001), while the IFG plays a central role in inhibiting motor responses (Aron, 2004) and the ACC detects response conflict (Botvinick et al., 2004). Behavioral studies indicate that BD patients are impaired in signal detection (Doyle et al., 2005, Clark et al., 2002) and motor inhibition (Swann et al., 2003). In a partially overlapping sample of youth with BD and youth HV, we found MFG hyperactivation in BD patients during successful change versus go trials (Nelson et al., 2007), similar to the MFG hyperactivation we report here in CBD compared to CHV. In addition, several studies show IFG hypoactivation during motor inhibition in both BD youth and adults (Passarotti et al., 2010, Mazzola-Pomietto et al., 2009); while we found IFG hypoactivation in ABD vs. AHV, we found the opposite pattern in CBD vs. CHV. The current study therefore extends the existing literature, by showing that MFG, ACC, and IFG dysfunction exists during response flexibility in both adults and youth with BD, although the direction of the dysfunction varies developmentally.

As in the frontal and parietal lobes, young BD patients show hyperactivation of middle and superior temporal gyri during successful change trials, while adults showed hypoactivation. In response flexibility paradigms, the middle and superior temporal gyri mediate the detection of behaviorally salient visual cues (Tamm et al., 2004, Braver et al., 2001). A previous behavioral study showed that adult BD patients are impaired in detecting behaviorally salient visual cues compared to healthy volunteers (Clark et al., 2002), while pediatric BD patients showed temporal gyri hypoactivation during a task requiring signal detection to inhibit motor responses, differences that were reversed with pharmacotherapy (Pavuluri et al., 2010). Taken together, temporal gyri dysfunction is important in BD during response flexibility, and may underlie the difficulty in detecting behaviorally salient stimuli important in switching motor responses.

While brain activity differed between BD patients and healthy volunteers during response flexibility, BD patients did not differ from controls in the speed at which they responded to change cues (CSRT) or go cues (GoRT). Adults showed longer GoRT than children (Table 6.2). Importantly, our ACC findings emerged only after adding age group x GoRT as a covariate in our model, supporting existing evidence that possible differences in the RT-BOLD relationship between youth and adults should be taken into account in studies measuring motor responses (Carp et al., 2012). The finding of increased change accuracy in adult HV compared to adult BD likely reflects the inability of the task algorithm to completely correct for changes in speed-accuracy tradeoffs between the groups.

This study has important limitations. First, we eliminated 42% of scanned subjects for excessive movement, poor performance, technical problems, or abnormal brain findings.

While this potentially limits the generalizability of our findings, this rate of exclusion is not

unusual in fMRI studies including young participants (Pliszka et al., 2006). Second, the effect of medication on imaging results could not be investigated thoroughly, since only one adult BD patient was unmedicated at time of testing. However, a previous investigation examining the impact of medication on fMRI findings suggest that medication increases the probability of Type II, but not Type I, errors (Phillips et al., 2008).

This is the first study to examine the neural mechanisms mediating response flexibility in early onset BD compared to adult BD. Our results indicate that the frontal, temporal, and parietal network that mediates successful response flexibility is dysfunctional in both child BD and adult BD. Specifically, dysfunction in this network is characterized by hyperactivation in BD youth and hypoactivation in BD adults. This extends existing evidence that the nature of the frontal dysfunction in BD varies developmentally (Weathers et al, in press) and indicates developmental differences in the direction of temporal and parietal dysfunction in patients with BD. Future longitudinal studies can determine whether this developmental difference in activation reflects different illness subtypes or, instead, different points on the developmental trajectory of BD.

Table 6.1. Subject Characteristics

Characteristic	Child BD (N = 15)	Adult BD (N = 23)	Child HV (N = 20)	Adult HV (N = 27)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Age	14.74 ± 2.23	40.85 ± 11.81	13.88 ± 1.98	35.56 ± 7.97
WASI Full-scale I.Q. ^{a,b}	109.13 ± 11.02	114.81 ± 10.35	112.95 ± 13.44	115.92 ± 9.49
YMRS ^c	7.20 ± 5.76	3.90 ± 4.90		
CDRS ^d	24.73 ± 5.61	NA		
SIGH-SAD ^e	NA	16.62 ± 11.40		
*Age of onset: Mania ^f	11.69 ± 3.79	21.82 ± 10.66		
Number of medications	1.69 ± 1.65	2.48 ± 1.53		
	N (%)	N (%)	N (%)	N (%)
Male	8 (53.3)	7 (30.4)	11 (55.0)	10 (37.0)
Euthymic ^g	12 (80.0)	11 (52.3)		
*Depressed	0 (0)	8 (38.1)		
Hypomanic	3 (20.0)	1 (4.8)		
Mixed State	0 (0)	1 (4.8)		
Bipolar I	12 (80.0)	14 (60.9)		
Bipolar II	3 (20.0)	9 (39.1)		
Any Comorbidity	12 (80.0)	15 (60.0)		
Any Anxiety Disorder	7 (46.7)	6 (26.1)		
*ODD	4 (26.7)	0 (0)		
CD	1 (6.7)	0 (0)		
Any Substance Abuse/Dependence	0 (0)	2 (8.7)		
*Unmedicated	6 (40.0)	1 (4.3)		
Atypical Antipsychotic	4 (26.7)	10 (43.8)		
Lithium	3 (20.0)	5 (21.7)		
Antiepileptic	6 (40.0)	15 (65.2)		
Antidepressant	5 (33.3)	9 (39.1)		
Stimulants	2 (13.3)	1 (4.3)		

^aMissing data from 2 adults with BD and 1 adult control.

^bNote, trend difference between adult BD and pediatric BD ($t=1.85$, $p=0.073$).

^cYoung Mania Rating Score; Missing data from 2 adults with BD.

^dChildren's Depression Rating Scale.

^eThe Structured Clinical Interview Guide for the Hamilton Rating Scale, Seasonal Affective Disorders Version. Missing data from 2 adult BD.

^fData missing from 2 children with BD and 1 adult with BD.

^gNote, trend difference between adult BD and pediatric BD ($\chi^2=2.89$, $p=0.089$).

* $p < 0.01$.

Table 6.2. Performance of subjects on the change signal task during scanning, presented by group.

	Child Healthy Volunteer N=20	Child Bipolar Disorder N=15	Adult Healthy Volunteer N=27	Adults with Bipolar Disorder N=23	Age by Diagnosis Factorial <i>F</i> statistic			Planned post hoc's (Tukey's test)
Variable	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Interaction	Diagnosis	Age	
Accuracy Go (%)	79.2 (12.7)	77.8 (12.4)	84.4 (11.2)	75.5 (16.1)	1.6	3.0	0.3	
Accuracy Change (%)	34.9 (9.6)	30.0 (10.8)	37.7 (13.2)	26.1 (15.5)	1.4	8.4**	0.0	Adult HV>Adult BD**
Go ReactionTime (ms)	696.8 (107.6)	669.9 (79.8)	761.8 (81.4)	778.5 (73.7)	1.3	0.1	20.6***	Adult HV>Child BD**; Adult BD>Child HV*, Child BD**
Inhibit Delay ^a (ms)	457.0 (121.8)	402.1 (81.8)	537.0 (100.6)	470.3 (99.1)	0.1	7.1**	10.6**	Adult HV>Child HV*, Child BD**
Change signal reaction time ^b (ms)	183.3 (45.3)	189.5 (80.2)	186.2 (69.7)	213.1 (78.5)	0.5	1.2	0.7	

Age added as covariate for adult groups.

^a Inhibit Delay=interval between onset of go and onset of change signals.

^b See text for method of calculation.

*p<0.05, **p<0.01, ***p<0.001

Table 6.3. Significant clusters of activation for age x diagnosis interaction on successful change versus go and successful change versus unsuccessful change contrasts

Primary Contrast	Region	BA	# Voxels ^a	MNI coordinates			F	p <	Between group differences
<u>Successful Change versus Go trials</u>	<u>Subregion</u>			<u>X</u>	<u>Y</u>	<u>Z</u>			
	Frontal Cortex								
	L Precentral Gyrus	6	183	-32	4	22	12.84	.001	CBD>ABD***, CHV**;
	R Middle Frontal Gyrus	6	123	34	16	42	12.38	.001	CBD>CHV***, ABD***, AHV**
	R Precentral Gyrus	4	41	20	-26	62	8.53	.005	CBD>ABD*; AHV>ABD*
	R Medial Frontal Gyrus	6	35	16	18	48	9.12	.003	CBD>ABD*
	R Cingulate Gyrus	24	24	16	2	42	7.69	.007	CBD>CHV**, ABD**
	L Postcentral Gyrus	2	21	-54	-16	46	9.03	.004	CBD>ABD***CHV>ABD*; AHV>ABD**
	Parietal Cortex								
	L Precuneus (Superior Parietal Lobule)	7	280	2	-50	48	11.29	.001	CBD>ABD*, CHV**; AHV>CHV*
	L Paracentral Lobule	5	97	-8	-28	52	9.57	.003	CBD>CHV***, ABD*
	R Inferior Parietal Lobule (Supramarginal Gyrus)	40	24	58	-52	38	9.00	.004	CBD>ABD***; CHV>ABD*
	Temporal Cortex								
	L Middle Temporal Gyrus	22	192	-60	-44	4	14.56	.000	CBD>ABD***, CHV***
	L Superior Temporal Gyrus	21	42	-64	-24	-2	14.79	.000	CBD>ABD***; AHV>ABD***
	R Superior Temporal Gyrus	22	38	52	-18	-14	9.41	.003	CBD>CHV***
	L Inferior Temporal Gyrus	37	24	-54	-68	2	7.82	.006	CBD>CHV*; AHV>CHV*
<u>Successful Change versus Unsuccessful Change trials</u>									
	Frontal Cortex								
	R Middle Frontal Gyrus	8	320	50	22	38	16.67	.000	CBD>ABD***, CHV**; AHV>ABD*
	L Cingulate Gyrus	24	88	-22	12	46	12.36	.001	CBD>CHV**; AHV>CHV**
	L Inferior Frontal Gyrus	45	71	-50	22	8	12.05	.001	CBD>CHV**; AHV>CHV*
	L Middle Frontal Gyrus	6	36	-42	6	46	12.02	.001	CBD>ABD**, CHV*
	R Medial Frontal Gyrus	8	24	10	46	36	11.29	.001	CBD>ABD**, CHV*
	Parietal Cortex								
	R Precuneus (Superior Parietal Lobule)	7	298	6	-50	48	12.75	.001	CBD>ABD**, CHV**
	R Inferior Parietal Lobule (Supramarginal Gyrus)	40	73	58	-52	38	9.76	.002	CBD>ABD***, CHV*
	Temporal Cortex								
	L Middle Temporal Gyrus	37	143	-62	-56	2	16.01	.000	CBD>ABD***, CHV**; AHV>ABD**
	R Middle Temporal Gyrus	39	125	48	-70	20	12.49	.001	CBD>ABD**; AHV>ABD**
	R Middle Temporal Gyrus	22	40	68	-40	6	10.00	.002	CBD>ABD**; AHV>ABD**

BA = Brodmann's Area

^a = cluster size at least 20 contiguous voxels, uncorrected

MNI = Montreal Neurological Institute

* = $p < .10$; ** = $p < .05$; *** = $p < .01$

CHV = child healthy volunteer; CBD = child bipolar disorder; AHV = adult healthy volunteer; ABD = adult bipolar disorder

Figure 1. Mean activation in (A) right middle frontal gyrus, (B) left middle temporal gyrus, and (C) left superior parietal lobule on successful change vs. go contrast

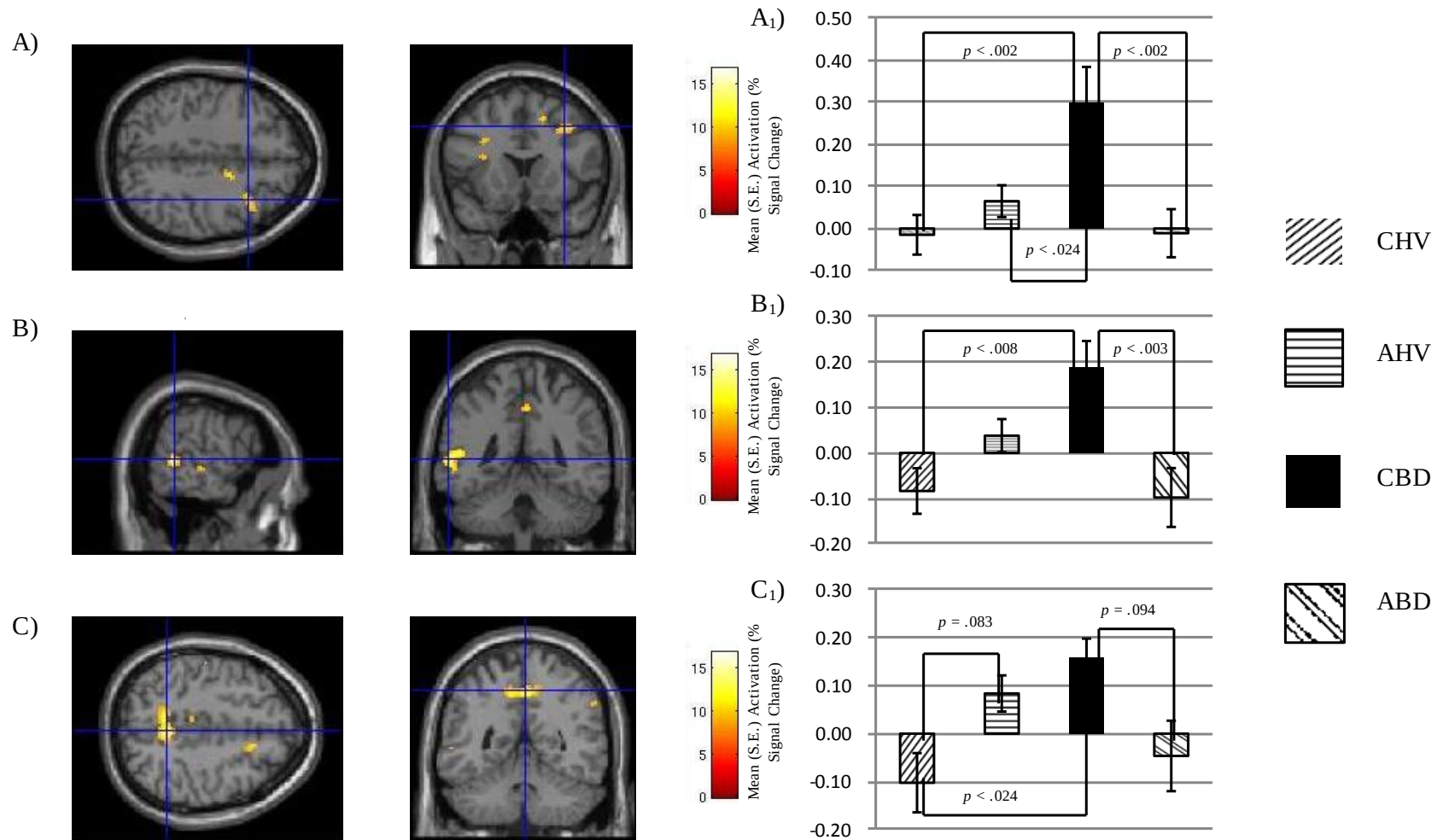


Figure 6.1. Mean activation in (A) right middle frontal gyrus, (B) left middle temporal gyrus, and (C) left superior parietal lobule.

Between group differences in percent signal change for right middle frontal gyrus (A_1), left middle temporal gyrus (B_1), and left

superior parietal lobule (C_1). CHV = child healthy volunteer; AHV = adult healthy volunteer; CBD = child bipolar disorder; ABD =

adult bipolar disorder

Figure 2. Mean activation in (A) left cingulate gyrus, (B) left inferior frontal gyrus, and (C) right superior parietal lobe on successful change vs. unsuccessful change contrast

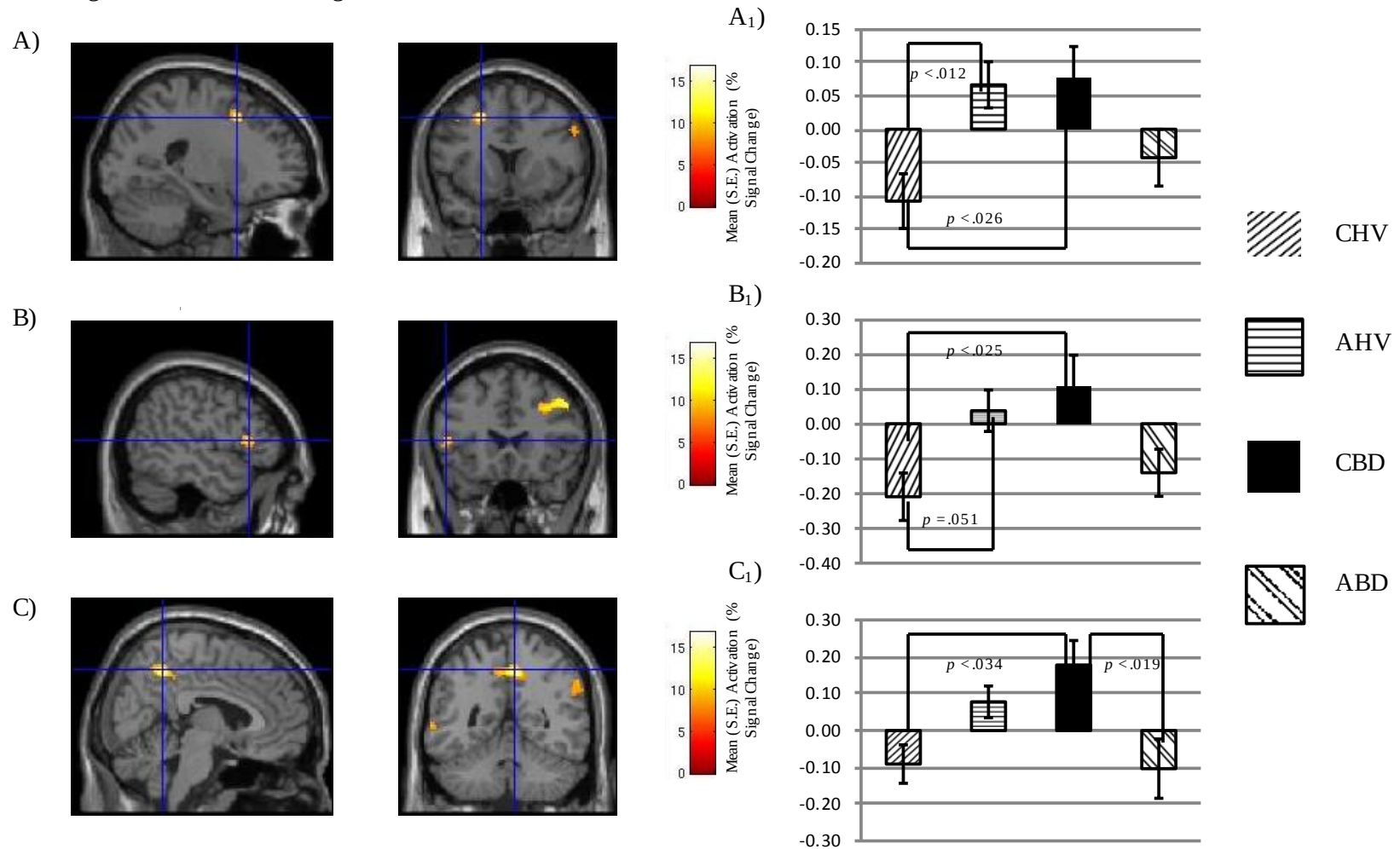


Figure 6.2. Mean activation in (A) left cingulate gyrus (B) left inferior frontal gyrus, and (C) right superior parietal lobe. Between group differences in percent signal change for left cingulate gyrus (A_1), left inferior frontal gyrus (B_1), and right superior parietal lobe (C_1). CHV = child healthy volunteer; AHV = adult healthy volunteer; CBD = child bipolar disorder; ABD = adult bipolar disorder

Chapter 7: General Discussion

7.1 Summary of Findings

Impairments in decision-making, motor inhibition, and response flexibility in BD have been linked to symptoms of increased risk taking, increased impulsivity, and a decreased ability to change behavioral responses deployed to emotionally salient stimuli, respectively. Research using brain functional imaging and neurodevelopmental perspectives can increase our understanding of the pathophysiology of BD. Specifically, research on the neural causes of neuropsychological deficits in BD can help in developing medicines aimed at reversing brain dysfunction, thereby reducing the symptoms related to impaired cognitive functioning in BD (Gitlin et al., 1995). Further, research using neurodevelopmental perspectives in BD can reveal what forms of cognitive impairment emerge early versus late in the illness, as well as whether child BD and adult BD share common pathophysiological mechanisms.

We examined sustained attention, verbal memory, executive function, and emotion regulation performance in our patients to align their cognitive functioning with that shown of euthymic patients in previous studies (Henry et al., 2008, Torres et al., 2007, Robinson et al., 2006). Our results broadly corroborated previous cognitive studies in euthymia, with patients showing decreased sustained attention, impaired executive function, speed of decision making and emotion dysregulation relative to HV (chapter 2). Effects on verbal memory were modest. These results support existing evidence that neuropsychological impairment persists after clinical recovering in BD (Bora et al., 2009, Henry et al., 2008, Torres et al., 2007, Robinson et al., 2006), and that the cognitive functioning of our patient group was aligned with groups reported in previous studies.

7.2 Risky choice

Risk-taking during the RCT was the same in adult BD patients and controls. Specifically, patients were no different from controls in the number of risky choices made during lottery selections over a range of both positive and negative expected values (EVs). While this was not what we predicted, we reasoned that the underlying pattern of brain activity might show relevant distortions in patients compared with controls, even when behavior during task performance was equivalent. However, our fMRI examination also failed to distinguish patients from controls in neural activation patterns during decision-making. Specifically, patients showed similar prefrontal, insula, and subcortical activation during the response-phase, anticipation-phase, and outcome processing phases of lottery selections (chapter 3). These results suggest that existing evidence of increased risk taking during decision-making in euthymic BD is not due to abnormal behavioral or neural responses to changes in risk between competing options, but instead may be due to subtle differences in the way reinforcement or learning mechanisms operate during decision-making in BD compared to HV (Adida et al., 2011).

Two important research questions emerge based on these preliminary results. The first is whether increased risk taking by BD during the IGT is definitively caused by abnormal neural activation in regions important in reinforcement learning, like the basal ganglia (Delgado et al., 2005, Frank et al., 2005), versus abnormal activation in regions important in emotional decision-making, such as the VMPFC and OFC (Frank et al., 2005). A neuroimaging study that can disentangle these two possibilities would support or refute the existing hypothesis that increased risky choices during IGT is due to differences in reinforcement learning in BD

compared to HV (Adida et al., 2011). Secondly, while the present study failed to find neural dysregulation during risky decision-making in euthymia, an important question is whether brain activation *becomes* abnormal when patients cycle into mania or depression. Evidence of changes in neural activation between euthymia and acute episodes, could help develop medicines that prevent those fluctuations, thereby reducing the likelihood of relapse. An ideal experiment would include longitudinal collection of fMRI data, using tasks that examine risky decision-making, in patients across euthymia, manic, and depressed moods.

To our knowledge, no study had used identical tasks in child and adult BD to investigate whether young patients show a pattern of increased risk taking during decision-making as described in some studies for adult patients. Therefore, we examined decision-making in early-onset BD patients using the RCT, and compared their performance to healthy controls and young patients with chronic irritability (severe mood dysregulation, SMD). Results showed that young patients were no different from HV or SMD in the number of risky lottery selections over a range of positive and negative EVs (chapter 4). These results suggest that child BD are no more risk-seeking than controls, and incorporate changes in risk during lottery selections in a similar fashion as HV and SMD.

Importantly, however, unlike our adult participants, our child groups used a simplifying heuristic when they make lottery choices across different EVs. Specifically, all lottery choices in children, irrespective of diagnosis, were guided by changes in the probability of outcomes, and not in changes of the magnitude associated with losing or winning (chapter 4, Table 2A). This differs from the results in adults on this task, which showed decision-making was guided by changes in probability, gain, and loss outcome information (chapter 3, Table 3.2). This difference between child and adult performance likely reflect youth's inability to employ

computational strategies during decision-making, potentially limiting our ability to detect between-group differences in risk-taking, per say, using this task. Therefore, future studies examining risk decision-making in child BD should use tasks that are sensitive to the development of decision-making strategies in childhood. An example of this would be a decision-making task that collapses probability and magnitude information into a single-dimensioned stimulus, thereby circumventing the use of simplifying probabilistic strategies in children.

7.3 Motor inhibition and response flexibility

Cross-sectional (age x diagnosis) fMRI designs are an important first step in understanding how neural dysfunction changes across the development of BD, as well as how the pathophysiologic mechanisms of child BD are similar or different from that in adult BD. No study has used this type of design to make direct comparisons of brain functioning during motor inhibition or response flexibility in child BD and adult BD, relative to age-matched controls. Here, we used this strategy to examine motor inhibition using the stop signal task in BD compared to HV. During motor inhibition performance, child and adult BD were no different from child and adult HV in their accuracy or latency in withholding motor responses to stop signals (chapter 5). However, a main effect of diagnosis emerged during successful inhibition trials. Moreover, the matched behavioral performance during motor inhibition was associated with significant age x diagnosis interactions during fMRI. These results indicate that, while subcortical (i.e. nucleus accumbens) and VPFC hypoactivation during motor inhibition is present in BD across the lifespan, ACC dysfunction varies developmentally, with child versus adult BD showing different patterns of neural dysregulation during unsuccessful motor inhibition.

Nucleus accumbens activation is important during conditioned reward learning (O'Doherty et al., 2003), while the VPFC is activated when suppressing basal ganglia output during motor performance (Aron, 2004). The demonstration that the VPFC and NAc are dysfunctional in BD patients across the developmental spectrum suggests that impaired inhibitory signals to the basal ganglia and aberrant associative learning mechanisms may arise early in the illness and persist throughout its course. These dysfunctional inhibitory and associative learning mechanisms may be related to symptoms of heightened reward-seeking and impulsivity characteristic of child and adult manic patients.

The ACC is activated during tasks engaging response conflict and error detection (Botvinick et al., 2004). We found that child BD hypoactivated the ACC, while adult BD hyperactivated the ACC, compared to controls, during unsuccessful inhibition trials. This means that BD patients do not engage the ACC appropriately during cognitive conflict induced by an error, which could diminish their ability to inhibit stimulus-incongruent responses to external cues as they manifest in real-world environments, such as when patients interact with teachers, parents, co-workers and friends.

We used a similar cross-sectional analytic design to examine response flexibility performance in child and adult BD relative to controls using the change task. Again, patient and control groups showed matched behavioral performance in their accuracy and latency in responding to change signals (chapter 6). However, this matched behavioral performance was associated with significant age x diagnosis interactions in brain functioning. The results indicated that, when having to switch a prepotent motor response to an alternate motor response guided by behaviorally salient cues, BD youth show increased neural activation in regions important in

signal detection, motor inhibition, response conflict, and sustained attention, while BD adults showed decreased activation in a subset of these regions, relative to controls. Neural hyperactivation in BD patients relative to controls may represent cortical inefficiency (Gruber et al., 2010), while hypoactivation in BD may represent difficulty engaging a particular brain region during a specific task (Pompei et al., 2011). Therefore, there is evidence for cortical inefficiency in child BD patients when replacing one motor response with another (present study), while there is evidence for such inefficiency in adult BD patients when failing to inhibit a prepotent motor response (Weathers, in press). Nevertheless, the brain dysregulation we detected during response flexibility in both child and adult BD may be related to the reduced ability to modify behavior deployed toward emotional stimuli, such as when fixating inappropriately on pleasurable activities while in a manic episode.

An important next step in understanding the development of abnormal brain functioning during motor inhibition and response flexibility in BD is using longitudinal studies that combine neuroimaging with repeated clinical assessments. Results from these types of studies may provide a potential neuroimaging-means of monitoring brain development, and therefore disease progression, in BD across the life span. Longitudinal fMRI studies will show if brain activity changes with time in youth with BD, to eventually mimic the neural dysfunction found in adult patients. This finding would suggest that the developmental trajectory of brain functioning is abnormal in BD, due to normal brain development interacting with underlying disease. Another possibility is that the brain dysfunction detected in early-onset BD stays the same as children grow into adults, suggesting child BD is a separable disorder from adult BD.

7.4 Impulse control, attention flexibility, and framing

When using the BIS, ID/ED, and framing tasks to assess executive functioning, we found our patients were no different from controls in self-reported impulsivity during BIS (chapter 2, Table 2.2) or decision-making during the framing task (chapter 2, Figure 2.3), but had increased numbers of attempts at extradimensional-shifts during ID/ED compared to HV (chapter 2, Table 2.3). Previous studies using the BIS in euthymic patients indicated increased total impulsivity relative to controls (Ekinci et al., 2011, Swann et al., 2003) Swann, 2003), with $p < .001$. However, those investigations did not report how many patients were medicated at the time of testing. This is important given evidence that medication, lithium in particular, decreases impulsivity in humans and animals (Ohmura et al., 2012, Hollander et al., 2005). This means our negative finding using the BIS may be due to increased medication use in our euthymic sample compared to previous studies. In contrast, our finding of increased extradimensional-shifts during ID/ED confirms the results from a previous study using this task in euthymic patients and their relatives (Clark et al., 2005), adding further evidence that patients show a diminished ability to shift attention to the new, behaviorally salient attributes of the visual stimuli after clinical recovery (Clark et al., 2005).

7.5 Emotion Regulation

Finally, we assessed affective reactivity and stability using the AIS, ALS, PANAS, and BAS/BIS scales (chapter 2, Table 2.2). Our results AIS and ALS results are similar to Henry (Henry et al., 2008), with patients showing increased emotional intensity (both positive and negative) and negative emotional reactivity during the AIS, and increased depressive, anxious, and elated emotional lability during the ALS, indicating patients continue to show heightened sensitivity in responding to emotionally salient stimuli (AIS findings), leading to increased fluctuations in mood (ALS findings) after recovery. During PANAS, our patients reported

elevated levels of trait positive and negative affect, and state negative affect, compared to HV, indicating patients continue to have abnormal positive and negative affective responses in euthymia. These PANAS findings were different from a previous study in euthymic BD, where patients were no different from controls in positive or negative affect (Knowles et al., 2007). Our findings may differ from Knowles (Knowles et al., 2007) however, since that study used self-reported responses to hypothetical, emotionally provocative scenarios as a measure of affective intensity.

During BAS/BIS performance, we found that our patients were no different from controls in BAS subscale measures (i.e. reward responsiveness, drive, and fun seeking), but did show increased BIS, meaning patients were more likely than controls to inhibit appetitive responses to rewarding stimuli. These results are different from Salvert (Salavert et al., 2007), which showed elevated BAS, but no increase in BIS, in euthymic patients compared to controls. Importantly, our increased BIS in patients may be related to elevated, but subsyndromal, depressive symptoms measured using the HAM-D (Meyer et al., 1999). Therefore, subsyndromal depressive symptoms in our patient group may underlie decreased approach to rewarding stimuli, evidenced by an increased BIS score compared to controls. Nevertheless, the impaired emotion regulation we detected in our patients adds to existing evidence that abnormal affective responses persist in patients after clinical recovery (Henry et al., 2008), and may underlie subsyndromal mood instability and increased likelihood of relapse.

7.6 Summary

This thesis contributes to our understanding of the neuropsychological and pathophysiologic mechanisms of BD in four important ways. First, we demonstrated that existing evidence of increased risk taking during decision-making in BD is not due to altered behavioral or neural

responses to changes in risk as assessed using the RCT in adult euthymic BD compared to HV. Future studies should determine if increased risky choices during the IGT is due to abnormal activation in brain regions important in reinforcement learning versus emotional decision-making. Second, we showed that early-onset BD are no different from healthy and patient controls during decision-making, assessed using the same lottery-based decision-making task we used our adult euthymic patients. This finding suggests that impaired decision-making is not central to the pathophysiology of child BD. Future studies should examine risk taking during decision-making in child BD using tasks sensitive to the development trajectory of decision-making strategies in youth. Third, we showed that brain activation during successful and unsuccessful motor inhibition is abnormal in BD relative to controls, but that child versus adult BD show different patterns of neural dysregulation compared to each other. Fourth, we showed that brain activation during successful response flexibility is dysfunctional in BD, but this dysfunction is again different in child versus adult forms of illness. These neuroimaging results when examining motor inhibition and response flexibility in BD, indicate one of two possibilities: (1) neural dysregulation associated with motor inhibition and response flexibility changes as young BD grow into adults, or (2) early-onset BD has different pathophysiological mechanisms compared to adult BD. Future neuroimaging studies using longitudinal designs can disentangle these two possibilities.

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