

2014

Neuroanatomical correlates of cognitive deficits in pediatric bipolar disorder

<https://hdl.handle.net/2144/14666>

"Downloaded from OpenBU. Boston University's institutional repository."

BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**NEUROANATOMICAL CORRELATES OF COGNITIVE DEFICITS IN
PEDIATRIC BIPOLAR DISORDER**

by

UZOAMAKA S. ASOBYE

B.S., University of Texas at Austin, 2012

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science

2014

© 2014 by
UZOAMAKA S. ASONYE
All rights reserved

Approved by

First Reader

Jarrett Rushmore III, Ph.D.
Department of Anatomy and Neurobiology
Boston University School of Medicine

Second Reader

Jair C. Soares, M.D, Ph.D.
Department of Psychiatry and Behavioral Sciences Chair
University of Texas Health Science Center at Houston

ACKNOWLEDGMENTS

Dr. Jair C. Soares, Chair of the Department of Psychiatry and Behavioral Sciences,
University of Texas Health Science Center at Houston

Dr. Benson Mwangi, Faculty, University of Texas Health Science Center at Houston

Dr. Isabelle Bauer, Post-Doc, University of Texas Health Science Center at Houston

Dr. Jarrett Rushmore, Faculty, Boston University School of Medicine

**NEUROANATOMICAL CORRELATES OF COGNITIVE DEFICITS IN
PEDIATRIC BIPOLAR DISORDER**

UZOAMAKA S. ASONYE

ABSTRACT

Objectives.

It has been illustrated in numerous studies that children with Bipolar Disorder (BD) consistently show deficits in declarative memory. There are a number of regions within the brain that have been inferred to correspond to these deficits. Currently, there are a limited number of studies that have analyzed the direct relationship between neuropsychological tests and anatomical brain regions. The purpose of this study was to establish a relationship between structural neuroanatomical measurements and cognitive tasks measurements in Pediatric Bipolar Patients.

Methods.

We administered the California Verbal Learning Test-II (CVLT-II) to 46 children and adolescents with BD and compared their scores 35 age-matched healthy controls. A MANCOVA between PBD and Healthy was performed and Long-Delay Free Recall (LDFR) and Long-Delay Cued Recall (LDQR) were significantly different. A multiple linear regression between LDFR and LDQC cognitive variables and anatomical volume and cortical thickness was performed in SPM and FreeSurfer libraries.

Results.

There was overall significance in CVLT-II Trial 1 ($p=0.042$), Long Delay Free Recall (LDFR) ($p=0.047$), and Long Delay Cued Recall (LDQC) scores (0.038), amongst the diagnostic groups (BD-I, BD-II, BD-NOS, Other, Healthy). Within Bipolar subjects, LDFR scores were positive correlated to the gray matter volume of the cingulate gyrus, Brodmann's area 6, parahippocampal gyrus and the thickness of the lateralorbitofrontal region. LDQC scores were positive correlated to the gray matter volume of the cingulate gyrus, Brodmann's area 7 and middle temporal gyrus. LDQC was also correlated to the volume of the superior frontal, pars triangularis, insula and the thickness of the rostral middle frontal region.

Conclusion.

These results reaffirm previous reports of the cognitive deficits present in children with bipolar disorder. This study also revealed a positive correlation between gray matter density of structures within the limbic system and performance on cognitive variables of the California Verbal Learning Test-II Children's version.

TABLE OF CONTENTS

TITLE.....	i
COPYRIGHT PAGE.....	ii
READER APPROVAL PAGE.....	iii
ACKNOWLEDGMENTS	iv
ABSTRACT.....	v
TABLE OF CONTENTS.....	vii
LIST OF TABLES	viii
LIST OF FIGURES	ix
LIST OF ABBREVIATIONS.....	xi
INTRODUCTION	1
METHODS	20
RESULTS	28
DISCUSSION	38
REFERENCES	43
CURRICULUM VITAE.....	52

LIST OF TABLES

Table	Title	Page
1	Demographics and Clinical Data	28
2	Performance on CVLTC-II	29
3	Summary of Gray Matter volume and Relationship to LDFR	32
4	Summary of measures of structural volume and cortical thickness and their relationship with LDFR	33
5	Summary of Gray matter volume and relationship with Long-Delay Cued Recall	34
6	Summary of structural volume and cortical thickness and relationship with Long-Delay Cued Recall	37

LIST OF FIGURES

Figure	Title	Page
1	Illustration of Mood Oscillations in Bipolar Disorder	4
2	Identifiers of Depressive Episode	5
3	List of California Verbal Learning Test-Children's Version Variables and Definitions	25
4	Average number of words recalled for LDQC and LDFR	30
5	Regions of Positive correlation of Gray Matter volume and LDFR performance	31
6	Regions of Positive correlation between cortical thickness in the Lateral Orbitofrontal Cortex and LDFR Performance	32
7	Regions of Positive correlation of Gray Matter volume and LDQC performance	34
8	Regions of positive correlation of cortical thickness in the rostral middle frontal gyrus and LDQC performance	35
9	Region of positive correlation of the superior frontal gyrus and LDQC performance	35
10	Region of positive correlation of the insula and LDQC Performance	36

11	Region of positive correlation of the pars triangularis and LDQC performance	36
----	--	----

LIST OF ABBREVIATIONS

ADHD	Attention Deficit/Hyperactivity Disorder
BP	Bipolar Disorder
CDRS	Children's Depression Rating Scale
CVLT-C	California Verbal learning Test-Children's version
DLPFC	Dorsolateral Prefrontal Cortex
DSM	Diagnostic and Statistical Manual
GM	Gray Matter
LDFR	Long Delay Free Recall
LDQC	Long Delay Cued Recall
MANCOVA	Multivariate Analysis of Covariance
MNI	Pediatric Bipolar Disorder
MRI	Magnetic Resonance Imaging
NOS	Not Otherwise Specified
OCD	Obsessive/Compulsive Disorder
PBD	Pediatric Bipolar Disorder
QDEC	Bipolar Disorder
SDFR	Short Delay Free recall
SDFR	Short Delay Cued recall
SPM	Statistical Parametric Mapping
TR1	Trial 1
WCST	Wisconsin Card Sorting Test

WM White Matter
WMH White Matter Hyperintensities
WMS Wechsler Memory Scale
YMRS Young's Mania rating Scale

INTRODUCTION

Once considered a rare occurrence in children and adolescents, Bipolar Disorder (BD) is increasingly being diagnosed in those under the age of 17 (Parens et al., 2010). Epidemiological studies have estimated the prevalence of pediatric BD (PBD) to be 1 to 1.5% in the general population (Pfeifer et al., 2008). The diagnosis of Pediatric Bipolar Disorder is relatively new, with most diagnoses spanning over the past two decades. Departing from the traditional view of BP being an adult illness, Geller and Luby, in a review article, stated

“Pre-pubertal onset manic depressive disorder...may present...with continuous, mixed manic, rapid-cycling of multiple brief episodes....Thus, children may be having a laughing fit and happily doing arts and craft when, without any environmental prompt, they suddenly become miserable and acutely suicidal...parents describe their children rapidly cycle sometimes numerous times a day.”
(Parry, 2012)

This and other articles discussing pre-pubertal onset of bipolar disorder in the scientific literature precipitated an abrupt change in the way physicians approached treating these patients. As a result, the diagnosis of pediatric bipolar disorder increased by 4000% from the year 1994-1995 to the year 2002-2003(Parry et al., 2012). The rapid increase in Pediatric Bipolar diagnoses, in such a short time frame, resulted in a general rise in concern and skepticism of these new cases. While, some would argue that the dramatic increase in PBD diagnosis reflects overdue recognition of its occurrence in children, others have intensely opposed this notion (Parens et al., 2010).

The negative reception to the increase in PBD diagnoses, by the public has three primary reasons. Firstly, in diagnosing adolescents with PBD, clinicians do not strictly follow the criteria as outlined by the DSM-V manual. Secondly, a high percentage of Pediatric patients do not experience a hypomanic or manic episode for a minimum duration of 4-7 days, respectively, as required by DSM-IV, before being considered bipolar (Pavuluri et al., 2005). Thirdly, bipolar disorder has long been accepted as existing on a spectrum (wide range of symptoms and levels of impairment), but the line between pathology and unaffected becomes even more blurry when diagnosing children.

Manic episodes in children may not present themselves with the classic symptoms that describe mania. Pediatric mania is characterized by severe irritability as opposed to euphoria, as seen in adults (Leibenluft et al., 2008). A symptom such as irritability, which can be found in many healthy children, being used as an identifier for bipolar disorder is very difficult for many people to accept. In the words of McClellan “The Labeling of tantrums as a major mental illness lacks face validity and undermines credibility in our profession.”(Parry et al., 2012) Lastly, the symptoms of Pediatric Bipolar disorder closely mirror those of other disorders, particularly Attention Deficit/Hyperactivity Disorder (ADHD). More often than not, children with Bipolar disorder are also diagnosed with other psychiatric disorders such as Obsessive Compulsive Disorder, Anxiety disorder and ADHD. The presence of co-morbidities makes it easy for one to question the appropriateness of a BD diagnosis in children.

With that said, there is still overwhelming support for the continuance of recognizing bipolar disorder as a spectrum in pediatric patients. There is clear evidence that exists,

showing that children with bipolar disorder have differences in brain anatomy when compared to age-matched, healthy controls (Blumberg et al., 2003; Chiu, S. et al., 2008; DelBello, M.P. et al. 2004). In particular, these patients exhibit abnormalities in structures such as the amygdala, hippocampus, and the prefrontal cortex.

Addressing the issue of BP and ADHD co-morbidity, a study conducted by Biederman and colleagues showed that these subjects possess neuroanatomical correlates of both disorders (Biederman et al., 1996). This finding shows that a diagnosis of ADHD does not undermine that of bipolar disorder in the same patient. There is a different neuropathological basis associated with each disorder.

The amount of scientific data that has confirmed the presence of bipolar disorder in pediatric patients at a neuroanatomical, cognitive and behavioral level is immense. This makes it difficult for one to deny the presence of this disease in young patients. Although much has been discovered regarding PBD, there is still great interest and promising research that will attempt to further elucidate this complex mood disorder.

States of Bipolar Disorder

Bipolar disorder (BD) is a type of mental illness that causes radical emotional changes and mood swings such as recurring episodes of mania and depression (Medicaldictionary). As illustrated in Figure 1, between these periods of mania and depression, the patient is in a normal non-depressed emotional state, also known as euthymia.

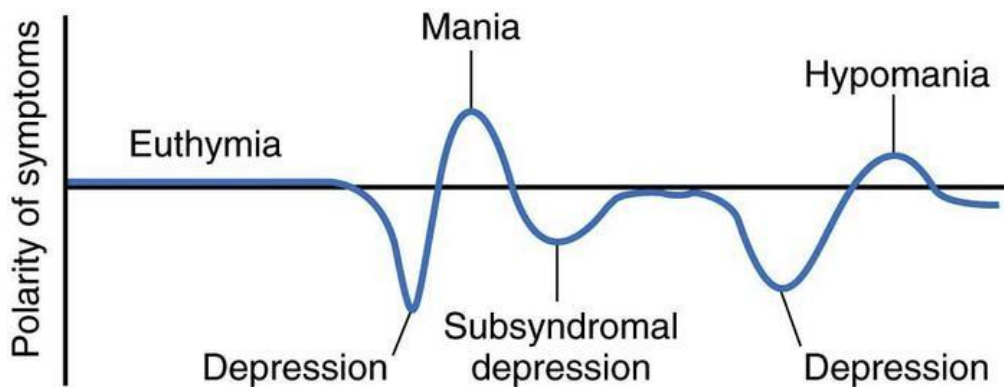


Figure 1: Illustration of Mood Oscillations in Bipolar Disorder. Retrieved from *Cleveland Clinic*, by S. Khalife, V. Singh & D.J. Muzina, 2014, Retrieved from <http://www.clevelandclinimed.com/medicalpubs/diseasemanagement/psychiatry-psychology/bipolar-disorder/> . Copyright (2000-2014) by The Cleveland Clinic Foundation.

Mania

Mania is a persistent elevation of mood that appears as increased excitation or irritability.

If a patient presents with an expansive or elevated mood, he or she must exhibit 3 of the following 7 symptoms: a decreased need for sleep, forced speech, racing thoughts, distractibility, inflated self-esteem, excessive involvement in risky behavior, and increased goal-directed activity (Parens, 2010). When the mood is characterized by irritability, the patient should present with at least 4 of the previously mentioned symptoms (Parens, 2010). In a manic state, these symptoms lead to cognitive and social functioning impairment (Leibenluft & Rich, 2008). *Hypomania* is a milder form of mania. Although there is a marked difference in behavior of people experiencing a hypomanic episode, their social and cognitive functioning is not as impaired as those experiencing mania. In DSM-V, the characterization of an episode requires a distinct

period of abnormally, persistently elevated or irritable mood for duration of at least seven days for mania and four days for hypomania (Am. Psychiatr. Assoc., 2000)

Depression

The Depressive phase of bipolar disorder presents with the same symptoms as unipolar depression. The symptoms for depression include depressed mood or irritability, decreased energy, a change in sleeping patterns, psychomotor retardation or agitation, and suicidal ideation. Although it may be challenging to diagnose a patient with the appropriate disorder, a clinician can use helpful identifiers summarized in the table below.

Episode features	Longitudinal illness history
Rapid onset and end of episode	Family history of bipolar disorder
Brief episodes (<2 weeks)	First episode at younger age (<25)
Psychotic features	Frequent episodes
Atypical features	History of brief major depressive episodes
Psychomotor retardation and anergia	History of mania or hypomania
Hypersomnia	History of antidepressant-induced hypomania
Mood lability	History of postpartum depression
Nonresponse to antidepressants	Cyclothymic or hyperthymic temperament
Response to lithium	

Figure 2: Identifiers of Depressive episode. Retrieved from *Bipolar Disorders: Basic Mechanisms and Therapeutic Implications* (p.6), by A.H., Young & J.C. Soares (Eds.), 2007, New York, Ny: Informa Healthcare.

It is important to identify the condition that a person is experiencing because the two states require different medications (lithium or antidepressants) for treatment and different long-term functional outcome and different course of the disease

Diagnosing PBD

The core controversy with diagnosing PBD is the characterization of mania in children. The two primary developmental differences in adult BD and PBD that have

been proposed are (1) the cardinal symptom of severe irritability in pediatric mania, as opposed to that of euphoria in adults and (2) a distinction between mood episodes separated by euphoria in adult BD, in contrast to rapid cycling and chronic symptoms in children (Leibenluft et al., 2008). Currently there are 3 distinct approaches taken in identifying children with BD. The first of which applies the criteria, as outlined by the DSM, for identifying mania in adults, in children as well (Leibenluft & Rich, 2008). In doing so, Clinicians must take into account behaviors that are age-appropriate when identifying a patient's symptoms as abnormal. This method suggests that the presentation of mania in adults and children follow a similar pattern. Whereas, the second approach, proposed by Geller and colleagues, suggests that rapid mood changes and complex cycling are characteristic of PBD (Geller et al., 1998). In their method, the diagnosis of a mania requires either an elevated mood or grandiosity (Geller et al., 1998). In the final approach, rather than focusing on a change in mood state from baseline, another group of researchers consider the presence of chronic, severe and extremely impairing irritability as a criterion for diagnosing mania (Biederman et al., 1998).

Clinicians are faced with the issue of deciphering which approach is most suitable for diagnosing PBD. The Academy of Child and Adolescent Psychiatry (AACAP) supports the use of DSM-IV-TR criteria for the assessment of BD in youths (McClellan et al., 2007—Leibenluft). Therefore, physicians should focus on the presence of an elevated and/or irritable mood and episodic symptoms when identifying PBD. The diagnosis of Bipolar Disorder falls under three sub-types: Bipolar-I, Bipolar-II and Bipolar-Nos. Children with *Bipolar-I* experience manic episodes with or without

recurrent depression (Maj et al., 2002). *Bipolar-II* consists of spontaneous hypomania with recurrent depressive episodes (Maj et al., 2002). The *Bipolar-NOS* sub-type consists of bipolar patients who either present unremitting, non-episodic dysregulation in mood and behavior or whose episodes fail to meet the duration requirement outlined by the DSM (Leibenluft & Rich, 2008).

Cognitive Functioning in PBD

In an attempt to identify endophenotypic markers of BD, there is great interest in understanding the cognitive deficits associated with this disorder (Leibenluft & Rich, 2008). Cognitive impairments in adult and pediatric BD have been identified, regardless of age and mood phase (Pavuluri et al., 2006; Dickstein et al., 2004; Martinez-Aran, 2004). This implies that cognitive dysfunction is more of a trait-like characteristic of BD, rather than a by-product of prolonged illness. These impairments result in learning difficulties that often lead to poor academic achievement and the need for special education services (Pavuluri et al., 2009). The cognitive domains that have been implicated in PBD include areas of memory (working and verbal), attention and executive function (Pavuluri et al., 2009). Each of these domains is discussed in detail below.

Working Memory

Working memory refers to a brain system that temporarily stores information where they can be manipulated to perform complex cognitive tasks such as language comprehension, learning and reasoning (Baddeley, 1992). This system can be subdivided

in to three components: (i) the central executive, otherwise referred to as the attentional-controlling system (ii) the visuospatial sketch pad which manipulates visual images and (iii) the phonological loop, which holds and processes auditory and verbal information (Baddeley, 1992). Working memory is necessary for children when performing tasks such as learning the alphabet, performing mental math problems, comprehending reading materials and understanding social cues. There are multiple tests available for measuring working memory. They include the Digit Span and Arithmetic and the WMS-III Digit Span raw Score and Spatial Span Raw Score.

The demonstration of impairment in working memory has mostly been in adult BD studies. One Longitudinal study of Pediatric Bipolar patients showed that these children perform significantly lower on tasks that engage working memory (Pavuluri et al., 2009). Specifically, this study showed that PBD patients were still lagging behind their age-matched controls. Data are not consistent in this respect; in a study carried out by Dickstein (2004) and colleagues, they did not find a difference in the working memory of PBD relative to controls.

Verbal Memory

Verbal memory is a concept that refers to the ability to learn, store and consolidate, and retrieve information (the memory of information that has been presented verbally). Verbal memory is most commonly tested in PBD by the recall of a list of words. This type of testing falls under the category of declarative (explicit) memory and more specifically semantic memory. According to Tulving (1972), semantic memory is the memory needed for the use of language and serves as storage for the organized

knowledge of words, other verbal symbols, and referents about the relationships amongst them (Tulving, 1972).

The *California Verbal Learning Test* is the most extensively used measure of learning, immediate and delayed recall. Consistent with the findings in adult bipolar disorder, pediatric patients' performance on tasks measuring verbal memory is significantly lower than age-matched controls (McClure et al., 2005). In this particular study, children were neither able to recall as many words nor distinguish target from distracter words during recognition testing, as well as controls. These impairments in recall were replicated in a study conducted by Glahn (Glahn et al., 2005), as well. Children with issues in declarative memory may have difficulty in learning and with language acquisition.

Verbal memory has been consistently identified as having a link to the hippocampal region of the brain (Tulving et al., 1998; Eichenbaum & Cohen 2001). The hippocampal memory system is composed of the cerebral cortical areas, parahippocampal region and the hippocampus (Eichenbaum et al., 2000). An initial report of human memory loss showed impairment in memory, independent of any other cognitive functions (Scoville et al., 1957). Further Cohen and Squire identified the hippocampal region as functioning selectively in declarative memory (Cohen et al., 1980).

Attention

Attention is a cognitive process that requires one to selectively concentrate on a particular aspect of their environment, while ignoring other distracters, and respond to

that stimulus (Anderson et al., 2004). There have been a number of potential attentional subsystems that have been proposed and they are described as either top-down or bottom-up processing (Young & Soares, 2007). Top-down processing involves the passing down of information, acquired through prior experiences, from higher to lower brain regions in preparing goal-directed selection for stimuli and responses (Young & Soares, 2007). Bottom-up processing describes the flow of information, starting from sensory input, through perceptual analysis and ending in motor output (Young & Soares, 2007). Bottom-up processing is associated with temporo-parietal and inferior frontal cortices, while top-down processing is associated with the intraparietal cortex and superior frontal cortex (Young & Soares, 2007).

Numerous studies have illustrated deficits in attention in the adults with bipolar disorder (Neu et al., 2001; Ferrier et al., 1999 and Basso et al., 2002). The Continuous performance task (CPT), can be used to measure sustained attention. Youths with bipolar disorder showed deficits in attention, even when ADHD status was entered as a covariate in statistical analysis (Doyle et al., 2005). In this sample, both drug-naïve and medicated children exhibited poor performance on cognitive tests assessing sustained attention, such as the Digit Span. Results from the Cambridge Neuropsychological Test Automated Battery found that children with PBD were impaired on the Intra/Extradimensional shift subtest, relative to normal children (Dickstein et al., 2004).

Executive Function

Executive function (EF) is generally used as umbrella term that describes a system that controls cognitive processes (Elliot, 2003). In the words of Funahashi, “executive

function is a product of the co-ordinated operation of various processes to accomplish a particular goal in a flexible manner (Funahashi, 2001).” These cognitive processes include problem solving, planning and execution, working memory and reasoning (Monsell et al., 2003). In the school setting, children with EF deficits are impulsive (e.g. they cannot wait to speak until called on), encounter difficulties in making and executing plans, and struggle to effectively use time-management skills and multi-task. Literature suggests that the prefrontal cortex mediates different aspects of executive function (Elliot, 2003).

The executive function is measured with pen and pencil and computerized tests such as the Cambridge Neuropsychological Test Automated Battery (CANTAB), Intra/Extradimensional Shift task, Wisconsin Card Sorting Test (WCST) and Stroop color-word test (Walshaw et al., 2009). A longitudinal study showed that children with PBD were not only impaired in the domain of executive function, but also had significantly less progress at the 3-year follow up, relative to normal controls (Pavuluri et al., 2009). Doyle and colleagues (2005) conducted a study that also showed that children with PBD exhibited deficits in executive function, like working memory. A qualitative review of executive function in PBD, conducted by Walshaw, found primary differences in executive function in the areas of interference control, working memory, planning, cognitive flexibility and fluency, relative to healthy children (Walshaw et al., 2009). Other studies have drawn similar conclusions (James, A. et al., 2011; Pavulri, M. et al., 2006). These findings are, therefore, relatively consistent in PBD literature.

Structural Brain Abnormalities

Multiple imaging studies have identified anatomical brain changes in children with bipolar disorder. This is done by measuring certain features of the brain such as cortical thickness, gray matter volume and the volume of structures within in the brain.

The chronology of structural changes in bipolar disorder is largely unknown. Studying the brain anatomy of children with PBD is advantageous because the confounds associated with Adult BD do not exist, such as duration of illness, effects of medication and number of episodes. Therefore, at early onset, MRI studies are necessary in order to better understand the underlying pathophysiology of that is involved in bipolar disorder. Specifically, we may learn of any unique traits that may exist in PBD. Brain abnormalities observed in Adult Bipolar Disorder do not necessarily overlap with those in children. In the next section we will discuss the anatomical regions found to be altered in PBD.

Prefrontal Cortex

The prefrontal cortex is an essential area of interest in understanding the pathology of BD. This region of the brain plays a crucial role in higher order cognitive functions such as executive functioning and decision making. There is a growing body of evidence that shows abnormalities in particular regions within this area of the brain.

Left Anterior Cingulate

The cingulate cortex lies in the medial wall of each cerebral hemisphere and the anterior cingulate (ACC) is associated with Brodmann areas (BA) 24, 25, 32 and 33 (Stevens et

al., 20110). The ACC is thought to play an essential role in the executive control of cognition (Carter et al, 1999). Carter suggests that the ACC is important for executive processes that support the detection of processing conflicts that may be associated with deteriorating performance on cognitive tasks (Carter et al., 1999). Additionally, the anterior cingulate cortex has been implicated in the regulation of emotional behavior, based on the findings from different neuroimaging studies (George, M. et al., 1995; Elliot, R. et al., 2000)

Further, other studies have indicated that the anterior cingulate may play a role in the pathology of pediatric bipolar disorder. Children and adolescents with bipolar disorder have been shown to have significantly smaller volumes in the left anterior cingulate, relative to age and gender matched healthy controls (Kaur et al., 2005). These findings were later confirmed in a study conducted by Chui and colleagues. In this study, pediatric bipolar subjects had a significantly smaller Left Anterior Cingulate (ACC) volume when compared to healthy controls. These differences did not appear to be due to medication use (Chiu et al., 2008).

Left Dorsolateral Prefrontal Cortex

Dorsolateral Prefrontal Cortex (DLPFC) is a region of the prefrontal cortex that includes Brodmann's areas 9 and 46. This region of the prefrontal cortex is involved in executive functions, working memory, and regulation of emotion (Young & Soares, 2007). Based on research findings, Nathaniel-James suggested that a specific function of the DLPFC may be that of selecting a set of responses suitable for a given cognitive task, otherwise known as response-sculpting (Nathaniel-James & Frith, 2002).

In a study in 2005, it was observed that pediatric subjects with PBD had reduced gray matter volume in the Left DLPFC relative to healthy controls (Dickstein et al., 2005). These findings have been replicated in the adult BD population as well. One Adult BD study concluded that a morphological signature of BD is a decreased neuronal and glial density within the dorsolateral prefrontal area (Grazyna, R. et al., 2001). Currently, the DLPFC is an understudied region in MRI studies concerning Pediatric Bipolar Disorder. Information on whether the DLPFC is a marker for BD is inconclusive.

Medial Temporal Structures

Amygdala

The amygdala has long been recognized as a critical feature in the neural circuitry responsible for the processing of emotion (Gallagher & Chiba, 1996). Aside from its regulation of emotional states internally, it has been shown that bilateral damage to the amygdala results in the decreased ability of a subject to adequately process information about emotions conveyed by complex perceptual cues (Young et al., 1996). The amygdala is essential for modulating the consolidation of long-term memories that are associated with emotionally arousing experiences (Mcgaugh et al., 1996).

The central role of the amygdala in the processing of emotions makes it, justifiably, a great area of interest for affective mood disorder studies. Volumetric studies indicate that the size of the amygdala is altered in BD. In the adult population, a study led by Strakowski discovered an enlargement in amygdala volume in BD subjects relative to healthy controls (Strakowski et al., 1999). Additionally, this finding was consistent in adult men when compared to both schizophrenic and normal comparison subjects

(Altshuler et al., 2000). Long-term use of lithium may have had an effect on the enlargement of this structure in BP patients, since it has been shown that lithium-treated patients have greater total gray matter volumes than untreated patients and controls (Sassi et al., 2002).

In contrast, Blumberg and colleagues found a volume reduction in the amygdala-hippocampal complex in adolescents and young adults (Blumberg et al., 2003). In isolation, the amygdala volume was still significantly smaller than the healthy controls' volume. Del Bello et al. discovered similar findings of a reduction in amygdala volume compared to healthy controls in adolescents (DelBello et al., 2004). There are a number of additional studies that replicate this discovery. This finding, of a reduction in amygdala volume, may be more specific to Pediatric bipolar patients. The effects of lithium on the brain may not be as apparent during the early stages of BD. The specific role this structure plays in the pathology of BD has yet to be clearly outlined.

Hippocampus

The hippocampus is essential for a specific function: declarative memory (Squire, 1992). This role in declarative memory is believed to be time-sensitive; the initial formation of memory is dependent on the hippocampus, but as a more permanent memory is formed its role is diminished (Squire, 1992).

A structural brain magnetic resonance imaging (sMRI) study, showed that PBD subjects have smaller hippocampal volumes than healthy comparison subjects (Frazier et al., 2005). Further analysis of this finding showed that the female BD subjects were predominantly driving the effect. Similarly, A study conducted by Blumberg (2003) and

colleagues supports these findings by showing a trend towards reduction in hippocampal volumes of PBD relative to healthy controls. A study carried out by Dickstein and colleagues were not able to replicate this finding and found no difference in the hippocampal volumes of children with BD and controls (Dickstein et al., 2005).

Thalamus

The thalamus is a key component in the brain anatomic circuits that are involved in the pathophysiology of mood disorders (Young & Soares, 2007). The thalamus functions as a relay system for transmitting sensory information to the cerebral cortex and translates impulses from appropriate receptors to crude sensations of pain, temperature and touch (Mosby, 2008). One study has shown a reduction in thalamic area amongst pediatric schizophrenia and bipolar patients relative to healthy controls (Dasari et al., 1999). The findings of abnormalities in the thalamus are inconsistent. While two studies found larger thalamic volumes in adult bipolar patients relative to healthy controls, six other studies (two were conducted in PBD) failed to replicate these findings (Young & Soares, 2007). One study has shown a reduction in thalamic area amongst pediatric schizophrenia and bipolar patients relative to healthy controls (Dasari et al., 1999).

White Matter Abnormalities

The loss of effective connectivity between the prefrontal areas and limbic regions, indicated by white matter changes, may contribute to the understanding of the pathophysiology of PBD (Young & Soares, 2007). White matter consists of mainly myelinated nerve fibers. Studies suggest a relationship between white matter hyperintensities (WMH), impaired cognition and different vascular risk factors (Paul, R.,

Cohen, R., Ott, B. & Salloway, S. (Eds.), 2005; Fazekas, F., 1989). White matter abnormalities have been reported in MRI studies;

In a diffusion tensor imaging study, a significantly lower Fractional Anisotropy was observed in white matter fiber tracts in pediatric bipolar patients relative to controls (Pavuluri et al., 2009). Pillai and colleagues conducted a similar study and also observed a significantly greater presence of WMH in pediatric bipolar subjects, relative to healthy controls. White matter abnormalities have been observed in both PBD and first-degree relatives of BD patients. Children with bipolar disorder and unaffected first-degree relatives had significantly lower Fractional anisotropy in white matter tracts when compared to healthy controls (Frazier et al., 2007). It should be noted that WMH is not specific to PBD, as they have been observed in other psychiatric diseases such as Conduct disorder/ ADHD, unipolar depression and schizophrenia.

Purpose of Study

Cognitive deficits in children with bipolar disorder persist, irrespective of mood state (Pavuluri et al., 2006). This makes the study of neuropsychological deficits particularly insightful because it may provide us with clues as to the neurophysiological and neuroanatomical abnormalities implicated in the pathophysiology of this disorder (Bearden et al., 2010). The severity of neuropsychological deficits is of importance to clinicians because they can serve as indicators of illness severity, functional outcome, and course of the disease. It has been illustrated in numerous studies that bipolar patients, both adults and children, consistently show deficits in declarative memory, specifically in measures of recall. The parahippocampal region of the brain, outlined previously, has

been inferred to correspond to such cognitive impairment (Tulving et al., 1998; Eichenbaum & Cohen 2001; Cohen et al., 1980)

Currently, there are a limited number of studies that have analyzed the direct relationship between neuropsychological tests and brain anatomy in Bipolar Disorder (Ali et al, 2000). This information would provide us with a *direct* link between features of the brain and cognitive dysfunction in PBD and, thus, lend insight into the mechanisms that have been disrupted in this disorder.

Therefore, the purpose of this study is to investigate the memory abilities of PBD subjects and explore the relationship between neuroanatomical structures and memory functioning in PBD. We selected memory because it has been consistently shown to be impaired in PBD.

Our aims are:

1. To test whether there are significant differences between PBD and Healthy controls in specific CVLT tasks performance.
2. Establish whether there is a significant correlation between cognitive tasks identified above and neuroanatomical morphometric signatures such as volume and cortical thickness.

First, we hypothesized that pediatric bipolar disorder patients will show cognitive deficits when compared to the age and gender matched healthy controls. Second, we hypothesized that there will be a relationship between structures that have been

implicated as abnormal in PBD, such as those within the limbic system, and any cognitive impairment that may be observed within the affected group.

METHODS

Subjects

This study was approved by the local Institutional review board at The University of Texas Health Science Center at San Antonio. Prior to participation in study, written informed assent and consent was obtained from all subjects and their guardians. The study participants included 46 children and adolescents with DSM-IV diagnosis of bipolar disorder and 35 Healthy controls, ranging from ages 8.06 to 17.96. These two groups were matched based on age, gender and ethnicity. Inclusion criteria was a DSM-IV diagnosis of bipolar disorder (I, II or not otherwise specified- NOS). Patients' diagnosis was determined through the use of a structured clinical interview of Diagnostic and Statistical Manual of Mental Disorders –IV (DSM-IV). BD patients had not abused drugs in the previous six months and did not suffer from medical problems. 15 out of 40 bipolar patients were medication naïve. Healthy controls (HC) had no history of any psychiatric disorders and substance abuse or neurologic disorders. Healthy individuals with a history of any Axis I psychiatric disorders in first degree relatives were excluded. Common exclusion criteria included in BD and HC included: pregnancy, neurologic disorders, head injury with loss of consciousness, family history of hereditary neurologic disorders and presence of metallic objects in the body. MRIs make use of strong magnets, so the presence of metal within the body of a subject may put them in potential danger.

MRI Protocol

Structural MRI images were acquired using a 1.5T GE Imaging System (General Electric Medical Systems, Milwaukee, WI) with a 3-D spoiled gradient recalled

acquisition (SPGR) protocol with the following parameters. Repetition time (TR) = 25 ms, echo time (TE) = 5 ms, flip angle = 40°, field of view (FOV) = 24 cm, Slice thickness = 1.5 mm and a matrix size = 256x192.

Clinical Testing

Young Mania Rating Scale (YMRS) is a rating scale that assesses manic symptoms. This scale is based on the patient's subjective report of their clinical condition based on the past 48 hours (MEASURE, 2006). This test is usually administered by a clinician or trained rater. A child that obtains a score of 12 or less is considered to be in remission (Young, 1978).

Children's Depression Rating Scale (CDRS) is a scale that aids clinicians in assessing childhood depression. An interview is conducted by the clinician with the child, parent and teacher, in order to complete the 17 item scale. A score of 40 or greater reflects depression and a child that obtains a score of 28 or less is considered to be in remission (Mayes et al., 2010)

MRI Acquisition

Image pre-processing

Statistical Parametric Mapping (SPM8)

Statistical Parametric Mapping refers to the construction and assessment of statistical processes used to test hypotheses regarding neuroimaging data (Guillaume, 2013). The SPM8 software package is designed for the purpose of analyzing these neuroimaging data sequences, using voxel-based morphometry (Guillaume, 2013). Put simply, voxel-based morphometry is a whole-brain, unbiased technique, that compares

the local concentration of gray matter of different brains on a voxel-by-voxel basis (Mechelli et al., 2005).

All T₁-weighted MR scans were visually inspected to rule out artefacts and spatially normalized into a common anatomical template to allow inter-subject statistical comparisons (Ashburner, 2007). The spatial normalization step was implemented in statistical parametric mapping (SPM8) toolbox. First, the T₁-weighted MR scans were segmented into different tissue types (e.g. gray matter, white matter and cerebrospinal fluid) (Ashburner, 2007). Second, using the diffeomorphic anatomical registration through exponential lie algebra (DARTEL) method, a study-specific brain anatomical template was created based on average tissue probability maps from all subjects (Ashburner, 2007). Third, in order to control for tissue ‘stretching’ and ‘compression’ effects sustained in the previous step segmented images from the first step were aligned into the study-specific template but with an additional tissue modulation step (Ashburner, 2007). In the final step, the spatially normalized scans were resampled into a $2 \times 2 \times 2$ voxel size and smoothed with an isotropic 8 mm Gaussian full-width at half-maximum (FWHM) smoothing kernel.

Free Surfer

Free surfer is a surface-based, brain imaging software that performs cortical reconstruction and volumetric segmentation. This software can be used to measure different morphometric properties of the brain such as cortical thickness and regional/structural volumes. In contrast to voxel-based, surface-based morphometry

typically involves the measurement of cortical thickness on a vertex-by vertex basis (CNA lab).

In a short summary, this process entails motion correction, removal of non-brain tissue, automated Talairach transformation, segmentation of white and gray matter volumetric structures, intensity normalization, tessellation of gray and white matter border, automated topology correction and surface deformation (Ecker et al. 2012). The volumes used in the analysis of sub-cortical volumes were extracted from aseg atlas including labeled regions for individual subjects (Fischl et al., 2002). Cortical thickness measures were extracted from Desikan-Killiany atlas (Desikan et al., 2006). The Query, Design, Estimate, Contrast (QDEC) application is a single binary application that was used to perform inter-subject/group averaging and inference on morphometric data produced by the FreeSurfer processing stream (FreeSurfer Wiki, 2013).

Neurocognitive Measurements

We administered the California Verbal Learning Test- Children's version (CVLT-C) to patients and healthy controls in order to assess their cognitive function. This test measures verbal learning and declarative memory using a multiple trial list-learning paradigm (Strauss, Sherman & Spreen, 2006).

The CVLT-II is administered as follows. First, the experimenter reads a 16-word list (List A) and asks the participants to recall as many words as possible in any order. This is repeated four more times for a total of five trials. Following this learning procedure, a different 16-word list (List B) is read to the subjects and participants are to

recall as many words as possible. List B is an interference/ intrusion list and is only recalled once. Next, participants are to recall as many words as they can remember from the first list (list A). This measures their short-delayed free recall. The list of 16 words fall under four distinct categories. The experimenter then, asks the subjects to recall the words from the first list after each category is read (short-delay cued recall).

Next, participants are given a break from recall tasks and are to engage in other executive function tasks for 20 minutes. Then, participants are to recall words from the first list A (long-delay free recall). Participants are not made aware of the fact that they would be recalling these words again. Next, the experimenter cues the subjects, using the categories, to recall list A for the final trial (long-delay cued recall).

The test lasts 15 to 20 minutes, excluding the additional 20 minutes needed to accommodate the delayed-recall interval.

Variable	Description
List A Total	Total number of words recalled across the five learning trials
List A1	Number of words recalled from the first trial
List A5	Number of words recalled from the fifth trial
List B	Number of words recalled from the interference list (List B)
List A Short-Delay Free Recall	Number of words recalled from List A immediately after exposure to the interference trial (List B)
List A Short-Delay Cued Recall	Number of words recalled from List A immediately after exposure to the interference trial (ListB), with semantic cueing
List A Long-Delay Free Recall	Number of words recalled from List A after the long delay (20 min)
List A Long-Delay Cued Recall	Number of words recalled from List A after the long delay (20 min), with semantic cueing

Figure 3: List of California Verbal Learning Test- Children’s Version variables and definitions. Adapted from *Compendium of Neuropsychological tests: Administration, norms and Commentary* (p. 736), by E. Strauss, E.M.S. Sherman & O. Spreen, 2006, Oxford: Oxford Press.

Statistical Analysis

Neurocognitive Statistical Analyses

Statistical analyses of neurocognitive and demographic data were performed using SPSS. Multiple one-way ANOVAs were performed to detect between group

(Bipolar and Healthy) differences for Age, sex, years of education, YMRS, and CDRS scores. The two groups did not differ on age (0.39), sex (0.61) and years of education (0.17). There were significant differences in YMRS ($p=0.00$) and CDRS scores ($p=0.00$). A Multivariate analysis of covariance (MANCOVA) compared cognitive scores, according to diagnosis (BP-I, BP-II and Healthy) adjusting for age and years of education. When a significant omnibus F statistic was observed, post hoc comparisons were computed. Results were significant with $p<0.05$.

Neuroanatomical statistical analyses

Multiple linear regression

A multiple linear regression was performed to explore the relationship between **gray matter volume** and cognitive variable of interest which were Long-Delay Free Recall (LDFR), and Long-Delay Cued Recall (LDQC). Age and Education entered to the model as covariates. The cluster size threshold was set at 51 voxels and at a FDR corrected significance level at $p<0.05$. The null hypothesis of no linear relationship between cognitive variables and neuroanatomy was tested using a one-sample t-test in SPM8, for a group level VBM analysis. In order to establish significance, voxel threshold was set at $p<0.05$ and clusters needed to exceed 51 contiguous voxels. This method was adapted from the Monte-Carlo neuroimaging algorithm to identify these parameters (Slotnick et al., 2003). This approach only allows for clusters of voxels, rather than individual voxels, that meet the criteria to be regarded as reflecting a significant positive linear relationship between a cognitive variable.

A second multiple linear regression was performed to explore the relationship between the **volume** of brain measures and memory scores Long-Delay Free Recall (LDFR), Long-Delay Cued Recall (LDQC). Multiple comparison correction was performed via Monte-Carlo simulation method. The statistical threshold was set at $p < 0.05$.

The use of different neuroimaging software served two purposes. We leveraged on these tools to extract multiple morphometric features that can inform us more about neuronal structure as opposed to one feature. This allowed us to take a multidimensional approach in assessing the underlying neural structure and its relationship to cognition in PBD.

Secondly, the use of these two different methods allows us to see whether findings from FreeSurfer are replicated in SPM and vice versa.

RESULTS

Demographic Characteristics

As illustrated in Table 1, there were a total of 81 subjects that participated in this study (PBD=46, controls=35). The subjects ranged in age from 8.07 years to 17.96 years. PBD subjects had significantly higher YMRS ($p=0.00$) and CDRS ($p=0.00$) scores.

Characteristic	Bipolar I Mean(SD)	Bipolar II Mean(SD)	Healthy Controls Mean(SD)	Significance
Age(Years)	12.62(3.00)	13.98(2.47)	13.76(2.87)	0.223
Sex(Females/Total)	13/26	6/14	18/35	0.865
Years of Education	6.72 (2.95)	8.21(2.91)	7.97(3.03)	0.209
YMRS	11.74(8.67)	9.00(5.86)	36.77(15.84)	$p<0.01$
CDRS	36.67(14.14)	.57(1.36)	17.71(1.27)	$P<0.01$
Age of illness onset	8.77(3.29)	8.79(3.53)	---	0.988

Table 1. Demographics and Clinical Characteristics of the sample.

Young Mania Rating Scale (YMRS); Children's Depression Rating Scale (CDRS); S.D.; Standard Deviation. Bold indicates significant group differences at alpha level 0.05.

Cognitive Performance

The results of the CVLTC-II are shown in Table 2. Analysis of cognitive performance was carried out according to diagnosis (BP-I, BP-II, and Healthy). MANCOVA analyses yielded significant differences on three cognitive variables: Trial 1 ($p=0.042$), Long-Delay Free Recall ($p=0.047$) and Long-Delay Cued Recall ($p=0.038$). Post-hoc analysis showed that BP-I subjects score lower on all these variables compared to healthy controls. The memory performance of BP-II subjects' was comparable to that of HC. BP-NOS recalled less words on Trial 1 compared to HC.

CVLT-C Variable	BD-I (n=26)	BD-II (n=14)	Healthy (n=35)	Mancova (F)	Significance (p)
<i>Trial 1</i>	5.65(1.90)	6.57(1.99)	6.74(1.46)	2.07	0.13
<i>Trial 2</i>	7.81(2.26)	9.00(1.71)	9.14(1.88)	2.50	0.09
<i>Trial 3</i>	9.00(2.70)	10.07(1.64)	10.31(1.84)	2.04	0.14
<i>Trial 4</i>	9.62(2.50)	11.00(1.41)	11.09(2.62)	2.07	0.13
<i>Trial 5</i>	10.12(2.82)	11.86(1.66)	11.09(2.63)	2.96	0.06
<i>SDFR</i>	8.58(3.20)	10.79(1.53)	10.11(2.64)	3.04	0.05
<i>SDQC</i>	9.42(2.58)	11.14(1.83)	10.66(2.36)	1.99	0.14
<i>LDFR</i>	9.04(2.68)	10.79(1.12)	10.94(2.49)	4.26	0.02*
<i>LDQC</i>	9.35(2.99)	11.64(1.28)	11.14(2.14)	4.48	0.02*

Table 2. Performance on CVLTC-II.

MANCOVA, multivariate analysis of covariance; CVLT-C, California Verbal Learning Test- Children's version; BP-I, Bipolar Disorder I; BP-II; Bipolar Disorder II, BP-NOS.

Bipolar Disorder- Not Otherwise Specified; SDFR, Short-Delay Free Recall; SDQC, Short-Delay Cued Recall; LDFR, Long-Delay Free Recall; LDQC, Long-Delay Cued Recall.

Means and Standard Deviations are reported unless otherwise specified. Bold indicates Significant group differences at alpha level 0.05. *= $p=0.05$ or below.

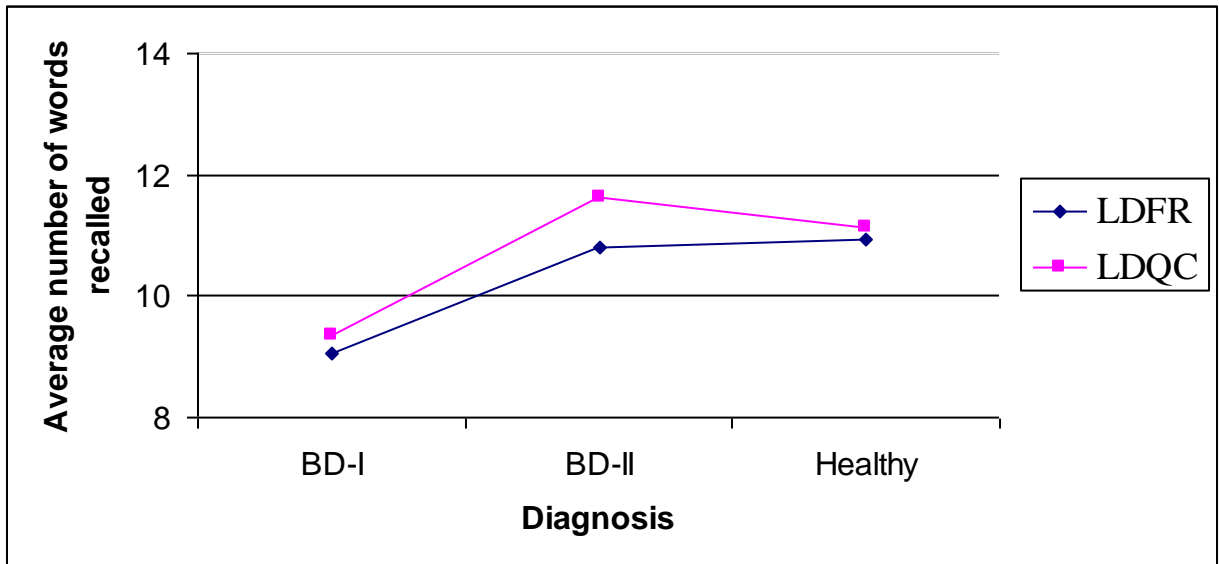


Figure 4. A line graph illustrating the average number of words recalled for LDQC and LDFR. BD-I (26), BD-II (14), and Healthy (35).

On the measure of Long-Delay Free Recall, Bp-I participants had significantly lower scores than healthy (0.013) participants. Bipolar-I Subjects had lower scores than Bipolar-II subjects, but they were not significantly different (0.051). No other groups were significantly different from another on this cognitive score. BP-I patients scores were significantly different from the healthy (0.027) and BP-II (0.024) groups for long-delay cued recall.

Multiple linear Regression Analyses

Multiple regression analyses showed that the gray matter volume of the middle frontal gyrus (Brodmann's area 6) predicted performance on LDFR, LDQC and Trial 1 in BP. The gray matter volume of the cingulate gyrus correlated positively with scores of the LDFR and LDQC in BP.

Long-Delay Free Recall

SPM Output

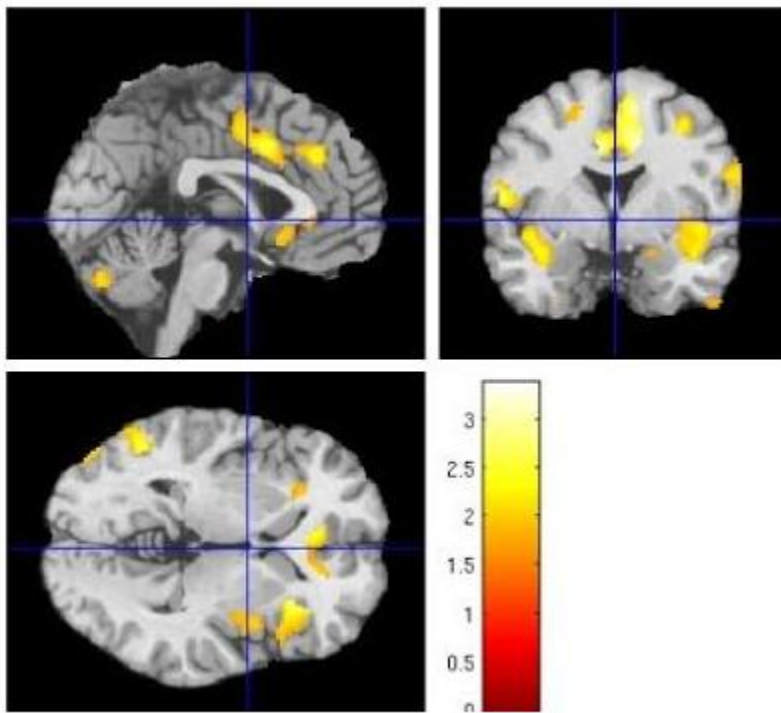


Figure 5. Regions of statistically significant positive correlations of gray matter volume with LDFR performance overlaid on the average whole-brain anatomical dataset. Colored voxels have $p < 0.05$ (corrected). Extent threshold=51 voxels. All images in radiological orientation. Refer to color legend.

Cognitive Score	Anatomical Region	MNI Coordinates	Z value
<i>Long Delay Free Recall</i>	Limbic lobe, Cingulate Gyrus	12,-4,42	3.15
	N/A	66,-28,38	2.92
	N/A	-38,-72,24	2.74
	Middle Frontal Gyrus, BA 6	34,2,48	2.71
	Limbic lobe, parahippocampal gyrus	32,-26,-22	2.65

Table 3. SPM Output. Summary of Gray matter volume and positive correlation with Long-Delay Free Recall.

Free Surfer Output

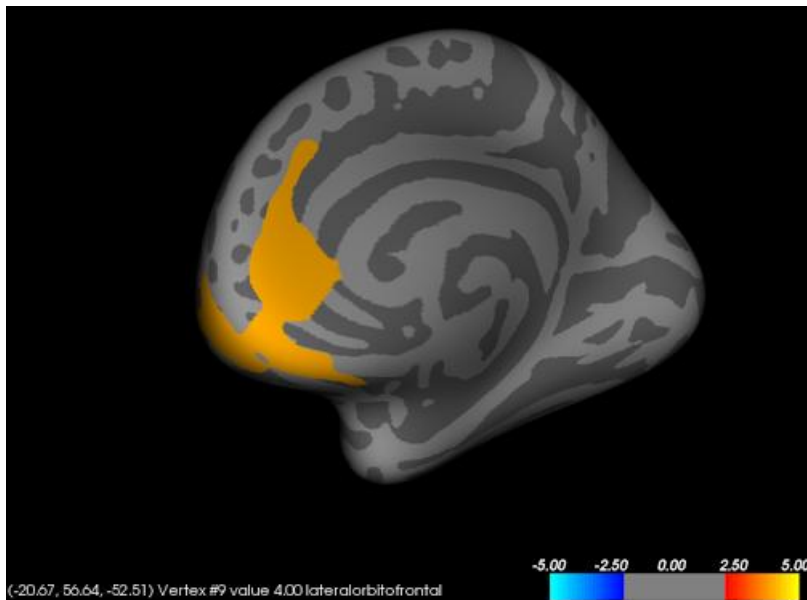


Figure 6. Regions of statistically significant positive correlations between cortical thickness in the lateral orbitofrontal cortex with LDFR performance overlaid on the average whole-brain anatomical dataset. Colored voxels have $p < 0.05$ (corrected). Refer to color legend.

FreeSurfer				
Cognitive Score	Hemisphere	Talairach Coordinates	Thickness	Max. Value
<i>Long-Delay Free Recall</i>	RH	-20.67, 56.64, -52.51	<u>lateralorbitofrontal</u>	4.00

Table 4. Free Surfer Output. Summary of measures of structural volume and cortical thickness of and their relationship with LDFR.

SPM Output

Long-Delay Cued Recall

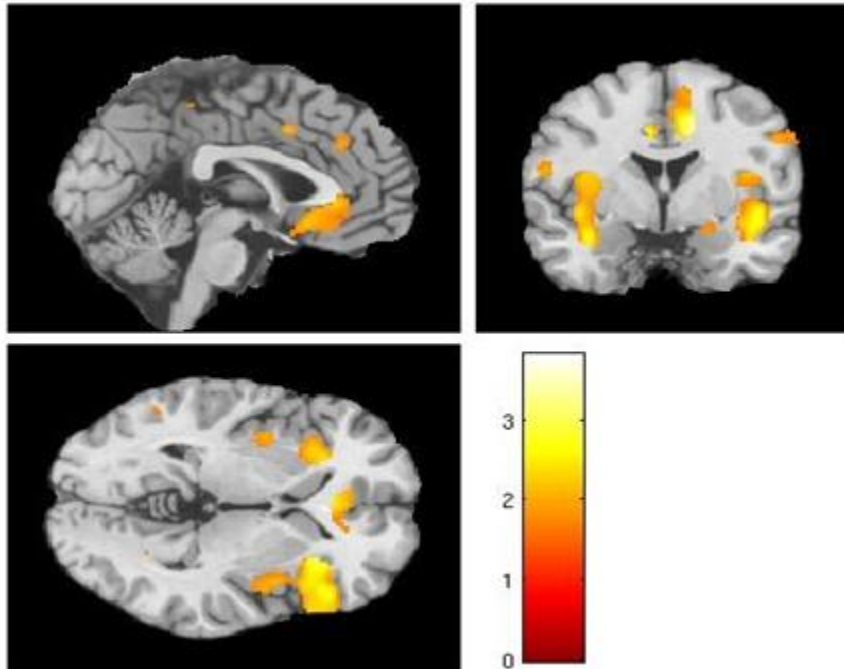


Figure 7. Regions of statistically significant positive correlations of GM volume with LDQC performance overlaid on the average whole-brain anatomical dataset. Colored voxels have $p < 0.05$ (corrected). Extent threshold=51. All images in radiological orientation. Refer to color legend.

Cognitive Score	Anatomical Region	MNI Coordinates	Z value
<i>Long-delay cued recall</i>	Parietal lobe, postcentral gyrus	62,-28,38	3.51
	Temporal lobe, middle temporal gyrus	-50,-60,8	3.35
	Limbic lobe, cingulate gyrus	-12,-2, 42	3.24
	Superior parietal lobule, Brodmann Area 7	-34,-60,46	2.79
	Sub-lobar, extranuclear	30,24,0	2.72

Table 5. SPM output. Summary of gray matter volume and positive correlation with Long Delay Cued Recall.

Free Surfer Output

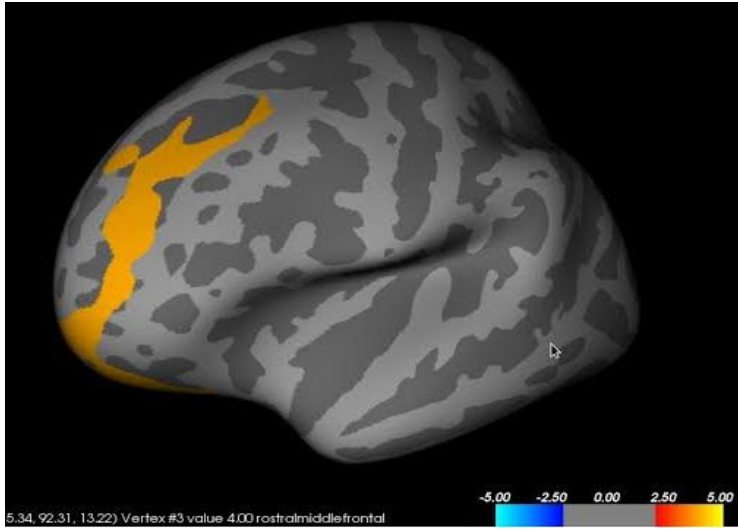


Figure 8. Regions of statistically significant positive correlations between cortical thickness in the rostral middle frontal gyrus with LDQC performance overlaid on the average whole-brain anatomical dataset. Colored voxels have $p < 0.05$ (corrected). Refer to color legend.

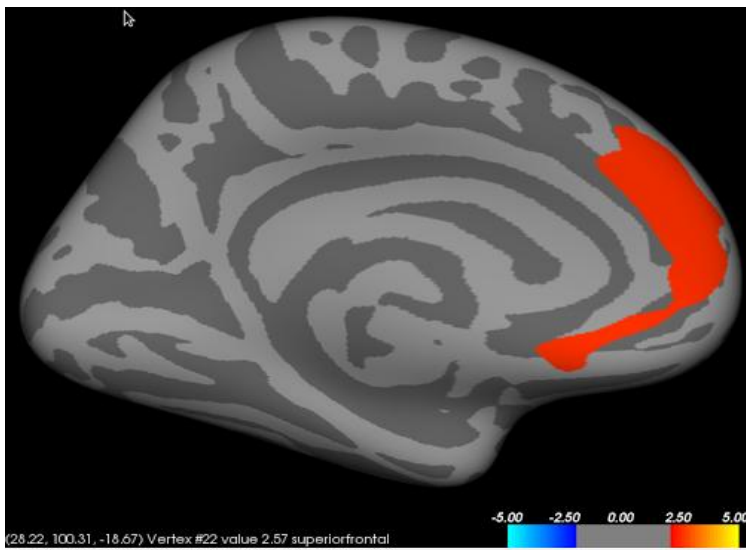


Figure 9. Region of statistically significant positive correlation between the volume of the superior frontal gyrus with LDQC performance overlaid on the average whole-brain anatomical dataset. Colored voxels have $p < 0.05$ (corrected). Refer to color legend.

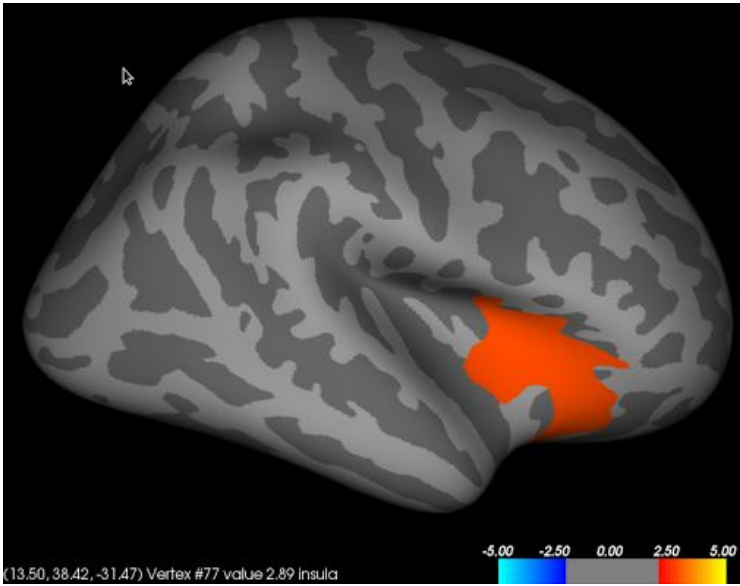


Figure 10. Region of statistically significant positive correlation between the volume of the insula with LDQC performance overlaid on the average whole-brain anatomical dataset. Colored voxels have $p < 0.05$ (corrected). Refer to color legend.



Figure 11. Region of statistically significant positive correlation between volume of the pars triangularis with LDQC performance overlaid on the average whole-brain anatomical dataset. Colored voxels have $p < 0.05$ (corrected). Refer to color legend.

<i>FreeSurfer</i>							
Cognitive Score	Hemisphere	Volume	Talairach Coordinates	Max. Value	Thickness	Talairach Coordinates	Max. Value
<i>Long Delayed Cued Recall</i>	LH	Superior frontal	28.22, 100.31, -18.67	2.57	Rostral middle frontal	5.34, 92.31, 13.22	4.00
		pars triangularis	-12.46, 54.29, -24.83	2.13	N/A	N/A	N/A
	RH	insula	13.50, 38.42, -31.47	2.89	N/A	N/A	N/A

Table 6. FreeSurfer Output. Summary of structural volume and cortical thickness and positive correlation with Long Delay Cued Recall. N/A (Not Applicable)

DISCUSSION

The main objective of this study was to confirm the existence of cognitive deficits in our pediatric bipolar sample and establish neural correlates for these deficits. To the best of our knowledge this is the first study that sought to establish a direct relationship between neuroanatomical structures and verbal memory in a general pediatric bipolar population.

Our first hypothesis, which states that pediatric bipolar subjects would perform significantly lower on cognitive variables in the CVLTC-II test relative to healthy controls, was confirmed by our findings. This outcome has been reported in previous studies that investigated verbal/declarative memory in PBD (Glahn et al., 2005). In this study, pediatric bipolar patients scored poorly on Long-Delay Free Recall, and Long-Delay Cued Recall cognitive variables. This might suggest that these patients experience the greatest difficulty in recalling words after a longer time has elapsed than controls. There were not significant findings in any of the short-delay variables. The Bipolar-I subjects were the most cognitively impaired amongst the three groups. This finding is consistent with a previous study carried out by Torrent and colleagues that found that Bipolar-II subjects performed at an intermediate level, between Bipolar-I and Healthy controls, in verbal memory (Torrent et al., 2006).

Multiple Regression Analyses revealed a positive correlation between the deficit cognitive scores of LDFR and LDQC and volume, thickness, and gray matter volume of many anatomical regions and structures such as the cingulate gyrus, parahippocampal gyrus, postcentral gyrus, pars triangularis, superior frontal lobe, middle temporal gyrus

insula, superior parietal lobule, middle frontal gyrus and lateral orbitofrontal lobe . Therefore, these structures may play an indirect role in the verbal memory of bipolar children.

Of particular interest are the structures that are found to positively correlate with Long Delay Free Recall and Long Delay Cued Recall. Some of these structures belong to the limbic system. The gray matter volume of the **cingulate gyrus**, a structure in the limbic system, showed a positive correlation with both LDFR and LDQC. The limbic system is the area of the brain that regulates mood, emotion and is also responsible for higher brain functions such as learning and formation of memories. In previous studies, structures within this system have been implicated in the pathophysiology of bipolar disorder (Kaur et al., 2005 & Frazier et al., 2005). The gray matter volume of **Brodmann's area 6** showed a positive correlation with LDFR.

LDFR also shows a positive correlation with one structure of the medial temporal lobe (MTL) and the limbic system, the **parahippocampal cortex**. A system of interconnected structures, including the entorhinal and parahippocampal cortices, in the medial temporal lobe is responsible for long-term memory encoding and retrieval (Buffalo et al., 2006). The MTL plays an instrumental role in declarative memory. The above findings support our second hypothesis, which states that structures that have been implicated as abnormal, such as those within the limbic system, in pediatric bipolar patients will also play a role in their cognitive deficits.

Although our findings have established relationships between brain morphometry and cognitive impairment in PBD, one should note that correlation does not equal

causation. The regression analysis outcomes only establish a *relationship* between cognitive variables and brain structures. Another limitation of this study is that 31 out of 46 pediatric bipolar subjects were taking psychotropic medications at the time of the study. Consistent use of psychotropic medications may alter one's brain structure and cognitive performance, thus, confounding our results.

The systematic investigation on the impact of psychotropic medications and cognition in patients with BD is limited. A study investigating the impact of psychopharmacologic treatments on cognition in PBD found that mood stabilizers (i.e. lithium) have a negative impact on processing speed and working memory (Henin, 2009). However, an investigation conducted by Pavuluri et al. (2006) found that PBD patients showed impairments in domains of attention, working memory, verbal learning and executive function, regardless of medication status. Although, cognitive deficits have been reported as an adverse effect of lithium treatment, it seems more likely that these impairments are characteristics of PBD (Grandjean & Aubry, 2009). Medication history is also important because of the impact that psychotropic drugs have on the brain. Lithium, the standard treatment in PBD, has been documented as a factor that is involved in neurogenesis (Yucel et al., 2007). There have been reports of Lithium-associated increases in total grey matter volume, anterior cingulate size and bilateral increases in hippocampal volume in BD (Moore et al, 2000; Sassi et al., 2002; Yucel, 2007).

Despite these considerations, our data illustrates clear cognitive deficits in PB patients relative to controls. These cognitive deficits have a positive correlation with the limbic system---a system that has been indicated as abnormal in bipolar disorder. This

system, when functioning normally in healthy individuals, plays an important role in verbal memory. Future research can investigate whether this system also correlates with cognitive deficits in adults who had an early onset of bipolar symptoms. This will inform us on whether bipolar adults have developed a separate set of mechanisms, in order to compensate for the early dysfunction of their limbic system. The data collected in this study could also be used to construct a model that would predict cognitive scores of each patient, based solely on their MRI scan. A model with an ability to perform this function, accurately, would provide clinicians with critical information regarding the severity of the patient's disease. Physicians would, then, be able to provide more individualized and effective treatment for children with bipolar disorder.

The only drug approved by the Food and Drug Administration for the treatment of PBD is lithium carbonate. The most effective form of pharmacological treatment is a combination therapy that involves a second-generation antipsychotic (e.g risperidone) and a mood-stabilizer (e.g Lithium Carbonate) (DelBello et al., 2002). PBD patients are not advised to use antidepressants, as it is said to precipitate symptoms of mania (Biedermen et al., 1996). Psychotherapy, used in conjunction with medication, is often essential in the recovery of PBD. Although there is no proven psychosocial treatment, Child and Family focused cognitive behavioral therapy was designed specifically for the treatment of PBD (Pavuluri et al, 2004b.) Along with effective treatment, early intervention plays an important role in achieving a better prognosis for patients with PBD.

Currently, the chronology of structural changes in bipolar disorder is largely unknown. Thus, this study serves as a contribution to a better understanding of the neural networks that underlie early-onset bipolar disorder symptoms, particularly cognitive dysfunction. Further cognitive neuroscience research is needed to further elucidate the natural progression of neuroanatomical structural changes in bipolar disorder, from childhood to adulthood.

REFERENCES

- Ali, O. S., Denicoff, K. D., Altshuler, L. L., Hauser, P., Li, X., Conrad, A. J., ... & Post, R. M. (2000). A preliminary study of the relation of neuropsychological performance to neuroanatomic structures in bipolar disorder. *Cognitive and Behavioral Neurology*, *13*(1), 20-28.
- American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Press (4th ed.).
- Anderson, J.R. (2004). *Cognitive Psychology and its implications*. New York, NY: Worth Publishers.
- Ashburner, J. & Friston, K.J. (2000). Voxel-based morphometry—the methods. *Neuroimage*, *11*, 805-821.
- Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *Neuroimage*, *38*, 95-113.
- Baddely, A. (1992). Working memory. *Science*, *225*(5044), 556-559.
- Bearden, C. E., Glahn, D. C., Monkul, E. S., Barrett, J., Najt, P., Villareal, V. , & Soares, J. (2006). Patterns of memory impairment in bipolar disorder and unipolar major depression. *Journal of Psychiatry Research*, *142*, 139-150.
- Bearden, C. E., Glahn, D. C., Monkul, E. S., Barrett, J., Najt, P., Kaur, S., . . . Soares, J. C. (2006). Sources of declarative memory impairment in bipolar disorder: Mnemonic processes and clinical features. *Journal of Psychiatry Research*, *40*, 47-58.
- Bearden, C.E., Woogen, M. & Glahn, D.C. (2010). Neurocognitive and neuroimaging predictors of clinical outcome in bipolar disorder. *Current Psychiatry Reports*, *12*, 499-504.
- Biederman, J., Faraone, S., Mick, E., Wozniak, J., Chen, L., Ouellette, C., ... & Lelon, E. (1996). Attention-deficit hyperactivity disorder and juvenile mania: an overlooked comorbidity? *Journal of the American Academy of Child and Adolescent Psychiatry*, *35*(8), 997-1008.
- Biederman J., Klein R.G., Pine D.S. & Klein D.F. (1998). Resolved: mania is mistaken for ADHD in prepubertal children. *Journal of the American Academy of Child & Adolescent Psychiatry*, *37*(10), 1091–96.
- Blumberg H.P., Kaufman J., Martin A., Whiteman R., Zhang J.H., Gore J.C., Charney D.S., Krystal J.H., Peterson B.S. (2003). Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder. *Arch Gen Psychiatry*, *60*,1201–1208.

- Bora, E., & Pantelis, C. (2011). Structural trait markers of bipolar disorder: Disruption of white matter integrity and localized gray matter abnormalities in anterior fronto-limbic regions. *Society of Biological Psychiatry*, *69*, 299-300.
- Bora, E., Fornito, A., Yucel, M., & Pantelis, C. (2010). Voxelwise meta-analysis of gray matter abnormalities in bipolar disorder. *Society of Biological Psychiatry*, *67*, 1097-1105.
- Buffalo, E.A., Bellgowan, P.S & Martin, A. (2006). Distinct roles for medial temporal lobe structures in memory for objects and their locations. *Learning and Memory*, *13*(5), 638-643.
- Carter, C.S., Botvinick, M.M., & Cohen, J.D. (1999). The contribution of the anterior cingulate cortex to executive processes in cognition. *Reviews in the Neurosciences*, *10*(1), 49-57.
- Casey, B. J., Giedd, J. N., & Thomas, K. M. (2000). Structural and functional brain development and its relation to cognitive development. *Biological psychology*, *54*(1), 241-257.
- Chiu, S., Widjaja, F., Bates, M.E., Voelbel, G.T., Pandina, G., Marble, J., Blank, J.A., Day, J., Brule, N. & Hendren, R.L. (2008). Anterior cingulate volume in pediatric bipolar disorder and autism. *Journal of Affective Disorders*, *105*(1-3), 93-99.
- Cohen, N.J. & Squire, L.R. (1980). Preserved learning and retention of pattern-analyzing skill in amnesia: dissociation of knowing how and knowing that. *Science*, *210*(4466), 207-210.
- Dasari, M., Friedman, L., Jesberger, J., Stuve, T.A., Findling, R.L., Swales, T.P. & Schulz, S.C. (1999). A magnetic resonance imaging study of thalamic area in adolescent patients with either schizophrenia or bipolar disorder as compared to healthy controls. *Psychiatry Research: Neuroimaging*, *19*(3), 155-162.
- DelBello, M.P., Zimmerman, M.E., Mills, N.P., Getz, G.E. & Strakowski, S.M. (2004). Magnetic resonance imaging analysis of amygdala and other subcortical brain regions in adolescents with bipolar disorder. *Bipolar Disorders*, *6*(1), 43-52.
- Desikan, R., Segonne, F., Fischl, B., Quinn, B., Dickerson, B., Blacker, D., ...& Killiany, R. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*, 968-980.
- Dickstein, D. P., Milham, M. P., Nugent, A. C., Drevets, W. C., Charney, D. S., Pine, D. S., & Leibenluft, E. (2005). Frontotemporal alterations in pediatric bipolar disorder: Results of a voxel-based morphometry study. *Archives of General Psychiatry*, *62*, 734-741.

- Dickstein, D. P., Treland, J. E., Snow, J., McClure, E. B., Mehta, M. S., Towbin, K. E., ... & Leibenluft, E. (2004). Neuropsychological performance in pediatric bipolar disorder. *Biological Psychiatry*, 55(1), 32-39.
- Donders, J. (2008). Subtypes of learning and memory on the California Verbal Learning Test—Second Edition (CVLT–II) in the standardization sample. *Journal of clinical and experimental neuropsychology*, 30(7), 741-748.
- Doyle, A. E., Wilens, T. E., Kwon, A., Seidman, L. J., Faraone, S. V., Fried, R., ... & Biederman, J. (2005). Neuropsychological functioning in youth with bipolar disorder. *Biological Psychiatry*, 58(7), 540-548.
- Drevets, W.C., Savitz, J. & Trimble, M. (2009). The subgenual anterior cingulate cortex in mood disorders. *CNS Spectrums*, 13(8), 663-681.
- Durston, S., & Casey, B. J. (2006). What have we learned about cognitive development from neuroimaging?. *Neuropsychologia*, 44(11), 2149-2157.
- Ecker, C., Marquand, A., Moura-Miranda, J., Johnston, P., Daly, E.M., Brammer, M.J., ... & Murphy, D.G.M. (2010). Describing the brain in autism in five dimensions---Magnetic Resonance Imagine-Assisted Diagnosis of autism spectrum disorder using a multiparameter classification approach. *The Journal of Neuroscience*, 30(32), 10612-10623.
- Eichenbaum, H. (2000). A cortical-hippocampal system for declarative memory. *Nature Reviews of Neuroscience*, 1(1), 41-50.
- Eichenbaum, H. & Cohen, N. (2001). From conditioning to conscious recollection: memory systems of the brain. *Oxford Psychology Series*. New York, NY: Oxford university Press.
- Elliott, R. (2003). Executive functions and their disorders. *British Medical Bulletin*, 65, 49-59.
- Elliot, R., Rubinsztein, J., Sahakian, B., & Dolan, R. Selective attention to emotional stimuli in a verbal go/no-go task: an fMRI study. *NeuroReport*, 11, 1739-1744.
- Engelsmann, F., Katz, J., Ghadirian, A.M. & Schachter, D. (1988). Lithium and memory: a long-term follow-up study. *Journal of Clinical Psychopharmacology*, 8(30), 207-212.
- Erus, G., Battapady, H., Satterthwaite, T. D., Hakonarson, H., Gur, R. E., Davatzikos, C. , & Gur, R. C. (2014). Imaging patterns of brain development and their relationship to cognition. *Cerebral Cortex*.
- Fazekas, F. (1989). Magnetic resonance signal abnormalities in asymptomatic individuals: their incidence and functional correlates. *The European Journal of Neurology*, 29, 164-168.

- Fischl, B., Salat, D., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., ... & Dale, A. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*, 33, 341-355.
- Fornito, A., Malhi, G. S., Lagopoulos, J., Ivanovski, B., Wood, S. J., Saling, M. M., ... Yucel, M. (2008). Anatomical abnormalities of the anterior cingulate and paracingulate cortex in patients with bipolar I disorder. *Psychiatry Research: Neuroimaging*, 162, 123-132.
- Frazier, J. A., Ahn, M. S., Dejong, S., Bent, E. K., Breeze, J. L., & Giuliano, A. J. (2005). Magnetic resonance imaging studies in early-onset bipolar disorder: A critical review. *Harvard Review of Psychiatry*, 13(3), 125-140.
- Frazier, J.A., Chiu, S., Breeze, J.L., Makris, N., Lange, N., Kennedy, D.N., & Biederman, J. (2005). Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. *American Journal of Psychiatry*, 162(7), 1256-1265.
- Frazier, J.A., Breeze, J.L., Papadimitriou, G., Kennedy, D.N., Hodge, S.M., Moore, C.M., Rohan, M.P, Caviness, V.S. & Makris, N. (2007). White matter abnormalities in children with and at risk for bipolar disorder. *Bipolar Disorder*, 9(8), 799-809.
- FreeSurfer Wiki. (2013). Retrieved from https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/QdecGroupAnalysis_freeview .
- Funahashi, S. (2001). Neuronal mechanisms of executive control by the prefrontal cortex. *Neuroscience Research*, 39, 147-165.
- Gallagher, M. & Chiba, A.A. (1996). The amygdala and emotion. *Current Opinion in Neurobiology*, 6(20), 221-227.
- Geller B., Williams M., Zimmerman B., Frazier J., Beringer L. & Warner K.L. (1998). Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms, grandiose delusions, ultrarapid or ultradian cycling. *Journal of Affective Disorders*, 51(2), 81-91.
- George, M., Ketter, T., Parekh, P., Horwitz, B., Herscovitch, R. & Post, R. (1995). Brain activity during transient sadness and happiness in healthy women. *American Journal of Psychiatry*, 152, 341-351.
- Glahn, D.C., Bearden, C.E., Caetano, S., Fonseca, M., Najt, P., Hunter, K., ... & Soares, J.C. (2005). Declarative memory impairment in pediatric bipolar disorder. *Bipolar Disorders*, 7, 546-554.
- Grandjean, E.M. & Aubry, J.M. (2009). Lithium: updated human knowledge using an evidence-based approach: part III: clinical safety. *CNS Drugs*, 23(5), 397-418.

- Guillame. (2013). Statistical Parametric Mapping. Retrieved from <http://www.fil.ion.ucl.ac.uk/spm/>.
- Henin, A., Mick, E., Biederman, J., Fried, R., Hirshfeld-Becker, D.R., Micco, J.A.,... & Wozniak, J. (2009). Is psychopharmacologic treatment associated with neuropsychological deficits in bipolar youth? *The Journal of Psychiatry*, 70(8), 1178-1185.
- Honig, A., Arts, B.M., Ponds, R.W. & Riedel, W.J. (1999). Lithium induced cognitive side-effects in bipolar disorder: a qualitative analysis and implications for daily practice. *International Clinical Psychopharmacology*, 14(3), 167-171.
- Houenou, J., Frommberger, J., Carde, S., Glasbrenner, M., Diener, C., Leboyer, M., & Wessa, M. (2011). Neuroimaging-based markers of bipolar disorder: Evidence from two meta-analyses. *Journal of Affective Disorders*, 132, 344-355.
- James, A., Hough, M., James, S., Burge, L., Winmill, L., Nijhawan, S., ... & Zarei, M. (2011). Structural brain and neuropsychometric changes associated with bipolar disorder with psychosis. *Bipolar Disorder*, 13(1), 16-27.
- Joseph, M. F., Frazier, T. W., Youngstrom, E. A., & Soares, J. C. (2008). A quantitative and qualitative review of neurocognitive performance in pediatric bipolar disorder. *Journal of child and adolescent psychopharmacology*, 18(6), 595-605.
- Kalmar, J. H., Wang, F., Spencer, L., Edmiston, E., Lacadie, C. M., Martin, A., . . . Blumberg, H. P. (2009). Preliminary evidence for progressive prefrontal abnormalities in adolescents and young adults with bipolar disorder. *International Neurological Society*, 15(3), 476-481.
- Kaur, S., Sassi, R.B., Axelson, D., Nicoletti, M., Brambilla, P., Monkul, E.S., Hatch, J.P., Keshavan, M.S., Ryan, N., Birmaher & B., Soares, J.C. (2005). Cingulate Cortex anatomical abnormalities in children and adolescents with bipolar disorder. *The American Journal of Psychiatry*, 162(9), 1637-1643.
- Keener, M. T., & Phillips, M. L. (2007). Neuroimaging in bipolar disorder: A critical review of current findings. *Current Psychiatry Reports*, 9(6), 512-520.
- Leibenluft, E. & Rich, B.A. (2008). Pediatric Bipolar Disorder. *Focus*, 6(3), 331-347.
- Luby, J. L., & Navsaria, N. (2010). Pediatric bipolar disorder: Evidence for prodromal states and early markers. *Journal of Child Psychology and Psychiatry*, 51(4), 459-471.

- Maj, Mario, Aksiskal, H.S., Lopez-Ibor, J.J. & Sartorius, Norman (Eds.). (2002). *Bipolar Disorders*. Hoboken, NJ: Wiley.
- Marsh, R., Gerber, A. J., & Peterson, B. S. (2008). Neuroimaging studies of normal brain development and their relevance for understanding childhood neuropsychiatric disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*, 47(11), 1233-1251.
- Martinez-Aran, A., Vieta, E., Colom, F., Sanchez-Moreno, J., Reinares, M., Benabarre, A., . . . Salamero, M. (2004). Cognitive impairment in euthymic bipolar patients: Implications for clinical and functional outcome. *Bipolar Disorders*, 6, 224-232.
- Mayes, T.L., Bernstein, I.H., Haley, C.L., Kennard, B.D. & Graham, E.J. (2010). Psychometric properties of the Children's Depression Rating Scale—Revised in adolescents. *Journal of Child and Adolescent Psychopharmacology*, 20(6), 513-516.
- McClure, E. B., Treland, J. E., Snow, J., Dickstein, D. P., Towbin, K. E., Charney, D. S., ... & Leibenluft, E. (2005). Memory and learning in pediatric bipolar disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 44(5), 461-469.
- McGaugh, J.L., Cahill, L. & Roozendaal, B. (1996). Involvement of the amygdale in memory storage: interaction with other brain systems. *Cross Mark*, 93(24), 13508-13514.
- Mckenna, B. S., Sutherland, A. N., Legenkaya, A. P., & Eyler, L. T. (2013). Abnormalities of brain response during encoding into verbal working memory among euthymic patients with bipolar disorder. *Bipolar Disorders*.
- Anonymous. (2006). MEASURE. Retrieved from <http://dcf.psychiatry.ufl.edu/files/2011/05/Young-Mania-Rating-Scale-Measure-with-background.pdf> .
- Mechelli, A., Price, C.J., Friston, K.J. & Ashburner, J. (2005). Voxel-based morphometry of the human brain: methods and applications. *Current Medical Imaging Reviews*, 1.
- Monkul, E. S., Malhi, G. S., & Soares, J. C. (2005). Anatomical mri abnormalities in bipolar disorder: Do they exist and do they progress? *Australian and New Zealand Journal of Psychiatry*, 39, 222-226.
- Monsell, S. (2003). Task Switching. *Trends in Cognitive Sciences*, 7(3), 134-140.
- Mosby. (2008). *Mosby's Dictionary of Medicine, Nursing & Health Professions* (8th ed.). Philadelphia, PA : Elsevier Health Sciences.

- Mwangi, B., Mathews, K. & Steele, J.D. (2012). Prediction of illness severity in patients with major depression using structural MR brain scans. *Journal of Magnetic Resonance Imaging*, 35, 64-71.
- Nathaniel-James, D.A. & Frith, C.D. (2002). The role of the dorsolateral prefrontal cortex: evidence from the effects of contextual constraint in a sentence completion task. *Neuroimage*, 16(9), 1094-1102.
- Parens, E. & Johnston, J. (2010). Controversies concerning the diagnosis and treatment of bipolar disorder in children. *Child and Adolescent Psychiatry and Mental Health*, 4(9).
- Parry, P.I., & Levin, E.C. (2012). Pediatric Bipolar Disorder in an Era of “Mindless Psychiatry”. *Journal of Trauma and Dissociation*, 13.
- Paul, R., Cohen, R., Ott, B. & Salloway, S. (Eds.). 2005. *Vascular Dementia*. Totowa, NJ: HUMANA Press.
- Pavuluri, M. N., Birmaher, B., & Naylor, M. W. (2005). Pediatric bipolar disorder: a review of the past 10 years. *Journal of the American Academy of Child & Adolescent Psychiatry*, 44(9), 846-871.
- Pavuluri, M. N., West, A., Hill, S. K., Jindal, K., & Sweeney, J. A. (2009). Neurocognitive function in pediatric bipolar disorder: 3-year follow-up shows cognitive development lagging behind healthy youths. *Journal of the American Academy of Child & Adolescent Psychiatry*, 48(3), 299-307.
- Pavuluri, M.N., Schenkel, L.S., Aryal, S., Harral, E.M., Hill, K.S., Herbener, E.S. & Sweeney, J.A. (2006). Neurocognitive function in unmedicated manic and medicated euthymic pediatric bipolar patients. *The American Journal of Psychiatry*, 163(2), 286-293.
- Pavuluri, M.N., Yang, S., Kamineni, K., Passarotti, A.M., Srinivasan, G., Harral, E.M., Sweeney, J.A. & Zhou, X.J. (2009). Diffusion tensor imaging study of white matter fiber tracts in pediatric bipolar disorder and attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 65(7), 586-593.
- Pfeifer, J.C., Welge, J., Strakowski, S.M., Adler, C.M. & DelBello, M.P. (2008). Meta-analysis of amygdale volumes in children and adolescents with bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 47(11), 1289-1298.
- Phillips, M. L., & Vieta, E. (2007). Identifying functional neuroimaging biomarkers of bipolar disorder: Toward dsm-v. *Schizophrenia Bulletin*, 33(4), 893-904.

- Rajkowska, G., Halaris, A. & Selemon, L. (2001). Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. *Society of Biological Psychiatry*, 49, 741-752.
- Rocha-Rego, V., Jógia, J., Marguand, A.F., Mourao-Miranda, J., Simmons, A. & Frangou, S. (2014). Examination of the predictive value of structural magnetic resonance scans in bipolar disorder: a pattern classification approach. *Psychological Medicine*, 44(3), 519-532.
- Sassi, R.B., Nicoletti, M., Brambilla, P., Mallinger, A.G., Frank, E., Kupfer, D.J., ... & Soares, J.C. (2002). Increased gray matter volume in lithium-treated bipolar disorder patients. *Neuroscience Letters*, 329, 243-245.
- Schenkel, L. S., West, A. E., Jacobs, R., Sweeney, J. A., & Pavuluri, M. N. (2012). Cognitive dysfunction is worse among pediatric patients with bipolar disorder Type I than Type II. *Journal of Child Psychology and Psychiatry*, 53(7), 775-781.
- Scoville, W.B. & Milner, B. (2000). Loss of recent memory after bilateral hippocampal lesions. 1957. *Journal of Neuropsychiatry and Clinical Neuroscience*, 12(1), 103-113.
- Singh, M. K., & Chang, K. D. (2007). Impact of bipolar disorder on selected areas of pediatric development: A research update. *Pediatric Health*, 1(2), 199-215.
- Slotnick, S.D., Moo, L.R., Segal, J.B. & Hart, J. (2003). Distinct prefrontal cortex activity associated with item memory and source memory for visual shapes. *Brain Research. Cognitive Brain Research*, 17(1), 75-82.
- Soares, J.C. & Young, A.H. (Eds.). (2007). *Bipolar Disorders: Basic Mechanism and Therapeutic Implications*. New York, NY: CRC Press.
- Squire, L.R. (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychological Review*, 1992, 99(3), 582.
- Stevens, F.L., Hurley, R.A., Hayman, L.A. & Taber, K. (2011). Anterior cingulate cortex: unique role in cognition and emotion. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 23, 121-125.
- Strakowski, S. M., Adler, C. M., Almeida, J., Atshuler, L. L., Blumberg, H. P., Chang, K. D., . . . Townsend, J. D. (2012). The functional neuroanatomy of bipolar disorder: A consensus model. *Bipolar Disorders*, 14(4), 313-325.
- Strakowski, S.M., DelBello, M.P., Sax, K.W., Zimmerman, M.E., Shear, P.K., Hawkins, J.M. & Larson, E.R. (1999). Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. *Archives of General Psychiatry*, 56(3), 254-260.

- Strauss, E., Sherman, E.M. & Spreem, O. (Eds.). (2006). *A Compendium of neuropsychological Tests: Administration, Norms, and Commentary*. Oxford: Oxford University Press.
- Torrent, C., Martinez-Aran, A., Daban, C., Sanchez-Moreno, J., Comes, M., Goikolea, J.M. & Vieta, E. (2006). Cognitive impairment in bipolar II disorder. *British Journal of Psychiatry*, 189, 254-259.
- Tulving E. (1972). Episodic and semantic memory. In E. Tulving & W. Donaldson (Eds.), *Organization of Memory* (pp.381-403). New York: Academic.
- Van Gorp, W. G., Altshuler, L., Theberge, D. C., & Mintz, J. (1999). Declarative and procedural memory in bipolar disorder. *Society of Biological Psychiatry*, 46, 525-531.
- Wagner, A. D., Shannon, B. J., Kahn, I., & Buckner, R. L. (2005). Parietal lobe contributions to episodic memory retrieval. *Trends in cognitive sciences*, 9(9), 445-453.
- Woods, S. P., Delis, D. C., Scott, J. C., Kramer, J. H., & Holdnack, J. A. (2006). The California Verbal Learning Test—second edition: test-retest reliability, practice effects, and reliable change indices for the standard and alternate forms. *Archives of Clinical Neuropsychology*, 21(5), 413-420.
- Young, A.W., Hellawell, D.J., Van de Wal, C. & Johnson, M. (1996). Facial expression after amygdalotomy. *Neuropsychologia*, 34(1), 31-39.
- Young, R.C., Biggs, J.T, Ziegler, V.E. & Meyer, D.A. (1978). A rating scale for mania: reliability, validity and sensitivity. *The British Journal of Psychiatry*, 133, 429-435.
- Yucel, K., McKinnon, M.C., Taylor, V.H., Macdonald, K., Alda, M., Young, L.T. & MacQueen, G.M. (2007). Bilateral hippocampal volume increases after long-term lithium treatment in patients with bipolar disorder: a longitudinal MRI study. *Psychopharmacology*, 195(3), 357-367.

CURRICULUM VITAE

