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Neuropsychological and emotion processing abnormalities in bipolar disorder I and II

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NEUROPSYCHOLOGICAL AND EMOTION PROCESSING ABNORMALITIES IN BIPOLAR DISORDER I AND II

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ABSTRACT

Neuropsychological and Emotion Processing Abnormalities In Bipolar Disorder I and II

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Bipolar disorder illness is marked by emotional lability and mood disturbance, as well as various neuropsychological deficits, and the neuroanatomical correlates of many of these deficits are beginning to be identified. Numerous studies have implicated specific cortical and sub-cortical abnormalities in areas associated with executive function, memory, motor function, and the processing of emotion. Although a large body of research has been devoted to the investigation of cognitive and emotion-processing deficits in bipolar disorder, relatively few studies have been devoted to the investigation of how these deficits differ among bipolar disorder subtypes. This is surprising in light of known symptomatological and phenomenological differences found among the illness subtypes. Moreover, the nosological status of bipolar disorder is still considered by many to be uncertain. The aim of this study is to address these ongoing issues by investigating and comparing emotion processing and neuropsychological deficits among bipolar I disorder, bipolar II disorder, and healthy control groups to further clarify the nature and extent of differences in impairment among these groups.

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CHAPTER 1

INTRODUCTION

A growing body of research is clarifying understanding of the various psychosocial, neurocognitive, and emotion processing deficits associated with bipolar disorder (Van Gorp, Altshuler, Dixon, & Theberge, 1996; Gourovitch, Torrey, Gold, Randolph, Weinberger, & Goldberg, 1999; Ferrier & Thompson, 2002; Phillips, Drevets, Rauch, & Lane, 2003). Many of these studies have also provided evidence of abnormalities of specific brain structures that are critical for the normal processing of information, including those that underpin the processing of emotion. In considering the integral nature of emotion processing in learning and memory, it is logical to assume that impairments in the processing of emotion likely contribute to the extent and nature of dysfunction commonly found in those with bipolar disorder. An accurate conceptualization of the nature and extent of the neurocognitive and emotion processing abnormalities associated with bipolar disorder has significant implications for those with the illness.

The potential benefits of increased understanding of the functional and structural abnormalities associated with bipolar disorder could lead to a refinement of the diagnostic criteria and facilitate earlier detection, more accurate diagnoses, improvement in treatment outcomes, and possibly even the development of prophylactic interventions for those at risk for this debilitating illness. More importantly, such an expansion of this knowledge base may serve to alleviate the human suffering and financial burden often realized by individuals, families, and communities as a result of the disorder.

Despite the chronic illness course inherent in bipolar disorder as well as clear differences among BP subtypes with regard to symptom presentation, age of onset, and prevalence rate, research has only recently turned attention to an examination of how neurocognitive and emotion processing deficits may differ among the subtypes.

The main purpose of this study is to investigate how neurocognitive and emotion processing profiles differ in bipolar disorder as compared to healthy populations. Differential patterns of performance in bipolar I disorder and bipolar II disorder populations were also investigated to determine whether performance measures are consistent with a spectrum conceptualization of bipolar disorder or whether these measures indicate distinct disorders among the subtypes. Considering the extant literature, it was predicted that the combined bipolar disorder groups would demonstrate a significant degree of impairment in working memory, verbal learning and memory, executive function, and emotion processing as compared to a normal control group. It was also hypothesized that the bipolar I disorder group would demonstrate a quantitatively greater degree of impairment in these domains as compared to the bipolar II disorder group, with the bipolar II disorder group performing at an intermediate level of performance between the bipolar I disorder and the normal control group, thus supporting a spectrum conceptualization of bipolar disorder illness.

CHAPTER 2

LITERATURE REVIEW

Bipolar disorder (BP) is a severe and debilitating mental disorder characterized by perceptual, affective, behavioral, cognitive, and psychosocial impairment. Due to the phenomenological variability found in BP, with illness course, symptom presentation and functional impairment in BP differing widely among individuals and across time, the disorder is often misdiagnosed and perhaps even more often inadequately treated. This is unfortunate considering the high degree of morbidity and chronicity often associated with the illness.

Lifetime prevalence rate estimates range from .4% to 1.6% in individuals with bipolar I disorder (BPI) and from .5% to as much as 5% in individuals with bipolar II disorder (BPII), (Berk & Dodd, 2005). BP appears to be distributed rather evenly among the genders, although there is some evidence that symptom presentation may differ to some degree as a function of sex. In males, the first episode is more often a manic episode, and manic episodes tend to predominate over the illness course. In contrast, the first episode among women is more often a major depressive episode, and major depressive episodes tend to predominate. This is an interesting finding and may indicate that women in general are at particular risk for depression. There is also some evidence suggesting that women experience more rapid cycling than do men. This is of note in that rapid cycling, which is characterized by the presence of four or more major depressive, manic, hypomanic, and/or mixed episodes in a twelve-month period, is associated with poorer prognosis (DSM-IV, 1994).

Research has indicated the presence of a strong genetic component in BP with higher rates of the disorder being found in first-degree biological relatives of individuals with BPI (4% - 24%) and individuals with BPII (1% - 5%). Although no specific genetic markers have been definitively identified, multiple regions on the human genome are indicated for genetic risk. One genetic study, in which 7 pairs of monozygotic twins discordant for BP were investigated, the unaffected twins demonstrated cognitive impairment in relation to a control group on various measures of memory. This finding may indicate a genetic predisposition or vulnerability and reaffirms the assertion of a strong genetic component in the disorder.

According to DSM-IV criteria, a diagnosis of BPI is made when the occurrence of one or more manic or mixed episodes, exclusive of any substance- or medically- induced mood disorder is established (DSM-IV, 1994). In the DSM-IV, a manic episode is:

> "…a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least one week (or any duration if hospitalization is necessary)" (p. 362).

Symptoms commonly associated with a manic episode include inflated self-esteem, a marked or decreased need for sleep, pressured speech, a flight of ideas, racing thoughts, distractibility, agitation, and increased involvement in destructive or personally harmful behaviors. Additionally, individuals with BPI usually experience one or more major depressive episodes, although the occurrence of such episodes is not necessary for a diagnosis of BPI to be made. Major depressive episodes are characterized by 2-weeks or more of persistently depressed mood and/or a loss of interest or pleasure in normal activities and commonly include irritability, significant weight loss or gain, decreased or

increased appetite, hypersomnia or insomnia, psychomotor agitation or retardation, fatigue, inability to concentrate, indecisiveness, feelings of worthlessness or guilt, thoughts of death, and suicidal ideation (p. 356). A mixed episode is characterized by a period of at least a week in which the patient meets criteria for both a manic and a major depressive episode (p. 365).

BPII, which is generally considered to be a milder form of the disorder and which according to some studies occurs more frequently in the population (Kessler, McGonagle, Zhao, Nelson, Hughes, Eshleman, Wittchen, & Kendler, 1994), was originally classified as bipolar disorder NOS in the DSM-IIIR and did not achieve its official title until publication of the DSM-IV in 1994. According to the DSM-IV, a diagnosis of BPII is given when an individual has experienced at least one major depressive episode, has had at least one hypomanic episode, and has never experienced a manic or mixed episode. Hypomanic episodes are similar in symptomology to manic episodes, although episodes are "not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features." Additionally, time criterion for persistence of symptoms for a hypomanic episode is four days as opposed to one week as required for mania (p. 368).

The literature remains divided with regard to the nosological status of BP illness, with some conceptualizing a “bipolar spectrum” (Klerman, 1981; Akiskal, 2002) or dimensional model, with BPII representing a milder form of the disorder (Serretti & Olgiati, 2005) and others arguing that BPI and BPII are better conceptualized as separate and distinct disorders (Harkavy-Friedman, Keilp, Grunebaum, Sher, Printz, Burke, Mann & Oquendo, 2006). Relatively few studies, however, have directly investigated

neurocognitive deficit differences in BPI and BPII. This is unfortunate in that there is some evidence suggesting that those with BPII may experience a more chronic course of illness, demonstrate greater risk for suicide, experience significantly more hypomanic and depressive episodes, and have shorter interepisode intervals than those with BPI (Judd, Akiskal, Schettler, Coryell, Maser, Rice, Sollomon & Keller, 2003; Joffe, MacQueen, Marriott & Young, 2004). For example, findings from a study in which self-perception in BP was investigated suggest that BPII may be associated with a lower degree of insight and illness awareness, a higher degree of relapse, more familial dysfunction, and higher rates of affective disorders within families than is BPI (Pallanti, Quercioli, Pazzagli, Rossi, Dell'Osso, Pini & Cassano, 1999). In a review of suicidal behavior among BPI, BPII, and MDD populations, researchers found evidence that the rate of suicide attempt may be higher in BPII than BPI. The study also indicated that BPII may be overrepresented among depressed suicide victims.

In that hypomanic episodes lack marked impairment and are often experienced as egosyntonic, those with BPII rarely seek treatment until in a major depressive episode, which no doubt contributes to the high rate of misdiagnosis and underdiagnosis of this subtype. Considering these factors, it is not hard to understand the difficulty associated with classification and accurate diagnosis of bipolar disorder subtypes. Findings of a study in which BP patients from the community were investigated highlight this difficulty. Within the sample, roughly 70% of BP subjects had previously been misdiagnosed. Of those who had received an incorrect diagnosis, 60% had been diagnosed with major depressive disorder, with 33% maintaining this incorrect diagnosis for 10 years or more. Moreover, these patients had over the years received an average of

3.5 additional incorrect diagnoses and had been seen by an average of four physicians before being correctly diagnosed (Hirschfeld, Lewis & Vornik, 2003). As clarified by this study, BP depression is frequently diagnosed and treated as unipolar depression. This is unfortunate in light of the potential dangers associated with the misdiagnosis and incorrect treatment of BP, which include possible triggering of manic episodes in individuals with BPI when given antidepressants without accompanying mood stabilizers and a poor track record for antidepressant therapy in the treatment of BP depression.

Neuroanatomical Abnormalities

Various structural and functional brain abnormalities appear to be associated with the pathophysiology of BP, and technological advances in neuroimaging are providing increasingly powerful and noninvasive means to view chemical, structural, and functional aspects of brain and neural circuitry specific to BP, frequently without the use of ionizing radiation. The most commonly used modalities to date include Magnetic Resonance Imaging (MRI), which uses a magnetic field to align atoms and reveal contrasts in the different soft-tissues of the brain, Functional Magnetic Resonance Imaging (fMRI), which monitors neural activity by measuring hemodynamic responses or changes in blood-flow in brain regions, Magnetization Transfer Imaging (MTI), which is a quantitative MRI technique that utilizes the presence or absence of macromolecules in brain tissue membranes to view neuroanatomy, Diffussion Tensor Imaging (DTI), a variation of MRI technology with which subtle brain circuitry and connections between different brain areas can be observed, Positron Emission Tomography (PET), which uses gamma rays to produce a three-dimensional image of functional brain processes, Single

Photon Emission Computed Tomography (SPECT), which uses small amounts of radioactive isotypes to measure neuronal changes, and Voxel-Based Morphometry (VBM), which uses statistical parametric mapping to view focal brain tissue differences. These technologies are proving to be powerful tools in the search for specific BP endophenotypes. In the pursuit of BP-specific functional and structural abnormalities, science continues to add to our BP knowledge base by linking abnormalities observed with the use of these neuroimaging techniques to core domains of BP pathology that points to the identification of endophenotypic markers for the illness. It is hoped that the identification of BP specific markers will serve to facilitate differential diagnosis, earlier illness detection, and the identification of at-risk populations for early intervention in BP.

Structural Imaging

Structural imaging studies have demonstrated robust changes in numerous cortical regions, although there has been some inconsistency across studies (McDonald, Zanelli, Rabe-Hesketh, Ellison-Wright, Shama, Kalidindia, Murray, & Kennedy, 2004; Kempton, Geddes, Ettinger, Williams, & Grasby, 2008; Konarski, Mcintyre, Kennedy, Rafi-Tari, Soczynska, & Ketter, 2008). Nonetheless, changes have been consistently observed even in the early course of the illness in BP (Hajek, Carrey, & Alda, 2005; Pfeifer, Welge, Strakowski, Adler, & DelBello, 2008). These early structural changes indicate that neuroanatomical abnormalities are not simply the sequelae of illness morbidity, recurrent mood episodes, or pharmacotherapy. Findings postmortem investigations have also consistently demonstrated structural pathology in BP and include neuronal size abnormalities as well as glial cell density reductions in various prefrontal and subcortical areas (Rajkowska, 2002).

Structural neuroimaging studies indicate the presence of abnormal grey matter densities within various cortical structures in BP and other mood disorders. In an MRI study in which subcortical grey matter brain regions in adolescents with BP were investigated, results revealed enlarged putamen in BP adolescents as compared to NC adolescents (DelBello, Zimmerman, Mills, Getz, & Strakowski, 2004). A similar study found an inverse correlation between putamen matter volumes and age in individuals with BP, and an association between duration of illness and putamen volumes was indicated, with those reporting a shorter duration of illness showing smaller putamen volumes (Brambilla, Harenski, & Nicoletti, 2001). The putamen, a rounded structure located at the base of the telencephalon or forebrain and part of the dorsal striatum and basal ganglia, utilizes dopamine projections to perform its functions in the regulation of movements and in influencing certain types of learning. A recent study found evidence that the putamen (in conjunction with the caudate nucleus and pulvinar) is also part of a cortico-subcortical anatomical network that when damaged leads to spatial neglect in humans (Karnath, Himmelbach, & Rorden, 2002).

Perhaps the most consistent findings of structural neuroimaging studies in BP have been abnormalities of limbic system structures in those with BP. In one such study, anterior cingulate grey matter reductions were found in BP subjects who were in remitted or euthymic states of the illness (Drevets et al., 1997). The anterior cingulate gyrus is a brain region thought to play a role in a variety of autonomic functions, including blood pressure and heart rate regulation, as well as various social and cognitive functions such as social reciprocity, decision making, anticipation of reward, empathy, and the production of emotion. In a recent study in which the anterior cingulate gyri of male

macaque monkeys were lesioned, the damaged monkeys lost the interest or ability for social interaction with female macaques (Rudebeck, Buckley, Walton & Rushworth, 2006). In that the subjects in the former BP study were in euthymic phases of BP illness at the time of imaging, the grey matter anterior cingulate reductions found may represent a BP trait deficit, which could explain some of the social dysfunction often realized by those with BP.

One study reported reduction of thalamic volume in BP adolescents (Dasari et al., 1999), and others have reported amygdalar abnormalities. These findings have been varied however with regard to abnormality specifics, with some studies finding amydalar enlargement and others finding volumetric reductions in BP patients (Berns, Martin, & Proper, 2002; DelBello, Zimmerman, Mills, Getz, & Strakowski, 2004; Strakowski, DelBello, & Sax et al, 1999). Studies have also varied as to which portions of the amygdala are affected in BP, with some studies reporting bilateral enlargement and others finding enlargement only in the left hemisphere (Strakowski et al., 1999; Altshuler et al., 2000; Frangou et al., 2002; Brambilla et al., 2003). The amygdala, which is involved in the identification of the emotional significance of stimuli as well as in the encoding and retrieval of emotional information in memory processes, has been identified by LeDoux (1996) as the most central structure in the processing of emotion. In light of BP symptomatology, the amygdala and other limbic structures have been the target of BP investigation for quite some time, and research findings of amygdala and other limbic structural abnormalities in BP are no surprise. One study in which limbic structures in BP subjects were investigated found evidence that suggests amygdala volume may be associated with symptom severity and/or illness chronicity, as greater

volume reductions were found in BP subjects who had experienced multiple manic episodes as compared to first break manic patients (Strakowski et al., 2002).

Various studies have also found evidence of prefrontal cortex abnormalities as well as abnormalities in the prefrontal-limbic pathways in those with BP (Haldane & Fangou, 2004; Berns, Martin, & Proper, 2002). One study found significant grey matter reductions in the left dorsolateral prefrontal cortex in unmedicated BP subjects as compared to a NC group. A trend in the same direction was also found in the right dorsolateral prefrontal cortex of the subjects (Brambilla et al., 2002). The dorsolateral prefrontal cortex is the highest cortical area of the brain and is involved in the most complex aspects of cognition, including manipulation of sensory information in working memory, the integration of sensory and mnemonic information, planning of deliberate action and motor movement, and organizational and regulatory aspects of emotional and intellectual functioning. Dorsal, ventral, and orbital prefrontal cortical grey matter volume reductions have also been reported by various neuroimaging studies in BP (Lopez-Larson et al., 2002; Frangou et al., 2002).

The various structural abnormalities found in these studies are consistent with BP symptomatology and have added significantly to our knowledge base and understanding of the phenomenology specific to BP, such as emotional lability, distractibility, and memory disruption (Lyoo, Kim, Stoll, Demopulos, Parow, Dager, Friedman, Dunner, & Renshaw, 2004; Altshuler, Bartzokis, Grieder, Curran, & Mintz, 1998; Phillips et al., 2003; Bertolino, Frye, Cilicott, Mattay, Rakow, Shelton-Repella, Post, & Weinberger, 2003; Bremner, Narayan, Anderson, Staib, Miller, & Charney, 2001; Bearden, Hoffman, & Cannon, 2001).

Findings of various structural imaging studies suggesting that BP medications, such as Lithium, may increase grey matter volumes provide a sense of hope for those with BP (Moore et al., 2000; Sassi et al., 2002). The general belief regarding these findings is that medications such as Lithium have neurotrophic effects and increase bcl-2, a neuroprotective protein (Manji et al., 1999). A study in which unmedicated verses medicated BP patients showed increased grey matter reductions in the posterior cingulate cortex lends support to this assertion (Nugent, Milham, & Bain, 2006). If correct, the clinical importance of mood stabilizers in providing neuroprotection to those with BP cannot be overstated, and this importance is highlighted by research findings that show greater age-related neural atrophy and grey matter decline in individuals with BP than is found in the general population (Brambilla et al., 2001).

Various neuroimaging studies have also indicated the presence of white matter volumetric reductions in BP (Strakowski et al., 1993; Zipursky et al., 1997; Brambilla et al., 2001). BP MRI studies have also found evidence of deep white matter hyperintensity lesions involving numerous abnormal neuronal signaling cascades and interrelated processes of glutamatergic neurotransmission, altered neurotrophin signaling, abnormal mitochondrial function, calcium influx alterations, and oxidative stress (an imbalance between reactive oxygen production and the system's detoxification capacity and/or ability to readily repair resulting damage), (Schloesser, Huang, Klein, & Manji, 2007; Kato, 2008; Quiroz, Gray, Kato, & Manji, 2008; Ng, Berk, Dean, & Bush, 2008; Stork & Renshaw, 2005; Zarate, Du, Quiroz, Gray, Denicoff, Singh, Charney, & Manji, 2003). Findings of glutamatergic system abnormalities in BP, and other disorders that are marked by mood disturbance, are thought to be associated with problems in cellular and

synaptic resilience and plasticity. These abnormalities are in turn are thought to play a major role in the pathophysiology of BP, as preliminary study findings indicate that glutamatergic systems are the target for the actions of some antidepressants and mood stabilizers used in the treatment of BP (Zarate, Du, Quiroz, Gray, Denicoff, Singh, Charney, & Manji, 2003). Abnormalities in molecular processes (second messenger metabolism alterations, cellular membrane abnormalities, changes in the molecular processes involving energy in the formation and breakdown of chemical bonds, etc.) have been identified within the prefrontal cortex, striatum, and other brain regions in BP and are consistent with the idea that decreased neural plasticity and synaptic resilience are part of BP pathophysiology (Schloesser, Huang, Klein, & Manji, 2007).

Deep white matter lesions, which are seen as bright spots in T2-weighted MRI scans and indicative of axonal injury, are sometimes referred to as "brain rust" and are thought to be ischemic in etiology and evidence of vascular degeneration, similar to what is typically found in aging populations and those with chronic cardiovascular disease (Dupont et al., 1987, 1995; Swayze et al., 1990; Figiel et al., 1991; Altshuler et al., 1995; McDonald et al., 1999). Additionally, these hyperintensities are thought to be associated with vulnerability for the development of late-life depression, greater impairment in executive functioning, more severe disability, poorer outcome and quality of life, and greater illness chronicity in BP (Moore et al., 2001; Yuan, Salvadore, Li, Zhang, Du, Chen, & Manji, 2009).

A meta-analysis found older BP subjects to have an increased number of these white matter hyperintensities as compared to younger BP and older NC subjects (although they have been found to some degree in all BP populations), and those with a BPI diagnosis are significantly more likely to develop white matter hyperintensities than are those with BPII (Altshuler et al., 1995; Botteron et al., 1995; Lyoo et al., 2002; Pillai et al., 2002). However, findings of a recent study which suggest that Valproic Acid may attenuate white matter intensities in those with BP as well as decrease vulnerability for further development of these hyperintensities in late-life BP are encouraging (Yuan, Salvadore, Li, Zhang, Du, Chen, & Manji, 2009).

Numerous MRI studies have also identified ventricular enlargement in BP, specifically enlargement of the lateral and third ventricles, which researchers have viewed as evidence of volumetric reductions of the thalami and/or hypothalami, as the lateral ventricle lies above and the third ventricles lie at the medial aspect of the thalami (Ferrier, & Thompson 2002; Videbech, 1997; Nasrallah et al., 1982; Pearlson et al., 1984; Dewan et al., 1988). These findings are consistent with BP symptomatology as the thalami are involved in the regulation of arousal and the relaying of information to various other parts of the cortex, and the hypothalami are involved in arousal response to emotional circumstances and motivated behaviors. However, findings have again been inconsistent, with some MRI studies failing to demonstrate ventricular enlargement in BP (Johnstone et al., 1989; Swayze et al., 1990; McDonald et al., 1991; Harvey et al., 1994). A related research finding that has been largely consistent across studies is that illness-

episode number is positively correlated with ventricular volumes, which suggests that illness chronicity and/or severity may be associated with enlargement of the ventricles in BP (Brambilla et al., 2001; Strakowski et al., 2002).

Functional Imaging

Due to the technology's temporal and spatial resolution abilities, fMRI is currently one of the most commonly used neuroimaging modalities in the investigation of functional deficits in BP, and studies utilizing this technology have contributed significantly to our understanding of the way in which cognitive functioning may differ in various phases of BP illness. Numerous studies have found evidence that suggests differential right hemispheric impairment during active BP episodes (Bruder, Stewart, Towey, Friedman, Tenke, voglmaier, Leite, Cohen, & Quitkin, 1992; Caligiuri, Brown, Meloy, Eyler, Kindermann, Frank & Lohr, 2004). In one study, which utilized fMRI to examine potential cortical asymmetry in individuals with BP during manic and depressed illness phases, researchers found that depressed BP subjects had difficulty suppressing right hemispheric activity when engaging in right-handed tasks (Caliguiri et al., 2004). In a similar study in which cerebral laterality in BP and unipolar depression was compared, evidence was found suggesting right hemispheric dysfunction and left visual field accuracy deficits in BP depression. Interestingly, these deficits were not found in unipolar depression (Bruder et al., 1992).

Right hemispheric dysfunction could explain much of the social and emotional impairment often experienced by those with BP as various studies have found evidence that the right hemisphere may be preferential in the lexical and prosodic aspects of emotional auditory information and is more sensitive to the affective semantic content of

stimuli. More interesting is the finding of one of these studies of a processing advantage for negatively valenced words in currently depressed individuals and in those not currently depressed but who have been depressed in the past, whereas never-been-depressed individuals have a processing advantage for positively valenced words (Atchley, Stringer, Mathias, Ilardi, & Minatrea, 2006; Atchley, Ilardi, & Enloe, 2003; Bobes, Martin, Olivares, & Valdes-Sosa, 2000).

Systemic problems involving other neural regions and circuits necessary for normal social functioning have also been found. In a recent study in which BP youth (ages 7-18) completed an fMRI facial emotion identification task with attention directed to emotional (hostility and fearfulness) and nonemotional (nose width) facial features, whole brain functional connectivity with the left amygdala was examined. Results of the study indicated that the BP subjects had reduced connectivity between the left amygdala and the right posterior cingulated-precuneus and right fusiform gyrus/parahippocampal gyrus. Reduction in connectivity in the BP subjects was observed independent of mood state or comorbid diagnoses (Rich, Fromm, Berghorst, Dickstein, Brotman, Pine, & Leibenluft, 2008). In that these regions of reduced connectivity have previously been implicated in the processing of facial expressions and social stimuli, these are important findings and add to mounting evidence of the functional abnormalities that underlie the neuropsychological deficits, emotional abnormalities, and psychosocial dysfunction seen in BP.

Other studies in which cortical and subcortical brain regions were investigated during active phases of BP illness have also been productive in clarifying the pathophysiology of BP. Studies in which PET and SPECT scan technology were utilized indicate the

presence of abnormalities in anterior cingulate function in manic and depressive phases of BP (George et al, 1993; Ito et al, 1996). Manic patients in these studies demonstrated increased activity in the left dorsal anterior cingulate cortex, an area vital to important cognitive functions, such as the production of empathy, modulation of emotional responses, reinforcement, and the anticipation of reward. In contrast, depressed BP subjects demonstrated decreased cerebral blood flow in the prefrontal cortex, a region of the brain involved in complex cognitive behaviors and higher order functions such as impulse inhibition and modulation, moderation of social behavior, mediation of conflicting cognitions, problem solving, foresight, short-term memory, set-shifting, mental flexibility, and the encoding of unfamiliar faces. Decreased cerebral blood flow was also found in depressed BP patient limbic and paralimbic regions, which are involved in the production of emotion, interpretation of emotional stimuli, formation of emotional associations in memory, and motivation, and nucleus accumbens, which receives dopaminergic projections and is involved in reward and reinforcement, the experience of pleasure and euphoria, and sexual arousal. These abnormalities are consistent with the emotional dysregulation and social dysfunction often seen in BP (George et al, 1993; Ito et al, 1996).

Neurochemical Abnormalities

Several theories regarding the role of neurotransmitters in BP have been asserted over the years. One such theory posits the existence of functional deficits in regard to the catecholamine neurotransmitters, specifically a depletion of norepinephrine or dopamine at the neuronal synaptic cleft in depressive episodes and an excess of these

neurotransmitters in mania (Schildkraut, 1965). One study investigated the relationship between visual tracking, motor speed, and catecholamine system function. Subjects were inpatients in participating centers of the National Institute of Mental Health Clinical Research Branch Collaborative Study on the Psychobiology of Depression. Results suggested that catecholamine systems may be associated with impairment in psychomotor processes as well as an increase in arousal in individuals with BP (Swann, Katz, Bowden, Berman, & Stokes, 1999).

A similar theory implicates the indolamine, serotonin. Still other theories have investigated potential functional deficits in regard to GABA and acetylcholine, which would suggest a more generalized neurochemical dysregulation in BP (Redmond & Leonard, 1997). Though neurochemical abnormalities appear to be associated to some degree with the dysfunction in BP, studies attempting to validate these theories as major etiological factors have failed to garner adequate support.

Neurocognitive Deficits

A broad range of neuropsychological deficits have repeatedly been shown to be associated with BP illness, and many of these deficits are thought to be of greater severity and to be manifest differently in BP than in other mood disorders. These deficits found in BP include impairment in learning, attention, verbal and visual memory, visuo-spatial perception, executive function, processing speed, psychomotor speed, and dexterity. (Bearden, Hoffman, & Cannon, 2001; Basso, Neel, Lowery, Purdie, & Bornsein, 2002; Wilder-Willis, 2003).

Several studies have sought to identify prodromal deficits in BP, and findings of these studies have important implications with regard to the identification of populations at particular risk for BP and potential benefits of early intervention. In a study involving seven pairs of monozygotic twins discordant for BP, the affected twins displayed deficits as compared to their unaffected twins and in relation to normal monozygotic twin controls on visual processing measures (which could possibly be due to right hemispheric deficits) as well as short- and long-term verbal memory tasks. On the Test of Facial Recognition, the affected twins performed significantly worse than did the unaffected twins or the normal controls. Additionally, on the Continuous Performance Task and on several measures of the California Verbal Learning Task (particularly, the short delay, cued recall and recognition hits), the affected twins performed more poorly than did their unaffected twins and normal controls (Gourovitch, Torrey, Gold, Randolph, Weinberger, & Goldberg, 1999). Cognitive deficits were not found to correlate with most measures of symptomatology, which suggests that impairment may be trait-related. Perhaps the most interesting finding in this study, however, was that the unaffected twins displayed more cognitive impairment on several short-term memory and verbal memory tasks than did the normal controls, although impairments were not as extensive as were those found in the affected twins. In another study in which individuals with BP were compared to their unaffected first degree family members and healthy controls, the BP group and their first degree family members performed significantly worse than controls on measures of visuospatial/constructional ability, executive function, and motor function, with the first degree relatives performing at an intermediate level between the other two groups (Frantom, Allen, & Cross, 2007).

Similarly, a retrospective study of premorbid functioning in BP reported the existence of various cognitive and motor impairments in individuals that later developed BP, and these deficits were found to be more pronounced in those subjects who later experienced psychotic features (Sigurdsson, Fombonne, Sayal, & Checkley, 1999). These findings suggest the existence of a genetic link or risk for those with a family history of BP or other mood disorder. This notion is supported by findings of a study in which diminished subgenual prefrontal cortical volumes were identified in subjects with a family history of mood disorder. These subjects, some of whom had been diagnosed with BP and some of whom had no diagnosis, were found to have subgenual prefrontal cortices that were 40% smaller than that of NC subjects (Drevets et al, 1997). In a similar study, researchers found 25% reductions in the subgenual prefrontal cortical volumes in first-break psychosis patients with a family history of mood disorder (Hirayasu et al., 1999).

In light of the fact that the number of affective episodes experienced and chronicity of illness is positively correlated with impairment severity in BP, these findings have obvious important implications. Identification of genetic markers and premorbid deficits in BP may help to clarify the pattern of neurocognitive morbidity unique to the disorder, enable detection of those at particular risk for illness development, promote accuracy in diagnosis, and facilitate efficacy in treatment and interventional considerations (Ferrier & Thompson, 2002).

Depressive Illness Phase

Various studies have attempted to compare neuropsychological impairment and dysfunction in the active phases of BP and the remitted or euthymic states of BP illness. One such study, in which cerebral laterality in BP depression and unipolar depression

was compared, utilized visual half-field and dichotic listening measures of perceptual asymmetry to investigate brain laterality differences between the groups. Findings demonstrated that individuals with BP depression had greater impairment than did the NC group or those with unipolar depression in identifying left visual field stimuli, but not right visual field stimuli. This is an interesting finding in that the unipolar depression and NC groups were found to have a left visual field advantage on the measures. This difference lends support to the contention of right hemispheric dysfunction in BP. Further, the BP subjects in the study exhibited abnormal asymmetry during auditory discrimination tasks, which may indicate early sensory and attentional processing deficits in BP (Bruder et al, 1992). Another study in which motor deficits in individuals with unipolar depression were compared to those in BP depression reported that although both groups demonstrated deficits in motor speed, dexterity, and visual tracking, psychomotor dysfunction was related to symptom severity in BP depression but not in unipolar depression (Swann et al, 1999). Additionally, a comprehensive review of the neuropsychological and neuroimaging literature on BP reported greater impairment in frontal-executive function, attentional processes, and memory function in individuals with BP depression than in unipolar depression (Bearden, Hoffman, & Cannon, 2001). A recent meta-analysis of the literature regarding neuropsychological dysfunction specific to BP found greatest impairment in phonemic fluency in those in the depressed phase of illness (Kurtz & Gerraty, 2009).

Manic Illness Phase

Various studies have also revealed cognitive deficits that unique to the manic phase of BP. In one study in which a discriminant function analysis was utilized, results

showed illness phase-specific deficits in sustained attention, verbal learning and memory in BP mania (Clark, Iversen, & Goodwin, 2001). In a recent meta-analysis of neurocognitive deficits in various phases of BP, research indicated that although impairment in verbal learning was found even in euthymic illness states, these deficits were exaggerated during manic and mixed illness phases (Kurtz & Gerraty, 2009).

Euthymic Illness Phase

Although the etiological specifics of BP illness are still not well understood, technological and scientific advances have increased our ability to investigate the potential genetic and environmental factors that may contribute to the development of BP. These advances have also enabled us to better understand the pathophysiology of the illness and the way in which BP is expressed over various illness phases as well as over the lifespan.

Historically, research focused primarily on the investigation of cognitive deficits within active phases of BP, and this myopic research focus hindered advancement of understanding regarding illness course. This isolated focus was largely due to the belief that BP had a relatively benign course, with euthymia seen as a state of illness recovery and those affected by the illness thought to experience little if any persistent cognitive deterioration or impairment. More recently, investigation has turned to these euthymic or remitted BP states, and converging evidence suggests a chronic illness course, with pervasive and persistent cognitive impairment being found across a range of tasks of attention, memory, and executive function even in remitted phases (Clark, Iversen, & Goodwin, 2002; Tavares, Drevets, & Sahakian, 2003; van Gorp et al., 1998). An added benefit of this research is that while gaining insight as whether observed impairments in

BP are trait-dependent or state-dependent, the neurobiological disturbances that underpin these behavioral deficits are also being identified.

One study which investigated neuropsychological deficits in BP euthymic states reported impairments in verbal learning and memory as measured by the California Verbal Learning Test and the Wisconsin Card Sorting Test. Various recent meta-analyses of neuropsychological functioning in euthymic BP have also been conducted. One of these studies reported a large effect size with regard to impairment on measures of verbal learning and delayed verbal memory as well as on measures of nonverbal memory, and small to moderate effect sizes on measures of visuospatial functioning (Kurtz & Gerraty, 2009). In another multi-study survey, significant impairment was found in letter and category fluency, verbal working memory, immediate and delayed verbal memory, auditory attention, set-shifting, sustained visual attention, response inhibition, and psychomotor speed in euthymic BP (Robinson et al., 2006). Another review of the literature regarding cognitive function in euthymic BP patients reported impairment in verbal memory, response inhibition, executive function, working memory, visual memory, and sustained visual and auditory attention (Arts et al., 2007). A fourth survey of studies of neurocognitive function in euthymic BP found greatest impairment in verbal learning and significant impairment in verbal fluency, sustained visual attention and memory, auditory attention, and working memory (Bora et al., 2009).

These studies and literature reviews are consistent in reporting generalized neuropsychological impairment in euthymic phases of BP, with particular impairment being found in working memory, verbal learning and memory, and executive function measures. They are also consistent in reporting a worsening of many of these deficits

during active illness states. Although deficits may be more significant and pronounced in active mood episodes in BP, it is clear that much of the psychological deficits are trait related and cause chronic and persistent dysfunction even in remitted states (van Gorp, Altshuler, Dixon, & Theberge, 1999; Martinez, Vieta, Colom, Torrent, Sanchez-Moreno, Reinares, Benabarre, Goikolea, Brugue, Daban, & Salamaro, 2004; Wilder-Willis, 2003).

Emotion Processing Deficits

Research regarding how the processing of emotional information is affected in individuals with BP has not been as extensive as has been the investigation of cognitive impairments associated with the disorder. Emotion processing and memory are bidirectional systems, and awareness of the interconnected nature of these systems is fundamental to understanding how affective disorders are maintained. Cognitive models of emotional disturbance in affective disorders generally assert that memories of painful or negatively charged affective experiences produce attentional biases for emotional information and stimuli in the environment. According to these models, these biases are not simply side-effects of affective disorders but play a significant role in the causation, morbidity, and maintenance of these illnesses. The contention is that even a slight emotional disturbance can increase the salience with which an individual perceives an experience, and this emotional saliency can become paired with stimuli present at the time of the event in memory. This leads to a cycle in which the individual over-estimates the negative emotionality of events based on activated memory stores, which in turn produces a greater degree emotional disturbance. According to M. B. Arnold's excitatory theory (1952), memory provides the basis for emotional appraisal. As incoming sensory

stimuli impact the individual, memory pathways that are congruent with the emotional salience of the stimuli are activated. This activation in turn triggers emotions consistent with the activated memories, thus strengthening the neural pathways and making them easier to access in the future. Additionally, a major component of the experience of emotion is thought to be the anticipation of the way in which current situations may relate to future outcomes. In similar fashion, anticipation can activate congruent neural pathways in memory and these memories influence appraisal decisions as to whether stimuli should be approached or avoided. The salience of a current emotional experience therefore, is thought to be the product of one's appraisal of the event in the context of activated memory for similar past events. Memories of painful emotional experiences, therefore, may not only serve to negatively alter perception of current emotional events, but may also reinforce and enhance negative interpretations of current and future events for those with BP (Arnold, 1952; Arnold, 1970).

Arnold's model was supported by a recent study in which sensitivity to facial expression of basic emotions was investigated in BP during depressed and manic phases of illness. Results of the study demonstrated mood-related biases with regard to sensitivity to the facial expressions of happiness and negative affect in general in depressed BP subjects (Gray, Venn, Montagne, Murray, Burt, Frigerio, Perrett, & Young, 2006). Findings of a similar study in which fMRI was utilized to examine the ability of euthymic BP subjects to recognize facial emotion also appear to support Arnold's model. In the study differential responses to fear and disgust were also examined in an effort to determine the neural correlates of facial emotion processing. Results indicated that facial expressions of fear produced greater neural activation in euthymic BP patients as

compared to a NC group, with increased left-sided hippocampal activation in the BP group (Malhi, Lagopoulos, Sachdev, Ivanovski, Shnier, & Ketter, 2007). Researchers speculate that BP patients may demonstrate more hippocampal activation in the identification of facial expressions of fear as a result of a higher degree of active engagement resulting from past priming experiences (past traumatic emotional events associated with BP illness, etc.).

Arnold's model was also foundational to later cognitive models of emotion. One such model proposed by Joseph E. Ledoux extended Arnold's theories and placed more emphasis on the neuroanatomy involved in the production of emotion and the role of memory in this process Ledoux, 1992; Ledoux, 1993; Ledoux, 1996). An Emotional Memory System was proposed by Ledoux in which the amygdala, a cortical structure of the limbic region, was identified as the most central structure of this system and necessary to the appraisal of the emotional significance and interpretation of incoming stimuli. According to Ledoux, the amygdala is also involved in the process of encoding and retrieving emotional information in memory by way of thalamic circuitry (Ledoux, 1996).

Various studies have investigated the way in which emotional memory and/or biases for emotional information may enhance or impair performance on cognitive tasks. In a study in which hemispheric lateralization was investigated to determine how it affects the processing of words with emotional content in currently or previously depressed individuals, subjects with a history of depression demonstrated a bias for words with negative emotional content. Response latencies were shorter and responses were more accurate for depressed subjects in the identification of words with negative emotional

content as compared to identification of positive target words, and this pattern was the opposite of that found in a NC comparison group (Atchley, Ilardi & Enloe, 2003).

A recent study exclusively examined emotion processing in BP by comparing group performance on matching tasks of facial emotion recognition and perception of facial identity. Results demonstrated that euthymic BP subjects were significantly impaired in their ability to identify various facial emotions as compared to the NC group but had no such impairment when asked to identify faces with no requirement of recognition of facial emotion (Bozikas, Tonia, Fokas, Karavatos, & Kosmidis, 2006). A similar study investigated gender differences as well as differences between BPI and BPII groups in recognition of facial emotion ability. Results demonstrated no gender differences. However, a significant group effect was found such that the accuracy performance of BPI subjects was significantly impaired whereas performance of BPII subjects was similar to that of NC subjects (Derntl, Seidel, Kryspin-Exner, Hasmann, & Dobmeier, 2009).

In another study in which researchers investigated the neurocognitive processes that underlie affective and cognitive empathic abilities in BP, affective empathy (defined as "the capacity to experience a vicarious response to another person") and cognitive empathy (defined as "the ability to adopt another's psychological perspective") were compared in euthymic BP and NC subjects. Theory of mind (defined as "the ability to understand the feelings, intentions, and motivations of others") and executive function was also investigated in these groups. BP subjects demonstrated significant deficits in cognitive empathy, theory of mind, and cognitive flexibility measures of executive function. In contrast, BP subjects demonstrated increased affective empathy and intact planning behavior. Interestingly, deficits in cognitive empathy were correlated with

performance on tasks of cognitive flexibility, which is consistent with prefrontal cortical dysfunction (Shamay-Tsoory, Harari, Szepsenwol, & Levkovitz, 2007). In another study of theory of mind abilities in BP, findings indicated significant impairment in depressed and manic BP subjects, but intact functioning in euthymic BP subjects (Kerr, Dunbar, & Bentall, 2003). However, in a more recent study, Bora et al. found evidence of impairment in advanced theory of mind tasks in remitted phases of BP (Bora, Vahip, Gonul, Akdeniz, Alkan, Ogut, & Eryavuz, 2005).

Another study in which perception of affective prosody (defined as "the nonlexical component of speech that can communicate information about the emotional state of others") was investigated in BPI. Results demonstrated impairment in the perception of affective prosody in euthymic female BPI subjects, specifically with regard to the emotions of fear and surprise (Bozikas, Kosmidis, Tonia, Andreou, Focask, & Karavatos, 2007).

These findings are significant for various reasons. The ability to correctly process and interpret emotional responses and accurately read the verbal and facial expressions of others is essential for normal functioning and healthy social interaction and reciprocity. Such impairment may account for the dysfunctional social and interpersonal behaviors often found in BP. Moreover, the fact all subjects in these studies were in remitted phases at the time of testing supports the assertion that BP is a chronic and debilitating disorder in all phases of illness, even in euthymic states. Several recent studies have confirmed this connection between emotion processing deficits and psychosocial dysfunction in BP (Malhi, Ivanovski, Hadzi-Pavlovic, Mitchell, Vieta, & Sachdev, 2007). A recent neuroimaging study in which mirror neuron activation was investigated in an effort to

identify the neural substrates responsible for social cognitive difficulties frequently seen in BP supports this contention. In the study, euthymic BP and NC groups underwent functional MRI while performing a virtual-reality task of social cognition (which incorporated cognitive and emotional dimensions) that simulated real-world social situations. During the task, subjects were required to guess possible reasons for the emotions expressed by virtual humans while viewing their facial expressions, subsequent to observing their verbal/nonverbal emotionally valenced (happy, angry, neutral) facial expressions. Results indicated that BP subjects had delayed response latencies and corresponding accuracy on emotional conditions of the task as compared to the NC group. Imaging showed that the NC group had activation of the right anterior cingulate cortex, inferior frontal, and insular cortex (regions thought to underpin empathic processes during observation of emotional expressions of others) during emotional conditions verses neutral task conditions. BP subjects had reduced activation of mirror neuron areas (right inferior frontal, prefrontal, and insula cortices), which are thought to be integral in enabling empathic understanding and interpretation of emotion in others, mainly during angry and happy conditions as compared to the NC group. These results suggest that, even in euthymic states, individuals with BP may have difficulty recruiting brain regions normally activated in social interactions, in the interpretation of emotional cues integral to understanding the emotional states of others (Kim, Jung, Ku, Kim, Lee, Kim, Kim, & Cho, 2009).

Bipolar I and Bipolar II Disorder Differences

Neurobiological Abnormalities

The amount of research that has been dedicated to the investigation of potential neurobiological differences in BPI and BPII has been minimal. In a review of the literature, McGrath et al (2004) determined that although genetic data suggest potential differences between BPI and BPII populations, the imaging and metabolic studies available for review were insufficient to provide support for differences and lacked adequate power for conclusive inferences to be made due to the small number of studies available.

In a neuroimaging study of cerebral asymmetry in psychotic mood disorders, BP individuals with psychosis demonstrated cerebral lateralization whereas BP individuals without psychosis and control subjects did not. This finding may indicate that right hemispheric deficits are more strongly associated with BPI in that the presence of psychosis in BP is more commonly found in BPI (Reite, Teale, Rojas, Arciniegas, & Sheeder, 1999).

In another neurioimaging study, regional cerebral blood flow was measured via PET scan in individuals with BPII during performance of a serial reaction time task. While in the scanner, four boxes were displayed horizontally on a computer monitor in front of the subject. One box at a time was illuminated, the order of illumination being determined by a complex sequence that was changed in the last half of the task. Participants were instructed to press specific keys on the keyboard in correspondence to the light sequence as quickly as possible. Cerebral blood flow was analyzed during performance of the task in an attempt to measure changes in blood flow associated with perceptual responses to

illumination sequences. Both BPII and NC groups were able to accurately encode portions of the motor sequence. However, the BPII individuals showed activation of different brain regions while responding to sequence changes during the task than did NC subjects. Moreover, while the NC group demonstrated typical activation of the right superior parietal cortex in response to a novel spatial-motor sequence, the BPII group showed reduced activation of this region and demonstrated a wide network of activation, including activation of the medial prefrontal cortex and limbic structures, not seen in the NC group. In that the task was intentionally designed to be affectively neutral, researchers speculate that this limbic activation may be indicative of a limbic hyper-reactivity in individuals with BPII and may be associated with a dysfunction of processes of arousal rather than dysfunction of attentional processes. Specifically, individuals with BPII may react to certain stimuli in ways that are congruent with the affective nature of their illness experience (Berns, Martin, & Proper, 2002). Unfortunately this study did not compare performance of BPI and BPII groups and thus provides no information as to potential differences between these groups.

Neurocognitive Deficits

Recent bipolar spectrum theories and similar dimensional models conceptualize BP subtypes as homogenous disorders that fall along a continuum of severity. Moving toward an accurate conceptualization of BP is vital to understanding etiological factors, formulating appropriate diagnostic criteria, and developing effective prophylactic and treatment modalities for BP. Despite continuing nosological disagreement and conflicting views as to the present illness conceptualization as reflected in current BP diagnostic

criteria, surprisingly few studies have focused specifically on differences in neuropsychological impairment in BP subtypes.

One recent study in which BPI and BPII suicide attempters were compared on various measures of neuropsychological functioning provides evidence contrary to the spectrum conceptualization of BP. In the study, individuals with BPI demonstrated an intermediate degree of impairment on measures of working memory, attention, and psychomotor functioning in relation to BPII and NC groups. Additionally, the BPII group demonstrated deficits on various measures distinct from those found in the BPI group. On a simple reaction time motor task and the Stroop Test of Attention, BPII individuals demonstrated significant deficits as compared to the BPI and NC groups. The authors of this study infer from these findings that individuals with BPII may demonstrate more global patterns of neuropsychological dysfunction in certain domains and that BPI and BPII therefore should be studied as separate and distinct disorders rather than homogeneous subtypes (Harkavy-Friedman, Keilp, Grunebaum, Sher, Printz, Burke, Mann & Oquendo, 2006).

Other studies, however, report evidence more supportive of the spectrum model, although these studies also provide some evidence of performance pattern differences in BPI and BPII neurocognitive profiles, suggesting that there may be elements of BP subtypes that are consistent with the spectrum conceptualization as well as elements that are supportive of distinct illness differences. One recent study in which euthymic BPI and BPII groups were compared on cognitive functioning measures found evidence supportive of the spectrum conceptualization with BPI patients demonstrating deficits in psychomotor speed, working memory, verbal learning, delayed memory, and executive

functioning as compared to a NC group and BPII patients demonstrating dysfunction on a subset of measures within each of the domains. BPII subjects demonstrated performance deficits on measures of psychomotor speed, working memory, and executive functioning as compared to the NC group, but no impairment on measures of verbal learning and delayed memory. Additionally, the BP groups did not differ significantly from each other on any of the domains tested (Dittmann et al., 2008). A similar finding was reported in another recent study in which BPI and BPII group performance was compared on various neuropsychological measures. In the study, the BPI group demonstrated significantly greater impairment on measures of verbal memory, psychomotor speed, and executive function than did the BPII and NC groups. Both BP groups demonstrated significant performance deficits on measures of working memory and psychomotor speed, with the BPII group demonstrating an intermediate degree of deficit on measures of psychomotor speed as compared to the BPI and NC groups. The groups in this study demonstrated no differences in visual memory performance (Hsiao et al., 2009). Yet another study comparing BPI and BPII group performance on various neuropsychological measures reported significant impairment in the BPI group on measures of memory as compared to the BPII and NC groups. Additionally, the BPI group showed significant impairment in attention and executive function as compared to the NC group, and the BPII group demonstrated impairment on a subset of measures in relation to the BPI and NC groups. Overall, 24% of the BPI group in this study demonstrated neurocognitive impairment whereas 13% of the BPII group demonstrated impairment (Simonsen et al., 2008).

Although research investigating neuroanatomical and neuropsychological differences among BP subgroups has been limited, the research that has been conducted in this

regard has generally supported the existence of differences among the subtypes that reflect differences in degree of impairment as opposed to distinct deficit differences. These findings most consistently support the spectrum conceptualization of BP illness, although more research is warranted in order for conclusive determinations to be made.

Conclusion and Hypotheses

A large body of literature has been devoted to the study of BP, and in recent years numerous studies have validated the existence of neurobiological abnormalities involving specific cortical and subcortical brain areas as well as molecular, cellular, and neural system abnormalities in individuals with BP illness. Various neuropsychological and emotion processing deficits, thought to be phenotypic correlates of neurobiological abnormalities, have also been identified, although findings have been inconsistent as to specifics of these deficits. Less yet is understood with regard to the way in which neurocognitive and emotion processing deficits may differ in BP subtypes even though understanding these differences in the pattern and magnitude of deficit among BP subtypes is arguably essential to the formulation of an accurate illness conceptualization (and therefore, diagnosis and treatment considerations). Differential presentation of illness course, phenomenology, and symptomatology in BP subtypes strongly suggests the presence of differing neuropsychological deficits.

With these considerations in mind, the current study investigated the way in which neurocognitive and emotion processing deficits differ in BPI and BPII populations by comparing performance of the two groups on various standard and experimental measures designed to assess abilities in Working Memory, Verbal Learning and Memory,

Verbal Fluency, Visual Learning and Memory, Visuoconstruction, Psychomotor, Executive Function, Attention, and Emotion Processing domains. Performance between these two groups in all domains was compared. Additionally, performance in all domains among the BPI group, BPII group, and NC group was compared. The intent of these comparisons was to determine whether the combined BP group performance supports neuropsychological and emotion processing dysfunction as compared to healthy controls. Moreover, an aim of this study was to add to the literature regarding disorder conceptualization by determining if pattern of neuropsychological performance in BP is subtype specific or consistent with a spectrum conceptualization of illness.

It was hypothesized that the three groups would demonstrate significant differences in performance in specific neuropsychological and emotion processing domains. It was additionally hypothesized that the BPII group would demonstrate an intermediate degree of impairment on these measures as compared to the BPI and NC groups, (with the BPI group demonstrating the greatest degree of deficit) thus lending support to the spectrum conceptualization of BP illness. Based on the extant literature, the following hypotheses were proposed:

Hypothesis 1

Significant overall differences among the groups will be found in performance within the domains of Working Memory, Verbal Learning and Memory for Non-Emotional information, Attention, and Executive Function.

Hypothesis 2

Significant overall differences among the groups will be found in performance within the domains of Learning and Memory for Visual and Verbal Emotional information.

Hypothesis 3

As compared to the NC and BPI groups, the BPII group will demonstrate an intermediate level of performance in all domains assessed, with the best performance seen in the NC group and the BPI group demonstrating the worst level of performance among the groups.

CHAPTER 3

METHODS

Participants

Participants for this study were recruited from the University of Nevada, Las Vegas and the community at large and comprised three groups. These groups consisted of:

1) Thirty-seven subjects diagnosed with BPI as determined by way of the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1997) will constitute a bipolar disorder I group (BPI Group).

2) Eighteen subjects diagnosed with BPII as determined by way of the SCID-I will constitute a bipolar disorder II group (BPII Group).

3) Eighteen healthy individuals will constitute a normal control group (NC Group).

All subjects were between 18 and 65 years of age. Reasonable attempts were made insofar as was possible to have approximately equal representation of gender in this study. All participants were required to provide informed consent and to have English as their primary language. Exclusion criteria for participation included a past or present Axis I psychiatric diagnosis (with the exception of BPI or BPII for BP groups), as determined by self-report, a past or present history of a chronic medical condition with known effects on CNS function, traumatic brain injury or other neurological disorder as determined by self report, English as a secondary language as determined by self-report, a current or recent (within past six months) diagnosis of a substance use disorder as determined by way of the SCID-I, current medication use (within the past week) that has known CNS function effects (with the exception of medications prescribed specifically for the treatment of BP), and/or a hearing impairment as determined by self report,

hearing aid use, and a brief screener. Aside from these general inclusion-exclusion criteria, individuals with a first-degree relative who had been diagnosed with BP, MDD, or schizophrenia were excluded from the healthy control group.

Measures

Following is a description of the individual tests administered to participants in this study.

Screening and diagnostic measures

The Structured Clinical Interview for DSM-IV

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al., 1997) is a semi-structured interview for diagnoses of DSM-IV Axis I psychiatric disorders. Administration of the SCID-I is to be conducted only by clinicians that have been trained in the DSM-IV diagnostic system (APA, 1994). This instrument has been utilized in the diagnosis of both psychiatric and general medical patients and individuals in the community for the purpose of mental health surveys and research. The inpatient version of the SCID-I will be utilized in this study, and all 12 modules will be administered, including the screening module. The screening module is composed of 12 questions that are used to guide or elicit further administration of subsequent modules. Each item is rated on a scale of 1 to 3 (1 = symptom is absent, 2 = sub-threshold symptom, or 3 = symptom is present). The SCID-I has demonstrated fair to good reliability, achieving Kappa values as high as .98 for some diagnoses. Too, it has shown high validity for the diagnosis of schizophrenia, with good sensitivity (.89), specificity

(.96), and agreement (.86) when compared to best estimate diagnoses made by psychiatrists on first-admission psychotic patients (Fennig et al., 1994).

Experience and Symptom measures

The Positive and Negative Affect Symptoms Scale

The Positive and Negative Affect Symptoms Scale (PANAS) is a 20-item questionnaire that assesses the emotional style used by individuals to cope with life events. Respondents indicate the extent to which the adjective presented in each item is representative of their current mood. Each item is rated on a scale of 1 to 5 (1 = very little or not at all, 2 = a little, 3 = moderately, 4 = quite a bit, or 5 = extremely). The PANAS has demonstrated high reliability with studies showing internal consistencies using Chronbach's α of between .85 and .89. Correlations between the scales of the PANAS and those of other depression and anxiety rating scales were also high and significant at the .01 level (Crawford & Henry, 2004).

Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale (HAM-D) is a 17-item depression rating scale that is administered by a qualified rater. The HAM-D evaluates depressed mood, vegetative and cognitive symptoms of depression, and comorbid anxiety symptoms. It provides ratings on current DSM-IV symptoms of depression, with the exceptions of hypersomnia, increased appetite, and concentration/indecision. The total HAM-D score, which provides a reliable indication of depression, can also be used to provide a valuable guide to progress. The HAM-D has exhibited high internal consistency, and support for its construct validity was demonstrated by its pattern of correlations with other measures of depression, anxiety, and depression-relevant cognition. Factor analyses of the full 23-

item and 17-item versions of the HAM-D each yielded 4 factors, which accounted for 49% and 53% of the variance in participants' responses, respectively (Dozois, 2003). These results provide strong support for the HAM-D as a reliable and valid instrument for the assessment of depressive severity.

Young Mania Scale

The Young Mania Scale (YMS) is an 11-item clinician administered rating scale used to determine symptoms of mania. This scale was administered to bipolar subjects only to assess mood state as it is used to assess disease severity in patients already diagnosed with mania in bipolar disorder. The rating of each item on the scale is based on the subjective report of the individual's condition over the previous forty-eight hours, as well as behavioral observations of the clinician. Each item is rated on a 0 to 4 scale, (absent to overtly present) with the exception four items, which receive double weighting and are rated from 0 to 8. This scale was administered by a trained clinician who assigned a severity rating for each item based on a personal interview. The YMS has shown high inter-rater reliability by demonstrating a high correlation between scores of 2 independent clinicians on both total score (0.93) and individual item scores (0.66-0.92). Further, the YMS overall score has been shown to be highly correlated with an independent global rating and with scores from two other commonly used mania rating scales (the Petterson and the Beigel Scales) when the scales were administered concurrently.

Premorbid and Current IQ Estimates

Vocabulary, Information, and Block Design Subtests

The Vocabulary and Information subtests of the Wechsler Adult Intelligence Scale-3rd Edition (Wechsler, 1997) were used to estimate premorbid IQ. The Information and Vocabulary subtests have the highest reliabilities among the verbal WAIS subtests (.89 and .96, respectively). They are considered as "hold" tests and do not change considerably over time, even in the presence of brain dysfunction (Vanderploeg, Schinka, & Axelrod, 1996). The mean of the Vocabulary and Information age-corrected scaled scores were used as an estimate of premorbid IQ (Bilder et al., 1992).

A dyadic short form of the WAIS-III scaled scores on the Vocabulary and Block Design subtests were used to estimate current IQ. This score is calculated using regression equations that have been normed on a mixed neurological/psychiatric sample to estimate the Full Scale IQ score (Ryan, Utley, & Worthen, 2006).

The Block Design subtest involves nonverbal problem solving skills, spatial visualization/organization abilities, sustained attention and visual motor coordination, the ability to analyze the whole from constituent parts, and has been found to be sensitive to right parietal dysfunction (Groth-Marnat, 1999). In the Block Design subtest, participants are shown a series of red and white spatial designs of increasing difficulty via a stimulus booklet. Participants are asked to duplicate the designs with red and white blocks, all of which are identical (2 red sides, 2 white sides, and two sides of half red and half white). This measure is a speeded task in which accuracy and speed of completion contribute to overall level of performance.

Neuropsychological measures

The neurocognitive tests utilized in this study assessed Working Memory, Verbal Learning and Memory, Verbal Fluency, Visual Learning and Memory,

Visuoconstruction, Psychomotor, Executive Function, Attention, and Emotion Processing abilities. Most of the measures used are widely utilized research instruments and have been effectively used on multiple occasions in previous studies attempting to assess neuropsychological and emotion processing function in individuals with BP. Collectively, these measures served as a comprehensive neuropsychological test battery and results therefore are thought to constitute a representative index of cognitive ability in the domains assessed. All measures were administered and scored in the appropriate standardized fashion through use of the testing manuals. Psychometric data of all tests were available in standard neuropsychological texts (Lezak, 2004). All test scores were double checked and double entered by qualified laboratory assistants.

All participants were administered the same battery of neuropsychological tests and received the following measures:

1) Vocabulary Wechsler Adult Intelligence Scale-III Subtest
2) Information Wechsler Adult Intelligence Scale-III Subtest
3) Block Design Wechsler Adult Intelligence Scale-III Subtest
4) Digit Span Wechsler Adult Intelligence Scale-III Subtest
5) Spatial Span Wechsler Memory Scale Subtest
6) The California Verbal Learning Test, Second Edition (CVLT-II)
7) Controlled Oral Word Association Test
8) The Biber Figure Learning Test- Expanded (BFLT-E)
9) Rey-Osterrith Complex Figure (ROCF)
10) Purdue Pegboard
11) Grip Strength

12) The Trail Making Test A and B

13) The Wisconsin Card Sorting Task (WCST)

14) The Stroop Color-Word Association Test

15) The Emotional Verbal Learning Test (EVLT)

16) The Facial Affect Learning and Memory Test, Second Edition (FALMT-II)

Digit Span

The Digit Span subtest of the Wechsler Adult Intelligence Scale-3rd Edition has a forward and a backward component, both of which consist of verbal number pattern sequences that are presented to participants in increasing length. In Digit Span Forward, subjects are asked to orally recite these sequences of numbers of increasing length after verbal presentation by the examiner. In Digits Backward, subjects are asked to repeat a series of numbers in the reverse order or presentation. Scores attained for Digit Span Forward and Digit Span Backward are combined for an overall total score. The total raw score was used in the analyses as a dependent variable in the assessment of phonological loop function.

Spatial Span

The Spatial Span Wechsler Memory Scale subtest (Wechsler Memory Scale, Wechsler, 1997) has a forward and a backward component, both of which consist of spatial pattern sequences that are presented to participants. In Spatial Span Forward, the experimenter points to block sequences of increasing difficulty and length one at a time. After each sequence, the participant is asked to point to the same blocks in the same sequence. In Spatial Span Backward, the participant observes the examiner point to a series of blocks of increasing length and difficulty but is then asked to point to the blocks

in the *reverse* order of presentation. A total overall score is derived by adding the Spatial Span Forward score to the Spatial Span Backward score. The Spatial Span total score of participants was used as a dependent variable measure of visuospatial sketchpad function in this study. This score was used as it is a visuospatial analog to the Digit Span subtest of the WAIS-III.

The California Verbal Learning Test

The California Verbal Learning Test, 2nd Edition, Adult Version (CVLT-II) (Delis, Kramer, Kaplan, & Ober, 1987) is an instrument designed to test non-emotional verbal memory in which the subject is asked to learn a list of 16 common shopping list items on 5 consecutive trials (learning). The subject is then asked to recall and recognize these items following a delayed interval (memory). The recall measure involves both cued and free recall. During the CVLT, subjects are told verbally a series of 16 words over five immediate-recall trials. The list consists of 4 words from each of four semantic categories (i.e. vegetables, furniture, transportation, and animals). After this immediate-recall task subjects are asked to recall the words following a twenty minute waiting period in order to measure long term memory. Therefore, the CVLT measures recall, recognition and list learning. However, interference effects and retrieval/encoding difficulties can also be evaluated with this measure.

Controlled Oral Word Association Test

The Controlled Oral Word Association Test, (COWAT; Sumerall, Timmons, James, Wing, & Oehlert, 1997) is considered to be a measure of verbal fluency and is also believed to secondarily draw on prefrontal or executive function. The measure is subdivided into two components: phonetic fluency subtest and a semantic fluency

subtest. For the phonetic fluency subtest, participants are required to freely generate as many words as possible beginning with a given letter (F, A, and S, respectively) within 60 seconds (per letter). Proper names or the same words with different endings or suffixes are not allowed. For the semantic fluency portion of the test requires semantic association and requires participants to freely generate the names of as many examples of a given semantic category (names of animals) as possible within 60 seconds. The semantic fluency portion of this measure is thought to activate right dorsolateral and medial frontal regions of the brain whereas the phonemic fluency portion is thought to activate left frontal and temporal regions of the brain (Loring, Meador, & Lee, 1994).

The Biber Figure Learning Test- Expanded

The Biber Figure Learning Test- Expanded (BFLT-E) is a modification of the original Biber Figure Learning Test, (BFLT; Glosser et al., 1989) and is a test of recognition and recall of visuo-spatial stimuli in the form of geometric shapes. It is composed of 15 various geometric designs made up of simple shapes, such as circles, triangles, and squares. These fifteen designs are presented sequentially at a rate of one every 3 seconds. After the designs are presented, participants are asked to draw as many of the designs as can be recalled in any order desired. A task of interference is then introduced which is composed of figures different from those included in the 15 original design stimuli. This interference task is then followed by an immediate free recall condition. An unrelated task is then administered for 20-30 minutes, after which a delayed learning recall trial is introduced wherein verbal, non-visuospatial tasks are interjected into the condition. A recognition task is then introduced in which the participant is asked to recognize the original designs which are intermixed with distracter items. The reproduced designs are each scored on a scale of 0 - 3 according to the

accuracy of the drawing. The BLFT-E inter-rater reliability has been found to be very good at .98. It has also demonstrated good test-retest reliability and criterion validity (Glosser, Guila, Cole, Lynne, Khatri, & Upama, 2002). Further, it is sensitive to non-language-dominant right temporal lobe functioning and visuoconstructional difficulties that are related to various types of brain damage or injury, and has been shown to be usefulness in the assessment of various components of visuospatial memory in patients with lateralized right mesial temporal lobe dysfunction.

Rey-Osterrith Complex Figure

The Rey-Osterrieth Complex Figure (ROCF; Rey, 1941; Osterrieth, 1944) is a commonly used measure that assesses visual memory and visuoconstructional abilities (Lezak, 1995). In the measure, the participant is shown a stimulus card on which a geometric, complex figure is depicted. The participant is asked to copy the figure and to subsequently reproduce it from memory without warning after a 3-minute delay (delayed recall trial) and a 30-minute delay (delayed recall trial). Delayed recall is thought to be more sensitive to true visual memory deficits than is the immediate recall condition (Loring, 1990). The copy portion of the ROCF was used in this study.

Purdue Pegboard

The Purdue Pegboard Test (Purdue Research Foundation, 1948) measures gross motor coordination and dexterity and psychomotor processing speed. It is sometimes used to measure brain lateralization and for localizing cerebral lesions (Spreen & Strauss, 1998). The pegboard contains two parallel columns of twenty-five holes in which pegs are placed one hand at a time and then with both hands simultaneously under timed conditions (30 seconds per trial). Scores for this measure are derived for each trial

according to how many pegs were placed within the allotted time limit and a mean score is then calculated.

Grip Strength

The Grip strength test measures the grip strength of each hand consecutively by way of a hand dynamometer. The hand dynamometer is first adjusted to the grip width of the participant's hand and the participant is then instructed to grip the device with as much strength as possible while keeping the arm flush against the side of the body. The mean of two trials with each hand is then recorded in kilograms.

Trail Making Test A and B

The Trail Making Tests A and B (TMT; Reitan and Wolfson, 1985) were utilized as measures of central executive function as they are designed to assess, among other things, an individual's cognitive set shifting ability. In Trails A, the participant is asked to connect a series of circles containing the numbers from 1 to 25 with a pencil as quickly as possible in numerical order. Similarly, in Trails B, the participant is asked to connect circles but to alternate from number to letter, with the circles numbered from 1 to 13 and the letters from A to L.

Parts A and B have a correlation of .49 (Spreen & Strauss, 1998), suggesting that they measure somewhat different constructs. Part B is typically considered to be a more complex task, and is thought to be a purer measure of cognitive set shifting and visual perceptual processing aspects of working memory than is part A, which is a simpler measure visual spanning and psychomotor speed abilities. The time required (in seconds) to complete each part was used as dependent variables.

The Wisconsin Card Sorting Test

In the Wisconsin Card Sorting Test, (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993) participants are given a pack of 64 cards on which are printed one to four symbols (triangle, star, cross, or circle in red, green, yellow, or blue). Subjects are given one card at a time from the deck. They are asked to place the cards one at a time under a set of 4 stimulus cards according to a predetermined principle (color, form, or number), which must be deduced by the examinee based on examiner feedback. The sorting principle shifts from color to form, then to number and is thereafter repeated for a second set. Subjects are given corrective feedback with each attempt at sorting in order to deduce the sorting principle, but no further directions or prompts are given. The categorization rule shifts after ten successful, consecutive responses, and subjects must then decipher the new sorting principle using examiner feedback. After an additional 10 correct, consecutive sorts, the sorting principle changes again without warning. This sequence continues until six categories are completed or all of the 128 cards are sorted.

The Wisconsin Card Sorting test can be administered manually or via compute. This test measures abstract concept formation and the ability to shift cognitive sets as feedback is given. This task has been used extensively in research involving clinical populations and has been shown to be sensitive to dorsolateral prefrontal cortex dysfunction (Sullivan, Mathalon, Zipursky, Kersteen-Tucker, Knight, & Pfefferbaum, 1993). The dependent measures used in this study were perseverative errors, categories completed, and failure to maintain set scores of the WCST.

The Stroop Color-Word Association Test

The Stroop Color Word Association Test (Stroop, 1935) is a test of selective attention. This version of the Stroop test consists of three parts in which the participant is asked to visually scan words and symbols as quickly as possible for one minute time periods. In the first portion of the task, participants are asked to read color names (a total of 100 words) randomly printed in black ink, e.g. blue, red, and green as rapidly as possible. In part two, participants are asked to name the actual color of X's printed in the three colors (blue, red, and green). In part three, considered the color-word interference task, participants are asked to read the color names while ignoring the color of the printed word (which is different than the actual word color). Although variations of this test exist, the most recent version utilizes a time limit of 45 seconds for each section. The number of correct items completed in each section is tabulated and an interference score is derived in the third section. The Stroop test is a measure of information processing speed as well as ability to focus on task demand. It is also considered to be a measure of ability to rapidly shift attentional set, i.e. suppressing the color of the print while naming the word.

The Emotional Verbal Learning Test

The Emotional Verbal Learning Test (EVLT; Strauss and Allen, unpublished manuscript) is similar to the CVLT in every respect with the exception that the words included in the word lists have strong emotional content. So, rather than words selected from semantic categories, word selection was based on emotional content and intensity. List A for the EVLT contains 16 words, four from each of the emotional categories of happiness, sadness, anger, and anxiety (Strauss & Allen, unpublished manuscript).

The Facial Affect Learning and Memory Test- Second Edition

The Facial Affect Learning and Memory Test- Second Edition (FALMT-II) was developed to measure emotional visuo-spatial memory. During the FALMT-II, subjects are shown a series of facial photographs which display a sequence of six different and discrete emotions (happiness, surprise, fear, sadness, disgust and anger). Pictures for the task were taken from Penn facial-affect pictures which was developed for the Penn Face Memory Test (Gur, Sarab, Hagendoorna, Maroma, Hughetta, Macya, Turnera, Bajcsyb, Posnerd, & Gur, 2002) created by Ruben E. Gur at the University of Pennsylvania, Neuropsychiatry Section. In the series, 70 actors and 69 actresses display, via facial expression, the emotions of happiness, sadness, anger, fear and disgust. They also display neutral expressions. Each emotion is expressed at three levels of intensity and under both posed and evoked conditions. The facial images are of high technical quality and have been accurately identified by raters. This database of emotional expressions can therefore be considered as a standard for comparison with clinical populations (Gur et al, 2002). This assessment instrument was loosely modeled after the CVLT-II and EVLT in structure in that number of trials is identical and in that it includes a delayed recall component for the assessment of long term memory.

Domains of Assessment

The measures used to assess neuropsychological functioning were grouped broadly into 10 neurocognitive domains: 1) Working Memory (Digit Span and Spatial Span subtests of the WAIS-III, forward and backward scores), 2) Learning and Memory for Verbal Non-Emotional information (CVLT-II trials 1-5), 3) Learning and Memory for

Visual Non-Emotional information (BFLT-E trials 1-5), 4) Attention (Trail Making Test A and Stroop Color-Word Association Test congruent and incongruent response times and total correct scores), 5) Visuoconstruction ability (Block Design subtest of the WAIS-III and ROCF copy trial), 6) Psychomotor ability (Purdue Pegboard and Grip Strength dominant and nondominant hand scores), 7) Verbal Fluency (COWAT Animals and FAS), 8) Executive Function (Trail Making Test B and WCST perseverated errors and failure to maintain set scores) and, 9) Learning and Memory for Verbal Emotional information (EVLT trials 1-5), and 10) Learning and Memory for Visual Emotional information (FALMT-II trials 1-5). The measures selected are widely used in both clinical and research settings, have been used in previous studies assessing neuropsychological functioning in BP and other psychological disorders. These assessments were also selected to collectively measure broad domains of cognitive functions that would be inclusive in a comprehensive neuropsychological battery.

Apparatus

For the FALMT-II, all stimuli (in the form of human faces) were displayed via a computer screen for 3 seconds per photograph by way of E-Prime software (Psychology Software Tools) with a viewing distance of approximately two feet. Verbal response was measured by a voice-operated microphone, which was connected to a serial response box that relayed the stimulus response interval to E-Prime Data-Aid software (Psychology Software Tools, Inc., Version 5.0) on the computer. The following measures were assessed: length of time taken for identification of specific emotions demonstrated in

each stimulus, length of time taken for recognition of the various faces used as stimuli, and subject accuracy on both measures (Armstrong, 2005).

The Stroop Color Word Association Test was also presented by way of E-Prime software (Psychology Software Tools). Stimuli, in the form of slides, were projected onto a computer screen, with a viewing distance of approximately two feet. Verbal responses were measured by a voice-operated microphone, which was connected to a serial response box that relayed the stimulus response interval to E-Prime Data-Aid software (Psychology Software Tools, Inc., Version 5.0) on the computer. Response time for recognition of congruent stimuli, response time for recognition of incongruent stimuli, and total correct items were assessed.

Procedures

Subjects were recruited from the community through private mental health practitioners interested in involvement in the study, mental health clinics in the community with an established relationship with the Department of Psychology at the University of Nevada Las Vegas, and various support groups within the community such as the National Alliance for the Mentally Ill (NAMI) and the Depression and Bipolar Support Alliance of Southern Nevada (DBSA). An informational flyer, providing contact information as well as a brief overview of the study, was posted at various places on the University of Nevada, Las Vegas campus as well as at various agencies in the community (see Appendix D). Direct recruiting by way of case managers and mental health personnel was also employed in conjunction with participating community mental health agencies. Participants from the University of Nevada, Las Vegas were recruited

through the Psychology Department's Subject Pool, on-campus mental health service providers, and through posted recruitment advertisements placed at various locations. UNLV subject pool students received compensation of extra credit points or partial fulfillment of their course requirements, equivalent to one credit hour for each hour of participation. Participants who did not complete the entire study were compensated for the actual time spent participating. All other individuals who participated were compensated at the rate of $5.00 per hour of participation in the study, with a $30.00 final compensation given to those who completed the study in its entirety. Recruiting participants in this manner ensured equal participation opportunity in regard to gender and ethnicity.

Upon recruitment, participants completed an informed consent form. Included in Appendix C are all consent forms for a) individuals with BP and healthy individuals recruited from the community b) healthy individuals and individuals with BP recruited from UNLV. Prior to participation a trained researcher met individually with each participant to explicate the consent form and to ensure understanding of the requirements involved in participation. All potential participants were read the consent form and given the opportunity to ask questions. Two consent forms were signed by the examiner and each participant. One consent form was then given to the participant and one was kept in a locked filing cabinet in the Neuropsychology Research Laboratory at UNLV. This process ensured that the privacy of participants will be maintained and that participation will be voluntary and under complete informed conditions. All other information pertaining to participants will be identified by way of alpha numeric code to ensure subject anonymity. Participants in the study, as will be explicated in the informed

consent form, will be given no information or feedback regarding test scores or test results. Raw data will be accessible only to study personnel, including Carol Randall and Daniel Allen, as well as research staff as is necessary.

Following informed consent, all participants were given the same battery of screening and diagnostic measures, and neuropsychological tests in a fixed order by the principal investigator or a trained research assistant/technician. All measures and tests were administered individually in a quiet, private room at the UNLV Neuropsychological Laboratory or at the respective mental health agency if the individual was unable to come to UNLV. The total test administration time was between 6 and 7 hours.

CHAPTER 4

RESULTS

Data Screening

Preliminary analyses were conducted prior to performance of the main analyses. Raw data from the various neuropsychological tests were inspected to ensure that assumptions for multivariate analysis of variance (MANOVA) were met. Descriptive statistics and box plots were carried out for each of the neuropsychological variables, with skewness and kurtosis examined to ensure the existence normal distribution of variables and box plots utilized to evaluate potential outliers. Outliers were defined as scores lying at least 3.0 standard deviations above or below the mean, and variables with skewness and kurtosis estimates within ± 3.0 were considered to be in the range acceptable for use of parametric statistical tests and procedures. In cases where variables were not normally distributed, transformations were to be used to increase the normality of the distribution. Upon preliminary screening of the data, however, no measures were found to be skewed or kurtotic, and no outliers were identified, so MANOVA, repeated-measures analysis of variance (ANOVA), and univariate analyses were performed using raw variable scores.

Preliminary Analyses

Following data screening, preliminary analyses were conducted to determine the existence of significant differences among the three groups (BPI, BPII, and NC) on variables that are known to have an impact on neurocognitive test performance, including age, years of education, premorbid IQ, current IQ, sex, and ethnicity. Differences

between the BP groups in global assessment of functioning (GAF score), number of psychiatric hospitalizations, and medication status were also examined.

Likelihood Ratio was utilized for analysis of categorical variable comparisons of the three groups, and a binomial test was used for a comparison between the BPI and BPII groups on medication status (categorical variable). ANOVA was used for continuous variable comparisons among the three groups as well as between the BPI and BPII groups, and these analyses were followed by post-hoc contrasts when overall significant differences were identified. The demographic characteristics and results of these analyses are presented in Table 1, Appendix A.

When demographic variables were compared among the BPI, BPII, and NC groups (see Table 1), the groups did not differ significantly on age, $F(2, 70) = 2.509$, $p = .089$, (BPI group: 35.78 ± 14.238 years, BPII group: 31.72 ± 10.764 years, NC group: 27.78 ± 10.713 years), level of education, $F(2, 70) = .168$, $p = .846$, (BPI group: 14.19 ± 2.515 years, BPII group: 14.56 ± 2.229 years, NC group: 14.39 ± 1.614 years), premorbid IQ (which was based on WAIS-III Information and Vocabulary subtest score averages), $F(2, 70) = 1.088$, $p = .342$, (BPI group: 12.378 ± 2.531, BPII group: 12.000 ± 1.847, NC group: 13.056 ± 1.662), or current IQ (which was calculated using the WAIS-III Vocabulary and Block Design subtests), $F(2, 70) = 1.035$, $p = .361$, (BPI group: 105.460 ± 14.292, BPII group: 104.833 ± 11.848, NC group: 110.333 ± 11.499). The groups were found to differ significantly on overall level of functioning, as measured by the Global Assessment of Functioning (GAF) scale, $F(2, 69) = 17.926$, $p < .001$, (BPI group: 57.53 ± 12.235, BPII group: 67.94 ± 9.200, NC group: 82.17 ± 20.960). For the GAF, post hoc analysis indicated that the NC group had significantly higher functioning than the BPII

group, who in turn had significantly higher functioning than the BPI group. When the BPI and BPII group GAF scores were compared, results were still significant F (1, 52) = 10.139, $p < .01$.

BPI and BPII groups were then compared on number of mental health hospitalizations and current symptom severity (as measured by HAM-D and YMS scores). The groups did not differ on number of mental health hospitalizations, F (1, 53) = 2.707, p =.106, (BPI group: 2.46 ± 3.141, BPII group: 1.11 ± 2.111) or symptom severity, as measured by HAM-D, F (1, 52) = 1.891, p =.175, (BPI group: 8.22 ± 5.623, BPII group: 6.18 ± 3.486) and YMS scores, F (1, 53) = .805, p =.374, (BPI group: 4.00 ± 3.082, BPII group: 3.28 ± 2.081).

HAM-D and YMRS scores showed that individuals in the BP groups were within the euthymic range on average based on the standard cutoff scores of HAM-D ≤ 8 and YMRS ≤ 6 (Hamilton, 1967; Young, Biggs, Ziegler, & Meyer, 1978), and none of the participants were experiencing a current mood episode as defined by the SCID at the time of testing. Moreover, given that the mean years of education for the combined BP groups was 14.35 years, most were employed and/or attending a University, and the mean current IQ for the BP groups was 105.25 (BP groups combined), it is apparent that the BP groups were composed of relatively high functioning individuals as opposed to those more severely affected by the disorder.

Likelihood Ratio analyses revealed no significant differences among the BPI, BPII, and NC groups on sex, {G (1) = .783, p =.676}, or ethnicity, {G (12) = 16.378, p =.175}. BP group comparisons revealed no significant differences between the groups on sex, {G (1) = .221, p =.638} or ethnicity, {G (6) = 7.535, p =.274}, and the binomial test

comparing medication status (medicated versus un-medicated) between the BPI and BPII groups was also non-significant {$z = 1.415$, $p > .05$, *Confidence Level = 84.3%*}. Results are displayed in Table 1 (Appendix A).

Sex distribution within each group was such that the BPI, BII, and NC groups were 67.60%, 61.10%, and 55.60% female, respectively. With regard to the distribution of ethnicity within each group, the BPI group was 67.60% Caucasian, 5.4% Asian American, 5.4% Hispanic, 2.70% African American, 2.70% Native American, 8.10% Biracial, and 8.10% Other (which category was made up of various less common ethnicities). The BPII group was 77.80% Caucasian, 11.10% Asian American, 5.60% African American, and 5.60% Native American. The NC group was 44.40% Caucasian, 22.20% African American, 11.10% Asian American, 11.10% Hispanic, 5.60% Biracial, and 5.60% Other. In that the three groups were relatively well matched in terms of these demographic variables and no significant differences were found among the groups in these demographic variables, sex and ethnicity were not used as covariates in the analyses. Results are displayed in Table 1 (Appendix A).

Main Analyses

After preliminary analyses were completed, Hypothesis one and two were investigated. MANOVA was used for analysis of the Working Memory, Verbal Fluency, Visuoconstruction, Psychomotor, Executive Function, and Attention domain. Separate MANOVA were performed for each domain, and submeasures included Digit Span and Spatial Span subtests of the WAIS-III (Forward and Backward trials) for assessment of Working Memory, the COWAT (FAS and Animals total scores) for assessment of Verbal

Fluency, Block Design (subtest of the WAIS-III) and ROCF (Copy Trial) for assessment of Visuoconstruction abilities, Purdue Pegboard and Grip Strength (Dominant and Non-dominant Hand scores for each test) for assessment of Psychomotor ability, WCST (Perseverated Errors and Failure to Maintain Set) and Trail Making Test B for assessment of Executive Function, and Trail Making Test A and Stroop Color-Word Association Test (Congruent and Incongruent Response Time and Total Correct Items) for assessment of Attention. Combined test scores were used to assess the domains, and tests in each domain served as dependent variables in the MANOVA, with group membership (BPI, BPII, and NC) serving as the between subjects factor. When the results of MANOVA was found to be significant, univariate ANOVAs and post hoc comparisons (Tukey B) were used to examine group differences on individual measures.

Repeated-measures ANOVA was used to evaluate Learning and Memory domain differences among the groups for Non-Emotional and Emotional Visual and Verbal information. In these analyses, the first five learning trials from the CVLT-II, BFLT-E, FALMT-II, and EVLT served as the repeated-measures, and group (NC, BPI, and BPII) served as the between-subjects variable. A separate repeated-measures ANOVA was run for each of the measures (CVLT-II, BFLT-E, FALMT-II, and EVLT). When the results of the repeated-measures ANOVA was significant, univariate ANOVAs and post hoc comparisons (Tukey B) were used to examine group differences on the individual learning trials. Table 2 (Appendix B) contains descriptive statistics for the domains, separate neuropsychological tests, multivariate, repeated-measures, univariate analyses, and post-hoc tests.

Hypothesis three was evaluated by comparing group rankings on domain measures. The Kruskal-Wallis Test was first used to obtain group mean rankings on the various domain submeasures and then to obtain overall mean rank scores for the three groups for all measures combined. Finally, the Mann-Whitney Test was utilized to separately compare group rank scores of the BPI and BPII groups as well as between the BPII and NC groups (see Table 3).

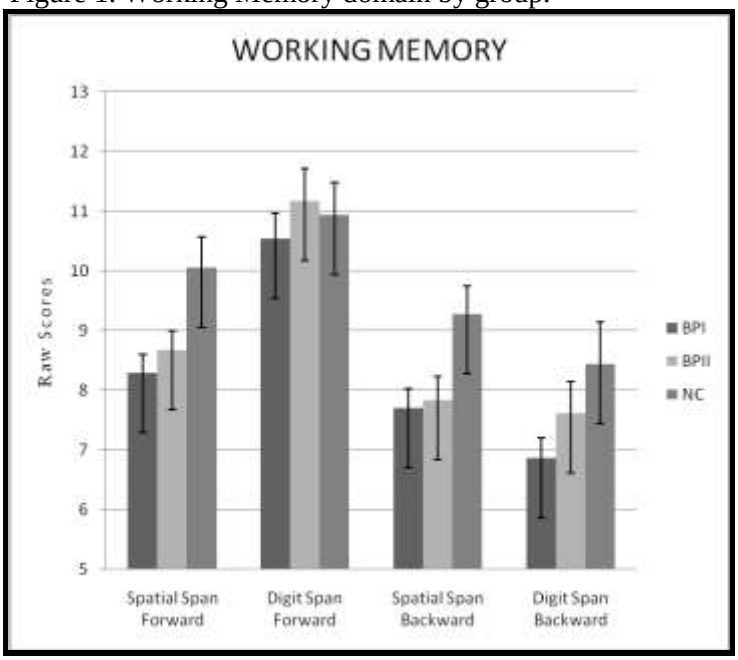
Analysis of Hypotheses

Hypothesis One

Significant overall differences among the groups will be found in performance within the domains of Working Memory, Verbal Learning and Memory for Non-Emotional information, Attention, and Executive Function.

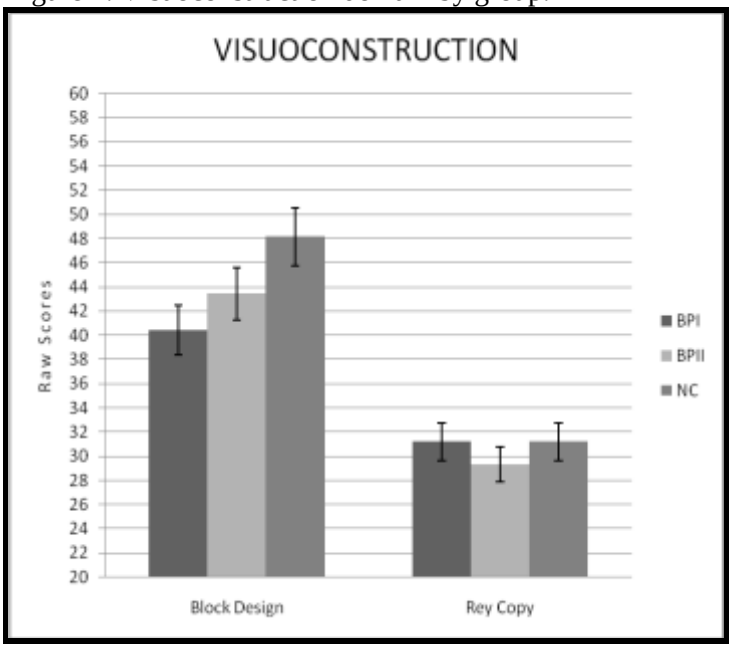
Analyses indicated significant performance differences among the groups in four of the eight neurocognitive domains, specifically in the domains of Working Memory, Visuoconstruction, Attention, and Verbal Learning and Memory for Non-Emotional Information, (see Figures 1-4 below). Expected differences among the groups were not present for the Executive Function domain.

Figure 1. Working Memory domain by group.



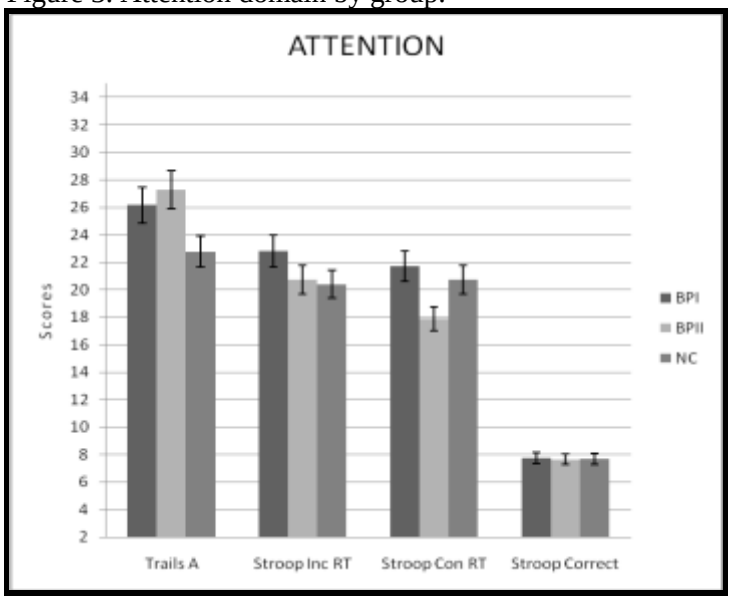
Note: Spatial Span Forward and Backward Trials, Digit Span Forward and Backward Trials; Raw Scores = total number correct; BPI = BPI group; BPII = BPII group; NC = Normal Control group.

Figure 2. Visuoconstruction domain by group.



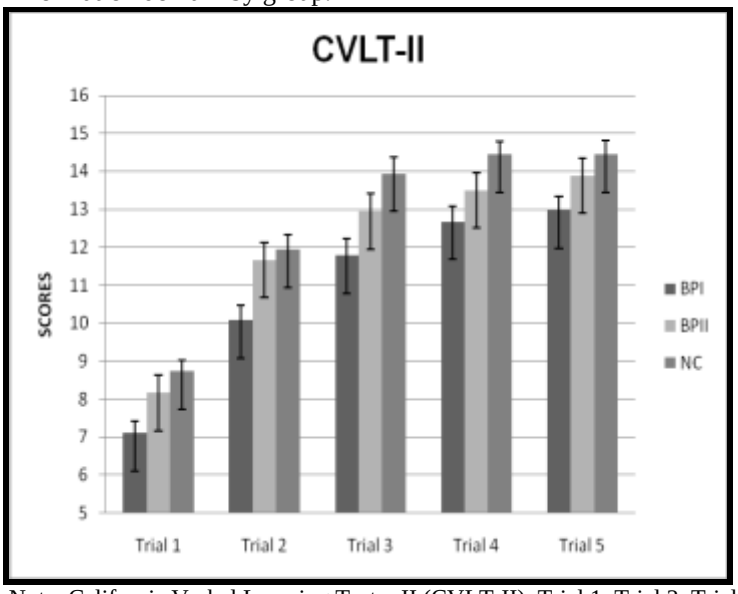
Note: Block Design = Block Design subtest of the WAIS-IV; Rey Copy = Rey Osterrith Complex Figure Copy Trial; Raw Scores = total number correct; BPI = BPI group; BPII = BPII group; NC = Normal Control group.

Figure 3. Attention domain by group.



Note. Trails A: Trail Making Test Part A; Stroop Inc RT: Color-Word Association Test, Incongruent Response Time; Stroop Con RT: Color-Word Association Test, Congruent Response Time; Stroop Correct: Color-Word Association Test, Total Number Correct; BPI = BPI group; BPII = BPII group; NC = Normal Control group.

Figure 4. Learning and Memory for Verbal Non-Emotional Information domain by group.



Note: California Verbal Learning Test – II (CVLT-II), Trial 1, Trial 2, Trial 3, Trial 4, and Trial 5; Scores = number of words recalled; BPI = BPI group; BPII = BPII group; NC = Normal Control group.

As predicted, no significant performance differences were found among the groups in the Verbal Fluency, Visual Learning and Memory for Non-Emotional information, and Psychomotor domains.

For the Working Memory domain, MANOVA was found to be significant, F (8, 136) = 2.191, p =.032, and Tests of Between-Subjects Effects indicated significant differences among the groups on Spatial Span Forward, F (2, 70) = 5.574, p =.006, and Spatial Span Backward, F (2, 70) = 4.419, p =.016. In the Working Memory Domain, Multiple Comparisons revealed significant differences between the BPI and NC groups on Digit Span Backward, p =.05, (BPI group: 6.865 ± 2.030, BPII group: 7.611 ± 2.279, NC group: 8.444 ± 2.975), Spatial Span Forward, p =.004, (BPI group: 8.297 ± 1.854, BPII group: 8.667 ± 1.414, NC group: 10.056 ± 2.182), and Spatial Span Backward, p =.014, (BPI group: 7.703 ± 1.942, BPII group: 7.833 ± 1.724, NC group: 9.278 ± 1.994). No significant differences were found between the BPI and BPII groups or between the BPII and NC groups on any of the submeasures, but group performance fell in the expected pattern on Digit Span Backward, Spatial Span Forward, and Spatial Span Backward (see Figure 1).

For the Visuoconstruction domain (see Figure 2), MANOVA was significant, F (4, 140) = 2.416, p =.05, although no differences were found among the groups on the separate measures of the domain, including Block Design, F (2, 70) = 2.036, p =.138, or the Copy trial of the ROCF, F (4, 140) = 1.478, p =.235. Moreover, Multiple Comparisons indicated no significant differences between the BPI and BPII, the BPI and NC groups, or the BPII and NC groups on Block Design, (BPI group: 40.432 ± 14.396, BPII group: 43.444 ± 12.641, NC group: 48.167 ± 11.698), and similarly, no significant

differences between any of the groups on the ROCF Copy trial were found (BPI group: 31.122 ± 3.805, BPII group: 29.306 ± 4.983, NC group: 31.194 ± 2.926). However, performance among the groups fell in the predicted pattern on the Block Design test, with the NC group performing better than either of the BP groups, and the BPII group performing at an intermediate level, between the BPI and NC groups.

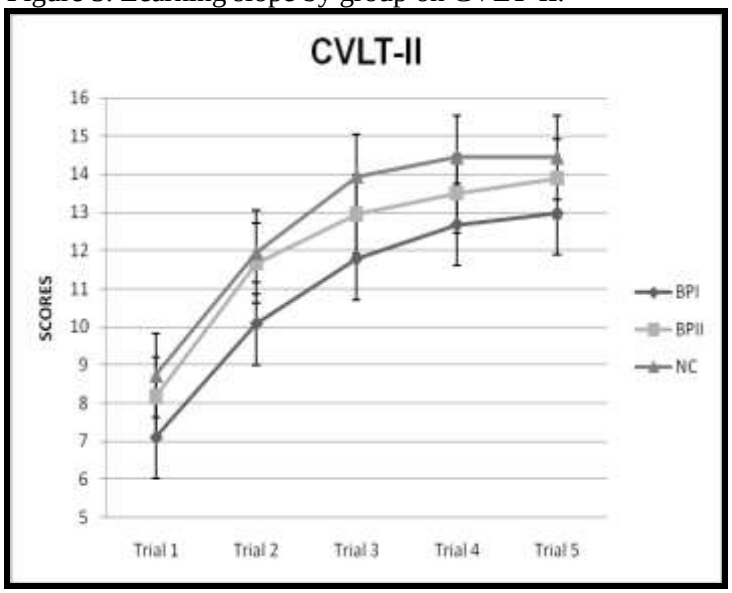
For the Attention domain (see Figure 3), MANOVA was significant, F (8, 136) = 2.778, p =.007, although Tests of Between-Subjects Effects demonstrated significant differences among the groups only on the Stroop Color-Word Association Test, Congruent Response Time, F (2, 70) = 3.932, p =.024. Multiple Comparisons revealed significant differences between the BPI and BPII groups on the Stroop Color-Word Association Test, Congruent Response Time, p =.018, (BPI group: 21728.757 ± 4333.155, BPII group: 17888.444 ± 5160.706, NC group: 20708.833 ± 5246.317), with the BPII performing better than the BPI (as well as the NC group, but not to a significant degree). No other significant differences were found between groups in this domain.

To examine Verbal Learning and Memory for Non-Emotional information, a repeated-measures ANOVA was used. CVLT-II learning trials 1 through 5 were the repeated measure, and group served as the between subjects variable. Results of this analysis indicated a significant within subjects effect for CVLT-II learning trial, F (4, 280) = 205.50, p < .0001, partial eta squared = .746, a significant between subjects effect for group, F (2,70) = 7.41, p < .001, partial eta squared = .175, and a non-significant trial by group interaction effect, F (8,280) = .51, p = .85, partial eta squared = .014.

Univariate ANOVAs used to compare performance among the groups on the individual trials of the CVLT-II indicated significant differences among the groups for

Trial 1, F (2,70) = 5.96, $p < .01$, Trial 2, F (2,70) = 6.33, $p < .01$, Trial 3, F (2,70) = 5.41, $p < .01$, Trial 4, F (2,70) = 4.17, $p < .05$, and Trial 5, F (2,70) = 3.3, $p < .05$. Post hoc comparisons (Tukey B) indicated that the BPI group performed significantly worse than the NC group on all of the learning trials. The BPII group did not differ from the NC group or the BPI group on any of the trials, although the performance of the BPII group was intermediate to these two groups on all trials (see Figures 4 and 5).

Figure 5. Learning slope by group on CVLT-II.



Note: California Verbal Learning Test – II (CVLT-II), Trial 1, Trial 2, Trial 3, Trial 4, and Trial 5; Scores = number of words recalled; BPI = BPI group; BPII = BPII group; NC = Normal Control group.

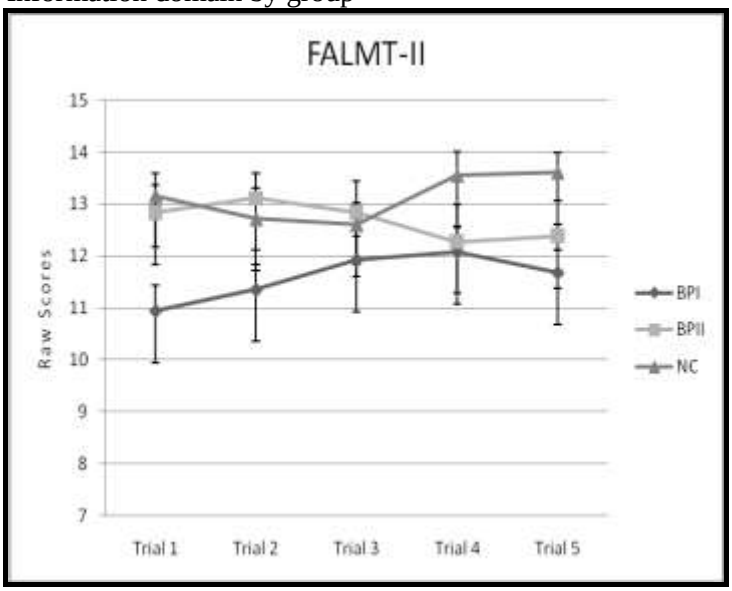
Hypothesis Two

Significant overall differences among the groups will be found in performance within the Learning and Memory for Verbal Emotional information and the Learning and Memory for Visual Emotional information domains.

Results of the repeated-measures ANOVA used to examine Learning and Memory effects for Emotional Visual information demonstrated a non-significant within-subjects

effect on the FALMT-II for trial, F (4, 280) = .42, p = .80, partial eta squared = .006, a significant between-subjects effect for group, F (2,70) = 3.52, p < .05, partial eta squared = .091, and a significant trial by group interaction effect, F (8,280) = 2.04, p < .05, partial eta squared = .055. Univariate ANOVAs used to compare performance among the groups on the individual trials of the FALMT-II indicated significant differences among the groups for Trial 1, F (2,70) = 6.05, p < .01, Trial 2, F (2,70) = 3.27, p < .05, and Trial 5, F (2,70) = 3.56, p < .05. No significant differences were present for Trial 3, F (2,70) = .96, p = .39, and Trial 4, F (2,70) = 1.76, p = .18 (See Figure 6 below).

Figure 6. Learning and Memory for Visual Emotional Information domain by group



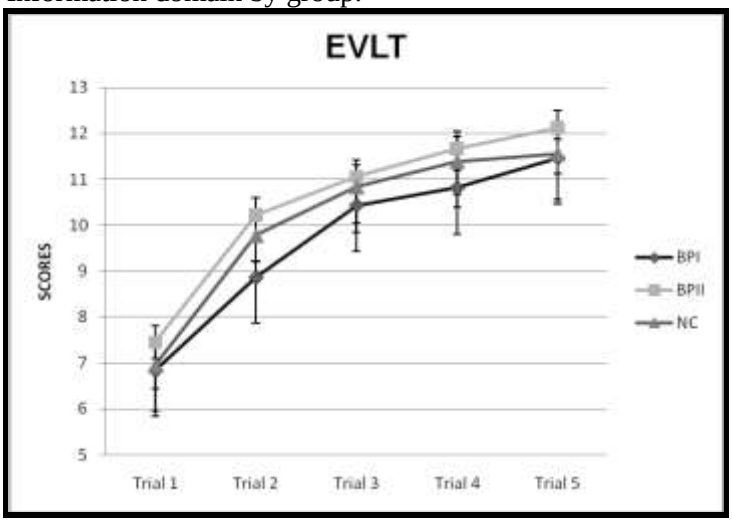
FALMT = Facial Affect Learning and Memory Test- II, Trial 1, Trial 2, Trial 3, Trial 4 and Trial 5. Raw Scores = number of items correctly identified; BPI = BPI group; BPII = BPII group; NC = Normal Control group.

Post hoc comparisons (Tukey B) indicated that for Trial 1, the BP1 group performed significantly worse than the NC and BPII groups. Tukey B indicated no significant differences between groups on Trial 2. On Trial 5, the BPI group performed significantly

worse than the NC group, and the BPII group did not differ from either the NC or the BPI group. As can be seen from Figure 6 above, the significant trial by group interaction effect was accounted for by the BPII group doing better than expected on two of the trials (Trials 2 and 3).

Comparable analyses were conducted to examine Learning and Memory for Verbal Emotional information (see Figure 7). EVLT learning trials 1 through 5 were the repeated measure, and group served as the between subjects variable. Results indicated a significant within subjects effect for EVLT learning trial, F (4, 280) = 145.72, $p < .0001$, partial eta squared = .676, a non-significant between subjects effect for group, F (2,70) = 7.418, p = .25, partial eta squared = .175, and a non-significant trial by group interaction effect, F (8,280) = .67, p = .71, partial eta squared = .019. As can be seen from Figure 6 below, the significant effect for EVLT Trial resulted from expected improvement in performance across the five trials.

Figure 7. Learning and Memory for Verbal Emotional Information domain by group.



Note: EVLT: Emotional Verbal Learning Test. Trial 1, Trial 2, Trial 3, Trial 4, and Trial 5; Scores = number of words recalled; BPI = BPI group; BPII = BPII group; NC = Normal Control group.

Hypothesis Three

As compared to the NC and BPI groups, the BPII group will demonstrate an intermediate level of performance in all domains assessed, with the best performance seen in the NC group and the BPI group demonstrating the worst level of performance among the groups.

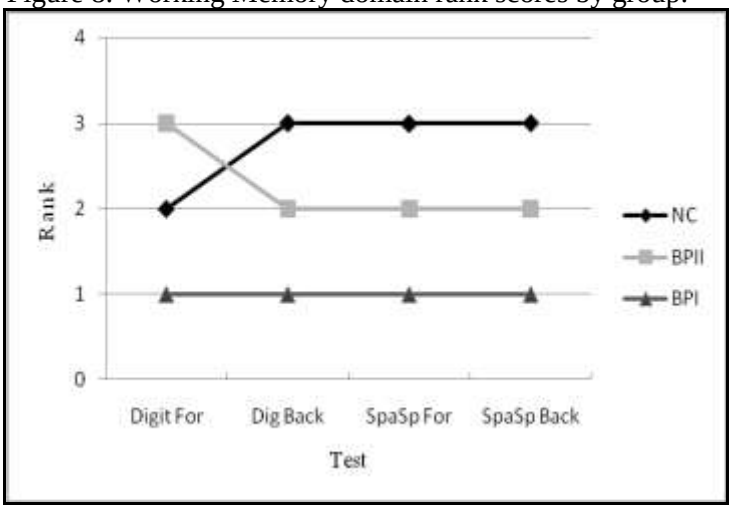
The Kruskal-Wallis Test results indicated a significant overall difference among rankings on the combined measures for each group, $H(2) = 59.258$, $p < .001$, (BPI group: 82, BPII group: 67, NC group: 28). The Mann-Whitney Test comparing mean rank scores of the BPI and BPII groups were also significant, $U(1) = 521.500$, $Z = -2.666$, $p = .008$, (BPI group: 45.63, BPII group: 33.37), with the BPI group performing significantly worse overall than the BPII group. Moreover, the Mann-Whitney Test comparing mean rank scores of the BPII and NC groups was significant, $U(1) = 209.500$, $Z = -5.992$, $p < .001$, (BPII group: 53.63, NC group: 25.37), with the BPII group performing significantly worse than the NC group. Distribution of the rankings by percentage for each of the three groups is listed in Table 3, below, and rank scores by group for each of the domains are presented in Figures 8-17.

Table 3. Rank percentages by group

Rank	Group		
	NC	BPII	BPI
1	**71.8%**	23.1%	5.1%
2	25.6%	**56.4%**	17.9%
3	2.6%	20.5%	**76.9%**

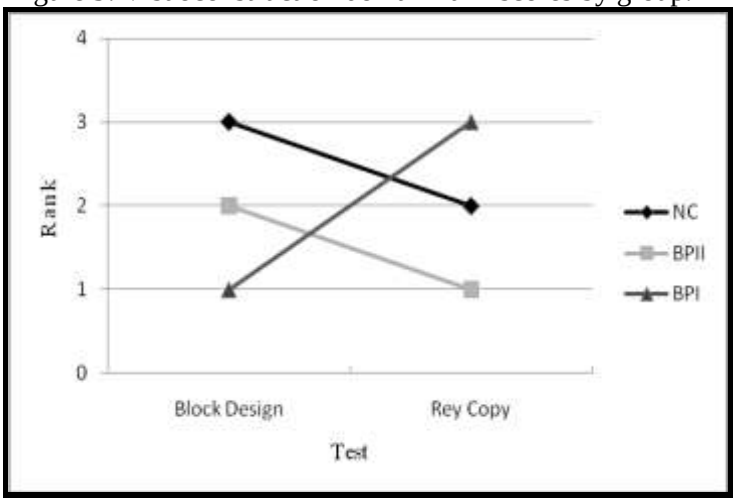
Note. 1= best performance rank score; 2 = intermediate performance rank score; 3 = worst performance rank score; NC = Normal Control group; BPII = BPII group; BPI = BPI group.

Figure 8. Working Memory domain rank scores by group.



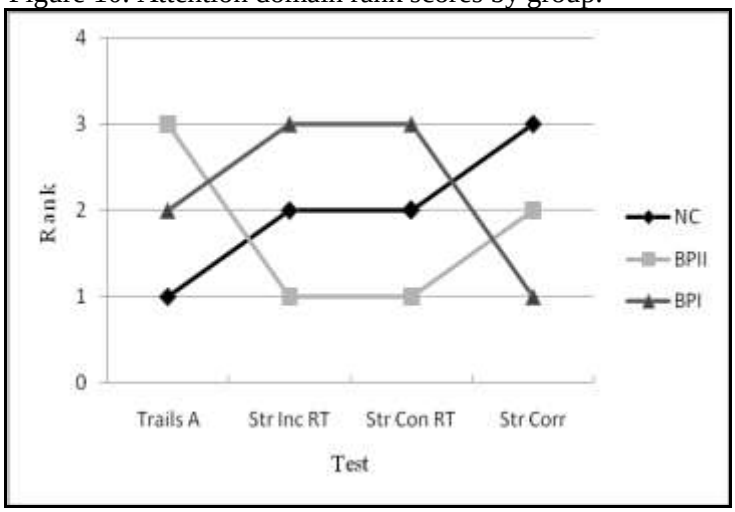
Note. Dig For = Digit Span Forward; Dig Back = Digit Span Backward; SpaSp For = Spatial Span Forward; SpaSp Back = Spatial Span Backward; NC = Normal Control group; BPII = BPII group; BPI = BPI group.

Figure 9. Visuoconstruction domain rank scores by group.



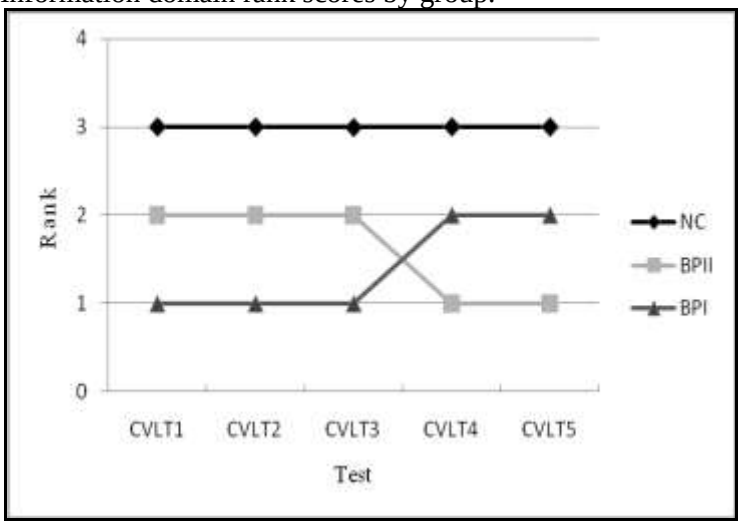
Note. Block Design = Block Design WAIS-III subtest; Rey Copy = Rey Osterrith Complex Figure Copy Trial; NC = Normal Control group; BPII = BPII group; BPI = BPI group.

Figure 10. Attention domain rank scores by group.



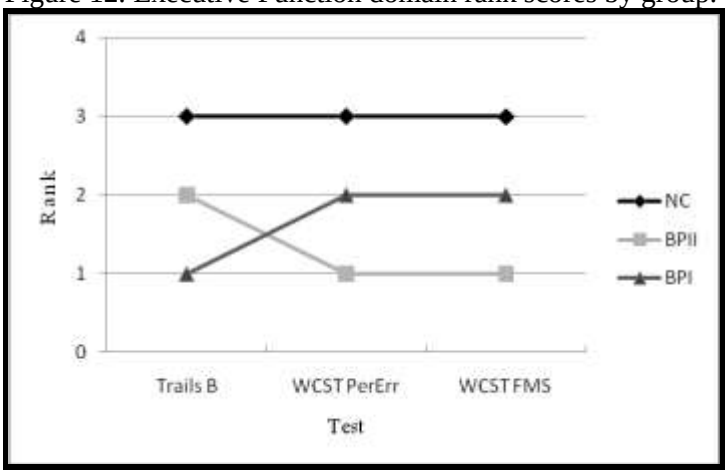
Note. Trails A = Trail Making Test Part A; Str Inc RT = Stroop Color-Word Association Test Incongruent Response Time; Str Con RT = Stroop Color-Word Association Test Congruent Response Time; Str Corr = Stroop Color-Word Association Test total correct items; NC = Normal Control group; BPII = BPII group; BPI = BPI group.

Figure 11. Learning and Memory for Verbal Non-Emotional Information domain rank scores by group.



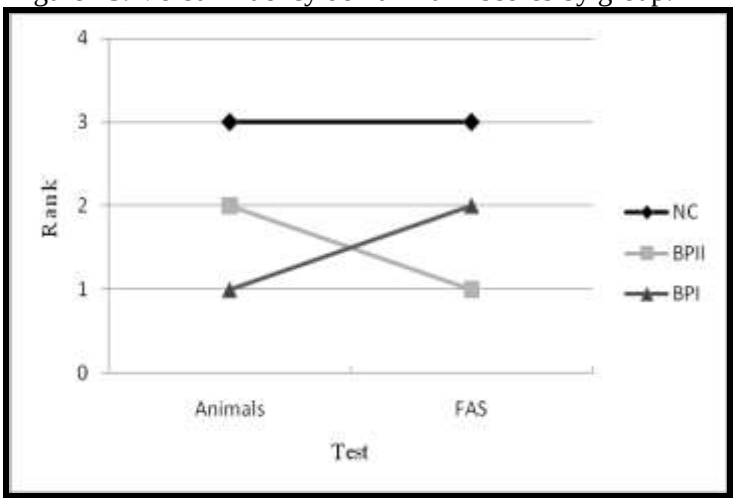
Note. CVLT = California Verbal learning Test- Second Edition (Trials 1-5); NC = Normal Control group; BPII = BPII group; BPI = BPI group.

Figure 12. Executive Function domain rank scores by group.



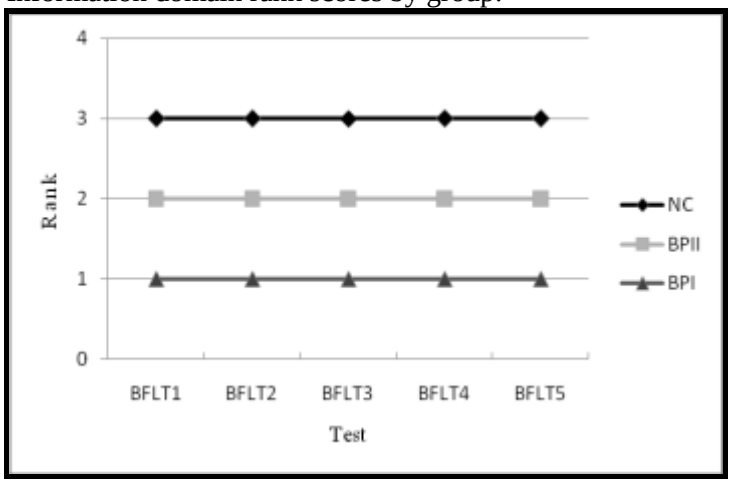
Note. Trails B = Trail Making Test Part B; WCST PerErr = Wisconsin Card Sorting Test, Perseverated Errors; WCST FMS = Wisconsin Card Sorting Test, Failure to Maintain Set; NC = Normal Control group; BPII = BPII group; BPI = BPI group.

Figure 13. Verbal Fluency domain rank scores by group.



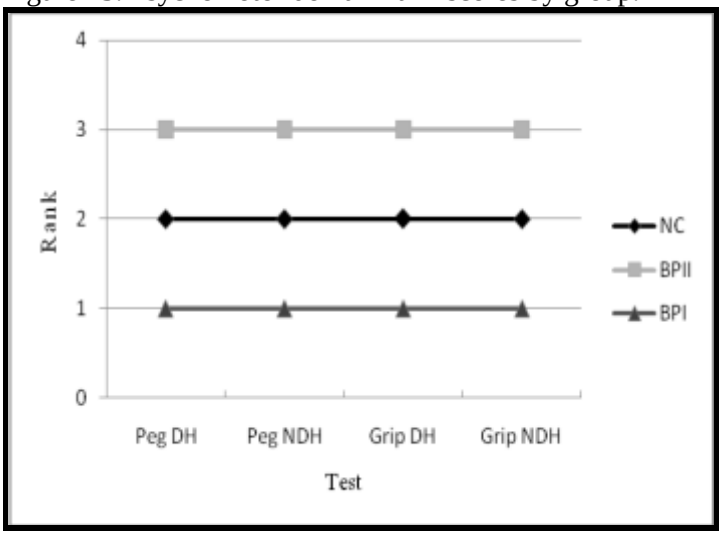
Note. Animals = Animals subtest of the Controlled Oral Word Test; FAS = FAS subtest of the Controlled Oral Word Test; NC = Normal Control group; BPII = BPII group; BPI = BPI group.

Figure 14. Learning and Memory for Visual Non-Emotional Information domain rank scores by group.



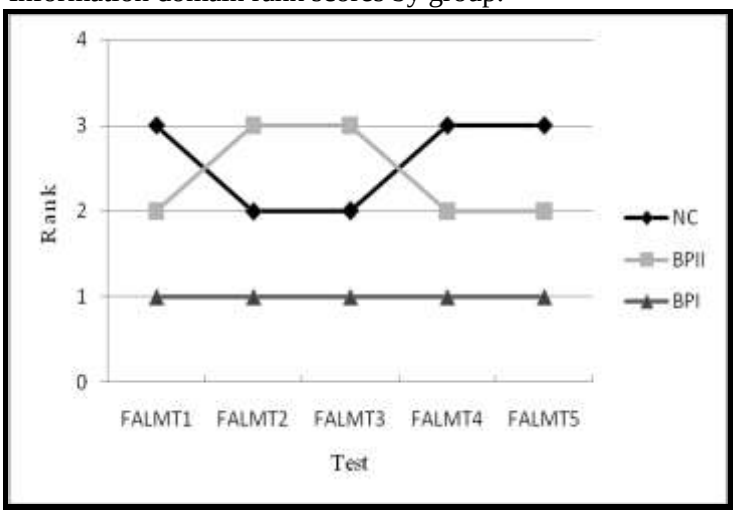
Note. BFLT = Biber Figure Learning Test- Extended (Trials 1-5); NC = Normal Control group; BPII = BPII group; BPI = BPI group.

Figure 15. Psychomotor domain rank scores by group.



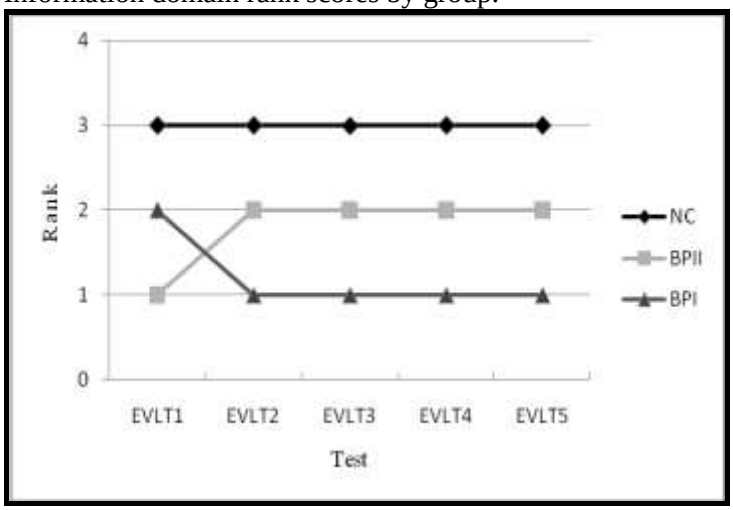
Note. Peg DH = Purdue Pegboard dominant hand score; Peg NDH = Purdue Pegboard non-dominant hand score; Grip DH = Grip Strength test dominant hand score; Grip NDH = Grip Strength test non-dominant hand score; NC = Normal Control group; BPII = BPII group; BPI = BPI group.

Figure 16. Learning and Memory for Visual Emotional Information domain rank scores by group.



Note. FALMT = Facial Affect Learning and Memory Test- Second Edition (Trials 1-5); NC = Normal Control group; BPII = BPII group; BPI = BPI group.

Figure 17. Learning and Memory for Verbal Emotional Information domain rank scores by group.



Note. EVLT = Emotional Verbal Learning Test (Trials 1-5); NC = Normal Control group; BPII = BPII group; BPI = BPI group.

CHAPTER 5

DISCUSSION

The existence of neuroanatomical abnormalities, neuropsychological deficits, and emotion processing dysfunction in BP has been supported by a growing body of empirical evidence, but the outstanding literature has been mixed as to the specifics of these deficits and abnormalities. This is not surprising in light of the difficulty in accounting for all potential mediating and moderating variables and confounds in such investigations, which include medication effects, length and severity of illness, comorbid diagnoses, IQ, personality factors, illness insight, environmental factors, psychosocial stressors, cultural factors, and more (Yen, Cheng, Huang, Ko, Yen, Chang, & Chen, 2009; Fleck, Shear, Madore, & Strakowski, 2008). Ecological validity is also often a concern in research involving neuropsychological assessment of serious clinical populations such as BP. This is true not only in terms of the ecological validity of testing in a laboratory setting as opposed to a natural environment, but also with regard to the exclusion criteria often utilized in such empirical research. Although excluding subjects with comorbid disorders (such as substance use disorders, etc.) may render a "clean" sample that is less susceptible to associated confounds, this may nonetheless produce a sample that is unrepresentative of the illness as it is found among the general population (Pauls, 2004; Michael & Wilhelm, 1996; Sbordone, 1996; Hartman, 1996).

Despite these challenges, or perhaps because of them, research design and methodology have gradually been refined, and innovative approaches have been devised to overcome these obstacles and to enable greater validity and reliability of research findings.

Empirical evidence derived from these sophisticated studies is serving to elucidate the pathophysiology of BP, including the way in which the illness is expressed neuropsychologically and behaviorally over the lifespan. These studies are also serving to increase understanding of the neuroanatomical disturbances that underlie the neuropsychological and behavioral illness manifestations seen in BP. Although specific findings vary with regard to the pattern and magnitude of deficit found in BP populations, some findings have been more consistently supported than others. Those neuropsychological deficits that are most consistently identified in studies involving euthymic BP populations include disturbances in working memory, verbal learning and memory, attention, and executive function processes (Clark, Iversen, & Goodwin, 2002; Tavares, Drevets, & Sahakian, 2003; van Gorp et al., 1998; Kurtz & Gerraty, 2009; Robinson et al., 2006; Arts et al., 2007; Bora et al., 2009).

Considering that BP is characterized by emotional lability and dysfunction and the mounting evidence in support of neuroanatomical abnormalities and corresponding cognitive dysfunction in BP, it is no surprise that evidence of emotion processing deficits have also been identified among those with the illness, not only in depressive and manic BP phases, but also in euthymic illness states. Emotion processing deficits found in BP include impairment in the identification of facial affect, abnormalities in cognitive empathy and theory of mind abilities, and deficits in interpreting the affective prosody of language (Atchley, Ilardi & Enloe, 2003; Bozikas, Tonia, Fokas, Karavatos, & Kosmidis, 2006; Shamay-Tsoory, Harari, Szepsenwol, & Levkovitz, 2007; Kerr, Dunbar, & Bentall, 2003; Bora et al., 2005; Bozikas, Kosmidis, Tonia, Andreou, Focask, & Karavatos, 2007; Kim et al., 2009).

The ability to accurately interpret the emotional valence and intensity of stimuli in the environment and the affective communications of others is critical to normal social interaction and functioning. Consequently, it is no wonder that social dysfunction is considered to be integral to the functional difficulties commonly realized by those with BP (Malhi, Ivanovski, Hadzi-Pavlovic, Mitchell, Vieta, & Sachdev, 2007).

Although more attention has been focused on deficits in BP over the last several years, few studies have investigated the way in which neurocognitive and emotion processing deficits may differ among BP subtypes. Findings of those few studies that have undertaken this venture generally support quantitative differences or differences in magnitude of impairment among BP subtypes (Dittmann et al., 2008; Hsiao et al., 2009; Simonsen et al., 2008). Severity differences in emotion processing deficits in BPI and BPII populations have also been supported (Derntl, Seidel, Kryspin-Exner, Hasmann, & Dobmeier, 2009), with those with BPII typically demonstrating an intermediate degree of impairment in relation to those with BPI and NC. Fewer findings support more heterogeneous patterns of performance among BP subtypes consistent with a distinct disorder conceptualization (as opposed to a spectrum of severity model).

In consideration of the confirmed existence of differences in phenomenology and symptomatology in BPI and BPII populations as well as research findings, albeit small in number, that support differential neurocognitive and emotion processing deficits among BP subtypes, the aim of this study was to investigate differences in neurocognitive functioning and emotion processing abilities in BP populations as compared to healthy populations and elucidate potential neurocognitive and emotion processing differences in BPI and BPII groups. The findings of this study were intended to add to the extant

literature addressing BP illness conceptualization. The hypotheses postulated in this study, therefore, were designed to reflect these aims. Research results as they apply to the various hypotheses will now be discussed.

Hypothesis One

Hypothesis one predicted that significant overall differences would be found among the groups in performance on measures within the domains of Working Memory, Verbal Learning and Memory for Non-Emotional information, Attention, and Executive Function. Study results partially supported this hypothesis as significant differences were found among the groups in four of the eight domains, including the domains of Working Memory, Verbal Learning and Memory for Non-Emotional information, Visuoconstruction, and Attention. Executive Function performance was not found to differentiate the groups.

In addition to the overall difference found among the groups in the Working Memory domain (see Figure 1), subsequent tests also revealed significant differences on the Spatial Span Forward and Spatial Span Backward subtests of the domain. These findings are not surprising in that deficits in Working Memory systems are arguably the most frequently found neuropsychological deficit in BP populations, even among those in euthymic states (Martínez-Arán, Vieta, Reinares, Colom, Torrent, Sánchez-Moreno, Benabarre, Goikolea, & Salamero, 2004; El-Badri, Ashton, Moore, Marsh, & Ferrier, 2001). However, research findings indicate that the presence of psychosis can underpin working memory deficits in BP populations, with some asserting that these deficits may be potent trait markers for psychosis in general (Allen, Randall, Bello, Armstrong,

Frantom, Cross, & Kinney, 2010; Warrick, Wood, Phillips, Francey, Pantelis, Yung, Cornblatt, & McGorry, 2006). In that 50% or more of individuals with BP experience psychotic features at some point over the course of illness (Goodwin & Jamison, 1990), this is an important consideration. Interestingly, when psychosis was used as a covariate in the Working Memory MANOVA, significance actually increased (p = .006). The reason for this is unclear, but this may be an artifact related to the relatively small sample sizes utilized in this study. In any case, psychosis does not appear to account for the overall differences found in the Working Memory domain in this study.

An additional consideration is the fact that deficits in working memory are sometimes attributable to executive function failures. This is a logical conclusion in that working memory is a multi-component, multi-system domain, composed of a subsystem devoted to the short-term processing of auditory or phonological information (sometimes referred to as the Phonological Loop), a subsystem primarily devoted to the short-term processing of visual, spatial, and kinaesthetic information (sometimes referred to as the Visuospatial Sketchpad), and a subsystem devoted to planning and recruiting, performance of operations necessary for short-term task completion, and integration and allocation of incoming information to lower-level processes (sometimes referred to as the Central Executive). This last subsystem, the Central Executive, which is primarily devoted to executive function processes, overlaps to a considerable degree with general executive processes (Baddeley & Hitch, 1974). However, given that no significant differences were found among the groups in the Executive Function domain (nor on any of the sub-measures within this domain), differences among the groups in the Working Memory domain are not likely attributable to executive function impairment.

Deficits found in the Working Memory domain are also sometimes attributable to visual memory impairment. In that two of the subtests within the Working Memory domain are visual measures (Spatial Span Forward and Backward subtests of the WMS-III) and significant differences were found among the groups on these subtests, this is another important consideration. However, given that significant differences were also found among the groups on the Digit Span Backward subtest of the Working Memory domain and that no such differences were found on the BFLT-E, which is specifically a visual memory task, Working Memory deficits appear to be supported and independent of visual memory impairment.

Research has identified the frontal cortex, anterior cingulate, and parts of the basal ganglia as integral to working memory function (Bledowski, Rahm, & Rowe, 2009; Kondo, Osaka, & Osaka, 2004). The anterior cingulate is a brain region thought to play a role in a variety of autonomic functions, including blood pressure and heart rate regulation, and to various social and cognitive functions such as social reciprocity, decision making, anticipation of reward, empathy, and the production of emotion. As reviewed previously, multiple studies have identified anterior cingulate grey matter reductions in euthymic BP and various anterior cingulate abnormalities in manic and depressed phases of BP illness (Drevets et al., 1997; George et al, 1993; Ito et al, 1996). Moreover, various studies have found evidence of prefrontal cortex abnormalities in BP, including grey matter reductions in the left dorsolateral prefrontal cortex, abnormalities of the right dorsolateral prefrontal cortex, and grey matter volume reductions of the dorsal, ventral, and orbital prefrontal cortical regions (Haldane & Fangou, 2004; Berns, Martin, & Proper, 2002; Brambilla et al., 2002; Lopez-Larson et al., 2002; Frangou et al.,

2002). The frontal brain regions, primarily the prefrontal cortices, are the highest cortical areas of the brain and are responsible for the most complex aspects of cognition, including manipulation of sensory information in working memory, the integration of sensory and mnemonic information, planning of deliberate action and motor movement, and organizational and regulatory aspects of emotional and intellectual functioning.

Neuroimaging studies have also confirmed abnormalities of the basal ganglia, including enlarged putamen in BP (DelBello, Zimmerman, Mills, Getz, & Strakowski, 2004; Brambilla, Harenski, & Nicoletti, 2001). The putamen, which is part of the dorsal striatum and basal ganglia, draws on dopamine projections to perform its functions in the regulation of movements and in influencing certain types of learning. Damage to this structure has been shown to cause spatial neglect in humans (Karnath, Himmelbach, & Rorden, 2002).

Given that these various structural and functional abnormalities have been identified in BP in areas and processes known to underpin working memory function, as well as the fact that mood and affect are known to significantly influence working memory, attention, and other cognitive processes, it is no surprise that significant differences were found among the groups in this domain. Moreover, in that working memory processes involve the temporary storage and management of information utilized in complex cognitive tasks, a disruption of working memory processes likely contributes much to the dysfunction typically seen in the illness, including executive function deficits.

Function of the working memory and attentional systems are intricately connected, and some theorists view working memory as no more than a combination of short-term memory and controlled attention (Kane & Engle, 2003). Various studies have

investigated this overlap between attention and working memory and the way these systems interact and contribute to the deficits found in BP. Significant impairment in attentional set shifting, sustained attention processes of working memory, and other aspects of attention have been found in BP (Clark, Iverson, & Goodwin, 2002), and significant overall differences found among the groups in this study in the domain of Attention (see Figure 3) is consistent with these previous findings. Tests of between-subjects effects also revealed significant differences among the groups on the Stroop Color-Word Association Test, Congruent Response Time domain sub-measure. This finding is somewhat confusing, however. Although accuracy scores have generally been found to be similar in BP and NC populations on Stroop tasks, delayed Incongruent Response Times have frequently been seen in clinical populations during presentation of stimuli with incongruent qualities (Howieson, Lezak, & Loring, 2004). These delayed response times in clinical populations during incongruent conditions are thought to be due to Stroop effects (extended reaction times when various components of the task are incongruent, ex the name of a color is printed in a color not denoted by the name, such as the word "green" is printed in red ink) exacerbated by attentional problems associated with the illness and difficulty in suppressing incongruent aspects of the stimuli (Weissman, Warner, & Woldorff, 2009). Supporting this theory are findings of various MRI studies which have indicated altered patterns of cortical activation in BP in brain areas known to be critical for execution of complex tasks, sustained attention, and inhibition (ex. relative deactivation within the orbital and medial prefrontal brain regions, etc.) during Stroop conditions (Kronhaus, Lawrence, Williams, Frangou, Brammer, Williams, Andrew, & Phillips, 2006; Gruber, 2002).

Given results of these studies and the demands placed on attentional processes in the incongruent condition of the Stroop task, a greater difference among the groups was expected to be found in Incongruent Response Time than in Congruent Response Time of the Stroop Color-Word Association Test. This finding, again, may be a consequence of small group size, and further investigation of Stroop effects in BP populations may be warranted.

The finding of an overall difference among the groups in the domain of Visuoconstruction abilities was not predicted (see Figure 2), even though some studies have found such impairment, not only in BP populations, but also in the first degree family members of those with BP. A case in point are findings of a recent study in which BP, first degree family members of BP patients, and normal controls were compared across various domains of neuropsychological functioning. Results of this study demonstrated significant impairment of both those with BP and the family member group in relation to the control group on Block Design and Judgment of Line Orientation tasks. Although no significant differences were found between the BP and family member group on these measures, the family member group performed at an intermediate level as compared to the BP and NC groups (Frantom, Allen, & Cross, 2008). The findings of this study suggest that visuoconstructional deficits may be neurocognitive endophenotypes for BP.

Significant differences were predicted among the groups on the Verbal Learning and Memory for Non-Emotional information domain, and repeated-measures ANOVA indicated a significant between subjects effect for group. Univariate tests revealed significant differences among the groups on all learning trials of the domain, and the BPI

group performed significantly worse than did the NC group on all trials (see Figure 4). Deficits in verbal learning and memory have consistently been reported in studies of BP, and some have even found deficits in this domain in the first degree relatives of individuals with BP (Arts, Jabben, Krabbendam, & van Os, 2008). However, not all studies have been consistent in this finding (Frantom**,** Allen, & Cross, 2008; Antila, Tuulio-Henriksson, Kieseppa, Eerola, Partonen, & Lonnqvist, 2007; Clark, Sarna, & Goodwin, 2005). These inconsistencies in the deficits found among BP populations in verbal learning and memory may be due to differences among studies in methodological approach or sample composition (combining BPI and BPII into one group, including or excluding those with psychotic features, etc.) and may not be the result of biological or genetic heterogeneity in BP as some have proposed. In that this study specifically compared neuropsychological function in well-matched BPI and BPII subtype groups, the finding of verbal learning and memory impairment in the BPI group may point to verbal memory impairment as an endophenotype specific to BPI. It is also possible that a more severely affected BPII sample would demonstrate impairment in this domain as well.

Abnormalities of prefrontal brain regions in BP have been supported in numerous studies, and memory research findings have implicated involvement of the left prefrontal cortex in the encoding of verbal memory. Specifically, left prefrontal cortical areas are thought to mediate verbal information encoding processes that subsequently facilitate retrieval of the information from memory (Casasanto, Killgore, Maldjian, Glosser, Alsop, Cooke, Grossman, & Detre, 2002; Fernandez et al., 1998, 1999).

Verbal learning and memory deficits frequently found in BPI populations may also be attributable to the extreme emotional lability and inherently stressful affective states associated with this BP subtype. In humans, the hypothalamic pituitary adrenal axis is activated in response to stressful emotional events, and glucocorticoid or cortisol (which enables the individual to respond to stressors by elevating glucose levels in the brain) is consequently released into the system. The hippocampus, which is involved in the consolidation (and possibly the retrieval) of new memories, contains glucocorticoid receptors, and studies have demonstrated that prolonged stress and release of glucocorticoids can serve to modulate memory, although specific findings with regard to which memory processes are actually effected (ex. encoding, working memory consolidation, retrieval, etc.) have been mixed (Wolf, 2003; Lupien & McEwen, 1997).

It has been clearly demonstrated, however, that declarative memory is adversely affected by chronically elevated cortisol levels, such as is likely the case in BPI (Lupien et al., 1998; Martignoni et al., 1992; Wolkowitz, Lupien, Bigler, Levin, & Canick, 2004). Findings of studies in which the acute effects of cortisol on memory were investigated have been mixed, with some demonstrating impairment of verbal declarative memory under such conditions (Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996; Newcomer, Craft, Hershey, Askins, & Bardgett, 1994; Wolf, Schommer, Hellhammer, McEwen, & Kirschbaum, 2001; Wolkowitz et al., 1990), some failing to find any effects (Hsu, Garside, Massey, & McAllister-Williams, 2003; Wolf, Convit, et al., 2001), and others demonstrating opposite findings (Domes, Heinrichs, Reichwald, & Hautzinger, 2002). These inconsistencies are thought by some to reflect a curvilinear relationship between glucocorticoids and verbal memory (Lupien & McEwen, 1997). Others have

suggested that stress and cortisol actually facilitate memory consolidation and that memory disruption is due to retroactive interference during retrieval processes (Roozendaal, 2002). Animal studies, in which glucocorticoid effects on memory consolidation have been isolated, have provided evidence that moderate levels of glucocorticoids can provide a facilitative effect to memory processes (Conrad, Lupien, & McEwen, 1999; Roozendaal & McGaugh, 1996; Sandi, Loscertales, & Guaza, 1997), and several human studies have also found such an effect, particularly with regard to consolidation of memory for visual information with and without affective content (Buchanan & Lovallo, 2001; Cahill, Gorski, & Le, 2003; Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson, 2003).

However, facilitative effects of stress and cortisol on verbal memory consolidation have not been so clearly demonstrated, with one study finding such effects on word recall consolidation (Abercrombie et al., 2003) and others finding no facilitative effects whatsoever (de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Wolf, Schommer, Hellhammer, Reischies, & Kirschbaum, 2002) . There is stronger evidence that retrieval of verbal memory is adversely affected by stress and elevated cortisol levels (Kuhlmann, Piel, & Wolf, 2005). The effect of glucocorticoid and stress on memory, therefore, appears to be domain specific.

The finding of multiple studies that prolonged stress and the release of glucocorticoid may facilitate the consolidation of visual memory while impairing retrieval of verbal memory is consistent with the findings of this study wherein those with BPI (those thought to be most severely impacted by the disorder) were shown to have verbal learning and memory deficits but no impairment of visual learning and memory abilities.

Moreover, the finding of visuoconstructional deficits in this and other studies is also consistent with findings of previous research in which right hemispheric abnormalities in BP have been suggested (Bruder, Stewart, Towey, Friedman, Tenke, voglmaier, Leite, Cohen, & Quitkin, 1992; Caligiuri, Brown, Meloy, Eyler, Kindermann, Frank & Lohr, 2004).

It was expected that overall differences would be found among the groups in the Executive Function domain, as the majority of outstanding literature supports deficits in this domain (Bearden, Hoffman, & Cannon, 2001; Basso, Neel, Lowery, Purdie, & Bornsein, 2002; Wilder-Willis, 2003; Gourovitch, Torrey, Gold, Randolph, Weinberger, & Goldberg, 1999; Clark, Iversen, & Goodwin, 2002; Tavares, Drevets, & Sahakian, 2003; van Gorp et al., 1998; Kurtz & Gerraty, 2009; Robinson et al., 2006; Arts et al., 2007; Bora et al., 2009). The high-functioning nature of the study sample, as evidenced by an average of only 2.02 lifetime hospitalizations, mean years of education totaling 14.31 years, mean current IQ of 105.26, and the fact that most were employed or attending the university at the time of testing, may help to explain a lack of significant findings. Additionally, the small size of the groups in this study undoubtedly reduced power, and this may be a contributing factor in the failure of executive function measures to differentiate among the groups.

Hypothesis Two

Hypothesis two predicted that significant overall differences among the groups would be found in performance within the domains of Learning and Memory for Visual Emotional information and Learning and Memory for Verbal Emotional information.

Repeated-measures ANOVA results showed that Hypothesis two was partially supported. A significant between-subjects effect was found in the domain of Learning and Memory for Visual Emotional information, and univariate analyses also showed significant differences among the groups on Trial 1, Trial 2, and Trial 5 of the FALMT-II, and post hoc tests indicated a that the BPI group performed significantly worse than did the BPII and NC groups on the FALMT-II Trial 1 and significantly worse than the NC group on Trial 5 of the measure (see Figure 5). An interesting aspect of this finding is that although these significant differences were found among/between the groups on performance of this measure (FALMT-II), which is a *visual* memory task with emotional content, no such differences were found on the EVLT, which is a *verbal* memory task with emotional content (Verbal Learning and Memory for Verbal Emotional information domain). This is the exact opposite of the findings of Hypothesis one in which significant differences were found among/between the groups on a *verbal* memory task without emotional content (CVLT-II), but not on a *visual* memory task without emotional content (BFLT-E).

Although this may at first appear to be paradoxical, these findings are likely due to the facial component of the FALMT-II test. The processing of facial affect, which is an integral aspect of normal social interaction, involves different brain regions than those involved in the processing of other visual information with an affective component. As discussed previously, various studies have indicated impairment of and reduced connectivity between those brain regions known to be integral to the processing of facial affect in BP, specifically, reduced connectivity between the left amygdala and the right posterior cingulated-precuneus and right fusiform gyrus/parahippocampal gyrus. This

reduction in connectivity in the BP subjects was observed independent of mood state or comorbid diagnoses (Rich, Fromm, Berghorst, Dickstein, Brotman, Pine, & Leibenluft, 2008). Additionally, deficits in the processing of facial emotion and facial expression have repeatedly been demonstrated in Schizophrenia, and some studies have also found such deficits in BP (Rich, Fromm, Berghorst, Dickstein, Brotman, Pine, & Leibenluft, 2008; Gourovitch, Torrey, Gold, Randolph, Weinberger, & Goldberg, 1999; Gray, Venn, Montagne, Murray, Burt, Frigerio, Perrett, & Young, 2006). Considering the degree to which the identification of facial expression and affect is necessary for normal social functioning, these are important findings.

Hypothesis 3

Hypothesis three predicted that the BPII group would demonstrate an intermediate degree of performance impairment in relation to the BPI and NC groups in all domains assessed, with the best performance being seen in the NC group and the worst level of performance being seen in the BPI group. This hypothesis was found to be supported as a significant overall difference was found among group rankings on the combined measures. Additionally, performance on a majority of measures (NC = 71.8%, BPII = 56.4%, BPI = 76.9%) for all groups fell in the expected performance pattern (see Table 3). Subsequent tests also indicated that BPI group mean-rank scores were significantly worse than were the mean rank scores of the BPII group, and the BPII group mean-rank scores were similarly found to be significantly worse than the mean-rank scores of the NC group.

Additionally, although degree of difference and variance is not accounted for in these figures, group rank scores fell in the predicted pattern of performance on the Digit Span backwards, Spatial Span Forward, and Spatial Span Backward subtests of the Working Memory domain (see Figure 7), the Block Design subtest of the Visuoconstruction domain (see Figure 8), the Stroop Color-Word Association Test Total Correct score of the Attention domain (see Figure 9), Trials 1-3 of the CVLT-II of the Learning and Memory for Verbal Non-Emotional information domain (see Figure 10), Trail Making Test Part B of the Executive Function domain (see Figure 11), the Animals subtest of the COWAT within theVerbal Fluency domain (see Figure 12), Trials 1-5 of the BFLT-E within the Learning and Memory for Visual Non-Emotional information domain (see Figure 13), Trials 1, 4, and 5 of the FALMT-II within the Learning and Memory for Visual Emotional information domain (see Figure 15), and Trials 2-5 of the EVLT within the Learning and Memory for Verbal Emotional information (see Figure 16).

The predicted pattern of performance on the Animals subtest (a semantic fluency test) but not on the FAS subtest (a test of phonemic fluency) of the COWAT within the Verbal Fluency domain was an especially interesting finding in that various studies have found evidence of impaired semantic fluency and intact phonemic fluency in individuals with BP and Schizophrenia, and in older populations (Kremen, Seidman, Faraone, & Tsuang, 2003; Phillips, James, Crow, & Collinson, 2004). Moreover, various Neuroimaging studies of brain activation during fluency tasks indicate that neural activity patterns during intact performance on semantic tasks are strongly left lateralized (frontal), whereas activity patterns during impaired performance on semantic tasks activate right (inferior and middle) frontal brain areas. These findings suggest that efficient recruitment

and functional integrity of language areas within the left-frontal brain regions are essential for successful performance on semantic fluency tasks (Meinzer, Wilser, Flaisch, Eulitz, Rockstroh, Conway, Rothi, & Crosson, 2009). Although the performance of the BP groups on the Animals subtest did not reach significance, the pattern of performance among the groups, as well as the performance of the BP groups (particularly the BPII group) on this measure relative to performance on the FAS subtest is consistent with these previous research findings.

Together, these results generally lend support to the spectrum of severity conceptualization of bipolar disorder and the assertion that BPII may be viewed primarily as a milder form of the illness than BPI. However, in that a small subset of measures indicated a distinct pattern of performance for the two groups (Psychomotor and Attention domain subtests, Rey Osterrith Complex Figure Copy Trial of the Visuoconstruction domain, etc.), there does appear to be some support for the idea that in some aspects of neuropsychological functioning, the subtypes are heterogeneous, although these particularly findings may be due to small sample sizes and the high-functioning nature of the groups in this study.

Considering this high-functioning nature of the clinical samples used, these findings have particularly important implications as it is logical to assume that these samples would perform at a level that more closely matches performance of the healthy population than would a sample more severely affected by the disorder, and yet significant differences were found and the postulated hypotheses of the study were largely confirmed. These findings add to the extant literature in the identification of neurocognitive and emotion processing deficits specific to BP and lend important

information to the ongoing debate regarding the nosological status of BP and the other affective disorders.

Limitations

A limitation of this study is that it is unknown if results were affected by the prescribed medications taken by BP subjects. The majority of participants in the BP groups were taking prescribed medications at the time of testing, and these medications included mood stabilizers (including anticonvulsants), antidepressants, antipsychotics, anxiolytics and stimulants, so a rigorous evaluation of the impact medications may have had on neuropsychological test performance was not possible. BP groups did not differ, however, with regard to medicated verses non-medicated status. Additionally, various studies in which medication effects on neurocognitive function in affective and psychotic disorders were assessed indicate that some medications may serve a neuroprotective function in these disorders (Moore et al., 2000; Sassi et al., 2002; Manji et al., 1999; Brambilla et al., 2001; Nugent, Milham, & Bain, 2006). Additionally, normalization of neurocognition and brain function resulting from medication treatments have been demonstrated in schizophrenia (Keefe et al., 2007; Wittorf, Sickinger, Wiedemann, & Klingberg, 2008), major depressive disorder (Fales et al., 2009), and bipolar disorder (Gruber et al., 2004; Phillips, Travis, Fagiolini, & Kupfer, 2008), although there is contradictory evidence in this regard, particularly in bipolar disorder (Savitz, 2005). Given that neurocognitive deficits do persist even in medication-free states in BP and schizophrenia (Goswami et al., 2001), it is likely that some neurocognitive deficits are genetically driven trait markers that represent functional changes in neural networks in

the disorders (Burdick et al., 2007; Savitz et al., 2005). Consequently, it is unlikely that medication effects can account for the neurocognitive and emotion processing deficits reported in this and other studies.

Another limitation of this study is that the sample may not representative of the "real world" BP populations (as previously mentioned), which typically demonstrate high substance use and other psychiatric disorder comorbidity rates. None of the participants in the BP groups in the current study had a current comorbid substance use or major psychiatric disorder diagnosis. This is another indicator that the clinical groups in this study were high-functioning groups overall. Future studies with samples that are more representative of those with bipolar disorder in the general population may be warranted in the identification of neurocognitive profiles specific to the illness and illness subtypes.

A third limitation of this study is that the sample sizes of the groups were relatively small. Finding BP subjects, particularly those who are outpatient, is a difficult venture from the outset, and the exclusion criteria for clinical groups in this study (which included comorbid psychiatric and substance use disorders) made this task all the more difficult. Moreover, finding BPII subjects is particularly challenging due to an unusually high rate of misdiagnosis of the subtype, as well as the fact that many individuals with BPII find the hypomanic states of the illness to be egosyntonic, which sometimes inhibits treatment seeking behaviors wherein diagnoses are typically made.

Despite these limitations, the investigation of neurocognitive deficits among BP populations, and particularly the way in which these deficits may differ in BP subtypes is a venture worthy of pursuit. This is especially true given the ongoing professional

disagreement in the field regarding the nosological status of the affective disorders and the limited effectiveness of current treatments for these disorders.

Implications and Future Directions

Bipolar disorder is a debilitating disorder characterized by disruption of various symptom domains, including psychosocial dysfunction, emotional lability/affective instability, and neurocognitive disruption. It is unclear as to whether the deficits found in the BP groups in this study indicate a unique pattern of neurobiological dysfunction, but these results add to the mounting literature supporting the existence of such deficits. This is important in that deficits in neurocognitive function have been shown to be associated with poorer functional outcomes in various psychiatric conditions, including schizophrenia (Brekke et al., 2005; Green et al., 2004).

Additionally, despite a growing body of research dedicated to BP and its subtypes, it remains unclear as to whether the subtypes subsumed under this diagnosis are representative of a spectrum of severity or whether they would better be conceptualized as discrete disorders. The results of this study lend support to the spectrum of severity conceptualization model. The argument can be made that the pattern of performance seen among the groups on many of the measures in this study, namely the BPI group demonstrating the greatest degree of impairment and those with BPII demonstrating a less severe degree of deficit (as evidenced by an intermediate level of performance between BPI and NC groups), may not be representative of the general "real world" BP population. Moreover, inconsistencies across studies with regard to deficits in BP and BP subtypes, and those encountered in this study, may actually indicate a lack of validity for

the BPII diagnosis itself. Nonetheless, in that the BP groups were particularly high-functioning, these results are likely an underestimate of true BP deficits and pattern of performance among subtypes. An important direction for further evaluation will be to investigate whether the pattern of neurocognitive deficits correspond to functional outcomes in BP populations. There is some evidence to support this assertion (Bello et al., 2008; Martínez-Arán et al., 2007).

Although the literature on neuropsychological deficits in BP has provided important insights regarding the pattern and magnitude of deficit in individuals with the illness, much is still unknown or unclear, particularly with regard to the way in which deficits may differ among BP subtypes. Early detection, accurate diagnosis, and the development of more effective treatment interventions would likely serve to attenuate the cognitive morbidity and functional impairment often realized in BP and other affective disorders. The identification of a unique profile for BP and BP subtypes, in which these findings are taken fully into account, could be beneficial to future psychotherapeutic and psychopharmacological approaches to treatment. Additionally, given the division in the literature with regard to the nosological status of the affective disorders and the continued lack of consensus as to the diagnostic criteria for BP and its subtypes, future research would do well to further this investigation.

APPENDIX A

TABLES

Table 1. Descriptive statistics and results of comparisons among groups on demographic and clinical variables

Variable	Group							
	BPI (*n* = 37)		BPII (*n* = 18)		NC (*n* = 18)			
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*F(2,70*	*p*
Age (years)	35.78	14.24	31.72	10.76	27.78	10.71	2.51	0.089
Education (years)	14.39	2.52	14.56	2.23	14.39	1.61	0.17	0.846
Premorbid IQ	12.38	2.53	12.00	1.85	13.06	1.66	1.09	0.342
Current IQ	105.46	14.29	104.83	11.85	110.33	11.50	1.04	0.361
							F(1,54	*p*
GAF Score	57.53	12.24	67.94	9.20			10.14	**<.01**
Hospitalizations	2.46	3.14	1.11	2.11			2.71	0.106
HAM-D	8.22	5.62	6.18	3.49			1.89	0.175
YMRS	4.00	3.08	3.28	2.08			0.81	0.374
							G	*p*
Female (%)	67.60		61.10		55.60		0.77	0.680
Ethnicity (%)							13.95	0.304
Caucasian	67.60		77.80		44.40			
African Amer	2.70		5.60		22.20			
Hispanic	5.40		0.00		11.10			
Asian Amer	5.40		11.10		11.10			
Native Amer	2.70		5.60		0.00			
Biracial	8.10		0.00		5.60			
Other	8.10		0.00		5.60			
							z	*CL*
Medications (%)							1.415	84.3%
Unmedicated	16.20		3.89					
Antidepress	48.60		50.00					
Mood Stab								
Anticonvuls	62.20		33.30					
Other	5.40		0.00					
Antipsychotics	48.60		11.10					
Anxiolytics	29.70		22.20					
Stimulants	8.10		5.60					

Note: BPI = Bipolar I group; BPII = Bipolar II group; NC = Normal Control group; SD = Standard Deviation; GAF = Global Assessment of Functioning; HAM-D = Hamilton Depression Rating Scale; YMRS = Young Mania Scale; Amer = American; Antidepress = Antidepressants; Mood Stab = Mood Stabilizers; G = Tukey B; z = z Test for Two Proportions; CL = Confidence Level

Table 2. Neurocognitive domains and measures for bipolar I (BPI), bipolar II (BPII), and normal control (NC) groups.

Score	BPI (n=37)		BPII (n=18)		NC (n=18)					
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*F*	(df)	*p*	Contrasts
Work Memory							2.191	(8,136)	< **.05**	
Digit Span										
For	10.541	2.567	11.167	2.333	10.944	2.287	0.442			
Back	6.865	2.030	7.611	2.279	8.444	2.975	2.797			BPI < NC
Spa Span										
For	8.297	1.854	8.667	1.414	10.056	2.182	5.574	(2,70)	< **.01**	BPI < NC
Back	7.703	1.942	7.833	1.724	9.278	1.994	4.419	(2,70)	< **.05**	BPI < NC
Verb Memory										
CVLT							7.410	(2,70)	**<.001**	
Trial 1	7.108	1.807	8.167	1.948	8.722	1.227	5.960	(2,70)	< **.01**	BPI < NC
Trial 2	10.081	2.373	11.667	1.847	11.944	1.589	6.330	(2,70)	< **.01**	BPI < NC
Trial 3	11.784	2.720	12.944	1.924	13.944	1.798	5.410	(2,70)	< **.01**	BPI < NC
Trial 4	12.676	2.484	13.500	1.978	14.444	1.464	4.170	(2,70)	< **.05**	BPI < NC
Trial 5	12.973	2.267	13.889	1.779	14.444	1.504	3.300	(2,70)	< **.05**	BPI < NC
Visuoconstruct							2.416	(4,140)	**0.05**	
Block Des	40.432	14.396	43.444	12.641	48.167	11.698	2.036			
Rey Copy	31.122	3.805	29.306	4.983	31.194	2.926	1.478			
Attention							2.778	(8,136)	< **.01**	
STROOP										
In RT	22820	4874	20753	7525	20393	4037	2			
Con RT	21728	4333	17888	5160	20708	5246	4	(2,70)	< **.05**	BPI < BPII
Tot Corr	77.514	3.124	76.444	3.974	76.889	2.374	0.727			

TMT A	26.162	9.203	27.278	5.819	22.778	5.429	1.745		
Exec Function							1.077	(6,138)	
WCST									
PErrors	13.622	10.644	13.111	9.139	10.167	7.965	0.797		
FMS	0.973	1.258	0.889	0.900	0.389	0.778	1.852		
TMT B	60.487	27.284	54.111	15.277	49.222	13.401	1.692		
Psychomotor							0.827	(10,134)	
Purdue Peg									
DH	13.440	2.732	14.868	2.116	14.166	1.773	2.251		
NDH	12.855	2.410	13.756	2.032	13.518	2.145	1.143		
Grip Str									
DH	31.946	14.642	35.778	11.383	32.917	16.020	0.438		
NDH	26.973	13.215	29.528	10.658	29.000	15.504	0.280		
Verb Fluency							1.276	(4,140)	
FAS	44.649	11.046	40.944	10.468	46.222	10.947	1.146		
Animals	21.946	5.055	22.722	4.775	24.389	4.996	1.461		
Vis Memory									
BFLT-E							0.673	8,136	
Trial 1	6.432	2.167	6.722	2.244	7.667	1.970	2.032		
Trial 2	9.757	2.842	10.278	2.321	11.111	1.844			
Trial 3	11.351	2.879	11.833	2.407	12.389	2.253			
Trial 4	12.189	2.413	12.556	1.917	13.611	1.685			
Trial 5	13.000	2.000	13.278	2.109	13.889	1.323	1.343		
Emo Process									
Visual									
FALMT								(2,70)	**<.05**

Trial 1	10.946	2.934	12.833	2.256	13.167	1.791	6.053	(2,70)	< **.01**	BPI<BPII, NC
Trial 2	11.351	2.983	13.111	2.026	12.722	2.469		(2,70)	<**.05**	
Trial 3	11.919	2.803	12.833	2.595	12.611	1.720				
Trial 4	12.081	3.031	12.278	2.986	13.556	1.917				
Trial 5	11.676	2.719	12.389	2.852	13.611	1.577	3.561	(2,70)	< **.05**	BPI<NC
Verbal										
EVLT										
Trial 1	6.838	1.555	7.444	1.580	6.944	1.626	0.917			
Trial 2	8.865	2.030	10.222	1.768	9.778	1.865				
Trial 3	10.432	2.433	11.056	1.474	10.833	2.007				
Trial 4	10.811	2.343	11.667	2.029	11.389	2.279				
Trial 5	11.460	2.468	12.111	2.166	11.556	1.947	0.513			

Note. BPI = Bipolar I group; BPII = Bipolar II group; NC = Normal Control group; SD = Standard Deviation; Work Memory = Working Memory domain; Digit Spa = Digit Span WAIS-III subtest; For = Forward; Back = Backward; Spa Span = Spatial Span WAIS-III subtest; Verb Memory = Learning and Memory for Verbal Non-Emotional information domain; CVLT = California Verbal Learning Test- Second Edition; Visuoconstruct = Visuoconstruction domain; Block Des = Block Design WAIS-III subtest; Rey Copy = Rey Osterrith Complex Figure Copy Trial; Stroop = Stroop Color-Word Association Test; In RT = Incongruent Response Time total; Con RT = Congruent Response Time total; Tot Corr = Total Correct; TMT A = Trail Making Test Part A; Exec Function = Executive Function domain; WCST = Wisconsin Card Sorting Test; PErrors = Perseverated Errors; FMT = Failure to Maintain Set; TMT B = Trail Making Test Part B; Purdue Peg = Purdue Pegboard Test; DH = Dominant Hand; NDH = Nondominant Hand; Grip Str = Grip Strength; Vis Memory = Learning and Memory for Visual Non-Emotional information domain; BFLT = Biber Figure Learning Test, Expanded Edition; Emo Process = Emotion Processing domain; Visual = Learning and memory for Visual Emotional information domain; FALMT-II = Facial Affect Learning and Memory Test – Second Edition; Verbal = Learning and Memory for Verbal Emotional information domain; EVLT = Emotional Verbal Learning Test;

APPENDIX B

RESEARCH FORMS

UNIVERSITY OF NEVADA, LAS VEGAS

INFORMED CONSENT FORM

Introduction: Carol Randall and Daniel Allen, Ph.D., from the Department of Psychology at UNLV, are seeking participants for a study that examines the processing of emotion in individuals with bipolar disorder. You are invited to participate in this research study.

Procedure: If you volunteer to participate in this study, you will be interviewed and then be administered tasks that are designed to test emotion processing and various other cognitive abilities. For these tasks, you will be asked to complete a number of different exercises such as remembering lists of words and naming pictures. During the interview, the examiner will ask you general questions such as your age and years of education, along with questions regarding your medical history. At the beginning of the study, you will be provided with instructions that will tell you how to complete the tests. The total time needed to complete this research project is approximately 6.0 hours, although it may take less time for you to complete the study.

Benefits of Participation: By participating in this study, you will gain a research participation credit for every hour of research participation. Participation time in this study is expected to be approximately ?credits.

Risks of Participation: There is a chance you may experience some mental fatigue during the assessments. To decrease the chance of fatigue, the researcher will allow breaks as necessary for your comfort. Although it is not expected to occur, should you feel uncomfortable answering any of the questions or performing any of the tasks, you are encouraged to discuss concerns with the researcher. Your participation is voluntary and you may refuse to answer questions or withdraw from the study at any time.

Contact Information: If you have questions about the study, or if you experience any harmful effects because of participation in this study, you are encouraged to contact Carol Randall or Daniel Allen at 895-0295.

For questions regarding the rights of research subjects, you may contact **the UNLV Office for the Protection of Research Subjects at 895-2794.**

Voluntary Participation: Your participation in this study is voluntary. You may refuse to participate in this study or in any part of this study. You may withdraw at any time without prejudice to your relations with the university. You are encouraged to ask questions about this study at the beginning or any time during the research study.

Confidentiality: All information gathered in this study will be kept completely confidential. No reference will be made in written or oral materials that could link you to this study. All records will be stored in a locked facility at UNLV for at least 3 years after completion of the study. After this three-year period, all test materials will be destroyed.

Participant Consent:

I have read or have had read to me all of the above information. I have had all of my questions answered and understand the purpose, procedures, risks and benefits of the study. I agree to participate in this study. I certify that I am at least 18 years of age. A copy of this form has been given to me.

_____ _____

Name Date

_____ _____

Signature Date

Witness

COMMUNITY OF LAS VEGAS, NEVADA

INFORMED CONSENT FORM

Introduction: Carol Randall and Daniel Allen, Ph.D., from the Department of Psychology at UNLV, are seeking participants for a study that examines the processing of emotion in individuals with bipolar disorder. You are invited to participate in this research study.

Procedure: If you volunteer to participate in this study, you will be interviewed and then be administered tasks that are designed to test emotion processing and various other cognitive abilities. For these tasks, you will be asked to complete a number of different exercises such as remembering lists of words and naming pictures. During the interview, the examiner will ask you general questions such as your age and years of education, along with questions regarding your medical history. At the beginning of the study, you will be provided with instructions that will tell you how to complete the tests. The total time needed to complete this research project is approximately 6.0 hours, although it may take less time for you to complete the study.

Benefits of Participation: By participating in this study, you will receive $5.00 per hour of participation in the study, with a $30.00 final compensation given upon completion of the study in its entirety.

Risks of Participation: There is a chance you may experience some mental fatigue during the assessments. To decrease the chance of fatigue, the researcher will allow breaks as necessary for your comfort. Although it is not expected to occur, should you feel uncomfortable answering any of the questions or performing any of the tasks, you are encouraged to discuss concerns with the researcher. Your participation is voluntary and you may refuse to answer questions or withdraw from the study at any time.

Contact Information: If you have questions about the study, or if you experience any harmful effects because of participation in this study, you are encouraged to contact Carol Randall or Daniel Allen at 895-0295.

For questions regarding the rights of research subjects, you may contact **the UNLV Office for the Protection of Research Subjects at 895-2794.**

Voluntary Participation: Your participation in this study is voluntary. You may refuse to participate in this study or in any part of this study. You may withdraw at any time without prejudice to your relations with the university. You are encouraged to ask questions about this study at the beginning or any time during the research study.

Confidentiality: All information gathered in this study will be kept completely confidential. No reference will be made in written or oral materials that could link you to this study. All records will be stored in a locked facility at UNLV for at least 3 years after completion of the study. After this three-year period, all test materials will be destroyed.

Participant Consent:

I have read or have had read to me all of the above information. I have had all of my questions answered and understand the purpose, procedures, risks and benefits of the study. I agree to participate in this study. I certify that I am at least 18 years of age. A copy of this form has been given to me.

_____ _____

Name Date

_____ _____

Signature Date

Witness

UNLV

BIPOLAR DISORDER

RESEARCH STUDY

- To be eligible, you must be between the ages of 18 and 65, primarily English speaking and have a diagnosis of Bipolar disorder.
- Participants will be asked to do various tests, which will take approx. 6 hours, and will be compensated $5 per hour with a $30 bonus for completion of all testing.
- Please contact Christina at 217-5365 or UNLVBipolarResearch@yahoo.com if you are interested or would like additional information.

Bipolar Research:
Christina
217-5365 or
UNLVBipolarResearch@yahoo.com

UNLV

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RESEARCH STUDY

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- If interested, speak to your case manager or email UNLVBipolarResearch@yahoo.com for additional information.

APPENDIX C

IRB APPROVAL FORMS

UNLV
UNIVERSITY OF NEVADA LAS VEGAS

Social/Behavioral IRB – Expedited Review
Modification Approved

NOTICE TO ALL RESEARCHERS:

Please be aware that a protocol violation (e.g., failure to submit a modification for any change) of an IRB approved protocol may result in mandatory remedial education, additional audits, re-consenting subjects, researcher probation suspension of any research protocol at issue, suspension of additional existing research protocols, invalidation of all research conducted under the research protocol at issue, and further appropriate consequences as determined by the IRB and the Institutional Officer.

DATE: **November 9**, 2006

TO: **Dr. Daniel Allen**, Psychology

FROM: Office for the Protection of Research Subjects

RE: Notification of IRB Action by Dr. J. Michael Stitt, Chair
Protocol Title: **Neuropsychological and Emotion Processing Deficits in Adults with Bipolar Disorder**
Protocol #: 0510-1779

The modification of the protocol named above has been reviewed and approved.

Modifications reviewed for this action include:

- The title of the study will change to "Neuropsychological, Emotional, and Functional Deficits in Adults with Bipolar Disorder.
- The addition of Daniell Knatz, Carol Randall, and Brian Leany to the research team.
- The addition of Mojave Adult, Child and Family Services to the research sites.
- The expected amount of completion time will change to 6 hours.
- The removal of the Minnesota Multiphasic Personality Inventory -II from the protocol and the addition of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders as a measure.
- An increase in the number of subjects from 50 to 150.
- Advertisements will now be released to the UNLV Public Relations Department.
- Contact letters will now be sent to local psychiatrists, psychologists, and psychotherapists.
- Participants will now be compensated monetarily at a rate of $5.00 per hour and $2.50 per half hour and will be given a $30.00 bonus in addition to the $5.00 per hour upon completion of the

- entire study. Research credits will now increase to 6 to participants from the subject pool.
- Participants who may contact by phone will now be screened as well as verbally consented for the screening.
- An additional Informed Consent will be added for individuals diagnosed with Bipolar Disorder from the subject pool.
- The inclusion of a demographic form, functional outcome measure and additional symptom and neuropsychological assessments.
- Three functional outcome measures will be added to the assessment battery.
- Three neuropsychological assessments will be added.
- One symptom measure will be added.

This IRB action will not reset your expiration date for this protocol. The current expiration date for this protocol is September 20, 2007.

PLEASE NOTE:
Attached to this approval notice is the **official Informed Consent/Assent (IC/IA) Form** for this study. The IC/IA contains an official approval stamp. Only copies of this official IC/IA form may be used when obtaining consent. Please keep the original for your records.

Should there be *any* change to the protocol, it will be necessary to submit a **Modification Form** through OPRS. No changes may be made to the existing protocol until modifications have been approved by the IRB.

Should the use of human subjects described in this protocol continue beyond September 20, 2007, it would be necessary to submit a **Continuing Review Request Form** *60 days* before the expiration date.

If you have questions or require any assistance, please contact the Office for the Protection of Research Subjects at OPRSHumanSubjects@unlv.edu or call 895-2794.

UNLV
UNIVERSITY OF NEVADA LAS VEGAS

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DATE: May 16, 2007

TO: **Dr. Daniel Allen**, Psychology

FROM: Office for the Protection of Research Subjects

RE: Notification of IRB Action by Dr. J. Michael Stitt, Chair
Protocol Title: **Neuropsychological and Emotion Processing Deficits in Adults with Bipolar Disorder**
Protocol #: 0510-1779

The modification of the protocol named above has been reviewed and approved.

Modifications reviewed for this action include:

- The addition of Jamie Harnik, Michelle Sernas, Ruwida Abdel-Al, Benjamin Watrous, Paul Stolberg, and Audrey Garcia to the research team.
- Additional questions about psychotic symptoms have been added to the screening process.
- Two additional flyers have been added to the protocol.

This IRB action will not reset your expiration date for this protocol. The current expiration date for this protocol is September 20, 2007.

Should there be *any* change to the protocol, it will be necessary to submit a **Modification Form** through OPRS. No changes may be made to the existing protocol until modifications have been approved by the IRB.

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Social/Behavioral IRB – Expedited Review
Modification Approved

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DATE: February 1, 2008

TO: **Dr. Daniel Allen**, Pychology

FROM: Office for the Protection of Research Subjects

RE: Notification of IRB Action by Dr. J. Michael Stitt, Chair
Protocol Title: **Neuropsychological and Emotion Processing Deficits in Adults with Bipolar Disorder**
Protocol #: 0510-1779

The modification of the protocol named above has been reviewed and approved.

Modifications reviewed for this action include:

- The addition of a "Bipolar Contact Protocol."
- The addition of a "Consent to be Contacted for Future Studies."
- The addition of two funding sources from researcher Danielle Bello (Council of Graduate Departments of Psychology) and the NSF-EPSCoR undergraduate research award to researcher Sally Barney.

This IRB action will not reset your expiration date for this protocol. The current expiration date for this protocol is September 5, 2008.

PLEASE NOTE:
Attached to this approval notice is the **official Informed Consent/Assent (IC/IA) Form** for this study. The IC/IA contains an official approval stamp. Only copies of this official IC/IA form may be used when obtaining consent. Please keep the original for your records.

Should there be *any* change to the protocol, it will be necessary to submit a **Modification Form** through OPRS. No changes may be made to the existing protocol until modifications have been approved by the IRB.

Should the use of human subjects described in this protocol continue beyond September 5, 2008, it would be necessary to submit a **Continuing Review Request Form** *60 days* before the expiration date.

If you have questions or require any assistance, please contact the Office for the Protection of Research Subjects at OPRSHumanSubjects@unlv.edu or call 895-2794.

Social/Behavioral IRB – Expedited Review
Modification Approved

NOTICE TO ALL RESEARCHERS:

Please be aware that a protocol violation (e.g., failure to submit a modification for any change) of an IRB approved protocol may result in mandatory remedial education, additional audits, re-consenting subjects, researcher probation suspension of any research protocol at issue, suspension of additional existing research protocols, invalidation of all research conducted under the research protocol at issue, and further appropriate consequences as determined by the IRB and the Institutional Officer.

DATE: July 14, 2008

TO: **Dr. Daniel Allen**, Psychology

FROM: Office for the Protection of Research Subjects

RE: Notification of IRB Action by Dr. J. Michael Stitt, Chair
Protocol Title: **Neuropsychological and Emotion Processing Deficits in Adults with Bipolar Disorder**
Protocol #: 0510-1779

The modification of the protocol named above has been reviewed and approved.

Modifications reviewed for this action include:

- The addition of Alex Hutchings to the research team.

This IRB action will not reset your expiration date for this protocol. The current expiration date for this protocol is September 5, 2008.

Should there be *any* change to the protocol, it will be necessary to submit a **Modification Form** through OPRS. No changes may be made to the existing protocol until modifications have been approved by the IRB.

Should the use of human subjects described in this protocol continue beyond September 5, 2008, it would be necessary to submit a **Continuing Review Request Form** *60 days* before the expiration date.

If you have questions or require any assistance, please contact the Office for the Protection of Research Subjects at OPRSHumanSubjects@unlv.edu or call 895-2794.

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