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The neuropsychological correlates of individuals at risk for bipolar I disorder

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THE NEUROPSYCHOLOGICAL CORRELATES OF INDIVIDUALS AT RISK FOR BIPOLAR I DISORDER

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ABSTRACT

Neuropsychological Correlates of Individuals at Risk for Bipolar I Disorder

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Bipolar disorder is now recognized as a severe psychiatric disorder characterized by extreme mood swings and cognitive deficits, most notably in the domains of verbal learning, executive function, and sustained attention. Neurocognitive deficits have been proposed as vulnerability markers or endophenotypes for the development of bipolar disorder. However, few research studies have examined whether neurocognitive deficits also exist in individuals at risk for bipolar disorder or first-degree relatives. This study examined neurocognitive function in individuals with bipolar disorder, their first-degree relatives, and a normal control group. Results indicated that individuals with bipolar disorder and their unaffected relatives demonstrated neuropsychological deficits in comparison to the normal control group in the domains of visuospatial/constructional abilities, executive function, and visual learning and memory. In general, the unaffected relatives demonstrated an intermediate level of performance in comparison to the normal control and bipolar group. After adjustment for mood symptomotology, significant differences remained only in the visuospatial/constructional and executive function

domains. Individuals with bipolar disorder also demonstrated a differential right versus left hemisphere deficit with respect to neurocognitive tasks, providing support for the theory of right hemisphere dysfunction in bipolar affective disorder. Deficits on specific neuropsychological tests, most notably Digit Symbol, Block Design, and Judgment of Line Orientation may be indicative of cognitive endophenotypes for bipolar disorder. Replication studies are needed to identify these deficits as neurocognitive phenotypes and to further examine hemispheric functioning in bipolar affective disorder.

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- *Soli Deo Gloria.*

CHAPTER 1

INTRODUCTION

Purpose of the Study

The purpose of this study was to determine whether there is a neurocognitive phenotype for the risk of developing bipolar affective disorder. Phenotypes are behavioral characteristics that are believed to represent underlying genetic vulnerabilities or predispositions, also termed the genotype of a particular disorder (Faraone, Seidman, Kremen, Pepple, Lyons, & Tsuang, 1995; Tsuang, Faraone, & Lyons, 1993). To accomplish this task, individuals at genetic risk for developing bipolar disorder, (i.e., first-degree relatives of individuals diagnosed with the disorder) were evaluated with neuropsychological tests and compared to individuals with relatively low risk (i.e., individuals with no family history of bipolar or affective mood disorder). Traditionally, risk factors in psychiatric disorders have been defined as characteristics such as gender, family history, or significant life events that are associated with the onset or expression of a particular illness (Kraemer, Kazdin, Offord, Jensen, & Kupfer, 1997). These risk factors can be used to determine groups that are considered low risk versus high risk for development of psychopathology in a given population of interest. Because a positive family history has been found to be the single most consistent and predictive risk factor in the development of affective disorders (for review, see Duffy, 2000), first-degree relatives are considered to be a high-risk group.

First–degree relatives, defined as parents, offspring, or siblings, share approximately 50% of their gene variation with the bipolar proband (or individual who manifests bipolar illness) in comparison to more distant or second-degree relatives such as aunts, uncles, and first cousins, who share only 25% of their genetic variation. Familial studies have consistently shown that the relative risk of developing bipolar I disorder is significantly elevated in first-degree relatives (4 to 24%) compared to approximately 1% in the general population (DSM-IV TR, 1994). Although the genetic risk in bipolar disorder is well known, the exact mode of genetic transmission remains elusive, in part owing to the difficulty in measuring the genotype or genetic predisposition of this disorder. Other methods have been proposed to clarify the genetic susceptibility in bipolar disorder, such as identifying biological and behavioral characteristics or phenotypes that are related to the expression of this complex disorder (Lenox, Gould, & Manhi, 2002). Neurocognitive function has been proposed as a potential marker for the genetic heritability of bipolar affective disorder (Glahn, Bearden, Niendam, & Escamilla, 2005).

Cognitive deficits have been documented in various domains in patients with bipolar disorder, with some preliminary evidence suggesting that certain deficits may exist prior to the onset of illness (Gourovitch, Torrey, & Gold, 1999; Sigurdsson, Frombonne, & Sayal, 1999). These subtle neurocognitive deficits may be present in non-affected first-degree relatives, given the substantial genetic component in bipolar affective disorder, and may provide insight into the neuropathology of bipolar affective disorder.

Few studies have examined neuropsychological function in first-degree relatives, particularly adult relatives of bipolar probands, and results to date are equivocal. Only individuals diagnosed with bipolar I disorder (exclusive of bipolar II and other bipolar

spectrum disorders) and their first-degree relatives were used in this study in order to maintain a homogenous subgroup for greater clarity of phenotypic expression. In contrast, individuals with no known history of bipolar disorder, depression, or schizophrenia served as the comparison group.

This study examined a broad spectrum of neurocognitive measures, including those measures that have consistently been found to demonstrate impairment in bipolar patients, in the hopes of detecting abilities that likewise may be deficient in the high-risk group of relatives, (i.e., potential neurocognitive phenotypes). Neurocognitive phenotypes are considered more causally related to the genotype than clinical symptoms and therefore are more useful in identifying individuals at risk for various disorders (Faraone et al., 1995). Because phenotypes often demonstrate no overt clinical signs or symptoms, they have also been termed endophenotypes. Endophenotypes are defined as potential diagnostic indicators that are not only more prominent in individuals diagnosed with a specific disease but are also believed to be genetically transmitted and are therefore evident in relatives of affected probands (Tsuang et al., 1993). This study will also serve a confirmatory function such that if cognitive deficits are detected, these differences will mirror those deficits already documented in bipolar patients but to a lesser extent. These results would be anticipated given the substantial genetic component of bipolar illness. Specifically, this investigation attempted to identify deficits in the areas of executive functioning, learning and memory, and visuospatial abilities in both bipolar patients and their first-degree relatives. Memory functions were explored in terms of both verbal (auditory) and visual modalities. Memory deficits, specifically in auditory or verbal learning, have been one of the most consistently identified areas of

cognitive deficits in bipolar patients (Ali, Denicoff, & Altshuler, Hauser, & Conrad, 2000; Atre-Vaidya, Taylor, & Seidenberg, 1998; Burt, Prudic, Peyser, Clark, & Sackheim, 2000; Coffman, Bornstein, Olson, Schwarzkopf, & Nasrallah, 1990; Denicoff et al., 1999; Ferrier, Stanton, Kelly, & Scott, 1999; Guiliano, Garroway, Stein, DeLong, Biederman, & Frazier, 2002; Rubinsztein, Paykel, & Sahakian, 2000; van Gorp, Altshuler, Theberge, & Mintz, 1999; Zubieta, Huguelet, O' Neill, & Giordani, 2001).

Lastly, this study examined whether individuals with bipolar affective disorder and at-risk relatives demonstrated a differential right hemispheric dysfunction or deficits in tasks associated with predominantly right hemisphere functioning, as there is ongoing debate regarding the association of affective disorder with lateralized dysfunction (Bearden, Hoffman, & Cannon, 2000; Flor-Henry, 1976, 1983; Gruzelier & Flor-Henry, 1979). Overall, findings of this study will serve to further elucidate whether neuropsychological tests and, more specifically, abnormalities in cognitive functioning, can serve as markers of genetic vulnerability or behavioral phenotypes as well as contribute to the understanding of the neuropathology of bipolar affective disorder.

Research Questions/Limitations in the Literature

Bipolar affective disorder is a severe psychiatric disorder characterized by recurrent mood swings of mania and/or depression and significant social and occupational impairment. Lifetime prevalence rates for bipolar disorder are estimated as 1.0 to 1.6% in the adult population and 1.2% in child and adolescent populations (Keck, McElroy, & Arnold, 2001), although some researchers propose that the prevalence for the bipolar spectrum, including Bipolar I and II disorders and variations thereof, is closer to 5% in

the adult population (Akiskal, Bourgeois, Angst, Post, Möller, & Hirschfeld, 2000). It has also been observed that bipolar disorder is now occurring in progressively younger ages in vulnerable offspring of parents with bipolar disorder, a phenomenon known as genetic anticipation (Post, Leverich, Xing, & Weiss, 2001). Additionally, bipolar disorder has been reported as being the sixth leading cause of disability worldwide in terms of global health burden (Murray, Lopez, & Jamison, 1994).

Although early studies suggested a relatively positive prognosis in terms of psychosocial outcomes, more recent statistics indicate that approximately 30 to 50% of patients with bipolar disorder fail to return to their premorbid levels of psychosocial adjustment after the initial episode (Altshuler, 1993; Goodwin & Jamison, 1990; Tohen, Waternaux, & Tsuang, 1990; Zarate, Tohen, Land, & Cavanaugh, 2000). Longitudinal studies have demonstrated occupational impairment persisting in up to 25% of bipolar patients after several years (Tsuang, 1979) and acutely (after six months) in approximately 65% of patients (Dion, Tohen, Anthony, & Waternaux, 1988). Dion and colleagues (1988) further reported that up to 64% of the acute patients were unable to live independently. Estimates of poor functional recovery after an affective episode ranged from 25% (Tsuang, 1979) to 75% (Keck, McElroy, Strakowski, West, Sax, & Hawkins, 1998; see Zarate et al., 2000, for review), with impairment in functioning affecting all aspects of psychosocial functioning (social, occupational, recreational, and intellectual), even with resolution of clinical symptoms. Dickerson and colleagues (2001) found relatively comparable social and cognitive impairment between a sample of outpatients with schizophrenia and bipolar disorder on 36 out of 41 outcome measures.

Neurocognitive dysfunction has been proposed as one reason for poor psychosocial outcome in a subgroup of patients with bipolar disorder (Zarate et al., 2000).

Since 1921 when Kraepelin distinguished the two major psychotic disorders, manic-depressive illness or bipolar affective disorder and dementia praecox, now known as schizophrenia, it was proposed that bipolar disorder was characterized by a relative sparing of cognitive function, with minimal evidence of cognitive impairment or deterioration. In his early writings, Kraepelin (1921) reported that the majority of patients suffering with manic or depressive episodes typically returned to normal functioning with little impairment in cognition and few residual symptoms. In contrast, patients with schizophrenia demonstrated persistent thought disorder, cognitive deficits, and impaired psychosocial and occupational functioning. This distinction has guided much of contemporary thought regarding bipolar disorder and is reflected in the relative paucity of research aimed at identifying cognitive impairments in patients with bipolar illness. In contrast to schizophrenia, researchers have only recently begun to investigate neurocognitive dysfunction in patients with bipolar disorder in a critical and comprehensive manner. Overall, these recent studies challenge the long-held view that bipolar disorder has a benign course with minimal cognitive impairment and support the findings of definitive cognitive impairment in a least a subgroup of patients with bipolar illness (Atre-Vaidya, Taylor, & Seidenberger, 1998; Coffman et al., 1990; Rubinsztein, Paykel, & Sakahian, 2000; Zarate et al., 2000). Altshuler (1993) has reported persistent cognitive deficits in up to 32% of bipolar patients with recurrent episodes. However, the prognostic role of neurocognitive impairment for determining long-term functional outcomes, as well as the role of neuropsychological tests in identifying potential

predispositions or vulnerabilities characteristic of bipolar illness, have not been fully explored. More specifically, it is still unknown whether individuals at risk for developing bipolar disorder, such as first-degree relatives, demonstrate specific cognitive deficits or abnormalities without clinical manifestation of bipolar illness as compared to individuals without a family history. The current investigation attempted to address the issue of neurocognitive markers in bipolar affective disorder as well as to further elucidate cognitive functioning in individuals with bipolar disorder.

Prior to 1975, most studies of cognitive function in patients with affective disorder (unipolar and bipolar) measured primarily intellectual function (Clark, Clayton, Andreasen, Lewis, Fawcett, & Scheftner, 1985; Donnelly, Murphy, Goodwin, & Waldman, 1982; Johnstone, Owens, Frith, & Calvert, 1985) and suggested a pattern of right hemisphere dysfunction (Abrams, Redfield, & Taylor, 1981; Clark et al., 985; Flor-Henry, 1983; Friedman, 1964; Gilliland, Wittman, & Goldman, 1943; Kerry, McDermott, & Orne, 1983; Waldfogel & Guy, 1951). Many of these early studies also examined unipolar versus bipolar depression and found that bipolar depression resulted in greater cognitive impairment that unipolar depression (Rubinow, Post, Savard, & Gold, 1984; Savard, Rey, & Post, 1980; Wolfe, Granholm, Butters, Saunders, & Janowsky, 1987). The most consistent finding regarding cognitive impairment in patients with affective disorders suggested that cognitive deficits, by and large, were related to the severity of depression (Goodwin and Jamison, 1990).

Over the next two decades, various studies were conducted to assess cognitive functioning in bipolar patients, most of which demonstrated that patients with bipolar affective disorder had more neuropsychological deficits than normal controls but less

severe impairment than schizophrenic patients. Many of these studies, however, had various methodological limitations, including a limited number of cognitive measures and lack of control of specific variables, including diagnostic classification (unipolar versus bipolar depression), duration of illness, severity of illness, age, educational history, and history of substance abuse. Another potential confound in many early studies was the patient's history of electroconvulsive therapy (Kessing, 1998). As a whole, these limitations have generated inconsistencies in findings and resultant difficulty with generalizations and cross-sample comparisons. Often bipolar groups were used strictly as control-comparison groups to other psychiatric groups, particularly patients diagnosed with schizophrenia, rather than as the variable of interest.

Another factor of variability in many of the earlier studies of cognitive functioning of bipolar disorder has been the clinical phase of illness at the time of study (i.e. manic, depressive, mixed, or euthymic states). Initially, many more studies examined cognitive deficits in depressed states, primarily unipolar or major depressive disorder, and fewer investigations were performed with bipolar patients during periods of remission or euthymic stages, thus leading to the belief that neurocognitive disturbances are state-dependent or more predominant in manic or acute phases of illness (Martínez-Arán et al., 2000). However, this research trend has shifted over the last decade, with more recent studies examining patients in the remitted or euthymic stages of bipolar illness. Nonetheless, there is still a relative paucity of research of cognitive deficits in patients with bipolar disorder in comparison to the literature of cognitive impairment in other psychiatric disorders, most notably major depressive disorder or schizophrenia.

Despite significant improvements in research design, methodological limitations continue to exist in more recent studies. In a review of neuropsychological studies of bipolar patients in the last two decades, Martínez-Arán and colleagues (2000, p. 3) summarized major limitations: 1) small sample sizes 2) lack of distinction of bipolar vs. unipolar patients 3) heterogeneity of research designs and instruments 4) lack of control groups 5) limited control of demographic variables 6) heterogeneity of clinical states and 7) lack of high-risk studies. The severity of illness or symptomology across clinical states is likewise difficult to control and not always documented, making it difficult to posit global conclusions regarding state versus trait deficits. Furthermore, many studies fail to account for residual clinical symptoms, particularly depressive symptoms, which may confound results (Ferrier & Thompson, 2002).

These limitations notwithstanding, studies to date have consistently identified a neuropsychological profile specific to bipolar illness. Nonetheless, the majority of these studies have demonstrated cognitive deficits in bipolar patients relative to normal controls in the areas of learning, memory, sustained and selective attention, verbal fluency, and executive functioning (Martínez-Arán et al., 2000). Less commonly, deficits in visuospatial processing, working memory, motor functioning, and general intellectual functioning have also been identified (Martínez-Arán, et al., 2000; Murphy & Sahakian, 2001).

Other reviews of neuropsychological investigations with bipolar populations over the past two decades have resulted in similar conclusions. In a critical and extensive review of the neuropsychological and neuroanatomical findings of bipolar disorder, Bearden et al. (2001) proposed several conclusions. First and foremost, these researchers posited

that bipolar disorder, contrary to popular belief, is associated with definitive cognitive impairment, and that these impairments may be more evident in particular subgroups such as chronic and/or elderly bipolar patients. Furthermore, they noted that although cognitive deficits are most significant/dramatic in states of clinical symptom exacerbation (mania or depression), there is evidence of cognitive impairment persisting in the euthymic or residual states. Specifically, cognitive tasks requiring conceptual ability or abstraction as well as memory processes have been shown to be impaired independent of mood dysfunction and possibly existent in the premorbid state (Goodwin & Jamison, 1990). As a whole, verbal skills appear to be less impaired than visuospatial and abstraction skills, although there is evidence that complex verbal learning and memory is significantly altered in bipolar populations. In general, elderly patients or patients with chronic illness demonstrate more severe and diffuse cognitive impairment relative to younger, euthymic patients. These researchers also concluded that findings of lateralization in bipolar disorder did not clearly demonstrate a specific right hemisphere lesion or dysfunction but rather could be interpreted as state-dependent changes or neurotransmitter imbalances, i.e., dysfunctions more apparent in manic states, as opposed to enduring cognitive deficits, which were associated with dysfunction in frontal-subcortical systems.

Similar to other researchers, Bearden and colleagues (2001) concluded that there was no specific neuropsychological profile or pattern of deficit that characterized bipolar disorder, although there is preliminary indication of a cognitive profile in depressed bipolar patients that is similar to patients with subcortical disorders such as Huntington's chorea (Massman, Delis, Butters, Dupont, & Gillin, 1992; Wolfe, Granholm, Butters,

Saunders, & Janowsky, 1987). This proposed cognitive profile involves similar although less severe deficits found in subcortical disorders, on tasks of speeded information processing, immediate and delayed memory, and executive functioning. It appears too early to define bipolar disorder as having a subcortical cognitive profile as only two studies to date substantiate this proposal, whereas another investigation (van Gorp, Altshuler, Theberge, & Mintz, 1999) found support for cortical rather than subcortical impairment.

Another neuropsychological review of bipolar disorder (Murphy et al., 2001) summarized studies with an emphasis on clinical mood state and cognitive functioning. Murphy and colleagues (2001) noted that neuropsychological deficits in clinical or unipolar depression have been investigated to a greater degree than bipolar depression, once again demonstrating the relative lack of neurocognitive studies involving bipolar populations. These researchers examined the cognitive literature with regards to differences found in patients during various phases of illness (depressive, manic, and euthymic states), categorizing the specific versus general cognitive deficits that occur in each phase of bipolar illness. Although this classification system lends itself to clarifying the deficits associated with each phase of illness, Murphy et al. (2001) acknowledged the inherent difficulties and potential confounds when comparing patients within or between groups in relation to symptom severity of illness.

As noted above, cognitive impairment in major depressive disorder is well documented, with most research demonstrating deficits in memory, (Cronholm & Otteson, 1961; Henry, Weingartner, & Murphy, 1973; Weingartner, Gold, Ballenger, & Smallberg, 1981), executive functioning and abstraction (Jones, Henderson, & Welch,

1988; Raskin, Friedman, & DiMascio, 1982; Savard, Rey, & Post, 1980) and psychomotor speed and perceptual processing (Miller, 1975; Weingartner, Cohen, Murphy, Martello, & Gerdt, 1981). In the few studies comparing unipolar or major depressive disorder with bipolar disorder (Savard, 1980; Wolfe et al., 1987), patients with bipolar affective disorder demonstrated more severe cognitive impairment. Studies involving bipolar patients in the manic phase of illness typically found moderate to severe impairment in tests of attention, visuospatial function, executive function, and memory processing, implicating a broad spectrum of cognitive deficits rather than circumscribed deficits (Henry, Weingartner, & Murphy, 1981; Murphy, Sahakian & Rubinsztein, 1999; Murphy et al., 2001; Taylor & Abrams, 1986).

Most of the studies involving bipolar patients in the euthymic stages of illness employed cross-sectional designs and revealed cognitive impairments, particularly in attention and visual processing, independent of active symptom state (Ferrier et al., 1999; Kessing, 1998; Rubinsztein et al., 2000; Tham, Engelbrektson, Mathe, Johnson, Olsson, & Aberg-Wistedt, 1997). After examining the various studies that differentiated clinical states and comparing them to one another, Murphy and Sahakian (2001, p. 123) proposed:

> The bulk of research suggests that in both mania and depression, patients are impaired on a range of cognitive tasks subserved by different neural regions. In addition, although the few studies that actually compare mania and depression employ a limited range of tasks, it appears that conventional neuropsychological tests of attention, memory, and executive function are unable to discriminate between patients with mania and depression. Together, these findings suggest that

global pathological change, rather than factors unique to either disorder, may account for observed deficits, and that similar processes may be involved despite markedly different presentations.

Collectively, the aforementioned reviews suggest that there is evidence of significant cognitive impairment in bipolar disorder in all three clinical phases of illness, including the euthymic phase. However, attempts to identify a prototypic neuropsychological profile for bipolar disorder have not been substantiated and remain a viable area of interest. More recently, research efforts have been devoted to identifying neuropsychological profiles that are distinct to the affective disorders, most notably bipolar disorder, in order to understand the genetic underpinnings and potential etiologies of this disorder. Research has also focused on identifying specific relationships between the observable behaviors or manifestations of the disease, the phenotype, and the genetic formulation or genotype. Traditionally, the identification of phenotypes in psychiatric populations has been examined primarily in schizophrenia, although recent work has begun in the areas of obsessive-compulsive disorders, panic disorders, attention-deficit hyperactivity disorders, and bipolar disorders (Tsuang et al., 1993). In most of the aforementioned psychiatric disorders, the genotype or genetic foundation is expressed clinically in a variable pattern; for example, the schizophrenia genotype may be expressed as schizoaffective disorder, schizotypal personality, or atypical psychotic disorder, and the bipolar genotype may be expressed clinically as bipolar II disorder or major depressive disorder (Tsuang et al., 1993). Typically, there is not a one-to-one correspondence between symptom presentation or clinical expression of a disorder and the corresponding genotype; as such, neurobiological phenotypes such as biological

markers or indicators of neuropsychological impairment may be more closely related to the actual phenotype than clinical symptoms and therefore more useful for identifying at-risk individuals.

Significance of the Study

The use of high-risk paradigms to identify phenotypes has been used in various medical and psychiatric conditions and is now being utilized to examine neurocognitive deficits in bipolar populations. Essentially, the high-risk paradigm compares first-degree relatives who do not clinically manifest a disorder or disease to those who are affected in order to study variables of interest in a cross-sectional or prospective manner. Although various biological markers and potential markers of genetic vulnerability are being considered (Lenox et al., 2002), neurocognitive tests are being explored in relatives of bipolar probands via the high-risk research design. A high-risk paradigm allows researchers to investigate whether neuropsychological deficits might represent neurobehavioral endophenotypes (i.e. behavioral manifestations of the genotype of bipolar disorder) by examining if specific cognitive functions or profiles are more prevalent in individuals at risk for developing bipolar disorder. Endophenotypes are behavioral traits that are associated or closely linked with the genetic underpinnings of an illness and may represent a genetic vulnerability in unaffected relatives (Pierson, Jouvent, Quintin, Perez-Diaz, & Leboyer, 2000); hence endophenotypes are more directly related to disease pathology compared to more general phenotypes. By definition an endophenotype or behavioral marker must be present before onset of illness and be more prevalent among relatives of identified patients compared to the general population

(Pierson et al., 2000). Additionally, endophenotypes or markers must be heritable, state-independent, and found to co-segregate within the family (Gershon & Goldin, 1986).

Identification of cognitive endophenotypes is of critical importance because they 1) facilitate genetic linkage studies that attempt to determine the mode of transmission in complex, genetically-linked illnesses such as bipolar disorder. Therefore, phenotypic indicators are useful because they can identify affected family members who cannot be classified by psychiatric symptoms alone or who may have subclinical symptoms (Tsuang et al., 1993). Some researchers have suggested that endophenotypes may be more useful and reliable at identifying phenotypes in genetic linkage analyses than traditional methods (Lenox et al., 2000); 2) assist researchers in predicting which individuals are at greater risk for developing bipolar disorder; 3) serve to increase the effectiveness of early diagnosis and intervention in individuals at risk for bipolar disorder; and 4) allow for improvements in overall diagnostic assessment.

Specific biobehavioral markers, most notably smooth pursuit eye movement, auditory P300 evoked potentials, and measures of visual sustained attention have been shown to be significant neurobiological predictors or phenotypes of schizophrenia (Faraone et al., 1995). Similar studies are being performed to identify biological markers in bipolar disease (El Badri, Ashton, & Moore, 2001; Gooding, & Tallent, 2001; Rosenberg, Sweeney, Squires-Wheeler, Keshavan, Cornblatt, & Erlenmeyer-Kimling, 1997; Tien, Ross, Pearlson, & Strauss, 1996). Likewise, deficits in neuropsychological performance have been proposed in both schizophrenia and bipolar illness as less direct but nonetheless significant risk predictors or phenotypes of the schizophrenia and bipolar genotypes (Faraone et al., 1995; Kremen, et al., 1998). The term "risk" in these

paradigms has been used to implicate neuropsychological deficits that serve as "putative endophenotypes" or deficits having characteristics that are linked causally to the pathological genotype (Kremen et al., 1998). This distinction does not imply that all individuals demonstrating these phenotypic behaviors will go on to develop a specific disorder, secondary to multiple protective and environmental factors, but rather that these behavioral characteristics are latent genetic vulnerabilities.

Because both schizophrenia and bipolar disorder have strong genetic components and potential underlying neurodevelopmental components (Done, Crow, Johnstone, & Sacker, 1994; Post, Leverich, & Xing, 2001; Sigurdsson, Fombonne, & Sayal, 1999), studies utilizing relatives of schizophrenic patients are instructive for bipolar research. Faraone and colleagues (1995) were able to document neuropsychological deficits in first-degree relatives that paralleled the cognitive deficits consistently found in schizophrenic patients, most notably deficits in abstraction, verbal memory, auditory attention, mental control, and verbal ability, and to document that certain cognitive tasks, specifically abstraction, verbal memory, and auditory attention, showed not only deficits compared to normal controls but also the proposed variability. They concluded that they had found partial support for phenotypic characteristics that differentiated schizophrenia relatives from normal controls.

Comparatively, high-risk paradigms with relatives of bipolar disorder have been scarce and have traditionally measured only a few cognitive measures, predominantly IQ measures, and, in restricted samples, those of children of bipolar patients (Decina et al., 1983; Kestenbaum, 1979; Gourovitch, Torrey, Gold, Randolph, Weinberg, & Goldberg, 1999; Waters, Marchenko, & Smiley, 1983; Worland, 1979). In a review of studies of

child and adolescent offspring of bipolar parents, Delbello and colleagues (2001, p. 332) commented that "unaffected offspring present a unique opportunity to study pre-and-post morbid cognitive and physiological endophenotypes and structural and functional abnormalities." The study of children and adolescents invariably lends itself to identifying cognitive deficits unrelated to the aging process as well as detecting behavioral deficits occurring prior to the onset of illness, excluding early-onset cases.

Additionally, most studies examining at-risk individuals have not included the bipolar probands or affected relatives for direct comparison. It would seem that at-risk studies should utilize the relatives with a bipolar diagnosis in order to more clearly elucidate genetic versus environmental components and to establish more definitively the neurocognitive profile of individuals at risk for developing the disorder.

In summary, studies aimed at investigating offspring or siblings of bipolar patients can further serve to elucidate whether neuropsychological deficits are trait markers indicating genetic vulnerability to bipolar disorder (endophenotypes), or whether observed deficits are more state-like and non-enduring. Identification of potential phenotypic markers of cognitive deficits can also facilitate genetic linkage studies aimed at locating specific genes responsible for the transmission of genetic vulnerability to the disease. Lastly, identification of specific neurocognitive deficits in high-risk relatives can potentially lead to more effective diagnosis and early intervention, particularly in cases of early onset and adolescent bipolar populations.

The aforementioned literature reviews all cited the relative lack of high-risk studies with bipolar relatives, demonstrating the need to clarify the relationship between neuropsychological deficits and clinical manifestation of bipolar disorder. In their

literature review, Bearden and colleagues (2001, p. 144) comment that inasmuch "as there have been so few studies of neuropsychological performance and neuroanatomy in relatives of bipolar probands, no conclusions can yet be drawn as to whether the abnormalities seen in bipolar patients reflect an underlying genetic vulnerability to the disorder." It is apparent that high-risk studies utilizing first-degree relatives of bipolar probands are lacking and potentially crucial in understanding the possible genetic and neuroanatomical substrates of bipolar illness.

CHAPTER 2

LITERATURE REVIEW

Genetic Factors in Bipolar Disorder

A brief summary of the role of heredity in bipolar affective disorder is crucial prior to discussing studies that examine the role of neuropsychological function as biobehavioral markers of genetic predisposition to this disorder. Bipolar affective disorder is generally recognized as having a strong genetic component; in fact, it has been suggested that bipolar affective disorder demonstrates the greatest genetic predisposition among the severe psychiatric disorders (Ewald, 2000). The relative risk of manifesting bipolar disorder in first-degree relatives is 5% to 10% (Taylor, Faraone, & Tsuang, 2002), and the concordance rate for monozygotic twins is estimated as being 58-74% (Taylor et al., 2002; Tsuang & Faraone, 1990). Unfortunately, neither association nor linkage studies have been able to definitively identify the mode of transmission or specific chromosomes involved in the heritability of this disorder.

Although monogenic Mendelian inheritance has been found to be highly unlikely in the majority of cases, it has not been entirely ruled out (Tsuang & Faraone, 2000). It is more probable, however, that the genetic transmission of bipolar disorder is a result of polygenic or oligogenic influences, similar to the proposed mechanism in schizophrenia. Polygenic models assume that it is the interaction of several genes on a large number of loci that is responsible for the transmission of the inheritable liability to the disorder,

whereas oligogenic models propose that the inherited attributes are caused by a few (two or more) major loci or genes. Some researchers have proposed that genetic transmission occurring at the autosomal chromosomes involve multiplicative loci (Craddock, Khodel, Van Eerdewegh, & Reich, 1995), while others (Philibert, Egeland, Paul, & Ginns, 1997) have found evidence for more additive or subtractive effects on the chromosomal sites. Specific chromosome sites that have been postulated in recent linkage studies involve chromosome regions 12q24, 16p13.3, 4p16, 10q, 21q, and Xq (Ewald, 2000; Nurnberger & Foroud, 2000) as well as chromosome 11 (Egeland, Gerhard, & Pauls, 1987; Joffe, Horvath, & Tarvydas, 1986), and chromosome 18p and 18q (Berrettini, Ferraro, & Goldin, 1994; Nurnberger & Foroud, 2000), suggesting that the mode of transmission may involve several genes simultaneously (Ewald, 2000). A recent review outlining the genetic linkage in bipolar disorder suggested that the strongest evidence to date for genetic susceptibility in bipolar disorder has shown involvement of genomic regions or loci on chromosomes 18, 4, and 21 and to a lesser extent on chromosomes 5 and 8 (Mathews & Reus, 2003). It is probable that each specific gene location or chromosomal loci may contribute a relative risk of 2-3% for developing the disorder (Ewald, 2000).

Early studies, prior to the advent of DNA markers, suggested that the transmission of bipolar affective disorder was related to the X, or sex chromosome, as seen by equivocal evidence implicating X-linkage transmission close to the loci for color blindness. Other studies examining linkage to glucose-6-phosphate-dehydrogenase (G6PD) and blood clotting factor IX have provided some additional support for the involvement of chromosome X in the development of bipolar disorder (Tsuang & Faroane, p. 235, 2000).

More recently, the concept of protective genes has been explored with the possibility that such genes may be located on chromosome 4 (Ginns, 1998).

Although the specific mechanism of inheritance in bipolar disorder remains unknown, there has been unequivocal support for a strong genetic contribution from family, twin, and adoption studies. Family and twin studies provide the best expression of the genetic underpinnings of bipolar affective disorder (Ewald, 2000). Family studies have consistently demonstrated a significantly greater proportion in the number of relatives who demonstrate bipolar disorder as well as unipolar depression as compared to normal controls or individuals not exhibiting a family history, with approximately 15-20% of first-degree relatives of bipolar probands exhibiting bipolar or unipolar depression (Ewald, 2000). Some support has also been found for familial aggregation of psychotic symptoms in relatives of bipolar probands, suggesting a possible genetic subtype (Potash & Wilour, 2001).

Because the prevalence of bipolar disorder in relatives of bipolar probands can be attributed to both environmental and genetic factors, it is useful to examine twin and adoption studies in order to more closely identify the relative contribution of genetic factors. Ewald (2000), summarizing the findings of twelve recent twin studies on bipolar disorder, reported an average concordance rate for monozygotic twins of approximately 50%, with some studies demonstrating up to an 80% proband-wise concordance rate for bipolar disorder in identical twins (Bertelsen, Harvald, & Hauge, 1977). The concordance rates for dizygotic twins are, of course, more variable and depend on the number and penetrance of the putative genes, generally demonstrating concordance rates of only 25 to 35%. Adoption studies lend further support to the role of genetics in bipolar

affective disorder; however, there have been fewer adoption studies, with only two studies examining bipolar disorder specifically (Ewald, 2000). Both of these studies demonstrated a trend for the risk of bipolar disorder to be greater in the biologic relatives of bipolar patients. Therefore, studies utilizing relatives of bipolar disorder would further contribute to the understanding of the genetic pathways of bipolar disorder.

Early Studies of Neuropsychological Function in Bipolar Disorder

The initial studies assessing cognitive functioning in bipolar affective disorder were stimulated in large part by hypotheses and research findings of Flor-Henry (Flor-Henry, 1976; Flor-Henry & Yeudal, 1979), which proposed that bipolar affective disorder, along with schizophrenia, was associated with lateralized disorganization of hemispheric function (right dysfunction with manic-depressives and left dysfunction in schizophrenia). Early studies examining intellectual functioning in bipolar patients (Dalby & Williams, 1986; Decina et al., 1983; Gilliland, 1943, Robertson & Taylor, 1985; Waldfogel & Guy, 1951) all suggested right hemisphere impairment, with evidence of visuospatial dysfunction and discrepancies in Performance IQ relative to Verbal IQ.

These findings prompted some researchers to conclude that affective disorders, including bipolar disorder, were characterized by right hemisphere dysfunction; findings to support these conclusions involved patients who exhibited deficits on tasks requiring spatial processing, including visual perception and integration, visuospatial construction, and gestalt perceptual abilities (Goodwin & Jamison, 1990). Another consistent finding, prior to the advent of lithium treatment, was a general, non-progressive impairment in

intellectual functioning that appeared to be reversible upon remission of acute symptoms (Martínez-Arán et al., 2000).

Other support for Flor-Henry's lateralization hypothesis has been derived from studies of lateralization of function including dichotic listening tasks, handedness and grip strength, as well as studies examining secondary mania caused by right hemisphere lesions resulting from cerebrovascular accidents and other neurological diseases (Bearden, Hoffman, & Cannon, 2001). Gruzelier and colleagues (1988) demonstrated right hemisphere impairment utilizing spatial learning tests in a mixed group of manic and depressive bipolar patients, with findings of greater visuospatial impairment compared to both controls and patients with schizophrenia. Lohr and Caliquiri (1997) demonstrated lateralization differences in bipolar affective patients and patients with schizophrenia on tasks measuring hand force instability, with bipolar subjects in manic states demonstrating right hemisphere dysfunction (left hand deficits) and schizophrenic patients showing more impaired right hand function or left hemisphere dysfunction. A more recent neuroimaging study by Caliquiri and colleagues (2003) examined cortical functioning during motor tasks and found more cortical activity in the left primary motor area in both manic and depressed participants as well as a failure to suppress ipsilateral activity in both hemispheres during a motor hand task, suggesting dysfunction in the right hemisphere and cortical aymmetry (Caliquiri et al., 2003). Another study supporting right hemisphere dysfunction in bipolar disorder was performed by Post and colleagues (1989, in cit. Goodwin and Jamison, 1990), in which patients with affective illness were administered questionnaires designed to assess proficiency or ease with various lateralized tasks such as musical abilities, emotional processing, language abilities, and

spatial-perceptual relations. Differences between patients with bipolar illness and controls were found exclusively in those tasks associated with spatial orientation, with a significant gender effect being found primarily in female bipolar patients.

Some individual studies of children at risk or diagnosed with bipolar illness have demonstrated significantly higher verbal IQ (VIQ) than performance IQ (PIQ) (Kestenbaum, 1979; Kron, Decina, & Kestenbaum et al., 1982; McDonough-Ryan, Shear, Ris, Delbello, Graman, & Rosenberg, 2000), although other investigations have been unable to document significant VIQ/PIQ discrepancies (Jak, Shear, Rosenberg, DelBello, & Strawkowski, 2002; Worland & Hesselbrock, 1980). A recent unpublished study, (Jak et al., 2002) examining the intellectual functioning in children diagnosed with bipolar disorder (ages 12-17), revealed no significant (> 12 point) discrepancies between VIQ and PIQ performance in comparison to a psychiatrically healthy, age-matched group of children. However, these researchers did find statistically significant differences in the overall Verbal IQ, Performance IQ, and Full Scale IQ's between the children with bipolar disorder and the normal-control children.

Other studies have failed to find support for lateralized dysfunction in bipolar disorder. Calev and colleagues (1986), using a matched-task methodology, reported no differential deficit in verbal versus non-verbal learning in a group of depressed and euthymic patients with major affective disorder. In a review of ten studies comparing Wechsler IQ scores between bipolar patients and normal controls, Bearden and colleagues (2001) reported an average difference of 6 points between the VIQ scores (mean =102.8) and PIQ scores (mean = 96.7), a relatively small and non-statistically significant difference. Overall, they concluded that evidence for laterality or right

hemisphere dysfunction has not been supported by the literature in terms of cognitive studies or neuroanatomic studies.

Similarly, Kluger and Goldberg (1990) reported the findings of a meta-analysis on Wechsler-Bellevue IQ studies comparing brain-injured (diffuse damage), right-hemisphere lesioned patients, left-hemisphere lesioned patients, and affective-disordered patients, in which the affective disorder group consistently demonstrated absolute lower values of performance IQ scores; once again, the verbal/performance discrepancy in the bipolar group was small, with a mean PIQ of 99.21 and mean VIQ of 103.65. The affective disorder group more closely resembled the brain injury group, suggesting more global, bilateral cerebral impairment rather than right or left hemisphere impairment. Although the reported VIQ/PIQ discrepancies do not always achieve statistical significance and lend doubt to hypotheses of lateralized differences, the observed differences in verbal and performance IQ's remain one of the most consistent patterns in the neurocognitive literature with bipolar populations. As such, there is ongoing discourse that psychoses and affective disorders are related to asymmetric lateralization of the hemispheres (Crow, 2000).

A limitation of many of these early cognitive studies in bipolar patients was the relative lack of neuropsychological measures used. The aforementioned studies all involved primarily measures of intellectual functioning or IQ measures. Although IQ scores provide some indication of the integrity of right and left hemispheric function, they are not nearly as sensitive to brain damage or cerebral dysfunction as are neuropsychological tests (Reitan, 1959; Reitan & Wolfson, 1985). Furthermore, many of these earlier studies failed to differentiate patients with unipolar or major depressive

disorders from bipolar patients with depressive episodes, thereby making it difficult to ascribe specific neurocognitive deficits to bipolar disorder. Investigations since the 1990's have begun to control for demographic variables, stage of illness, medication status, and substance abuse. Furthermore, more recent studies are utilizing multiple neurocognitive measures, and in many instances, relatively extensive neuropsychological test batteries in order to identify a specific neuropsychological profile or cognitive deficits that may typify bipolar affective disorder.

For the sake of clarity, the remaining sections of the literature review will discuss studies of neuropsychological functioning in terms of illness stage (euthymic, manic, depressive, or mixed/undefined) including relevant studies involving psychiatric or neurological comparison groups, most notably patients with schizophrenia. Because bipolar patients cycle through episodes of mania, depression, euthymia, and mixed states, it appears relevant to examine the relationship between mood state and cognition. Literature pertaining to recent neuroimaging and neuroanatomic studies will also be summarized briefly. Lastly, high-risk studies involving relatives of bipolar probands will be critically reviewed.

Neuropsychological Function in Manic Bipolar Patients

Cognitive assessment of manic patients is difficult to perform for many reasons, most notably because acute symptomology interferes with cooperativeness, which impacts the reliability and validity of assessment procedures. Nonetheless, mania associated with bipolar disorder has been shown to significantly affect patterns of learning, verbal association, and long-term memory, with milder deficits noted in the areas of executive

functioning and short-term memory (Clark, Iverson, and Goodwin, 2001). In general, intellectual functioning may be impaired in the acute or symptomatic stages with most of the impairment noted in WAIS performance subtests (Hoff et al., 1990; Dalby & Williams, 1986; Morice, 1990). It should be noted that earlier studies used the distinction of unipolar versus bipolar depression, which has now been revised in the DSM-IV-TR (American Psychiatric Association, 1994) to major depressive disorder and bipolar disorder, respectively.

Several studies have been conducted comparing bipolar patients with mania to patients with schizophrenia (Hoff et al., 1990; Morice, 1990; Silverstein, Harrow, & Bryson, 1992; Goldberg, Gold, & Greenberg, 1993; Silverstein, Harrow, & Bryson, 1994; Strauss, 1984; Thomas, Kearney, Napier, Ellis, Leudar, & Johnston, 1996). Some of these studies did not find neurocognitive differences between bipolar manic and schizophrenic patients, with both groups demonstrating deficits in executive functioning on the Wisconsin Card Sorting relative to normal controls (Morice, 1990) and on measures of visual organization, visuospatial functioning, attention, memory, verbal learning, and fine motor coordination (Hoff et al., 1990). The latter study did not utilize a normal control group. On the other hand, other investigators have demonstrated similar patterns of cognitive impairment between patients in the acute stages of mania and schizophrenia but differential patterns of cognitive recovery during subacute stages (McGrath, Scheldt, Welhelm, & Clair, 1997). In the acute stages, both bipolar patients and schizophrenia patients were impaired in executive abilities as measured by a composite score on the Stroop test, the Wisconsin Card Sorting Test, Trails A and B, and verbal fluency. In the subacute stages, the manic patients had improved on the Wisconsin

Card Sorting Test (categories achieved) whereas the schizophrenia patients showed improvement on the Stroop Test and the difference score on Trailmaking Test A and B. These findings suggest potentially different trait markers for bipolar and schizophrenic groups, but perhaps similar state-dependent cognitive deficits inasmuch as both groups demonstrated impaired attention and concentration abilities in the acute phases of illness.

Thomas and colleagues (1996) examined language and speech fluency in a group of acutely admitted patients with schizophrenia or mania and compared them to a non-psychiatric control group. They reported that patients with mania demonstrated errors of commission with regards to their speech as well as errors of omission in a paper-and-pencil attentional task (Shape Cancellation Test). Other investigators have found deficits in selective attention (Oltmanns, 1978) and perceptual span (Strauss, Bohannon, Stephens, & Pauker, 1984) in patients with mania equivalent to those found in patients with schizophrenia.

Studies investigating patients in manic states relative to normal controls have identified diffuse cognitive impairment (Coffman, Bornstein, & Olsen, 1990; Murphy, Sahakian, Rubinsztein, Rogers, Robbins, & Paykel, 1999) as well as specific deficits in vigilance and sustained attention (Clark, Iverson, & Goodwin, 2001; Sax et al., 1999), verbal fluency (Lebowitz, Shear, & Steed, & Strakowski, 2001), executive functioning and planning (McGrath et al., 1997; Morice, 1990), dichotic listening (Bruder, Schnur, Fergeson, Mukhergee, Leite, & Sackheim, 1994), memory and planning (Murphy et al., 1999), and memory for patterns and spatial recognition (Murphy et al., 1999). In general, bipolar patients in manic states demonstrate a profile of global, rather than specific, cognitive deficits, similar to patients with major depressive disorders.

Investigating the emotional bias in cognitive processing in patients in manic versus depressive bipolar states, Murphy and colleagues (1999) found that manic patients had difficulty in focused attention and the ability to inhibit inappropriate or incorrect responses, whereas depressed patients demonstrated more difficulty in shifting their focus of attention. Further, affective biases were found in the processing of information such that bipolar patients exhibited a response or attentional bias for "happy" responses and depressed patients for "sad" responses. In a sample of clinically referred children with manic symptomology, Wozniak et al. (1995) identified deficits in various WISC-R subtests, including Vocabulary, Block Design, Arithmetic, and Digit Span, compared to control subjects, as well as significant differences in Performance IQ and Full-Scale IQ relative to normal controls. They also found significant differences in arithmetic achievement scores (WRAT-arithmetic) and on Global Assessment of Functioning scores.

In summary, cognitive deficits in manic states appeared to reflect diffuse cognitive impairment, along with impairment in specific domains of functioning, including language/fluency, memory, attention, abstraction and planning (executive function), and visuospatial perception. Executive functioning appeared to be most consistently impaired particularly with respect to abstract conceptual formation/planning and set-shifting (Albus et al., 1996; Morice, 1990; Murphy et al., 1999), whereas verbal fluency was relatively spared (Calev et al., 1989; Gruzelier et al., 1988). The presence of psychotic symptoms has been shown to further contribute to cognitive impairment in the manic stages (Albus et al., 1996).

Neuropsychological Function in Depressed Bipolar Patients or Mixed States

The few investigations examining neurocognitive function in bipolar depression have compared patients with unipolar or major depressive disorder and bipolar depressed patients and have demonstrated that neuropsychological tasks are generally more impaired in bipolar depression. Greater deficits have been found in bipolar depression patients relative to unipolar depression patients in the domains of executive functioning (Borkowska & Rybakowski, 2001; Savard, Rey, & Post, 1980), verbal learning and fluency (Borkowska & Rybakowski, 2001; Wolfe et al., 1987), and psychomotor speed (Blackburn, 1975). Burt and colleagues (2000) utilized a battery of tests, primarily verbal and visual learning tasks, to examine the effects of aging and diagnoses on neuropsychological function in a group of young and elderly unipolar and bipolar depressed patients. Their findings revealed that unipolar and bipolar patients did not differ in measures of global intelligence, but that elderly bipolar patients performed more poorly than all three other groups (young bipolar and young and elderly unipolar patients) on most measures of memory, irrespective of the number of affective episodes. In particular, delayed memory retrieval for declarative memory tasks was the most impaired in the elderly patients with bipolar disorder. Verbal learning deficits were not as pronounced in the elderly patients with bipolar disorder. The researchers concluded that these findings suggested a greater deterioration of memory functioning in patients with bipolar disorder compared to patients with unipolar disorder.

Other studies have demonstrated mixed results when performing head-to-head comparisons between patients in unipolar versus bipolar depressive states. Abrams and Taylor (1980) were unable to document differences in cognitive functioning between

patients with bipolar versus unipolar depression. Sweeny and colleagues (2000) found equal impairment in patients with bipolar and unipolar depression on tasks of episodic memory as compared to normal controls, whereas other researchers have documented greater impairment in unipolar vs. bipolar depressed patients and normal controls on tasks of visual-motor sequencing, executive function, and immediate memory and attention (Paradiso, Lamberty, Garvey, & Robinson, 1998). In this latter study, however, the two patient groups were tested in a non-symptomatic, remitted state of depression.

A few studies have compared cognition in states of mania and depression with the general conclusion that similar neurocognitive profiles exist in these two states of bipolar disorder. Bulbena and Berrios (1993) followed patients prospectively on tests of attention, memory, visuospatial function, and choice reaction time in acute symptomatic states and upon remission. They demonstrated that both patient groups, those in manic and depressive states, were equally impaired on immediate and delayed memory recall tasks and on a visuospatial task relative to controls in the acute stage. On follow-up examination, both patient groups had improved except for their scores on Benton's Judgment of Line Orientation, a measure of visuospatial ability. Goldberg et al. (1993) likewise found equal impairment on tests of executive function, reading, and facial recognition in patients with acute mania and depression. Furthermore, the bipolar group was equally impaired on Trail Making B and a facial recognition task compared to a group of acutely hospitalized schizophrenic patients. Murphy and colleagues (2001) reported equal impairment between patients with mania and clinical depression on a computerized task of decision-making, demonstrating slower deliberation times as well as lower overall scores in correct responses as compared to a normal control group.

Furthermore, the patients with mania demonstrated impairment in the quality of decision-making, with a tendency to choose the less likely of two possible outcomes more frequently than their depressed counterparts. In contrast, Sweeney and colleagues (2000) found significantly more impairment in bipolar patients in mixed or manic states relative to bipolar depressed patients. The former group demonstrated deficits in episodic and working memory, spatial attention, and problems solving; the bipolar depressed patients had deficits related to episodic memory only.

Other investigations of neurocognitive function in bipolar disorder have been reported in which the specific mood state was mixed or not specifically delineated. Examining patients with schizophrenia, bipolar disorder, major depression, and other mixed psychotic disorders in their index episode, Verdoux and colleagues (2000) found no significant differences between the four groups in tasks of executive functioning as measured by the Wisconsin Card Sorting Test and Stroop test. Only memory tasks differentiated the four diagnostic groups, with patients with schizophrenia demonstrating poorer performance. Once again, a normal control group was not utilized for comparison making it difficult to assess the degree of impairment.

Lui and colleagues (2002) examined four groups of inpatients (patients with schizophrenia, patients with major depression without psychotic features, and patients with bipolar disorder, with and without psychotic features) at admission and discharge using the Continuous Performance Test (CPT). In comparison to community sample normative data, all patient groups, except the nonpsychotic major depression group, exhibited significant impairment on the CPT, a test that measures sustained attention task. On administration, patients with schizophrenia performed the worst, followed by the

bipolar patients with psychotic features, and then the bipolar patients without psychotic features. In contrast to the patients with schizophrenia, the bipolar group demonstrated some improvement in CPT performance at discharge. Similarly, Rund and colleagues (1992) examined vigilance using the CPT test and the Span of Apprehension Test (SAT) in a group of patients with schizophrenia and affective disorders, including mixed bipolar patients, and found that there were no differences between the two patient groups in terms of the number of correct hits on the CPT nor on the SAT; both patient groups were found to be equally impaired with respect to sustained attentional abilities compared to normal controls.

Atre-Vaidya and colleagues (1998) investigated several neuropsychological domains in a mixed group of acute and asymptomatic patients with bipolar disorder and found deficits in verbal memory and learning, verbal fluency, visual organization and reasoning, and spatial orientation compared to age-equivalent normative data. Other investigations comparing patients with schizophrenia and bipolar disorder to normal controls revealed that the cognitive profile was similar between the former two groups (Hawkins, Hoffman, Quinlan, Rakfeldt, Docherty, & Sledge, 1997; Zihl, Gron, & Brunnaeur, 1998). Hawkins and colleagues (1997) found relative weaknesses in both psychiatric groups in Digit Symbol, Trail Making A, and Trail Making B, although only the schizophrenia group performed significantly worse than the normal control group. Zihl et al. (1998) noted that patients with affective disorders and schizophrenia were equally impaired on tasks of attention, problem solving, and memory relative to a normal control group, with the exception of poorer performance on the Wisconsin Cart Sorting Test by the patients with schizophrenia. Another study comparing chronically hospitalized geriatric patients with

affective disorders (DSM-III-R diagnosis of major depression or bipolar depression) to geriatric chronically-ill patients with schizophrenia failed to find differences in cognitive function on measures of verbal learning and recall, the Boston Naming Test, and praxic drawing tests (Harvey, Powchik, Parrella, White, & Davidson, 1997).

Sweeney and colleagues (2000) compared the neuropsychological performance of bipolar patients in a mixed or manic state to those in a depressed state on the Cambridge Automated Neuropsychological Test Battery (CANTAB) and found differential deficits in these two subgroups of bipolar patients. Specifically, they found that the mixed/manic bipolar patients demonstrated significant deficits in various cognitive domains including episodic and working memory, spatial attention, and problem solving, whereas the depressed group revealed specific deficits in episodic memory only. These researchers concluded that there are distinct cognitive profiles in mixed/manic states of illness relative to the depressed state of illness.

Other researchers have not found such distinct differences in cognitive profiles between manic, mixed, and depressed states. In the only apparent study to date examining neuropsychological performance among bipolar patients with depressed, manic, and mixed states as well as normal controls, Basso and colleagues (2002) retrospectively evaluated 86 inpatients with a diagnoses of bipolar I disorder based on a routine diagnostic evaluation completed during hospital admission. Overall, the three groups of patients with bipolar disorder performed worse than the controls on measures of executive function, speed of information processing, dexterity, and verbal memory. Furthermore, the three patient groups (depressed, manic, or mixed) demonstrated no statistically significant differences in test battery performance. Although several of the

patients demonstrated psychotic features, neither the main effect of psychoses nor the interaction term was significant for differences among the three patient groups These preliminary finding require replication but suggest that neuropsychological deficits are not well differentiated by mood state.

Collectively, these studies revealed that bipolar patients in states of depression or mixed states demonstrated deficits in the areas of attention, verbal memory, visuospatial function, and executive function, with chronic or elderly bipolar patients performing similarly to chronically ill patients with schizophrenia. There is also some evidence to suggest that patients in mixed and manic states have more global deficits relative to those individuals in depressed states. The following section will review cognitive function in bipolar patients in asymptomatic or euthymic states.

Neuropsychological Function in Euthymic Bipolar Patients

In contrast to an early investigation reporting minimal cognitive impairment in verbal learning and verbal and visual memory in chronically ill manic-depressives (Kerry, McDermott, & Orme, 1983), more recent research provides evidence for definitive areas of cognitive impairment in remitted, euthymic bipolar patients. The most consistent impairments have been found in the domains of executive function (Ferrier et al., 1999; Gilvarry, Barber, van Os, & Murray, 2001; Guiliano, A., Garroway, Stein, DeJong, Biederman, & Frazier, 2002; Krabbendam et al., 2000; Martínez-Arán et al., 2002; McKay, Tarbuck, Shapleske, & McKenna, 1995; Rossi, Arduini, Daneluzzo, Bustini, Properini, & Stratta, 2000), verbal memory (Denicoff et al., 1999; Krabbendam et al., 2000; Seidman et al., 2002; Tham, et al., 1997; van Gorp et al.,1998; Zubieta, Huguelet,

O'Neil, & Giordano, 2001), visuospatial processing (Albus, Hubmann, Wahlheim, Sobizack, Franz, & Mohr, 1996; El Badri et al., 2001; Krabbendam et al., 2000; MacQueen, Young, Galway, & Joffe, 2001; Tham et al., 1997; Zubieta et al., 2001), and attention/vigilance (Albus et al., 1995; Clark et al., 1999; Denicoff et al., 1999; Jones, Duncan, Mirsky, Post, & Theodore,, 1994; MacQueen et al, 2001; Seidman et al., 2002; Wilder-Willis, Sax, Rosenberg, Fleck, Shear, & Strakowski, 2001). Less consistently, deficits have been reported in visuospatial memory (Rubinsztein, Paykel, & Sahakian, 2000), verbal fluency, (Ferrier et al., 1999), facial affect discrimination (Yurgelun-Todd, Gruber, Kanayama, Kilgore, Baird, & Young, 2000) and psychomotor speed (Seidman et al., 2002; Tham et al., 1997; Zubieta et al., 2001).

Although cognitive deficits in patients with bipolar disorder appear to be associated with recurrent episodes (Denicoff et al., 1999: Kessing 1998) and chronicity of illness (Gilvarry et al., 2001), deficits in visual motor processing and attention have been documented in a sample of first episode affective disorder patients consisting of unipolar and bipolar patients (Albus et al., 1996). These researchers further noted that the first-episode bipolar patients with psychotic features performed most comparably to patients in their first episode of schizophrenia. El Badri et al. (2001) also found visuospatial impairment in a sample of young, euthymic bipolar patients as well as underlying EEG abnormalities in the right temporoparietal and left occipital regions known to be involved in visuospatial processing. These studies suggest that certain deficits occur early on in the disease process, may be premorbid in nature, and persist in the euthymic state (Albus et al., 1996; Ed Badri et al., 2001).

Visual processing deficits have also been found in chronic remitted patients with bipolar disorder. Bulbena and Berrios (1993) demonstrated that visuospatial function, measured by Benton's Judgment of Line Orientation Test, remained impaired even after recovery from major depressive or manic episodes. Deficits in facial affect discrimination and memory for designs have also been reported in a group of remitted or stable bipolar patients (Addington & Addington, 1998; Yurgelun-Todd et al., 2000). Furthermore, Rubinsztein and colleagues (2000) have documented impairment on tests of visuospatial memory in a group of bipolar patients in remission, prompting these researchers to conclude that the underlying dysfunction is probably in posterior temporal cortical regions. Van Gorp et al. (1999) documented a double dissociation in a sample of euthymic patients such that deficits were found on tasks of declarative memory (verbal list learning) but not on procedural memory (rote motor learning) in patients with bipolar disorder. Collectively, these deficits in visuospatial memory and processing, and verbal memory in remitted bipolar patients lend support to the hypothesis of trait abnormalities or dysfunction in medial temporal lobe structures, as well as the parieto-occipital association cortex (or hetero-modal cortex).

In contrast to the relative consistency of findings regarding visuospatial functioning, certain executive functions have been found to fluctuate with respect to clinical state, with some studies demonstrating persistent impairment in euthymic states and others reporting recovery of impairment in the euthymic states. Rubinsztein and colleagues (2000) reported that impairment in executive functioning, as measured by tasks of attentional set shifting and decision making, remitted in the euthymic state. In general, performance on the Wisconsin Card Sorting Task, a task of executive function, has been

found to be impaired more consistently in patients with a chronic history of illness (Albus et al., 1996; Denicoff et al., 1999; McKay et al., 1995) or in manic states (McGrath et al., 1997; Morice, 1990). Other studies, however, have reported neurocognitive deficits on the Wisconsin Card Sorting Test even after resolution of an affective episode (Coffman et al., 1990; Rossi, Arduini, Daneluzzo, Bustini, Prosperini, Stratta, 2000; Martínez-Arán et al., 2002).

Denicoff and colleagues (1999) demonstrated that a more severe course of prior illness, and greater duration and number of affective episodes, were associated with poorer performance on tasks of abstraction, attention, and memory. MacQueen and colleagues (2001) likewise demonstrated that performance on a backward masking task was associated with number of illness episodes, particularly depressive episodes. Other studies involving euthymic bipolar patients (Kessing, 1998; Rubinsztein et al., 2000; van Gorp et al., 1998) have found an association between both illness duration and number of manic/depressive episodes. As such, it is important to examine cognitive functioning in family probands or high-risk individuals to discern whether some of these cognitive deficits are present premorbidly or accrue over time.

In addition to deficits in visuospatial processing and executive functioning, deficits in verbal learning and memory have been reported consistently in euthymic bipolar patients (Coffman et al., 1990; Krabbendam et al., 2000; Seidman et al., 2002; van Gorp et al., 1999; Zubieta, et al., 2001). Specifically, tasks of declarative memory, such as recalling a list of words over multiple trials, and associative verbal learning have been shown to be impaired in bipolar patients in the euthymic state. Deficits in verbal learning have also

been demonstrated in pediatric bipolar populations, specifically with the Children's version of the California Verbal Learning Test (Giuloiano et al., 2002).

The research on cognitive deficits in euthymic patients suggests that there are relative deficits in the areas of verbal learning, visuospatial organization and perception, and some tasks of executive functioning that persist in the euthymic stage of bipolar illness. Impairment in verbal memory seems to be one of the most consistently documented impairments (Atre-Vaidya et al., 1998; Ferrier et al., 1999; Krabbendam et al., 2000; Van Gorp et al., 1998). Verbal memory deficits may therefore represent trait-like characteristics, and as such, potential indices of cognitive trait markers or phenotypes of bipolar affective disorder, since they occur independently of mood states and, in some instances, are observable upon index episodes.

Neuroanatomical and Neuroimaging Findings in Bipolar Disorder

Neuroanatomical and neuroimaging studies have recently burgeoned in the area of bipolar research with preliminary evidence demonstrating structural brain abnormalities in the caudate nuclei (Noga, Vladar, & Torrey, 2001) and in temporolimbic structures, (Altshuler, Curran, & Hauser, 1995; Beardon et al., 2001; Elkis, Friedman, & Wise, 1995; Strakowski, Delbello, & Sax, 1999; Videbech, 1997; van Gorp, Altshuler, Theberge, & Mintz, 1999). Volumetric studies utilizing CT and MRI scans have also revealed abnormalities in the third ventricle, frontal lobes, cerebellum, and temporal lobe (Beyer & Krishnan, 2002). A recent review of structural imaging and post mortem findings suggests that basal ganglia structures may be the putative anatomical structures in mood disorders (Baumann & Bogerts, 1999). These neuroanatomic findings suggest

that there may be multiple, stable biological indices underlying bipolar disorder. A most recent review on the functional neuroanatomy of bipolar disorder proposed that abnormalities in the prefrontal cortex, striatum, and amygdala may be present early in the course of illness, whereas abnormalities in the lateral ventricles and other prefrontal regions (e.g., left inferior) develop with illness progression (Strakowski, Delbello, & Adler, 2005).

The most consistent magnetic resonance imaging abnormality has been the identification of white matter hyperintensities in the periventricular white matter, subcortical gray matter, and deep white matter brain regions (Beardon et al., 2001). The significance of white matter lesions remains unknown but is believed to be related to cerebrovascular changes across psychiatric and non-psychiatric groups. Approximately 8-25% of bipolar patients demonstrate cortical or cerebellar atrophy on CAT scan measurements (Beardon et al., 2001), with the latter finding being the only brain abnormality that is more prevalent in a bipolar population relative to a schizophrenic population. Ventricular enlargement is also a common structural finding in bipolar disorder, as it is in schizophrenia, causing some researchers to speculate that it is a non-specific finding and indicative of psychosis (Bearden et al., 2001).

Although there is a high degree of overlap in structural abnormalities between bipolar illness and schizophrenia, bipolar affective disorder demonstrates more structural abnormalities in the basal ganglia, particularly in the nucleus accumbens and in the hypothalamic regions (Baumann & Bogerts, 1999). Fewer claims have been made regarding the neurodevelopmental origin of bipolar disorder. Nonetheless, it seems possible that abnormalities in brain structure and function found in both schizophrenia

and bipolar disorder share commonalities in gene expression, resulting in various anomalies in brain growth and development in both of these disorders (Bearden et al., 2001).

The association between cognitive function and neuroanatomical or neurophysiological findings has not been studied substantially. Coffman and associates (1990) found significant relationships between MRI-derived size of cerebral regions and performance on various subtests of the Halstead-Reitan Neuropsychological Battery, whereas Dewan et al., (1988) found no significant relationship between computed tomography ventricular brain ratios and performance on the WAIS and the Halstead Reitan Neuropsychological Battery. Other researchers have identified a significant correlation between MRI volumetric measurements of the hippocampus and prefrontal cortex with performance on the Continuous Performance Test in a group of bipolar patients with mania, with larger hippocampal volumes associated with better performance (Sax, Strakowski, & Zimmerman, 1999). In contrast, Ali and colleagues (2000) examined the neuropsychological function in twenty-six bipolar patients and reported a significant but negative correlation between right hippocampal volume and neuropsychological functioning. More specifically they found deficits in verbal working memory, verbal fluency, and sustained attention that were associated with enlargement of the right hippocampus. This study did not utilize a normal control group, making the results of this finding more difficult to interpret. Yurgelen-Todd and colleagues (2002) examined affective discrimination using fMRI and found a reduction in dorsolateral prefrontal cortex activation and heightened amygdalar activation in bipolar affective patients when viewing fearful stimuli.

A few studies have examined the association between white matter hyperintensities and cognitive function. Dupont and colleagues (1995) found that white matter intensities as visualized on MRI were correlated with poorer performance on nine out of twelve cognitive tests, specifically on tasks of verbal fluency, psychomotor speed, psychomotor sequencing, and verbal recall, relative to a normal control and unipolar depressed group. Deficits of psychomotor speed were also found by Hickie et al. (1995) such that psychomotor speed decreased as white matter hyperintensities increased in a group of bipolar and unipolar patients. Other investigators, however, have failed to find correlations between white matter hyperintensities and performance on measures of memory, speed, and cognitive flexibility. Krabbendam and colleagues (2000) reported no significant relationship between cognitive impairment and white matter lesions in bipolar patients in remission, suggesting that other types of brain abnormalities may be associated with cognitive dysfunction. Given the variable findings of the relationship between neuroanatomical structures and cognitive function, it seems that further research is warranted to identify the neuroanatomical substrates of bipolar disorder.

Neuropsychological Function in High-Risk Populations

Similar to the general literature on cognitive findings in bipolar disorder, the earliest studies of high-risk populations involved the measurement of intellectual functioning. Cognitive functioning, measured in part by intelligence testing and academic performance, has been described as being an indirect measure of impaired brain functioning (Waters, Marchenko, & Smiley, 1983). Therefore, studies which examined measures of intelligence, rather than more specific measures of neurocognitive function

in at-risk offspring, may have underestimated the severity of impairment owing to lack of sensitivity of the measures. Two of these early studies (Decina et al., 1983; Kestenbaum, 1979) suggested that high-risk children of bipolar parents performed significantly worse on the Performance IQ relative to the Verbal IQ on the Wechsler Intelligence Scale for Children (WISC). In a case study, Kestenbaum (1979) reported WISC results on thirteen children with a family history of bipolar disorder, with six of the thirteen demonstrating a specific pattern of verbal IQ greater than performance IQ and considerable subtest scatter. Absolute VIQ/PIQ discrepancies are not given except in two of three case vignettes in which the relative differences were found to be 27 points and 21 points, respectively. These six children also demonstrated clinical symptomology of depressed mood, learning difficulties, and/or hyperactivity.

Other researchers (Decina et al., 1983; Kron et al., 1982) documented a significant VIQ/PIQ difference (greater than 15 points) on the WISC-R in 39% or 12 out of 31 children at risk for bipolar disorder, with a statistical trend of the mean verbal/performance IQ discrepancy being most evident in offspring of bipolar I parents (mean =10.9) compared to the offspring of bipolar II (mean= 4.4) patients. Comparatively, a VIQ/PIQ discrepancy of greater than 15 points was found in only 11% of the control group. Of interest is the fact that the reverse pattern has been found in children of schizophrenic parents and other psychiatric disorders such that the performance IQ is significantly greater than the verbal IQ (Gruzelier, Mednick, & Schulsinger, 1979; Kestenbaum, 1982). It was also noted that those children who demonstrated hypomanic or expansive mood symptoms were more likely to demonstrate cognitive impairment. Interestingly, these researchers also found an overrepresentation

of left-handedness in their at-risk bipolar sample with 9 out of 31 children endorsing left-hand dominance compared to only 1 out of 14 children from the control group, which they interpreted as possible evidence of dysfunctional lateralized brain function, in support of Flor-Henry's lateralization hypothesis.

A more recent study by McDonough-Ryan and colleagues (2000) demonstrated that children of bipolar adults performed worse on the Performance IQ as well as on WRAT-3 arithmetic measures as compared to normal control children. Furthermore, the high-risk children demonstrated a significantly greater VIQ/PIQ discrepancy compared to the normal control children. Longitudinal studies appear to be warranted to determine if these cognitive deficits can predict the development of psychopathology or bipolar disorder in high-risk offspring. A comprehensive neuropsychological test battery would also help to delineate a more complete cognitive profile that may be indicative of significant risk in children of bipolar probands.

In contrast to the aforementioned studies, Worland and Hesselbrock (1980) did not find significant differences in Full Scale, Verbal, and Performance IQ scores in a sample of 331 male and female children of schizophrenic, bipolar, or chronically ill parents compared to a group of normal control children (without family history of medical or psychiatric disorders). Similar findings have been reported in adult offspring of bipolar patients, some of which had developed affective disorders, in which non-significant IQ differences were found between these offspring and well offspring with respect to Full scale, Performance, and Verbal IQ scores. (Waters et al., 1981). Waters and colleagues (1981) likewise did not obtain differences in Verbal and Performance IQ scores, but data on Verbal and Performance IQ were available on only 12 of 38 subjects in their sample.

In summary, it appears that the literature regarding intellectual functioning in bipolar probands and high-risk populations is equivocal, particularly with respect to VIQ/PIQ differences. When used as sole measures, Verbal vs. Performance IQ differences may not be sensitive in differentiating individuals who may develop bipolar affective disorder. On the other hand, this pattern of performance should not be entirely disregarded as insignificant, as it has been found on a rather consistent basis in both adult and child populations. High-risk paradigms utilizing specific neurocognitive measures, which reflect brain functioning more directly and are more sensitive to cerebral dysfunction than IQ tests, may prove to have greater utility as predictive indicators of genetic vulnerability to bipolar affective disorder. The remaining high-risk studies to be described have utilized either specific neuropsychological measures or complete neuropsychological tests batteries to assess potential cognitive deficits in high-risk individuals.

One recent investigation examined the neuropsychological performance of adult monozygotic twins discordant for bipolar disorder and normal twins in an attempt to differentiate the genetic factors from the environmental factors with respect to cognitive abilities (Gourovitch et al., 1999). These researchers utilized a twin paradigm, using discordant twin pairs and unaffected twin pairs, to identify both disease-specific impairments and high-risk or genetic factors. Various patterns of results implicate different contributions of genetic and environmental factors. For example, if unaffected twins perform significantly better than the affected twins, but equivalent to the normal twins, this would implicate that the abnormalities in the affected twins are likely due to the disease process itself. On the other hand, if the affected twins and unaffected twins perform relatively equivalent and significantly worse than the normal twins, genetic

factors may be more explanatory. A pattern demonstrating intermediate performance by the unaffected twins (between the affected twins and the normal controls) would indicate both genetic factors and factors associated with risk factors for the development of the disease, e.g. environmental and other risk factors.

Using this twin paradigm, Gourovitch et al. (1999) administered an extensive neuropsychological battery consisting of measures of attention, visuospatial skills, language, learning, memory, and abstract problem solving, to a sample of seven monozygotic twin pairs discordant for bipolar disorder and seven and one-half normal control twin pairs (one twin was excluded secondary to noncompliance). The twins with bipolar disorder were all receiving medication and were tested in various states of illness (3 euthymic, 2 depressed, and 2 in manic states). In support of genetic vulnerability, results indicated that the unaffected (discordant) twins performed worse than normal control twins on tasks of short-term memory (Brown-Peterson task), verbal learning (CVLT learning trials), and on the overall Wechsler memory quotient. Memory deficits were found to be less pervasive than those observed in the affected twins and involved deficits primarily in retrieval rather than memory consolidation.

The affected twins were also found to be impaired on measures of attention and verbal memory relative to the unimpaired twins and normal controls, suggesting that these deficits are perhaps more related to disease parameters and less likely indicative of genetic vulnerabilities. Specifically, the affected twins performed worse on the CPT vigilance task, the California Verbal Learning Test (CVLT) short delay cued recall, and the CVLT recognition task in comparison to the unaffected twins and normal controls. Additionally, the affected twins performed more poorly than the unaffected twins on the

Test of Facial Recognition. Unlike previous studies demonstrating multiple domains of visuospatial deficits, the affected twins were found to have deficits circumscribed solely to a face recognition test in comparison to the unaffected twin pairs. An intermediate pattern of performance was also found, with the unaffected twins performing worse than the normal twins but better than the affected twins, on the recall measure of the Brown Peterson task and on the California Verbal Learning Test total recall across five trials. This pattern of results suggests influences from both genetic and other risk factors associated with the development of the disease.

A third pattern of results was obtained such that both the affected and unaffected twins performed worse than the normal controls on the Wechsler Memory Scale mental control and memory quotient, the CVLT long delayed free recall and cued recall, and the CVLT discriminability score relative to normal controls. Therefore, results of this study yielded support for all three patterns of outcomes (environmental, genetic, and mixed) with respect to cognitive deficits, suggesting there is a need for further empirical studies to sort out the various contributions of environment and genetic factors.

The small sample size (N=7 in each twin group) in the aforementioned study precludes drawing definitive conclusions. Nonetheless, a portion of the results suggests that certain neurocognitive deficits, (i.e., specific verbal memory deficits), in unaffected relatives may represent genetic risk factors or vulnerabilities in bipolar affective disorder. Verbal memory deficits have also been identified consistently in euthymic patients. Given that both the affected and unaffected twins had mild impairments in learning and retrieval of information suggests a potential risk factor or possible endophenotype.

Replication of these findings with a larger sample size might lend further support to this hypothesis.

Using the high-risk paradigm to compare female relatives of patients with schizophrenia, female relatives of patients with bipolar disorder, and normal controls, Kremen and colleagues (1998) administered a comprehensive neuropsychological test battery comprised of seven broad cognitive domains (abstraction-executive functioning, verbal memory, visual memory, perceptual motor speed, mental control, auditory sustained attention, and motor function). The majority of the bipolar probands had psychotic features, thereby making them a good comparison group to the schizophrenia group. The first-degree relatives consisted of parents, siblings, and children. After adjusting for estimated intellectual ability based on WRAT-R reading scores, the relatives of patients with schizophrenia demonstrated deficits in verbal and visual memory and auditory attention, compared to the relatives of bipolar patients and normal controls. After statistical correction using current IQ, deficits remained only in verbal and visual memory in the relatives of patients with schizophrenia. No such deficits were found in the relatives of the bipolar patients.

Kremen et al. (1998) concluded that verbal memory, visual memory, and some auditory attention deficits appear to be specific risk indicators for schizophrenia, in support of previous investigations documenting similar deficits in schizophrenic patients. Additionally they concluded that these deficits appear to be differentially significant in contrast to other comparison groups such as the bipolar group and a normal control group. In this study, the relatives of normal controls and bipolar patients performed similarly on all cognitive tasks. This was one of the few studies that did not demonstrate

any deficits in the at-risk bipolar relatives in contrast to a normal control group. In fact, the relatives of bipolar patients had greater mean performances than normal controls in several domains, including Wechsler verbal and visual memory subtests, WAIS-R digit symbol, Stroop Test for colors and interference task, WAIS-R digit symbol, WRAT-R arithmetic, and the dichotic listening task.

The Kremen et al. (1998) findings were consistent with two other studies that found specific cognitive deficits in at-risk relatives of schizophrenic patients but not affective disorder patients (Cornblatt & Erlenmeyer-Kimling, 1985; Harvey, Winters, Weintraub, & Neale, 1981) and one unpublished report (Moldin, 1995). However, these studies examined test performance primarily between relatives of schizophrenia and unipolar patients (Harvey et al., 1981) and other affective disorders such as schizoaffective disorders (Cornblatt & Erlenmeyer-Kimling, 1985) rather than bipolar disorders. Moldin and colleagues (1995) compared adult relatives of probands with schizophrenia and bipolar disorder on the Continuous Performance Test, the California Verbal Learning Test, and the Wechsler Memory Scale-Revised, and found cognitive deficits in sustained attention and verbal memory only in the schizophrenia group.

Although the study by Kremen and colleagues (1998) had several strengths, including the use of an extensive neuropsychological battery and a homogeneous patient population (chronic, psychotic) from which the relatives were drawn, it nonetheless presented with a few limitations. The bipolar sample size was relatively small (N=15), decreasing the statistical power in detecting differences between the groups. Acknowledging this limitation, the researchers made further comparisons between the groups by examining effect sizes. Further analyses, however, demonstrated no significant differences between

the relatives of bipolar patients and normal controls, with most of the effect sizes being .16 or less. The group differences between the bipolar and/or control group relative to the schizophrenia group, however, remained significant only in the domains of visual and verbal memory (d >.8), when effect sizes were considered.

Another potential confound in the Kremen et al. (1998) study was the use of only female participants. Previous investigation by Kremen and colleagues (1997) demonstrated sex differences in relatives of schizophrenic probands with respect to neurocognitive measures (males worse than females), and therefore it may be crucial to include both male and female relatives in analyzing cognitive functions. It is perhaps premature to conclude that these specific neuropsychological deficits represent a latent genetic vulnerability or phenotype only in schizophrenia, as there have been too few high-risk studies examining cognitive functioning in relatives of bipolar patients.

A more recent high-risk study examined relatives of schizophrenic patients, relatives of bipolar patients, and normal control subjects on measures of visual information processing, verbal fluency, memory, and executive functioning (Keri, Kelemen, Benedek, & Janka, 2001). These researchers hypothesized that the relatives of the psychiatric probands would demonstrate similar cognitive deficits based on recent data implicating common genetic background for schizophrenia and bipolar affective disorder (Berrettini, 2000). The sample consisted of 25 unaffected siblings of patients with schizophrenia, 20 unaffected siblings of patients with bipolar disorder, and 20 normal healthy controls without family or self-psychiatric history. The findings of Keri et al. (2001) revealed that the relatives of patients with schizophrenia had significant deficits in visual information processing as evidenced by a visual backward masking task and in working memory for

spatial information, whereas the relatives of both the bipolar and schizophrenia probands demonstrated comparable deficits in long term verbal recall involving word lists. Verbal working memory for immediate recall and recognition, abstraction abilities, and letter fluency were relatively intact in both groups of relatives as compared to the normal control group. The verbal learning deficits found in the bipolar relatives were very specific, i.e., delayed recall of word lists, as compared to the more global verbal deficits that have been documented in patients who manifest bipolar disorder (Wolfe, Granholm, Butters, et al., 1987; Goldberg et al., 1993; Gourovitch et al., 1999; McKay, 1995; Van Gorp, 1998; Wolfe et al., 1987; Zubieta et al., 2001). The authors concluded that the verbal delayed recall deficit, the common impairment in the unaffected siblings of the patient groups, suggested potential dysfunction in the frontal-anterior hippocampal system. Furthermore, the study was significant in demonstrating differential patterns of impairment in the two sibling groups, with visual backward masking and short-term visuospatial memory deficits more apparent in the relatives of patients with schizophrenia, and long-term verbal recall deficits a common impairment in both high-risk groups. Once again, verbal memory deficits were implicated as potential cognitive markers in the relatives of bipolar probands.

The sample of relatives in the Keri et al study (2001) were drawn from a patient population that was relatively high functioning in the community, with fewer hospitalizations and shorter length of illness than those relatives in the Kremen et al. (1998) study. Interestingly, these high-functioning relatives, who demonstrated relatively high IQ's, educational levels, and GAF scores, nonetheless demonstrated deficits in delayed verbal recall. The authors, conceding study limitations of a small sample size

and lack of comprehensive cognitive measures, suggested that future studies include larger samples and more comprehensive test batteries (Keri et al., 2001).

Another study examined executive function specifically as a vulnerability marker by comparing euthymic bipolar and schizophrenic patients to their unaffected relatives and a normal control group (Zalla et al., 2004). The patients with schizophrenia performed poorly on all four measures of executive functioning (Wisconsin Card Sorting Test, Verbal Fluency, Stroop Word Color Test, and Trail Making Test). Additionally, both the schizophrenia and bipolar probands and their first-degree relatives all demonstrated deficits or lower performance on the Stroop Test relative to normal controls. The hypothesis that deficits in executive functioning, suggestive of genetic susceptibility, would be evident in the first-degree relatives compared to the normal controls, was not supported. The authors concluded that the deficit on the Wisconsin Card Sorting Test is not specific to diagnosis but rather to the "spectrum of complex psychiatric diseases of familial vulnerability." The lack of further group differences was attributed to the relatively small sample size and potential bias in selectivity of those who agreed to participate in the study.

In one of the few studies investigating potential biological markers and cognitive functioning, Pierson et al. (2000) investigated event-related potentials (ERP's) using EEG in relatives of bipolar probands (19 first-degree relatives belonging to multiply-affected bipolar families). Event-related potentials have been described as being markers of genetic vulnerability, with the most researched index being the P300 wave. Subjects were exposed to an auditory task in which they were required to make a motor response as rapidly as possible after aural presentation of a stimulus. Reaction times as well as

various EEG waveforms were recorded. The results indicated lower P300 amplitudes, longer latencies, and decreased reaction time, when first-degree relatives were compared to healthy controls. It was further noted that relatives showed a lack of P300 amplitude dominance in the right hemisphere, which could reflect a biological endophenotype or marker for bipolar disorder. The predominance of the event-related potential abnormalities was also described as reflecting frontal abnormalities, although this was not significant after statistical correction. This study is cited as the first study to report ERP abnormalities in relatives of bipolar probands in association with a cognitive task.

Duffy and colleagues (2001) investigated measures of inattention and hyperactivity in a high-risk sample of children of bipolar parents. In response to the numerous claims that attention deficit hyperactivity disorder (ADHD) and bipolar disorder appear to be associated and highly comorbid, particularly in children and adolescents, these researchers sampled 53 male and female offspring from parent probands between the ages of 10 and 25 years. Twenty four of the fifty-three offspring met criteria for at least one lifetime psychiatric diagnosis. These researchers utilized the Talland Cancellation Test (Talland, 1965) and a self-report measure of ADHD symptomology, the ADHD Symptom Rating Scale (DuPaul, 1991), to determine whether deficits of sustained attention were more prevalent in this high-risk population and whether this objective measure of attention was associated with the self-report measure. The children also completed the Beck Depression Inventory. No control group was utilized, but the children were further classified as those without any history of psychiatric illness and those with some diagnosable psychiatric illness, with only 4 of the 53 offspring demonstrating Bipolar I, II, or NOS, and one child with a diagnosis of ADHD.

No differences in sustained attention were found between children of bipolar parents with and without a lifetime psychiatric diagnosis. A significant relationship was found between the subjective ratings of ADHD and Beck Depression scores. Unfortunately, no comparison group or normative data were utilized to determine whether performance of the Talland Cancellation Test represented a significant deviation from normal performance. Once again, only one specific measure of cognitive (attentional) abilities was utilized rather than a battery of tests.

Another high-risk study examined the association between schizophrenia spectrum personality traits and neurocognitive deficits in relatives of patients with schizophrenia and affective psychosis (Gilvarry, Russell, Hemsley, & Murray, 2001). It was hypothesized that there would be a greater prevalence of spectrum traits in relatives of schizophrenia probands than in relatives with affective psychoses, and that the former would demonstrate poorer neuropsychological performance. Furthermore, it was proposed that relatives with schizophrenia spectrum personality characteristics in either group of relatives would demonstrate neuropsychological deficits similar to those obtained in the schizophrenia patient population. One hundred and twenty-nine first-degree relatives of patients with schizophrenia ($N = 91$) were compared to 106 relatives of patients with affective psychoses, ($N = 66$, 37 patients with manic or depressive bipolar disorder and 29 patients diagnosed with schizoaffective disorder). Relatives consisted of mother, father, or siblings. No control group was utilized.

Due to fairly extensive clinical interviews of the relatives, the authors examined only a few neurocognitive measures, including the National Adult Reading Test (NART, Nelson 1982), which is a measure of premorbid IQ, Trail Making Test, parts A and B

(Reitan, 1958, 1978) and Thurstone's Verbal Fluency Test (Thurstone, 1938). Analyses were performed comparing both the relatives to each other and the relatives to the affected probands. Schizophrenia spectrum traits were dichotomized as low or high by using item endorsement on the International Personality Disorder Evaluation (IPDE, Loranger et al., 1994) for paranoid personality disorder, schizoid personality disorder, and schizotypal personality disorder. Only one individual achieved full criteria for a personality disorder (paranoid personality disorder), with all other relatives demonstrating subthreshold criteria.

Contrary to the first hypothesis, the researchers found that schizophrenia personality spectrum traits were equally distributed in the relatives of patients with schizophrenia and in the relatives of affective disordered patients. Prior to controlling for spectrum personality traits, differences in IQ and verbal fluency were found in the two groups of relatives, with the schizophrenia relatives demonstrating lower estimated IQ scores and lower verbal fluency ($p<.007$ and $p<.03$, respectively). These statistical differences remained when one compared relatives of both schizophrenia and affective disorder patients who scored low on paranoid, schizotypal, and schizoid traits. However, no differences in verbal fluency or estimated IQ (NART) scores were found when relatives of both patients groups were compared who scored high, i.e., greater than or equal to 2, on these personality features. Therefore, relatives who scored comparably high on the schizophrenia personality spectrum traits could not be differentiated in terms of IQ or verbal fluency scores. Nonetheless, the researchers concluded "relatives of affective psychotic patients had significantly higher IQ and generated more words on the verbal fluency test than relatives of schizophrenic patients" (Gilvarry et al., p. 96, 2001).

No differences were found in full scale IQ between both groups of relatives as a whole and the patient probands when comparing those who scored high on the paranoid personality traits (PPT). There were, however, IQ differences between the patient groups and those relatives with schizotypal and schizoid personality traits (both low and high), with the relatives of both groups demonstrating higher full-scale IQ's. When comparing patients with schizophrenia to their relatives directly, no differences were noted between the proband and high-scoring PPT relatives, however, both high and low-scoring schizoid personality trait (SZPT) relatives and schizotypal personality trait relatives (STPT) had higher IQ's compared to the patient group. When comparing the relatives of affective psychotic patients to the probands, low-scoring relatives on all three spectrum traits had significantly higher IQ's than the patient group. No IQ differences were found between high-scoring relatives (PPT, SZPT, and STPT) and the patient group.

The researchers found only partial support for the last hypothesis suggesting that relatives with pronounced schizophrenia spectrum personality traits would demonstrate neurocognitive deficits similar to their affected relatives. This finding was reported only in the paranoid personality disordered relatives such that relatives with high paranoid spectrum traits, either schizophrenic or affective disordered relatives, demonstrated IQ scores comparable to their affected kin.

The limitations of this study include a very limited sample of neurocognitive measures on which to base the conclusion that relatives of schizophrenic patients demonstrate poorer neuropsychological performance than relatives of affective psychotic patients. Only verbal fluency scores and a measure of estimated IQ, NART scores, were found to be different between the groups of relatives, and this difference was apparent

only when comparing the relatives who scored low on the personality spectrum traits. Those who scored high on the personality traits could not be distinguished by NART scores or verbal fluency scores. No differences were found in the performance on Trail Making Test A or B.

It is probable that these relatives were not truly personality-disordered, as the personality measure was dichotomized and only one relative met full criterion for a personality disorder, that of paranoid personality disorder. It is also difficult to comment on the true differences between the groups of relatives, as the affective psychotic relative group was sampled from a heterogenous group of both bipolar and schizoaffective patients, and analyses were not performed to differentiate these groups. Furthermore, no control group was utilized. The general purpose of the study was to examine schizophrenia spectrum traits with regards to neuropsychological function; however, very few measures of cognitive function were performed. As acknowledged by the researchers, more comprehensive neuropsychological testing is warranted for both groups of relatives (Gilvarry et al., p. 98, 2001).

An innovative study of first-degree relatives of bipolar probands investigated the effects of acute tryptophan depletion on neurocognitive performance in relation to normal controls (Sobczak, Riedel, Booij, Aan Ret Bot, Deutz, & Honig, 2002). In an attempt to identify a biological vulnerability in bipolar disorder, these researchers utilized a placebo-controlled, double blind, cross-over design to assess whether individuals at risk for developing bipolar disorder demonstrated differential response to acute tryptophan depletion. Because serotonin has long been implicated in learning and cognitive functions, altering the levels of available tryptophan, the precursor to serotonin, is

described as a direct method of investigating the results of reducing central 5-HT or serotonin activity. Acute tryptophan depletion was accomplished by having subjects drink a mixture comprised of 14 amino acids along with 4% tryptophan or no tryptophan (control condition). Blood plasma concentrations of tryptophan were assessed via liquid chromatograpy.

The neuropsychological battery administered by Sobczak et al. (2001) consisted of a planning task, the computerized Tower of London (Owen, Sahakian, Hodges, Summers, Polkey, & Robbins, 1995), Picture Learning Task (Lezak, 1995), Visual Verbal Learning Test (Lezak, 1995), Sternberg Working Memory Task (Sternberg, 1975), Verbal Fluency Test (Luteijn & van der Ploeg, 1983), Stroop Color Word Test (Stroop, 1935), Dichotic Listening Task (Kimura & D'Amico, 1989), and a Concept-shifting/Attentional Set Shifting Task (Vink & Jolles, 1985).

As hypothesized, first-degree relatives of bipolar patients demonstrated impairment in planning and memory tasks. Relatives with a family history of bipolar I disorder demonstrated impaired reaction times at baseline on the Tower of London Task compared to normal controls, which increased with acute tryptophan depletion. This finding was interpreted as family history creating a biological vulnerability to the detrimental effects of tryptophan depletion, (i.e., a serotonin-mediated vulnerability). Deficits in verbal memory recall and recognition were also found in relatives with family history of bipolar I disorder, independent of acute tryptophan depletion. With acute tryptophan depletion, both normal controls and positive family history relatives were impaired in delayed recall of visual and verbal information or memory tasks, indicating deleterious effects on long-term memory in both groups. Acute tryptophan depletion did not alter performance on

auditory or visual attentional tasks nor on working memory tasks. These researchers proposed a serotonin-mediated frontal lobe dysfunction as being a potential biological marker in bipolar I disorder. Previous studies have demonstrated deficits in planning and executive function in bipolar patients that remit after clinical recovery (Rubinsztein et al., 2000), and this current study supports a biological vulnerability in cognitive functions, most notably planning abilities and verbal memory, which is present in non-affected relatives in a serotonin-depleted state. Therefore, planning deficits and/or verbal learning in bipolar disorder may be mediated by serotonin. Mood did not appear to have a significant role in the observed differences in cognitive function, and the researchers documented a significant decrease in plasma tryptophan, lending support to their experimental manipulation. Sobczak et al. (2001) proposed that the specific cognitive impairments in planning and memory could indicate a possible biological marker or cognitive endophenotype. Of interest are the findings of a recent neuroimaging study which supports the involvement of ventral and medial prefrontal and amygdalar abnormalities in a subgroup of bipolar patients (Blumberg, Charney, & Krystal, 2002), structures which correlate with dysfunction in executive functioning.

The aforementioned study appears to be the only investigation that manipulated a biological measure and examined cognitive function in a high-risk group of bipolar parents. This study is significant in elucidating a potential biological vulnerability as reflected in performance on cognitive tasks; high-risk neuroimaging studies of offspring or siblings of bipolar patients have not been conducted to date, so it is difficult to ascertain whether functional or structural brain abnormalities reflect underlying genetic vulnerabilities in a high-risk population (Bearden, Hoffman, & Cannon, 2001).

A most recent study (Ferrier, Chowdhurry, Thompson, Watson, & Young, 2004) examined neurocognitive function in unaffected first-degree relatives of patients with bipolar disorder but did not compare their performance to those of affected family members of bipolar probands. The study investigated the domains of attention and executive function, psychomotor performance, and declarative learning and memory only. Results indicated that the first-degree relatives exhibited impaired performance on Backward Digit Span, Spatial Span, and visuospatial memory (CANTAB spatial recognition). This study failed to replicate deficits in verbal declarative memory, which had been documented in two previous high-risk studies by Gourovitch et al. (1999) and Keri et al. (2001).

It is apparent from the aforementioned review of neurocognitive studies with bipolar relatives that no definitive conclusions can be drawn due to the fact that very few studies have been conducted to date. The most consistent finding from the neuropsychological high-risk literature thus far has been the identification of deficits in verbal memory and verbal learning. Interestingly, few measures assessing visuospatial memory or memory for non-verbal learning have been utilized. It would seem important to investigate more specifically non-verbal or visual memory tasks as well as other right-hemisphere tasks given that patients with bipolar disorder have been shown to exhibit some impairment on these tasks. Also, examination of right hemisphere function may help to further clarify Flor-Henry's lateralization hypothesis regarding right hemisphere deficits in bipolar patients.

Although several non-verbal memory tests have been designed, there is criticism as to whether any of the existing measures represent pure visual memory constructs

(Heilbronner, 1992). One of the biggest criticisms has been that most visual memory tests contain a visuoconstructive component that involves either reproducing a design by drawing or manually constructing a design (Heilbronner, 1992). Therefore, it has been proposed that delayed visual memory recall procedures may have greater validity than immediate memory reproductions. One such measure that has been developed to assess impairments in long-term visual memory independent of visuoconstructional abilities is the Biber Figure Learning Test (BFLT, Glosser, Goodglass, & Biber, 1989). The recently expanded version (BFLT-E; Glosser, Cole, Khatri, DellaPietrea, & Kaplan, 2002) has been shown to reliably detect non-verbal, visuospatial memory impairments in patients with neurological dysfunction, particularly temporal lobe disorders.

This investigation utilized a battery of cognitive measures to compare the relative performance of patients with bipolar disorder, their first-degree relatives, and normal controls on measures of verbal and non-verbal learning, attention/processing speed, executive functioning, motor assessment, visuospatial construction, and visual memory. In accordance with the literature review, it is anticipated that relatives of bipolar patients will be relatively intact in the areas of motor function and psychomotor coordination and in the domain of working or short-term memory. Several a priori hypotheses will be investigated regarding various neurocognitive domains. Based on the existing literature of cognitive deficits in high-risk individuals, it was hypothesized that:

1) First-degree relatives of individuals with bipolar disorder will perform worse than controls but better than the bipolar probands on tasks assessing verbal and visual learning and memory, executive functioning, and visuospatial abilities.

2) Compared to normal controls, participants with bipolar disorder will exhibit impaired performance on verbal learning and memory (CVLT), attentional and executive tasks (Stroop, CPT, Digit Symbol, Trail Making Tests A and B), visuoconstructional/spatial abilities (Block Design, Rey Osterrieth Complex Figure-copy, Judgment of Line Orientation, Facial Recognition), and visual memory (Biber Figure Learning Test, Wechsler Memory Scale-Faces 1 and 2, and Rey Immediate Recall/Delayed Recall).

3) No differences will be present between the unaffected relatives, normal controls, and bipolar patients on working (short-term) memory tasks (Digit Span and Visual Memory Span), and motor tasks (Finger tapping, Grip strength, and Purdue Pegboard).

4) In terms of hemispheric functioning, there will be a differential right-hemisphere deficit in the bipolar probands, compared to the unaffected relatives and normal controls, as measured by a right versus left hemisphere composite index comprised of tasks associated primarily with right or left hemisphere.

CHAPTER 3

METHOD

Participants

Participants in this study were recruited from the University of Nevada, Las Vegas and the community at large and ranged in age from 18 to 66 years. Participants were comprised of three distinct groups. The first group consisted of 19 individuals diagnosed with Bipolar I disorder and are designated as the BP group. The second group (FDR) consisted of 19 first-degree relatives (siblings, parents, or offspring) of the bipolar group. The third group, defined as the normal control (NC) group, consisted of 19 individuals who did not have a lifetime diagnosis of Bipolar I disorder or a family history of severe and chronic mental illness, including bipolar I disorder or schizophrenia.

Participants from the community were recruited through community-based mental health clinics that have an established relationship with the University of Nevada, Las Vegas' Department of Psychology, community support groups such as the National Alliance for the Mentally Ill (NAMI) and Depression and Bipolar Support Alliance (DBSA), as well as private mental health practitioners who agreed to participate in the recruitment. Participants from the University of Nevada, Las Vegas were recruited through the Psychology Department Subject Pool and through posted advertisements on the campus. The UNLV subject pool students received compensation in the form 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 wish to complete the entire study would have been compensated for the actual time spent participating, although all subjects in both the subject pool and other forms of recruitment completed the entire study. All other individuals who participated were compensated $40.00 upon completion of the study. Recruitment efforts were made to ensure that equal opportunity was given to both male and female individuals desiring to participate and efforts to match participants in terms of age and education were also made.

Individuals included in the bipolar group (BP) were 1) diagnosed with bipolar I disorder and 2) had at least one first-degree relative in the community who was willing to participate. Bipolar diagnosis was verified by use of the Structured Clinical Interview for DSM-IV (SCID I for DSM-IV) as described in the measures section. Likewise, individuals included in the bipolar relative (FDR) group were included if they were 1) a first-degree relative (parent, offspring, or sibling) of an individual with a diagnosis of bipolar I disorder and 2) had never received an affective or thought disorder diagnosis themselves (nor any other diagnosis suggestive of a serious mental disorder). The normal control (NC) group consisted of individuals who had not been diagnosed with an affective disorder or schizophrenia and who had a negative family history for these disorders in their first-degree relatives. The SCID for DSM-IV screening module was used in all participants to screen for the presence or history of any significant mental health disorders as well as substance and alcohol abuse. If there was any question of

bipolar disorder in the first-degree relatives, the appropriate modules of the SCID for DSM-IV was utilized to rule out lifetime or current presentation of bipolar I disorder.

In addition to meeting the inclusion criteria, individuals were screened to ensure that they did not meet any conditions of the exclusion criteria. Individuals were excluded from participation if they: 1) did not demonstrate English as being their primary language; 2) had a history of traumatic brain injury or any other medical condition or neurological disease/damage that could cause cognitive deficits; 3) had a history of alcohol or substance abuse or dependence within the last six months; 4) had a diagnosis of mental retardation or any diagnosis of cognitive dysfunction; 5) were currently on prescription or over-the-counter medications that could produce significant cognitive effects, other than those medications used to treat bipolar disorder in the BP group; and 6) were unable to comprehend or provide informed consent (or have a legal guardian). Those individuals who met both inclusion and exclusion criteria were asked to participate with informed consent procedures and were scheduled for testing.

Procedure

Prior to initiation of any study procedures, informed consent was obtained from all participants. Individuals with bipolar disorder were recruited either directly via community agencies or indirectly through first-degree relatives. An informational flyer providing a brief overview of the study and contact information was posted at various community agencies and public domains, such as libraries (see Appendix I). Direct recruiting methods via case managers and mental health personnel were also performed

in coordination with participating mental health agencies. Following informed consent, the participant identified as an individual with bipolar disorder was asked as part of the research design to contact any of his/her first-degree relatives in the community who might be willing to participate; as such, the bipolar proband served as the intermediary person for gaining permission to contact the first-degree relatives. The participant with bipolar disorder was given an informational sheet (see Appendix I) to give to the first-degree relative(s), that gave consent to be contacted directly by the investigator. The phone number of the primary investigator was also provided should the relatives have any additional questions or desire to contact the primary investigator directly. If the first-degree relative chose to participate after this initial contact, informed consent of the relative was obtained. A similar process was utilized if the initial point of contact was with the first-degree relative, such that the first-degree relative served as the intermediary for providing information to the individual with bipolar disorder and for accessing permission for informed consent. At no time during this initial recruitment phase were the relatives of participants approached directly by the primary investigator without them being informed of the purpose of the research. This procedure allowed relatives to maintain their privacy if they did not desire to participate. After this initial screening, individuals were scheduled for testing and underwent formal informed consent procedures.

Normal controls were recruited for participation primarily through the Department of Psychology subject pool via the Experimetrix website (UNLV Department of Psychology) as well as from the community at large. If any individuals from the

University of Nevada Las Vegas met the criteria as an individual with bipolar disorder or a first-degree relative of an individual with bipolar disorder, the process for informed consent was utilized, appropriate screening was performed, and research credit for participation was given. The majority of the NC group was recruited from the UNLV subject pool, although a few NC individuals were recruited from the community to assist in matching the experimental groups for age and education. Appendix II contains the four informed consent forms that were utilized and includes: a) the informed consent form for normal controls in the community, b) the informed consent for the individuals with bipolar disorder or the first degree relatives in the community, c) the informed consent for individuals with bipolar disorder or first-degree relatives at UNLV, and d) the informed consent form for normal controls at UNLV.

Following informed consent, all participants were given the same battery of neuropsychological tests in the same order by the principal investigator or an assistant/technician trained by the primary investigator or research advisor. Additional questionnaires and scales were administered as outlined in the Measures section. The structured clinical interview, rating scales, and all cognitive 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 typically 3.5 to 4.0 hours.

A demographic questionnaire was given to all participants (See Appendix I). In addition, the individuals with bipolar disorder were interviewed with the appropriate modules of the Structured Clinical Interview for DSM-IV (SCID-DSM-IV; First et al,

1995) to verify diagnosis of Bipolar I disorder. First-degree relatives and normal controls were screened with the SCID screening module to exclude lifetime diagnoses of serious mental disorders and/or substance abuse. All individuals were also assessed for symptom severity using the Hamilton Depression Rating Scale (Hamilton, 1960) and the Young Mania Scale (1978) to determine symptom severity at the time of testing.

All participants received a battery of neuropsychological tests in a fixed order as follows: 1) Lateral Dominance Test, 2) California Verbal Learning Test-I (CVLT-I), 3) Faces I of the Wechsler Memory Scale-II, 4) Judgment of Line Orientation, 5) Facial Recognition, 6) CVLT-I Delayed, 7) Faces II of the Wechsler Memory Scale-II, 8) Finger Tapping Test, 9) Grip Strength, 10) Letter Fluency (FAS), 11) Biber Figure Learning Test-Expanded version, 12) WAIS-III Vocabulary subtest, 13) Trails A and B, 14) Biber Figure Learning Test- Delayed, 15) WAIS III Block Design, 16) Wechsler Memory Scale Digit Span, 17) Wechsler Memory Scale Spatial Span, 18)WAIS-III Digit Symbol, 19) Continuous Performance Test, 20) Rey-Osterrieth Complex Figure Test-copy condition, 21) Category Fluency, 21) Rey 3-minute Delay, 22) Purdue Pegboard, 23) WAIS-III Information, 24) Rey 30-minute Delay, 25) Stroop Color-Word Test, and 26) Wisconsin Card Sorting Test

Each of the measures utilized in this investigation are described briefly in the following section. All of the neuropsychological tests, as well as the clinician-administered rating scales and the structural clinical interview, are commonly used tests that have been found to be valid and reliable for research purposes.

Measures of Symptomology

The Structured Clinical Interview for DSM-IV Axis I Disorders- Research version (SCID-I for DSM-IV; First, Gibbon, Spitzer, & Williams, 1996) is a semi-structured interview developed for obtaining DSM-IV Axis I diagnoses. It is administered by clinicians trained in the DSM-IV diagnostic system (APA, 1994) and is utilized with both psychiatric and general medical patients, as well as with individuals in the community for the purpose of mental health surveys and research. It is commonly used in studies to determine incidence/ prevalence of psychiatric disorders within patient groups as well as characteristics of individuals at risk, including family members. Although it may be used with adolescents, it is most widely used with adults 18 years or older with at least an eighth grade education. The research version of the SCID-I was used in this investigation. The research version is extensive and was designed to be modified according to the researcher's need or particular study question in terms of which modules to utilize, (i.e. the entire SCID does not have to be administered but is tailored to address the research question). In addition to the screening module, which was used to rule out the presence of major mental health disorders in all three groups, Module A (Mood episodes) and Module D (Mood Disorders) were used to verify the bipolar I diagnosis in the individuals with bipolar disorder.

The screening module of the SCID-I consists of 12 questions that are used to elicit further evaluation in subsequent modules. Scoring or rating of the SCID modules involves rating each response of diagnostic criteria either as 1 (symptom is absent), 2

(subthreshold symptom) or 3 (symptom is present). Diagnosis was also verified, whenever possible, by review of any available medical records.

The Young Mania Scale

The Young Mania scale (Young, Biggs, Ziegler, & Meyer, 1978) is an eleven-item clinician administered scale used to measure the severity of mania; it is not a diagnostic instrument. Each item or category to be rated is based on the subjective report of the individual's condition over the previous forty-eight hours as well as the behavioral observations of the clinician. Each item is rated from a 0 to 4 scale, (absent to overtly present) except for four of the items, which received double the weighting and are rated from 0 to 8. For example, item 1 is elevated mood, which is rated from 0 (absent) to 4 (euphoric; inappropriate laughter; singing). This rating scale was administered to all three comparison groups to assess for presence of manic symptoms, although it was anticipated that only the BP group would endorse manic symptoms. A score of 6 or less typically characterizes an asymptomatic state. It was anticipated that the majority of community-dwelling patients would not be acutely manic at the time of testing, but they may demonstrate subthreshold symptoms or hypomania. Patients who were acutely and severely manic, as identified by the SCID-I for DSM-IV, were not utilized.

The Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale (HDRS; Hamilton, 1960, 1967) is the most widely used observer-based rating scale for treatment outcome and clinical pharmaceutical studies of depression. Similar to the Young Mania scale, it is a clinician-administered scale for measuring the severity of depression and is not to be used as a

diagnostic tool. There are variations of the Hamilton Depression Rating Scale but the version that was used in this study was the 21 item scale in which each item is rated on either a five-point scale (0-4) or on a three-point scale (0-2). The five point anchor scores are designated as: 0=absent, 1=mild, 2=moderate, 3=severe, 4=extreme symptoms. The three-point rating scale is structured with ratings 0=absent, 1=mild, 2=obvious, distinct, or severe. A score of 8 or less is characterized as asymptomatic with a continuum thereafter. A sample item of the HDRS is as follows: 1) Depressed mood (sadness, hopeless, helpless, worthless) rated as 0 (absent), 1 (feeling states indicated only on questioning), 2 (feeling states spontaneously reported verbally), 3 (communicates feeling states non-verbally), 4 (patient reports virtually only these feeling states).

Neuropsychological Test Battery Domains

The cognitive tests used in this study were grouped broadly into the neuropsychological domains of Executive Function, Attention/Psychomotor speed, Verbal Learning and Memory, Visual Learning and Memory, Working Memory, Visuoconstructional/Spatial organization, and Motor Tasks. These measures were selected in part because they are widely used research instruments and have been used in previous studies assessing cognitive function in patients with bipolar disorder. Collectively, these measures served to measure a broad domain of cognitive functions that would be considered a comprehensive neuropsychological test battery and a representative index of cognitive abilities. Certain measures were selected to assess laterality in brain function, (i.e. right vs. left hemispheric functioning). Tests such as the

Wisconsin Card Sorting Test are general or non-lateralizing, while other measures, such as Faces I of the Wechsler memory scale and the California Verbal Learning Test represent primarily right or left hemispheric function, respectively. All measures were administered and scored in a standardized fashion using the test manuals. Psychometric data of all tests are available in standard neuropsychological texts (Lezak, 1995; Spreen & Straus, 1998), or are provided if not readily available.

Measures of Executive Function

Executive function/frontal abilities were measured using the Wisconsin Card Sorting Test (WCST, Grant & Berg, 1948; Heaton, Chelune, Talley, Kay, & Curtiss, 1993), the Controlled Oral Word Association, Trail Making Test B, and Digit Symbol. In the Wisconsin Card Sorting Test, participants are asked to categorize test cards to one of four stimulus cards placed in front of them. The stimulus cards consist of a red triangle on the first card, two green stars on the second, three yellow crosses on the third, and four blue circles on the fourth card. The test cards consist of different geometric forms, which have a different shape, number, and color. The subject is given one card at a time and asked to sort according to an underlying principle, the first one being that of color, which he or she must infer. The subject is 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 the subject 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 computer. This test measures abstract concept formation and the ability to shift cognitive sets as feedback is given. The Wisconsin Card Sorting Test has been shown to be sensitive to dorsolateral prefrontal cortex dysfunction (Sullivan, Mathalon, Zipursky, Kersteen-Tucker, Kight, & Pfeerbaum, 1993). The dependent measures used in this study were the number of categories achieved, number of perseverative errors, and failure to maintain set.

The Controlled Oral Word Association Test, (COWAT) is considered to be a measure of spontaneous word fluency and is believed to be subserved by executive or prefrontal cortical functioning. Participants are asked to generate as many words beginning with a given letter (phonetic fluency) or a specific category (semantic fluency) within a designated period of time. The most commonly used letters in the phonetic fluency component are the letters F, A, and S, which will be the letters used in this present investigation. Participants are asked to generate as many words beginning with the letter F, A, or S in the order specified by the examiner within a 60 second time period. Proper names are not allowable nor are the same words with different endings or suffixes. All three letters are administered. The second portion of the COWAT involves category or semantic association in which a participant is asked to generate as many items of a particular category within 60 seconds, with the most common categories including animals and supermarket items. The semantic category of animals was used in this study. The semantic category fluency test has been shown to activate primarily right dorsolateral and medial frontal region (Cardebat, Demonet, & Viallad, 1996), whereas the letter

fluency category has been found to be more sensitive to left frontal and temporal regions (Loring, Meador, & Lee, 1994). Both fluency tasks are scored by summing the total number of words generated in 60 seconds, and removing the intrusion errors and perseverative responses.

Digit Symbol is a subtest of the WAIS-III (Wechsler, 1997) and is considered to be a measure of immediate or selective attention as well as executive functioning. In this task, the participant is shown a key consisting of the numbers 1 through 9 and a corresponding symbol in a box below each digit. They are then asked to fill in the appropriate symbol, as quickly as possible, among several rows of blank squares in which a randomly assigned number is printed above the square. The time limit for this task is 2 minutes, and the dependent measure is the total number of squares completed with the correct symbol minus the number of errors.

Trail making Test B is considered a task of visual search, visuospatial sequencing, and cognitive set shifting and is generally considered an executive function task. 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 a more complex task of cognitive set shifting and visual perceptual processing, as opposed to part A, which is a simpler measure of psychomotor speed and visual span. The time required (in seconds) to complete each part was used as the measure of performance.

Measures of Attentional Control/Psychomotor Speed

Three measures were used to assess attentional abilities and/or abilities of psychomotor speed including the Stroop Color-Word test (Stroop, 1935; Golden, 1978), the Degraded Stimulus version of the Continuous Performance Test (CPT; Nuectherlein & Arsanow, 1992), and Trail Making Test A (TMT; Reitan & Wolfson, 1985).

The Stroop Color-Word Test (Stroop, 1935; Golden, 1978) is considered a test of selective attention and inhibition. 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 part the participant is 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 the participant is 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, the participant is 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 uses a time limit of 45 seconds for each section (Golden, 1995). The number of correct items completed in each section is tabulated as well as interference score derived in the third section. The Stroop test is a measure of information processing speed as well as the ability to focus on the task demand and to rapidly shift attentional set, (i.e. suppressing the color of the print while naming the word).

Sustained attention or vigilance was measured using the computer version of the Degraded Stimulus Continuous Performance Test (Nuechterlein & Asarnow, 1992). The

Continuous Performance Test involves viewing a series of quasi-randomly presented series of numbers, on a continuous basis one at a time. The stimuli are 50% degraded (0-9 scale) and are presented at various intervals (mean=100 ms) with a stimulus duration of 200 ms. The participant is asked to press a mouse key each time a predesignated target stimulus, the number zero, occurs on the computer screen. Various indices of responsiveness and sensitivity are utilized with the computer version, including the CPT d' index, which refers to the ability to discriminate the target stimuli from random (non-target) noise and the CPT Beta index, which represents the amount of perceptual evidence that is necessary for the participant to distinguish a target stimulus from a non-target stimulus. The CPT d' is obtained by assessing the hit rate versus false hits, with a CPT d' of 0 indicating a chance level of discrimination. CTP hit rate, d', Beta response, and sensitivity were used as dependent variables in this study. The Continuous Performance Test has been used extensively to differentiate schizophrenic patients from normal controls and other patient groups (Albus et al., 1996; Addington & Addington, 1998; Jones et al., 1994; Liu et al., 2002).

Trailmaking Tests A or Trails A (TMT; Reitan and Wolfson, 1985) was utilized as a measure of pure psychomotor speed. 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. Errors are recorded and included in the total time. The time required (in seconds) to complete Trails A was used as the measure of performance.

Measures of Working Memory

Two measures of working memory were used in this study, one assessing auditory short-term memory and the other assessing visual short-term memory. Auditory working memory was assessed using the Digit Span subtest of the WAIS-III (Wechsler, 1997) and visual memory was measured via the Spatial Span Forward and Backward subtests (Wechsler Memory Scale, Wechsler, 1997b).

In the Digit Span Forward and Backward subtest, the examiner verbally presents a series of numbers and the participant is asked to repeat the numbers verbatim, first in a forward sequence (Digits forward) and then in a reverse order (Digits backward). The task begins with a string of two numbers and progresses to a string of eight numbers or until the participant fails two consecutive trials. The total number of correct trials is summed for both digits forward and backwards. Digit Span involves attentional processes of being able to hold sequences of strings of numbers in working memory and reiterate the sequences in the auditory channel. Scaled scores were utilized as the dependent measure.

The Wechsler Memory Scale Spatial Span (Wechsler, 1997 b) is considered the visual analog of the Digit Span subtest, with a Forward tapping and Backwards tapping component. The Spatial Span subtest measures an individual's ability to hold a visual spatial sequence of locations in working memory and reproduce the sequence, thereby being a measure of visual working memory. The Digit Span subtest measures an individual's ability to hold a visual spatial sequence of locations in working memory and reproduce the sequence, thereby being a measure of working memory. The participant is

presented a three dimensional board of ten blue blocks in which the examiner taps out a fixed sequence of patterns at a rate of 1 block/second. The sequences begin with the tapping of two blocks and progresses to more difficult patterns. The participant is asked to mimic the presentation of the tapping exactly in the Forward Span condition, and to tap the squares in a reverse order in the Tapping Backwards span. Scores are the sum of the number of trials successfully completed in both conditions. Scaled scores were utilized as the dependent measure.

Learning and Memory measures

The California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) was used as a measure of declarative verbal learning and memory. Declarative memory, as opposed to procedural memory, is typically represented by tasks involving the recall of word lists presented over multiple trials. The CVLT is a verbal list-learning task in which a list of sixteen common shopping items (List A), representing various categories such as spices, tools, fruits, etc., are presented over five consecutive trials. Words are presented at the rate of one per second, and participants are asked to recall as many words as they can from List A following each presentation. After five consecutive presentations, a second list (List B) is introduced as a distracter list, and the participant is asked to recall items once again from list A. Following the recall trials, the participants are cued with the categories of fruit, clothing, tools, and spices (Cued recall) and are again asked to recall as many items as possible in each category. Following a 20-minute delay in which non-verbal tasks are performed, the participants are asked to recall as many items from list A in both a free recall and cued situation. A recognition trial then

follows in which participants select the words from List A that are presented with 16 distracter items. Therefore, the CVLT-I measures learning, recall, recognition; interference effects and retrieval/encoding abilities. The dependent variables used in the study included the total number of words recalled on Trials 1-5, the number of words recalled upon immediate recall of List A, delayed recall of List A, and recognition. Hit rate, response bias, and discriminability were also measured.

The Biber Figure Learning Test-Extended (BFLT-E; Glosser et al., 1997) was used as a measure of visual or non-verbal learning and memory. The BFLT-E has been described as the visual analog of the California Verbal Learning Test (Glosser, Cole, Khatri, DellaPietra, & Kaplan, 2002; Kurtzman, 1996; Traci, Mattson, King, Bundick, Celenza, & Glosser, 2001), such that both tests involve a series of five learning trials, an interference task, as well as an immediate recall and delayed recall conditions, and a recognition trial.

The BFLT-E, a modification of the original Biber Figure Learning Test, (BFLT; Glosser et al., 1989), consists of 15 geometric designs constructed of simple shapes (circles, squares, and triangles) which are put together to form novel stimuli. The fifteen designs are presented one at a time at a rate of one every 3 seconds. Following presentation of the designs, the participant is asked to draw as many of the figures as he/she can recall in no particular order. Similar to the CVLT, an interference task is introduced with distracter figures followed by an immediate free recall condition. A delayed learning recall trial is introduced 20 to 30 minutes later, interspersed with verbal (non-visuospatial) tasks. A recognition task is introduced in which the participant is

asked to recognize the original designs intermixed with distracter items. The designs reproduced are scored on a range of zero to three for each response according to the accuracy of drawing. Although the CVLT and the BFLT-E are not identically matched in terms of difficulty level and item content, they can serve as relative measures of verbal and non-verbal learning (Tracy et al., 2001). The inter-tester reliability for the BLFT-E has been found to be .98 (Glosser et al., 2002). The BLFT-E has also been shown to have good test-retest reliability and criterion validity (Glosser et al., 2002) and to demonstrate sensitivity to non language-dominant right temporal lobe functioning. Dependent variables of this measure included learning trials 1-5, immediate recall, delayed recall, immediate memory, hit rate, discriminability, and total false alarm rate.

In addition to the Biber Figure Learning Test-Expanded, the 3-minute delay and 30-minute delay condition of the Rey-Osterrieth Complex Figure Test was used to assess visual memory. Heilbronner and colleagues (1989) have proposed that delayed visual memory recall procedures may be truer indices of visual memory than more immediate administrations, and therefore delayed conditions of the Biber Figure Learning Test and the Rey- Osterrieth Complex Figure Test have been included in this investigation as indices of visual memory.

The Rey-Osterrieth Complex Figure (Rey, 1941; Osterrieth, 1944) is a commonly used test to assess visuoperceptual and visuoconstructional abilities as well as visual memory (Lezak, 1995). The test consists of a stimulus card with a complex figure of geometric forms consisting of crosses, squares, triangles, and a circle, in which the participant is asked to copy the figure and to subsequently reproduce it from memory

without warning. The test can be administered with the copy condition, a 3-minute delay recall trial, and a 30-minute delay recall trial or conversely with just the copy and 30-minute delayed trial. Delayed recall has been shown to be more sensitive to true visual memory deficits than the immediate recall condition (Loring, 1990). Various scoring systems have been used, but typically all involve scoring the 18 individual components or units. The scoring system by Meyers and Meyers (1995) was used in this investigation. The copy condition, the 3-minute, and the 30-minute recall scores were evaluated as dependent measures.

Immediate and delayed visual memory was also assessed with Faces I and Faces II subtest of the Wechsler Memory Scale-III (Wechsler, 1997 b). Memory and recognition for faces (both familiar and unfamiliar) has been found to be primarily a right hemisphere function (Benton, 1980). In Faces I task, the participant is exposed to 24 target faces for 2 seconds each. Following this exposure, the participant is shown a total of 48 faces, including 24 of the previously viewed faces and 24 new faces, and asked to indicate whether he/she was shown each particular face (immediate memory recognition). The total score for this section is 48. Approximately 30 minutes later, the participant is shown a second series of 48 faces and is asked to recognize whether the faces were those previously presented (delayed visual memory) and the total correct is recorded. Scaled scores of Faces I and II were used as the dependent variables.

Visuospatial/visuoconstructional measures

Four measures were used in this study to assess visuoconstructional and visuospatial abilities including the Rey-Osterrieth Complex Figure Test,(Rey, 1941), copy condition,

the Block Design subtest of WAIS-III (Wechsler, 1997 a), Benton Judgment of Line Orientation (Benton, Hamsher, Varney, & Spreen, 1983), and Benton Facial Recognition (Benton et al., 1983). These measures were chosen as they are well-validated tasks and are known to tap primarily right hemisphere functioning.

The Rey-Osterrieth Complex Figure (Osterrieth, 1944; Rey, 1941) was described in the preceding section. The copy condition was used as a measure of visuospatial and constructional abilities. The participant is shown the complex figure, which remains in sight, and is asked to reproduce the figure to the best of their ability so "that if I were looking at the picture, I would know it was this picture." This condition is not timed and is scored on a scale of 0 to 36 points, similar to the delayed conditions. Raw scores were used as the dependent measure.

The Block Design subtest of the WAIS-III was used to assess visuoconstructional abilities. The Block Design subtest has been shown to involve nonverbal problem solving skills as well as analysis of the whole into component parts, spatial visualization/organization, sustained attention and visual motor coordination. It has also been shown to be a sensitive indicator of right parietal dysfunction (Lezak, 1995), and to correlate highly with general intelligence. It is often used as an indicator or estimation of premorbid intelligence, although it does not have the same stability as verbal tests such as Vocabulary and Information.

In Block Design, the participant is shown a series of progressively more difficult red and white spatial designs via a stimulus booklet. The participant is asked to duplicate the designs with red and white blocks. The blocks are identical with 2 red sides, 2 white

sides, and two sides of half red and half white. This is a speeded task in which performance is rewarded by accuracy and speed of completion. Rotations of the design greater than thirty degrees are scored as failures. The task consists of 14 possible designs with a total score of 68. The task is terminated if the participant obtains 3 consecutive failures. Total score is based on correct reproduction of the block design and the time for completion. Scaled scores were used as the dependent measure.

Various tests of facial recognition and affect discrimination have been used in studies of patients with bipolar disorder (Walker, McGuire, & Bettes, 1984; Addington & Addington, 1998; Yurgelun-Todd, 2000). In this study, the Benton Facial Recognition task was used as a measure of visuospatial discrimination and processing without a memory component. The participant is asked to match the stimulus face to six possible faces presented on the stimulus card. The first six items involve matching to just one of six frontal views. The remaining sixteen items involve different views and lighting conditions and participants are asked to match the stimulus face to three separate views on the stimulus card. The long form used in this study includes 22 items with a possible score of 54. Total raw scores were calculated for the dependent measure.

Judgment of Line Orientation (Benton et al., 1983) was the last measure utilized as a visuospatial task. This test has been found to be predominantly a right hemisphere task (Lezak, 1995). Judgment of Line test (JOL; Benton et al., 1983) involves the matching of angled line pairs to a semi-circle of lines numbered one to eleven. The participant is asked to choose which two lines from the semi-circle are the same as the pair of the

stimulus lines. There are a total of 30 items. A five-item practice trial is given with corrective feedback. The total correct out of 30 was used as the dependent variable.

Motor Measures

Various measures were used to assess motor strength, motor coordination, and hand preference, including the Lateral Dominance Examination, Finger tapping, Grip Strength, and Grooved Pegboard. Typically these motor tests are utilized to assess potential lateralizing deficits (right vs. left dysfunction) as well as to measure gross and fine motor coordination and pure motor strength. The Lateral Dominance Examination (Reitan & Wolfson, 1985) is a series of questions in which the participant is asked to demonstrate his/her preference for performing various uni-manual tasks such as writing, eating, or throwing a ball as well as to demonstrate his/her mode of preference for uni-pedal tasks such as kicking a ball. At times, a participant will demonstrate mixed dominance such as right-handed preference for upper extremity activities but left-foot preference for pedal activities (or ambidexterity). Eye dominance can also be assessed rapidly by having the participant peer through a simulated object, such as a telescope. Grip strength assessment is a component of the Lateral Dominance Examination in which the strength or intensity of voluntary gripping is assessed via a hand dynamometer. After adjustment of the hand dynamometer to the participant's hand, the participant is asked to squeeze the handle as hard as possible with his/her hand at the side of the body. Typically, one practice trial is performed, followed by two consecutive trials with a 10 second break. The mean of the two trials is calculated in kilograms. The Lateral Dominance Examination was used

primarily for establishing handedness in terms of hemispheric functioning. Measures of grip strength were recorded for the dominant and non-dominant hand.

The Finger Tapping Test (Reitan, 1969; Reitan & Wolfson, 1985), also called the Finger Oscillation Test, is considered a relatively pure measure of psychomotor speed and control and is used to detect subtle motor and cognitive impairment (Spreen & Strauss, 1998). Typically, one compares the performance on the dominant hand relative to the performance of the non-dominant hand, with the guideline that the preferred or dominant hand should be approximately ten percent faster (Reitan & Wolfson, 1985). A significant discrepancy in one hand may indicate a dysfunction in the contralateral hemisphere. There is much variability in the population, however, with respect to strength in the preferred hand, so that this test should not be used in isolation to infer laterality of brain dysfunction. In conjunction with other findings, this test can be a sensitive measure of the presence and laterality of a brain lesion (Spreen & Strauss, 1998).

In the Finger Tapping Test, participants are instructed to tap a lever as rapidly as possible with their index finger of the preferred hand for a total of five consecutive 10-second trials. They are instructed to use only the index finger without raising or using the other fingers of the hand. A break is generally given after the third trial. Thereafter, they are asked to repeat the tapping with the non-dominant hand also for five trials. An average of these five trials is calculated and used as the Finger Tapping score, unless there is a variation of more than 5 taps from the highest to the lowest trial. In this case, additional trials are performed, up to ten trials, and the average of the trials within five

taps or less of each other is utilized as the score. The average score for the five trials was computed for both the dominant and non-dominant hands.

Lastly, the Purdue Pegboard Test (Purdue Research Foundation, 1948) was used as a measure of manipulative hand and finger dexterity. The Purdue Pegboard Test is a speeded test, which can be used as a potential lateralizing measure to assist in localizing cerebral lesions to right, or left hemisphere, once again implicating dysfunction in the contralateral hemisphere (Spreen & Strauss, 1998). Because right and left differences are variable and may change over time, this measure should not be used in isolation for lateralizing effects but rather in conjunction with the other motor tests.

The Purdue Pegboard is a board containing two parallel columns of twenty-five holes. Pins or pegs are contained at the top of the board in right and left-hand cups. Participants are instructed to place as many pegs as possible in the holes, initially with their preferred hand, then their non-dominant hand, and lastly, with both hands, each for a 30-second time period. For the right hand, participants are asked to take a peg from the right-hand cup and to insert them starting at the top of the right-hand column, without skipping any rows. Thereafter, the same procedure is performed with the left hand, with placement of the pegs in the left columns as quickly as possible. The pins are thereafter removed and the participant is asked to perform the task with both hands simultaneously. The task is demonstrated for each subtest, and the participant performs up to three trials of each task. Scores are derived for all three parts. For the right and left hand, the number of pins inserted in each of the right and left columns, respectively is calculated (A mean is calculated if multiple trials are used). For the bimanual condition, the number of pairs of

pins inserted is calculated. Raw scores in terms of total time were used as the dependent measures for the dominant and non-dominant hands.

Estimates of Premorbid and Current Intelligence

Two subtests from the WAIS-III (Wechsler, 1997a), Vocabulary and Information, were used to calculate an estimated IQ or measure of premorbid intelligence. The Information and Vocabulary subtests have the highest reliabilities among the verbal WAIS subtests, .89 and .96, respectively (Vanderploeg, Schinka, & Axelrod, 1996), and are traditionally considered as "hold" tests that do not change considerably over time, even with brain dysfunction. The Vocabulary subtest consists of 33 items in which the participant is asked to define words of progressive difficulty. The items are rated as zero, one, or two point responses depending on the accuracy of the definition. The test is discontinued after four consecutive errors. The Information subtest of the WAIS consists of a series of questions that are known to test one's general fund of information and that require broad knowledge of current and historical facts. No credit is given for guesses or partial answers. The test is discontinued after consecutive errors. An example of an item would be "Who painted the Sistine Chapel?" No credit is given for guesses or partial answers. The test is discontinued after consecutive errors. The mean of the Vocabulary and Information age-corrected scaled scores was used as the estimate of Verbal IQ (Bilder et al., 1992).

Current estimated IQ was calculated by using a dyadic short form of the WAIS-III, Vocabulary and Block Design subtests, based on regression equations to estimate the Full

Scale IQ score (Ringe, Saine, Lacritz, Hynan, Cullum, 2002). These regression equations have been normed on a mixed neurological/psychiatric sample and were found to estimate Full Scale IQ within 10 points in 81% to 93% of the sample (Ringe et al., 2002). This estimated current IQ was used as a descriptive measure for the current sample.

Data Analyses

Preliminary Analyses.

Prior to performing the main analyses, data were checked for out of range variables that would indicate inaccuracy in data entry. Thereafter, all dependent variables were examined to ensure that they were normally distributed and that there were no outliers. Descriptive statistics, including skewness and kurtosis, as well as box plots, were used for this purpose. Variables with skewness and kurtosis estimates that were within $\pm$ 1.0 were considered normally distributed, and outliers were defined as data points greater than 2.5 standard deviations above or below the group mean. In cases of outliers, the data were rechecked to ensure that these values were all valid cases.

Following data screening, analyses were then conducted to determine if there were differences among the three groups, the bipolar group (BP), the first-degree relatives (FDR), and the normal control group (NC), on variables that are known to be associated with neuropsychological test performance, including age, years of education, premorbid IQ, and mood ratings. Differences among the groups for sex and ethnicity were also examined. Analysis of variance (ANOVA) was used for continuous variables and chi-square for categorical variables, followed by post hoc Scheffé tests. The demographic

characteristics and results of these analyses are presented in Table 3. No significant differences were present among the three groups for age F (2, 54) = .51, p = .60, education F (2, 54) =2.53, p = .08, or premorbid IQ F (2, 54) = 2.93, p = .06. Premorbid IQ was calculated by taking the average of the Information and Vocabulary subtests from the WIAS-III, a calculation which has been used before in studies of individuals with chronic and severe mental illness (Bilder et al., 1992). Additionally, chi-square analyses indicated non-significant differences for ethnicity and sex χ^2 (10, N = 57) = 10.43, p =.40, and χ^2 (2, N = 57) = 4.17, p = .13, respectively. Although non-significant, the first-degree relative (FDR) group was somewhat older than the BP group, which was older than the NC group, and the NC group had approximately one more year of education than the FDR and BP groups.

Current estimated IQ, based on the WAIS-III Vocabulary and Block Design subtests, was also calculated and is reported in Table 3. ANOVAs indicated significant differences among the three groups on this variable F (2,54) = 7.14, $p < .001$, with post hoc tests indicating greater estimated IQ in the normal control group relative to both the first-degree relatives and the bipolar groups ($p < .05$), who did not differ from each other. Current estimated IQ was not used as a covariate in the main analyses for a number of reasons. First, IQ scores are sensitive to brain dysfunction, although not as sensitive to brain dysfunction as neuropsychological tests, and are often lower than what might be expected in individuals with chronic psychiatric disorders, such as bipolar affective disorder. Second, the current estimated IQ was based on Vocabulary and Block design, the latter task which is strongly associated with right hemisphere functioning. Because it

was proposed that individuals with bipolar disorder would exhibit deficits consistent with right hemisphere dysfunction, covarying out the effects of Block Design would obscure real differences in brain function between the bipolar, FDR, and normal control groups. Finally, it is common practice in studies of chronic mental illness to control for premorbid IQ differences, rather than current IQ differences, among patient and control samples, given the aforementioned considerations. Current IQ estimates, however, do provide information that is helpful in characterizing the sample, allowing for comparison purposes across studies, and therefore the data are included in Table 3.

Additional clinical and demographic characteristics of the individuals in the bipolar group are presented in Table 4, including years of illness duration, number of hospitalizations, symptom severity (depression and mania), as well as medication status. ANOVA revealed significant differences in mood symptomology among the three groups, F (2,54) = 7.27, $p < .002$, with post hoc testing demonstrating that the BP group had higher mean levels of mania and depression relative to the NC and FDR group ($p <$ .01. There were no differences in mean depression or mania scores between the NC and FDR groups, and all groups were found to have non-clinical levels of depression or mania, using standard cut-off scores for the Young Mania Scale and Hamilton Depression Rating Scale.

All participants in the BP group were judged to be clinically stable at the time of evaluation, as none were experiencing a manic, depressive, or mixed episode as determined by the SCID-I, although a few individuals ($N = 4$) in the BP group demonstrated clinically elevated symptom scores on either the Hamilton Depression

Rating Scale or the Young Mania Scale. However, the BP group was relatively euthymic in terms of manic and depressive symptoms as a group with mean scores of 6.16 and 6.89, respectively, on the Young Mania Scale and Hamilton Rating Scale of Depression, as can be seen in Table 4. Although the mean group values are suggestive that the groups were euthymic at the time of testing, the mania and depression scores were included as covariates in the main analyses because of reported associations between mood state and neurocognitive functioning in mood disorder. Mean illness duration for the BP group was 11.32 years, with an average of 2.89 lifetime hospitalizations. All individuals in the BP group were community dwelling and were receiving either outpatient psychiatric services or no services. None of the BP group had been acutely hospitalized in the last six months.

Evaluation of Main Hypotheses

Following these preliminary analyses, MANOVA was utilized to evaluate hypotheses one, two, and three, in order to examine overall performance among the three groups in the seven neuropsychological domains. The neuropsychological test scores of the various domains served as the dependent variables, and group membership (BP, FDR, and NC) served as the between subjects factor. Separate MANOVAs were performed for each neurocognitive domain. Univariate *F* tests and post hoc comparisons were subsequently used to examine differences among the groups on the individual tests when significant results were attained on the MANOVA.

For hypothesis Four, which examined hemispheric differences using composite scores, three sets of composite scores were calculated. The first composite represented cognitive functions in the left and right hemispheres (cognitive composite), the second composite represented motor functions in the left and right hemispheres (motor composite), and the third composite consisted of both cognitive and motor tasks (total composite), reflecting right and left hemisphere functioning. Only data from right-handed individuals was included in these analyses as lateralization of the two hemispheres in terms of language and visuospatial abilities has been shown to vary as a function of handedness (Lezak, 1995). The composite scores were calculated by transforming neurocognitive variables of interest to *z*-scores, and then using the average of the *z*-scores as the composite. For the cognitive composites, only tests reflecting higher order cognitive processing were included.

The right cognitive composite score was computed by summing and averaging the *z*-scores of Block Design, Biber Figure Learning Trials 1-5, Biber immediate recall, Biber delayed recall, Faces I, Spatial Span, and Judgment of Line Orientation. Correspondingly, the left cognitive composite score was computed by summing and averaging the *z*-scores of left hemisphere tasks, including the California Verbal Learning Test (CVLT) Trials 1-5, CVLT short delay free recall, CVLT long delay free recall, FAS verbal fluency, Vocabulary, Information, and WAIS-III Digit Span. In developing the composites, an attempt was made to include comparable or matched tasks, such as Digit Span and Spatial Span, corresponding to right and left hemisphere function.

The motor composite scores were calculated in a similar manner. The right motor composite was derived by summing and averaging the *z*-scores of the three lateralizing motor scores of Grip strength, Purdue pegboard, and finger tapping for the left hand. The left motor composite was derived by summing and averaging the *z*-scores for Grip strength, Purdue pegboard, and finger tapping performed by the right hand. Total composite scores for left and right hemispheres were calculated by combining the aforementioned cognitive and motor measures. Analyses of the three separate composites were performed in order to examine the relative contributions of both the motor and cognitive tasks to the overall differences in hemispheric functioning among the groups.

Subsequent to computing the composite scores, the scores were subjected to repeated measures ANOVA to examine main and interaction effects with respect to the hemispheric function and group membership. All *z*-scores were standardized to a mean of zero and a standard deviation of one, with the NC group used as the comparison baseline. Clinical status (BP, FDR, and NC group) was the between-subjects factor and the right and left cognitive composite scores were the within subjects' factor. Only individuals who were right hand dominant were included in these analyses in order to make inferences regarding lateralization effects.

CHAPTER 4

RESULTS

Preliminary Analyses

Data screening was performed and no out-of-range variables were identified. Results of the preliminary analyses including descriptive statistics for each neuropsychological variable are presented in Table 1. Variables with skewness and kurtosis estimates that were within $\pm$ 1.0 were considered normally distributed, and outliers were defined as data points greater than 2.5 standard deviations above or below the group mean. As can be seen from the Table 1, a number of the variables (15/48) exceeded the skewness and/or kurtosis criteria of $> \pm$ 1.0, most notably facial recognition, Biber recognition, Biber false alarm rate, CPT false alarm rate, and Rey copy condition. Box plots indicated that outliers were present for several variables, including Vocabulary, CVLT discriminability, Faces I, Benton Facial recognition, Benton Judgment of Line, Grip strengths, Biber (Trials 1-5, Immediate Recall, Delayed Recall, Immediate Memory, False Alarms, Hit rate, and Discrimination), Trails A and B, Digit Span, CPT (False Alarm rate, Beta), Rey Delayed, Category Fluency, Stroop total words, Purdue pegboard left, and WCST perseverative errors. In cases of outliers, the data were rechecked to ensure that these values were all valid cases. All values identified as outliers were found to be valid cases.

Given that a substantial number of the variables were non-normally distributed, both parametric and nonparametric multivariate analyses were performed. This approach to the data was selected, rather than transforming variables or outliers, because it allowed for the control of violations of homogeneity of variance and normality simultaneously, without changing the raw data. Although multivariate analysis of variance (MANOVA) has been found to be relatively robust with respect to violations in assumptions of normality and homogeneity (Tabachnick and Fidel, 2001), nonparametric analyses were performed to ensure that significant differences among the groups were not being overly influenced by the non-normal distribution of scores. To perform the nonparametric analyses, all of the dependent variables were converted from continuous scores to ranked scores, and the ranked scores were then subjected to standard multivariate and univariate analyses as appropriate. The comparison between the parametric and nonparametric analyses is shown in Table 2, which depicts the overall MANOVAs as well as the univariate test results for all seven neurocognitive domains. Although the nonparametric and parametric results were parallel in most cases, hypotheses and significant findings will be reported and discussed primarily in terms of the nonparametric analyses.

Evaluation of Study Hypotheses/Main Analyses

Following the preliminary analyses, MANOVA was utilized to evaluate hypotheses one, two, and three, which were concerned with overall differences in the neuropsychological domains among the three groups. Tables 5-11 contain descriptive

statistics as well as the results of the nonparametric univariate analyses and post hoc (Scheffé) tests for all seven neuropsychological domains.

Hypothesis One:

First-degree relatives of individuals with bipolar disorder will perform worse than controls but better than the bipolar probands on tasks assessing verbal and visual learning and memory, executive functioning, and visuospatial abilities.

Results of the MANOVAs for the four neurocognitive domains of interest provided partial support for the first hypothesis. As depicted in Table 2, MANOVA revealed significant overall differences in the domains of visual learning, executive functioning, and visuospatial/constructional abilities among the three comparison groups. The pattern of differences among the groups generally indicated that the NC group performed significantly better than the BP and FDR groups, who did not differ significantly from each other, as demonstrated in Figure 4. Thus, while the differences between the NC and BP group were present as predicted, the pure intermediate position of the FDR group, between the NC and BP groups, was not consistently found as hypothesized (NC > FDR > BP), or did not reach statistical significance, on many of the neuropsychological variables.

With regard to the specific neurocognitive domains, no significant overall differences were found in terms of the verbal learning and memory domain F (2, 54) = 1.38, p = .20. As depicted in Tables 5, 6, and 7, however, there were significant differences in each of the remaining three domains with respect to neuropsychological performance in the first-

degree relative (FDR) group relative to the other two comparison groups. Findings for each individual domain will be reported individually in the following section.

In the domain of visuoconstructional and spatial abilities, MANOVA revealed significant differences among the three groups $F = 3.50$ (2, 54), $p < .01$. Subsequent univariate and post hoc tests (See Table 5) demonstrated that the FDR group performed significantly worse than the NC group on two of the four tasks, including Block Design ($p < .02$) and Judgment of Line Orientation test ($p < .05$). There were also trends for the FDR group to perform better than the BP group on Block Design ($p = .10$) and Rey Complex Figure, copy condition ($p < .10$). Thus, consistent with Hypothesis 1, there were trends toward a pure intermediate pattern of performance in the first-degree relatives (NC > FDR > BP) on two of the four visuospatial tasks, including Block Design and Rey Complex Figure copy. Results of the pattern of performance of the BP group will be discussed under the discussion for Hypothesis 2.

Several significant differences were also noted in the visual learning and memory domain, after MANOVA revealed overall differences among the three groups F (2, 54) $=1.72$, $p < .04$. As shown in Table 6, univariate and post hoc analyses indicated that the FDR group performed significantly worse than the NC group on several measures of visual learning and memory, including Biber Figure Learning Trials 1-5 ($p < .05$), Biber long delay free recall ($p < .05$), Rey Complex Figure 3-minute delay ($p < .04$), and Faces I ($p < .02$). Additionally, there was a trend towards poorer performance in the FDR group relative to NC group ($p = .10$) on Faces II. The FDR group performed equivalent to the BP group on all tasks in the visual learning and memory domain.

In the domain of executive function, MANOVA likewise revealed overall differences among the three groups F (2, 54) = 2.42, $p < .01$. As depicted in Table 7, ANOVAs and post hoc comparisons between the FDR group and the other two comparison groups also revealed significant differences. First-degree relatives performed significantly better than the BP group on Digit Symbol ($p < .001$) but not significantly different than the NC group. There was also a trend for the FDR group to demonstrate more perseverative errors on the Wisconsin Card Sorting test ($p = .11$) and slower processing speed on Trails B ($p = .08$) in comparison to the NC group.

Because there were differences among the groups on the measures of depression and mania, these analyses were repeated with Hamilton Rating Scale of Depression scores and Young Mania scores as covariates in separate MANCOVAs. Results indicated that the MANCOVAs for the visuospatial, executive function, and verbal learning domains did not change in terms of significance for the overall differences. However, the visual learning domain was no longer significant when controlling for manic F (3, 53) = 1.48, $p = .10$ and depressive symptomology F (3, 53) = 1.53, $p = .08$, separately. In order to determine the influence of covarying out mania and depression scores on neurocognitive test scores, estimated marginal means and unadjusted means were examined and depicted in Table 12. Examination of the marginal means suggests that mania and depression contributed to some small changes in the neurocognitive test scores. However, these effects varied across the various neuropsychological measures. For the Biber Figure Learning test, the overall effect was to increase the scores of the BP group to levels similar to that of the FDR group, and to slightly decrease the NC group's scores. For the

Rey Complex Figure Test, little effect was present, although the tendency was to increase overall differences among the groups. Finally, for the WMS-III Faces I and II, differences among the groups were actually increased after adjustment for the effects of mood. Based on these findings, while mood did appear to affect the neuropsychological test scores, effects were not consistent, and it may be that the overall MANOVA results became non-significant as a result of reduced power caused by including covariates in the model rather than a differential effect of mood symptoms.

Based on these results, the predicted pattern of intermediate performance for the FDR group relative to the BP and NC group did not attain statistical significance for many of the neuropsychological variables. As can be seen in Figure 4, however, it was often the case that the FDR group demonstrated an intermediate level of performance, particularly in the domains of visual learning and memory, visuoconstructional abilities, and executive function. Overall, the FDR group performed worse than the NC group and nearly equivalent to the BP group on a number of the neuropsychological measures. The FDR group actually performed worse than the BP group on measures of verbal learning and memory. After controlling for level of mood symptoms among the three groups, there remained indications of impaired performance in the FDR group only in the domains of visuoconstructional abilities and executive function.

Hypothesis Two:

Compared to normal controls, participants with bipolar disorder will exhibit impaired performance on verbal learning and memory (CVLT), attentional and executive tasks

(Stroop, CPT, Digit Symbol, Trail Making Tests A and B, letter and semantic fluency), visuoconstructional abilities (Block Design, Rey-Osterrieth Complex Figure- copy), and visual learning and memory (Biber Figure Learning Test, Facial Recognition, and Rey Osterrieth Complex Figure-3 minute and 30 minute delayed).

Hypothesis Two was also partially supported in terms of impaired performance in the bipolar group relative to the normal control group in three of the five proposed domains of neurocognitive functioning. As can be seen in Tables 5, 6, and 7 significant differences were found in the domains of visuoconstructional/spatial abilities, visual learning and memory, and executive functioning. As previously mentioned, the verbal learning and memory domain approached significance for group differences F (2, 54) =1.38, p = .20. No significant differences were found among the three groups in the domain of attention and psychomotor speed F (2, 54) = 1.03, p = .43) as can be seen in Tables 2 and 9.

With respect to the visuoconstructional domain, overall differences were significant among the three groups F (2, 54) =.3.50, $p < .01$. As shown in Table 5, post hoc tests (Scheffé) revealed that the BP group demonstrated lower or impaired performance relative to the NC group on three of the four visuoconstructional or spatial tasks, including Rey Figure Copy ($p < .005$), Block Design ($p < .01$), and Judgment of Line Orientation, ($p < .001$). No significant differences were noted on Facial Recognition, F (2, 54) = 1.69, p = .19, although a similar pattern of performance was observed among the groups with NC group performing better than the FDR group, who in turn had better performance than the BP group.

The visual learning and memory domain also revealed significant overall differences among the three groups, F (2, 54) = 1.72, $p < .04$. Univariate and post hoc analyses demonstrated that the BP group was impaired on several measures of visual learning and memory as depicted in Table 6. Based on Scheffé multiple comparisons, the BP group performed significantly worse than the NC group with respect to Biber learning Trials 1-5 ($p < .02$), Biber delayed recall ($p < .001$), Biber false alarm rate ($p < .003$), and Biber discriminability ($p < .04$). Further support for impairment in visual memory was found in the BP group, relative to normal controls, on Faces I ($p < .001$) and Faces II ($p < .01$) of the Wechsler Memory Scale. Trends towards impaired performance in the BP group on additional visual measures included the 3-minute delay condition of the Rey Complex Figure Test, ($p < .10$) as well as Biber immediate memory condition ($p < .07$) and Biber hit rate ($p < .08$).

MANOVA also revealed significant overall differences in the executive function domain F (2, 54) = 2.42, $p < .01$, with post hoc differences demonstrating significant impairment in the BP group versus NC group (Refer to Table 7) on Digit Symbol ($p < .001$), Trails B ($p < .01$), and Wisconsin Card Sorting Test perseverative errors ($p < .01$). Additionally, a trend was noted for the BP group to have greater incidents of failure to maintain sets on the Wisconsin Card Sorting test compared to the NC group ($p < .10$).

MANCOVAs were performed on all five of the cognitive domains, with measures of depression and mania used as covariates. Results indicated that MANCOVAs for the cognitive domains did not change the overall differences for the visuoconstructional, executive function, verbal learning, and attention/psychomotor speed domains but, as

previously noted, the visual learning domain fell short of significance when mood symptoms were controlled. As aforementioned, this lack of differences among the groups may have been the result of a statistical artifact (reduced power).

Therefore, after partialing out the effects of mood symptomology, the BP group was found to be impaired on two of the five hypothesized domains, with the non-significant difference for the visual learning domain likely resulting from reduced power resulting from inclusion of mood symptoms as covariates. As such, partial support was found for Hypothesis Two, which predicted cognitive impairment in the BP group, although deficits were found in only two of the five hypothesized neurocognitive domains.

Hypothesis Three:

No differences will be present between the unaffected relatives, normal controls, and bipolar patients on working (short-term) memory tasks (Digit Span and Visual Memory Span), and motor tasks (Finger tapping, Grip strength, and Purdue Pegboard).

Hypothesis Three was supported in the initial analyses. As can be seen in Table 2, the overall MANOVA (nonparametric) for the working memory domain revealed no significant overall differences between the three groups F (2, 53) = 1.58, p = .20. The univariate analyses for the working memory domain are depicted in Table 10. Likewise, there no were overall group differences in the MANOVA for the motor domain, F (2, 53) = 1.47, p = .15, also depicted in Table 2. The univariate analyses for the motor domain are shown in Table 11. The motor domain was analyzed comparing dominant versus non-dominant motor findings, rather than right versus left, as there were five individuals who

demonstrated left hand dominance. Parametric analyses using MANOVA likewise revealed no differences between the groups on the working memory domain, but there were overall differences in the motor domain (Refer to Table 2), with subsequent post hoc tests demonstrating differences in dominant grip strength and Purdue pegboard. For the purpose of consistency, however, findings will be discussed in primarily terms of the nonparametric analyses as well as results of the MANCOVAs.

Once again, MANCOVAs were performed using Hamilton Depression Rating Scale and Young Mania scale scores as covariates to adjust for mood symptomology at time of testing. Overall differences in the working memory domain remained unchanged and non-significant when mania or depression were used as covariates, with MANCOVA results of F (2, 51) = 1.01, p = .41, and F (2, 51) = .80, p = .53, respectively. The MANCOVAs for the motor domain, however, revealed significant differences among the three groups when adjusting for depression scores F (3, 52) = 1.89, $p < .05$ as well as for mania scores F (3, 53) = 2.20, $p < .02$. Further ANCOVAS were performed to analyze univariate differences with respect to both depression and mania scores on all six motor measures. When using Hamilton Depression Rating Scale scores in the analyses, significant differences were found on Purdue Pegboard Dominant hand F (3, 53) = 3.82, $p < .03$ and Purdue Pegboard Non-Dominant Hand F (3, 53) = 4.77, $p < .01$. Post hoc analyses revealed that the NC had greater Purdue Pegboard scores on both the dominant and non-dominant hands compared to the BP group. When separate ANCOVAs were performed for each of the motor tests using Young mania scores, all test results were non-significant.

In summary, support for Hypothesis Three was found such that there were no overall differences in the main analyses (nonparametric MANOVAS) among the three groups with respect to working memory and motor abilities as hypothesized. When mood symptoms were accounted for, however, there were specific motor differences between the NC and BP group in terms of Purdue Pegboard performance, with the BP group demonstrating poorer performance for both dominant and non-dominant hands.

Hypothesis Four:

In terms of hemispheric functioning, there will be a differential right-hemisphere deficit in the bipolar probands, compared to the bipolar relatives and normal controls, as measured by a right versus left hemisphere cognitive composite index.

Three separate repeated measures ANOVAs were performed to examine overall differences in tasks involving right and left hemispheric functioning, corresponding to 1) a total composite score that combined both motor and cognitive abilities, 2) a cognitive composite score, and 3) a motor composite score. In the repeated measures ANOVAs, composite score served as the repeated measure (left vs. right) and clinical status was the between groups variable. The ANOVA for the left vs. right total composite score demonstrated significant differences among the groups $F\,(1, 51) = 8.45$, $p < .005$, and a significant group X total composite score interaction $F\,(2, 50) = 3.81$, $p < .03$. This interaction using the total right and left hemisphere total composite scores is depicted in Figure 1.

Subsequent ANOVAs for right and left hemisphere functioning revealed significant differences between the groups in right hemisphere functioning F (2, 50) = 10.04, $p <$ .001 as well as left hemisphere functioning F (2, 50) = 5.21, $p < .009$. Subsequent post hoc tests (Scheffé) on the right hemisphere total composite demonstrated significant differences between the NC and FDR group ($p < .009$) and the NC and BP group ($p <$ .001), with the NC group demonstrating higher overall mean performance (in standardized z-scores) compared to both the BP group and FDR groups. The post hoc tests for the left hemisphere functioning likewise revealed significantly greater performance in the NC group relative to the FDR group ($p < .02$) and the bipolar group ($p < .05$). There were no differences in right and left hemisphere total composite scores between the BP and FDR groups. Paired t-tests indicated no within-group differences on right versus left composite scores for the FDR group, but the BP group demonstrated overall lower mean performance on right hemisphere tasks compared to left hemisphere tasks t (16)= -3.40, $p < .004$. In summary, the FDR and BP group demonstrated significantly lower mean right and left cognitive composite scores relative to the NC group but did not differ significantly from each other with respect to right and left composite scores. Only the BP group, however, demonstrated a significant differential deficit, however, when comparing right to left hemisphere cognitive composite scores or repeated measures.

Similar analyses were performed with only cognitive tasks corresponding to right and left hemispheric functioning in order to assess pure cognitive composite scores without the contribution of the motor tasks. The overall ANOVA for the cognitive composite

scores revealed a significant group X cognitive composite (left vs. right) score interaction F (2, 51) = 4.48, $p < .02$. This interaction is depicted in Figure 2. Univariate analyses further indicated significant differences between the three groups on both the right cognitive composite (F (2, 51) = 9.72, $p < .001$ and the left cognitive composite (F (2, 51) = 3.46, $p < .04$). Subsequent post hoc testing indicated that the NC demonstrated significantly greater mean performance on the right cognitive composite relative to both the FDR group ($p < .009$) and the BP group ($p < .001$), with the FDR and BP group demonstrating no significant differences on the right hemisphere cognitive composite. Post hoc tests further revealed that there were significant differences only between the NC and the FDR group on the left composite ($p < .05$), with no differences between the BP and NC or FDR and BP groups. Thus, the FDR group performance on the left composite was significantly worse than the NC group, but not significantly different from the BP group. Further analyses using paired t-tests revealed once again no differences between right and left hemisphere tasks within the FDR group but significant differences in right and left hemisphere tasks in the BP group ($p < .001$), with poorer mean performance on the right hemisphere tasks. Similar to the results of the total composite score, the BP and FDR group demonstrated significantly lower performance on the right composite scores in comparison to the NC group but did not differ significantly from each other. With respect to right versus left cognitive tasks, only the BP group, and not the FDR group, demonstrated significant within task differences (within repeated measures) or a differential deficit in right versus left hemisphere tasks. Analyses using both the total composite right and left composite scores and right and left cognitive

composite scores were similar and in support of Hypothesis Four. The repeated measures ANOVA on the motor composite scores revealed no significant differences between the three groups on the motor composite scores as well as no significant motor composite X clinical status (group) interaction, as depicted in Figure 3.

Overall, Hypothesis Four was supported in that there was a significant group X composite score interaction, as predicted, using both the total composite scores and the cognitive composite scores, but not the motor composite scores, demonstrating relatively poorer performance for the BP group on right and left hemisphere tasks compared to the NC group. Impairment on right and left hemisphere tasks (lower mean performance) was found in both the BP probands and FDR group on the total composite scores. Additionally, the BP group demonstrated impairment on right composite scores, but not on the left composite scores, when assessing purely the cognitive tasks (cognitive composites without the motor component). The FDR group performance was equivalent to the BP group on both right and left cognitive composite scores. Additionally, only the BP group demonstrated lower mean performance (within subjects) with repeated measures of the right versus left cognitive tasks, which is in support of Hypothesis Four predicting a relative right versus left differential deficit in the BP group.

CHAPTER 5

DISCUSSION

This study examined the neurocognitive function in individuals with bipolar disorder and their first-degree relatives in order to determine if there are neurocognitive phenotypes for individuals at risk of developing bipolar disorder. The study also attempted to further clarify the specific neuropsychological deficits that exist in individuals with bipolar disorder and to examine the premise that bipolar disorder is characterized by right hemispheric dysfunction. Four specific hypotheses were explored to answer these questions. As a whole, all four hypotheses were at least partially supported by the data and will be discussed individually in terms of the specific findings and potential implications.

Hypothesis One

The first hypothesis addressed specifically the neuropsychological performance of the first-degree relatives or the FDR group in comparison to the normal controls and the bipolar probands. The premise of identifying subtle deficits in relatives of individuals with bipolar disorder was based on the notion that subclinical traits or cognitive deficits in these relatives represent neurocognitive endophenotypes or markers for the genetic predisposition for bipolar disorder. It was predicted that the FDR group would

demonstrate intermediate deficits, falling between the NC (normal control) group and BP (bipolar group) in terms of absolute performance, which would suggest both genetic risk as well as environmental and other factors contributing to the development of the disease.

The overall MANOVAs for the individual domains revealed significant differences among the groups (NC, FDR, and BP) for the visuospatial, verbal learning, and executive domains. For Hypothesis 1, while there was often an intermediate pattern of performance with the FDR group performing intermediate to the NC and BP groups, this pattern was specific to the visual learning and memory, visuoconstructional/spatial, and executive domains, and not apparent in the verbal learning domain (Refer to Figure 4). As can be seen in Tables 5, 6, and, 7, the means of the three groups typically followed this intermediate pattern with the NC group performing better, followed by the FDR group and the BP group. In many instances, however, the differences between the FDR and BP group did not attain statistical significance. Thus, even though the hypothesized intermediate pattern was present, post hoc analyses typically indicated that the FDR and the BP groups performed similarly to each other and worse that the normal control group. The most notable exception to this pattern was observed in the verbal learning and memory domain as can be noted in Table 8. In this domain, the FDR group performed worse than the BP group on most measures of verbal learning and memory (CVLT total learning trials, short-delay free recall, short delay cued recall, long-delay free recall, long delay cued recall, and discriminability), although these differences were non-significant as the overall verbal MANOVA did not reach statistical significance. Overall, the FDR

group evinced significant deficits in the visuoconstructional/spatial, visual learning, and executive functioning domains.

A more detailed analysis of the visuoconstructional domain indicated that the FDR group demonstrated impaired performance relative to the NC group on the WAIS-III Block Design and on Judgment of Line Orientation. Additionally, there was a trend towards the FDR group performing better than the BP group on Block Design, which would correspond to the predicted intermediate pattern of performance on this specific task. The few at-risk studies that have been performed with adult relatives of bipolar probands have not typically utilized either Block Design or Judgment of Line Orientation (Ferrier, Chowdhurry, Thompson, & Young, 2004; Gilvarry et al., 2001; Keri et al., 2001; Kremen et al., 1998; Zalla et al., 2004). Gourovitch and colleagues (1999) did not find significant differences in Judgment of Line Orientation in their study comparing monozygotic twins discordant for bipolar disorder and normal control twins, although these findings should be interpreted cautiously due to a small sample size (7 discordant twin pairs). However, even with the limited sample, the differences in Judgment of Line between the affected and unaffected twins produced a moderate effect size (Cohen's d = .51), with the affected twins performing worse than the unaffected twins.

Similar to this investigation, Ferrier and colleagues (2004) reported visuospatial deficits in the domain of spatial recognition (CANTAB) in a group of first degree relatives of bipolar probands. Interestingly, this study performed a relatively comprehensive neuropsychological test battery and found a few, circumscribed deficits in the first-degree relatives, specifically on Spatial Span, Backwards Digit Span, and

visuospatial recognition. In general, deficits in visuoconstructional and visuospatial abilities are well documented in bipolar probands (Atre-Vaidya et al., 1998; Coffman et al., 1990; Gruzelier et al., 1988; Jones et al., 1994; Sapin, Berrettini, Nurnberger, & Rothblat, 1987; Tham et al., 1997), but this finding remains to be consistently replicated in unaffected relatives.

With respect to executive function, first-degree relatives demonstrated impaired performance on Digit Symbol compared to the NC group and a trend towards performing better than the BP group, once again suggesting an intermediate pattern of performance. Additionally, there was a trend ($p < .10$) for the FDR group to demonstrate more perseverative errors on the Wisconsin Card Sorting Test and have slower perceptual-motor performance on Trails B compared to the NC group. Because little difference was present among the groups on Trails A, the Trails B finding was probably not the result of psychomotor speed or visual scanning difference among the groups, but rather indicative of difficulties associated with mental flexibility and switching. Executive function has been found to be impaired in bipolar probands across all mood states (euthymic, depressed, and manic) of the disorder (Ferrier et al., 1999; Martínez-Arán et al., 2004). Tests of perceptual-motor speed such as Digit Symbol have also been found to be impaired in individuals with bipolar disorder (Albus et al., 1996; Dupont, Jernigan, Butters, Delis, Hesselink, & Heindel, 1990; El Badri et al., 2001; Tabarés-Seisdedos et al., 2003), including bipolar patients assessed at index episode of the disorder (Albus et al., 1996). It is interesting to note that the Digit Symbol task, although a relatively simple task involving visual perception and motor speed, is one of the most sensitive tests for

brain dysfunction (Lezak, 1995).

No significant differences were found in the verbal domain, although overall differences between the groups approached significance F (2, 54) = 1.31, p = .20. Nonetheless, univariate and post hoc analyses demonstrated some differences, most notably for the first-degree relatives to perform significantly worse than the NC group on total CVLT learning trials ($p < .05$), total false alarms ($p = .06$), discrimination ($p < .02$), and recognition hits ($p < .07$). Keri and colleagues (2001) found verbal recall deficits (long delay recall) in relatives of individuals with bipolar disorder and proposed that verbal recall deficit was a common impairment in relatives of individuals with both bipolar disorder and schizophrenia. They did not assess mood symptoms at the time of testing, so it is difficult to make direct comparisons to the current sample, which were by and large euthymic, and were not in an active mood state at the time of testing.

Similarly, Gourovitch et al. (1999) found verbal list learning deficits in unaffected twins discordant for bipolar disorder. However, that study had a limited samples size (N = 7 twin pairs), and included bipolar probands in various stages of illness (3 euthymic, 2 depressed, and 2 manic). Interestingly, trends were noted in the current study for deficits in the FDR group but not in the BP group, with the FDR group consistently performing worse than the BP group in the verbal domain. However, when comparing the current results to those of Gourovitch et al. (1999) and Keri et al. (2001), the general pattern of deficient performance on verbal learning in memory tasks in unaffected relatives was similar, particularly for the CVLT Trials 1 – 5. Further investigations in verbal learning

and memory will assist in clarifying whether verbal recall deficits are potential neurocognitive markers in unaffected relatives.

For the visual learning domain, MANOVA revealed overall differences among the three groups, although the domain failed to reach statistical significance after controlling for mood symptomology among the groups. It is important to note that these analyses of covariance were undertaken primarily because the BP group had higher levels of symptoms than the other groups. However, the SCID findings indicated that none of the BP participants were in a manic, depressive or mixed episode at the time of testing. Also, on average, the BP group's scores on the HDRS and Young Mania Scale were not clinically elevated, providing further support for the idea that the symptoms were not at a level that they might significantly influence performance on the neuropsychological tests. Finally, examination of estimated marginal means following covariance procedures made it apparent that neither depression nor mania consistently influenced test scores. Given these considerations, it is likely that the MANCOVAs failed to reach significance because of reduced power that results from introducing additional factors or covariates into the MANOVA.

Findings that reached significance in the visual learning and memory domain prior to covariance procedures included tasks involving visual memory for patterns/designs (Biber Figure Learning), delayed visual memory for a drawing (Rey-Osterrieth Complex Figure test), and visual memory for faces (Faces I and II). In most of these instances, the NC group performed better than both the FDR and the BP group. Because the Biber Figure Learning Test has not been studied with regard to bipolar populations and because

it relies heavily on right hemisphere functioning, it is important to make note of these findings. Specifically, MANOVA without adjustment for mood symptomology demonstrated that the FDR group performed less well than the NC group on Biber total learning trials as well as Biber long delay free recall. The FDR group also demonstrated impaired performance on immediate (3-minute) delay of the Rey-Osterrieth Complex Figure test and on Faces I of the Wechsler Memory Scale, with trends noted on poorer performance on Faces II. Once again, the FDR group tended to perform relatively comparable to the BP group in this domain. Collectively, these findings suggest that visual learning and memory may also be a potential area of cognitive dysfunction in first-degree relatives and bipolar probands and an area worthy of further study.

Investigators have proposed that a pattern of performance in which unaffected relatives and probands perform comparably but worse than a normal control group is indicative of possible markers of genetic risk (Gourovitch et al., 1999; Zalla et al., 2004), and that an intermediate pattern in which the relatives perform better than the probands and worse than the normal controls suggests both genetic risk as well as environmental factors (Gourovitch et al., 1999). Other researchers stress that cognitive markers that are true endophenotypes must cosegregate within families, such that individuals with bipolar disorder must demonstrate poorer performance than their unaffected relatives and the relatives should correspondingly demonstrate impaired performance relative to normal controls (Glahn, Bearden, Niendam, & Escamilla, 2005). Glahn and colleagues propose that this pattern of impairment is indicative of a true endophenotype except in the cases of monozygotic twins, in which case the unaffected twins may demonstrate impairment

similar to the affected twins as described by Gourovitch et al. (1999). This criterion of co-segregation within families with the unaffected relatives demonstrating an intermediate level of performance is the acceptable standard within the literature (Glahn et al., 2005; Lenox et al., McQueen et al., 2005), and remains one of the four necessary and sufficient criteria for identification of endophenotypes.

There were indications of both types of patterns (NC > FDR > BP and NC > FDR = BP) in this study. On several tasks which attained significance, the NC group tended to perform better than the FDR group and BP, which were not statistically different from each other (NC > FDR = BP). These tasks included Block Design, Judgment of Line Orientation, Biber Trials 1-5, Biber Long Delay Free Recall, Faces 1, and Digit Symbol, and Dominant Grip Strength. Trends ($p < .01$) towards this were seen on Trails B, Wisconsin Cart Sorting Test perseverative errors, Faces II, and Rey 3-Minute Delay. When the more stringent analyses of covariance were utilized (accounting for mood symptomology), this pattern was observed in only four of the above tasks, excluding the Biber tasks. Again, there were strong trends towards a pure intermediate pattern of results on Block Design and Digit Symbol.

Collectively, these findings suggest several cognitive tasks that implicate a potential genetic risk or cognitive endophenotype for bipolar disorder in the unaffected relatives, most notably those of Block Design, and Digit Symbol, and to a lesser extent, Judgment of Line Orientation. Replication of these findings is needed in order to determine whether one or all of these tasks can truly be considered cognitive endophenotypes or markers.

Hypothesis Two

The second hypothesis examined the neurocognitive performance of the individuals with bipolar disorder (BP group) with respect to five cognitive domains (verbal learning and memory, visual learning and memory, visuospatial, attentional, and executive function). It was predicted that the BP group would demonstrate impaired performance in all of these domains compared to the NC group and the FDR group. Main analyses (MANOVA) revealed that overall differences were obtained in three of the five domains. As such, only partial support was obtained for Hypothesis Two, with the BP group evincing deficits only in the visuospatial, visual learning and memory, and executive function domains.

On the visuoconstructional/visuospatial domain, the BP group was found to demonstrate poorer performance than the NC group on three of the four tasks assessed, including Rey-Osterrieth Complex Figure (copy condition), Block Design, and Judgment of Line Orientation. Trends were also found for impaired performance in the BP group relative to the FDR group on Rey Figure copy and on Block Design. These results remained significant even after correction for mood symptomology. Rubinsztein and colleagues (2000) reported impairment in visuospatial recognition in bipolar probands in a manic state which persisted after recovery to a euthymic state, in contrast to corresponding improvement in executive function following recovery. These researchers proposed a neuropsychological profile indicative of posterior temporal lobe involvement with recovery in frontal dysfunction. Bulbena and Berrios (1993) reported deficits in Judgment of Line Orientation in a group of bipolar probands during episodes of mania

and depression, which persisted during follow-up in a euthymic stage. Additional deficits in visuospatial tasks have been documented in the literature in various states of illness (Atre-Vaidya et al., 1998; Coffman et al., 1990; El Badri et al., 2001; Gruzelier et al., 1988; Rubinsztein et al., 2000; Sapin, Berrettini, Nurnberger, & Rothblat, 1987; Tham et al., 1997), although these findings have not been found to be as significant or consistent as those deficits reported in the domains of verbal learning, executive function, and sustained attention.

Executive function was also found to be impaired in the BP group relative to the NC group and to a lesser extent, the FDR group. Impairment in executive function has also been well documented in the literature, particularly in euthymic or remitted individuals with bipolar disorder, and this finding was replicated in this study. The BP group demonstrated more perseverative errors on the Wisconsin Card Sorting test as well as impaired performance on Digit Symbol and Trails B relative to the NC group. There was also a trend for the BP group to have a significantly greater number of failures to maintain set on the WCST compared to normal controls. Hawkins and colleagues (1997) also documented relative impairment on Trails B and Digit Symbol in a group of bipolar patients, in comparison to individuals with schizophrenia. The deficits, however, were not significantly different from the normal control group in their sample.

The current findings do not support the suggestion by Rubinsztein and colleagues (2000) who proposed that recovery of executive functions occur as patients remit from mania to euthymia. While it may be that some improvement in executive functions does coincide with remission of manic symptoms, the current results indicate that executive

functioning deficits persist even in euthymic states, and should therefore be viewed as potential trait features of Bipolar I disorder.

Fewer differences were found between the BP group and the FDR group, with the BP group demonstrating poorer performance on Digit Symbol and trends towards poorer performance on WCST (perseverative errors) compared to the FDR group. Digit Symbol was the only task on which the BP group performed significantly worse than both the FDR and NC groups, approaching a pure intermediate pattern. This finding was recently replicated in a study comparing individuals with bipolar disorder and their unaffected relatives (McIntosh, Harrison, Forrester, Lawrie, & Johnstone, 2005). In that study, the BP group performed significantly poorer than first-degree relatives and normal controls on Digit Symbol Substitution Test, a test similar to Digit Symbol. Additionally, Tabarés-Seisdedos et al. (2003) reported significant impairment on Digit Symbol in bipolar probands. These deficits were reported as more apparent in individuals with a family history of psychosis in their first-degree relatives. Tabarés-Seisdedos and colleagues (2003) suggest that this deficit in visual-motor processing is familial and may be heritable, which is one criteria for defining cognitive markers or endophenotypes (Glahn et al., 2004). These findings are in support of prior studies that have demonstrated deficits in executive function/speed of information processing, which have led some researchers to suggest that deficits in executive function are traits markers that may constitute cognitive endophenotypes (Glahn et al., 2004; McIntosh et al., 2005).

As discussed under Hypothesis 1 findings, the visual learning and memory domain was no longer significant after correcting for mood symptomology. Nonetheless, it is

important to note that several significant findings were observed in the unadjusted main analyses (both MANOVA and ANOVAs) with respect to the BP group. Prior to covariate adjustment, the BP group demonstrated significant impairment compared to the NC group on six measures of visual learning and memory. As previously noted, the BP group performed comparably to the FDR group on several of these visual memory measures, implicating not only impairment due to illness parameters but also a potential genetic risk. A recent study of non-verbal memory impairment in bipolar disorder revealed impaired performance on the Rey-Osterrieth immediate recall condition, owing to poor encoding strategies (Deckersback, McMurrich, Ogutha, Savage, Sachs, & Rauch, 2004). In the current investigation, the BP group demonstrated a trend ($p < .10$) towards impaired performance on the 3-minute Rey copy condition. Other researchers (Addington & Addington, 1998; Rubinsztein et al., 2000; Yurgulen-Todd et al., 2000) have also found impairment in visuospatial memory in euthymic or remitted individuals with bipolar disorder. Collectively, the strong trends on the visual learning domain observed in this investigation, along with previous findings in the literature, suggest that the visual learning and memory domain merits further study and consideration.

Deficits in the BP group were not observed in either the attentional domain or the verbal learning domain as hypothesized. Prior studies have found impairment in sustained attention, typically measured by various continuous performance tests, but this finding was not replicated in this study. One potential explanation for negative findings with respect to the attentional domain is the premise by some researchers that impairment in sustained attention may be more a state-dependent, rather than a trait-dependent

marker (Clark, Iversen, & Goodwin, 2001; Liu, Chiu, Chang, Hwang, Hwu, & Chen, 2002). Both of these investigations demonstrated that impairments in sustained attention are more closely related to acute mania (Clark et al., 2001) and tend to improve during states of symptomatic remission (Liu et al., 2002). In fact, Liu and colleagues (2002) reported that individuals with bipolar disorder who were outpatients in clinical remission demonstrated Continuous Performance Test scores comparable to the general population. On the other hand individuals with bipolar disorder (with and without psychotic features) in the acute phases of illness were found to have CPT deficits as severe as those of individuals with schizophrenia (Liu et al., 2002). These investigators proposed that sustained attention deficits may play more of a mediating role as state-dependent vulnerability markers rather than trait markers. In the current investigation, performance on the CPT, the only measure of sustained attention, was found to be comparable among the three groups, which might be explained in part by the relatively euthymic nature of the BP group.

Similarly, verbal learning and memory deficits were not found in the present study with respect to the bipolar probands as hypothesized. Several studies have reported verbal learning and memory deficits in individuals with bipolar disorder (Ali et al., 2000; Clark et al., 2001; Denicoff et al., 1000; Seidman et al., 2002; van Gorp et al., 1998; 1999; Zubieta et al., 2001). As a whole, tasks of verbal learning and executive function have received the most consistent support as potential cognitive markers associated with bipolar disorder (Glahn et al., 2004). Interestingly, the verbal learning domain was closer to reaching significance after controlling for mood symptomology ($F = 1.4$ (3, 53), $p =$

.16). Lack of statistical power to detect differences due to the sample size may have contributed to the lack of replication for this relatively robust finding in the literature.

Another potential reason for the BP group not demonstrating significant impairment in multiple domains, particularly the verbal learning domain, may be that this sample of individuals was relatively high functioning in terms of illness severity. Studies have shown that cognitive deficits are typically associated with duration of illness as well as number of affective episodes (Clark et al., 2002; Denicoff et al., 1999; Zubieta et al., 2001). Martínez-Arán and colleagues (2004) reported that cognitive dysfunction in verbal learning and memory was specifically related to number of manic episodes. In their study investigating neuropsychological function across various stages of illness, Martínez-Arán et al. (2004) reported widespread cognitive impairment in a bipolar sample consisting of depressed, manic, and euthymic participants. The mean illness duration varied across the sample from 16.6 years for the depressed patients, to 15.4 years for manic/hypomanic patients, and 14.0 years for the euthymic patients. The total number of affective episodes ranged from 17.7 for the depressed group to 13.0 for the euthymic group. As a whole, the BP group in the current investigation demonstrated mean illness duration of 11.32 years and a mean number of 2.89 hospitalizations, which suggests that this sample of bipolar probands may not be as cognitively impaired in terms of chronicity and severity of illness. Although the number of affective episodes was not assessed or controlled for, the relatively low incidence of hospitalizations and low mean duration of illness in this sample of bipolar probands suggests that the average number of affective episodes may be relatively low.

Medication status may also have contributed to the relatively good functioning in the bipolar group and perhaps for the lack of larger differences between the bipolar probands and unaffected relatives. Recent studies have indicated that lithium and valproic acid may actually have a neuroprotective effect on cognition rather than a negative impact (Drevets, 2000; Manji, Moore, & Chen, 2000). Most of the participants in this sample (89%) were utilizing medications, typically a mood stabilizer and/or an atypical anti-psychotic, with a few also reporting use of anti-depressants ($N = 6$) and anxiolytics ($N = 5$), which could promote overall higher cognitive functioning that individuals who were not stabilized on medications. As previously mentioned, the FDR group actually performed worse than the BP group on CVLT learning trials (although the MANOVA failed to reach significance), which might be indicative of a neuroprotective function of medication in the BP group.

In summary, the BP group demonstrated cognitive impairments in the visuospatial and executive domains, with trends towards impaired performance on visual and verbal learning and memory, lending partial support to Hypothesis Two.

Hypothesis Three

In Hypothesis 3, it was predicted that there would be no differences in working memory and motor tasks among the three groups. The overall nonparametric MANOVAs indicated that there were no differences in working memory or motor abilities, as predicted, but significant differences were found among the three groups with

respect to the motor domain in the parametric analyses and after adjustment for mood symptomology.

The first finding that working memory is not impaired in individuals with bipolar affective disorder has received mixed support in the literature. Some studies have found differences in working memory (Ferrier et al., 1999; Gourovitch et al., 1999; Martínez-Arán et al., 2004; Thompson, Ferrier, Hughes, Gray, & Young, 2000), with some researchers positing working memory as a cognitive endophenotype (Ferrier et al., 1999). Other studies have examined working memory in relation to sustained attention and inhibitory control (Harmer, Clark, Grayson, & Goodwin, 2002; Larson et al., 2005), and have shown no significant differences in working memory between individuals with bipolar disorder and healthy controls. For example, Larson and colleagues contrasted a spatial working memory task, the Delayed Response Task, with Object Alternation Task, a measure of inhibitory control, and found no differences on the latter task between individuals with bipolar disorder (in manic and euthymic stages) and normal controls.

Various verbal and spatial tasks have been used to assess working memory function across studies, which could account for the variation in findings regarding this domain. For example, the Brown-Peterson task has been used as a working memory measure and has been found to be impaired in monozygotic twins discordant for bipolar disorder (Gourovitch et al., 1999). In the same study by Gourovitch and colleagues (1999), however, working memory as measured by Digit Span was not found to be impaired in the affected or unaffected twins.

Additionally, few studies examining cognition in bipolar disorder have utilized measures of spatial working memory (Glahn et al., 2004). In the current investigation, the WAIS –III Digit Span and the Wechsler Memory Scale Spatial Span were utilized as working memory tasks, representing auditory and visual working memory, respectively. Both tasks involve a simpler component or forward task, which taps primarily short-term memory and attention and a more complex, component or backwards task that involves more of a working memory component. As such, some studies differentiate between the forward and backwards condition. For example, Ferrier et al. (1999) reported impaired performance on Digits Backward but not Digits Forward and attributed this impairment to executive function subserved by working memory. These findings were not replicated in this current study, even when Digits Forward and Digits Backward were analyzed separately. No overall differences were likewise found when Spatial Span Forward and Backward were examined separately.

In addition, working memory has also been shown to fluctuate with respect to phase of illness; there seems to be some association with greater impairment during manic episodes (Murphy et al., 1999: Sweeney et al., 2000). Although a few of the bipolar probands in this study demonstrated hypomanic symptomology, none of these individuals met criteria for a current manic episode. Therefore, it is possible that working memory deficits were not elicited due to the relatively euthymic nature of this sample.

The hypothesis regarding the motor domain was supported in the main analysis when the ranked or nonparametric data were analyzed with MANOVA, such that there were no overall differences in the motor measures between the three groups, $F(2, 53) = 1.47$, $p =$

.15. As can be noted in Table 2, the MANOVA for the motor domain was significant when non-ranked or parametric data were used, and subsequent to adjustment for residual mania and depression with MANCOVA, the significant differences among the three groups remained. In order to maintain consistency with reporting of significant findings, the nonparametric data were utilized as the overall finding because of the non-normal distribution of the data set in general.

Univariate analyses (ANCOVAs) and post hoc analyses revealed that significant differences remained only in the analyses involving Hamilton Depression Rating Scale scores with respect to Purdue Pegboard test. The BP group performed worse than the NC on both the dominant and non-dominant hands, demonstrating slower fine motor coordination in terms of total pegs placed within 30 seconds. No differences were noted on grip strength or finger tapping among the three groups after controlling for residual mood symptoms.

Motor tasks have not traditionally differentiated individuals with bipolar disorder from normal controls. A few studies have demonstrated significant deficits in motor functions. Wilder-Willis and colleagues (2001) found motor differences in a sample of clinically stable bipolar probands such that the bipolar patient group was found to have poorer performance on Grooved Pegboard performance compared to a normal control group. Interestingly, these researchers found significant results independent of psychiatric symptoms as measured by the Young Mania Rating Scale and the Scale for the Assessment of Positive Symptoms. Thus, this study found differences prior to adjustment for mood symptoms, although no adjustments were made for depressive

symptoms. The sample size was small, however, with only 14 bipolar patients and 12 normal controls. Another study investigating cognitive function in euthymic individuals with bipolar I disorder demonstrated impaired performance in the patient group on two tasks of motor speed and coordination, the Manual Imitation Test and the Bead-Tap test. The sample size was likewise small ($N = 15$), and all of the bipolar probands had a history of psychotic symptoms, suggesting potentially more severe forms of illness.

Additionally, recent investigations have attempted to identify lateralized hemispheric dysfunction with respect to motor function. For example, Lohr et al. (1997) found differences in hand force instability in which participants were instructed to press a strain gauge with their index finger while observing a target on a computer screen. The sample consisted of 65 right-handed older patients (> 45 years old). Using a motor asymmetry score, they found greater left-right hand difference scores in BP patients, implicating right hemisphere dysfunction, as compared to individuals with schizophrenia, schizoaffective disorder, and normal controls.

Calligiuri et al. (2004) utilized functional magnetic resonance imaging to examine hemispheric differences in simple motor tasks. Based on prior research, they proposed hemispheric differences in cortical activity related to the nature of the motor tasks. The primary and secondary motor cortices of the left hemisphere are believed to be more involved in tasks involving sequential movement, task novelty, and choice reaction times, and the right primary and secondary motor cortices are more active in tasks involving accuracy in timing and simple reaction times (Caliquiri et al., 2004). The study examined the performance of 13 right-handed individuals with bipolar disorder on two reaction

time tasks (a simple reaction time task and a choice reaction time test). Functional magnetic resonance imaging was utilized to document activity in right and left primary motor cortex and supplementary motor areas during both tasks.

Results of the Caliquiri et al. study (2004) indicated that bipolar subjects in depressed states had longer reaction times than subjects in manic states and normal controls, and correspondingly the manic BP subjects had longer reaction times than the normal controls. The neuroimaging findings revealed group differences in terms of cortical activation in the primary motor and supplementary motor areas. The bipolar depressed subjects demonstrated abnormal activation of the ipsilateral right supplementary motor area (failure to suppress unwanted activity in right supplementary motor area during right-handed tasks). This finding was interpreted as increased right hemisphere cortical activity. The bipolar subjects with mania likewise exhibited abnormal activity during choice reaction times in the supplementary motor areas of both hemispheres. Abnormal hemispheric activation was also found in the primary motor areas for the bipolar individuals with manic symptomology only. The researchers concluded the presence of right hemisphere dysfunction related to these neuroimaging findings. It is important to emphasize that these findings were observed during a non-euthymic state of illness and may therefore represent more state-dependent characteristics. Nonetheless, these motor findings are in support of right hemisphere dysfunction.

Overall, the motor findings of this current investigation suggest that global motor deficits are not evident in bipolar probands or in their unaffected relatives but rather were confined to a motor coordination task of the Purdue pegboard task. Therefore, tasks

utilizing speed, reaction times, and motor coordination may warrant additional study to determine whether these motor functions are impaired in bipolar disorder, as there is some evidence from this current investigation and other studies to suggest that these may be impaired, particularly in non-euthymic states of illness. Also, working memory deficits were not supported in the current investigation, although only two measures of working memory were used to examine this domain. In summary, Hypothesis Three received strong support with no significant differences noted in the BP group in the domains of working memory and motor function, as assessed by the nonparametric findings.

Hypothesis Four

The Fourth Hypothesis proposed that there would be a differential right-hemisphere deficit in the bipolar probands, compared to the unaffected relatives and normal controls, as measured by right versus left cognitive composite scores. This hypothesis was supported in that the BP group did demonstrate a differential right versus left hemisphere deficit in terms of composite scores when compared to both the NC and FDR group. As per repeated measures ANOVAS, significant main effects were found for differences among the groups on the right and left composite scores as well as a significant group X composite score interaction (Refer to Figures 1 and 2). Subsequent analyses revealed that both the BP and the FDR group had significantly lower mean right and left composite scores as compared to the NC group on the total composite scores, but did not differ significantly from each other. Interestingly, the FDR group was found to have

significantly lower mean *z*-scores on both right and left hemisphere composite scores in comparison to the NC group when analyzing both the total and cognitive composite scores, whereas the BP group had lower mean z-scores on the right and left hemisphere scores only when using the total composites. Additionally, paired t-tests demonstrated that only the BP group, and not the FDR group, demonstrated a statistically significant discrepancy in right versus left hemisphere tasks, with poorer performance on right hemisphere tasks relative to left hemisphere tasks, which is consistent with a differential right hemisphere dysfunction as hypothesized. As a whole, the FDR group did not show differential deficit performance on right and left hemisphere tasks. Thus, differential performance in hemispheric functioning was evident in the BP group but not in the FDR group, although the FDR group did have significantly lower right and left hemisphere *total* and *cognitive* composite scores in comparison to the NC group.

The differential right hemisphere dysfunction, as demonstrated by the aforementioned analyses, was found to occur when analyses were done using both cognitive tasks and motor tasks combined to form the composite scores. However, when assessing strictly motor tasks, the differences were not significant, suggesting that the motor tasks did not contribute significantly to the observed hemispheric task differences between the groups. This is consistent with the analyses of the motor domain, which demonstrated differences primarily on the Purdue Pegboard task between the NC and BP group. Analyses of the motor tasks revealed that both dominant and non-dominant hand performance was impaired on the Purdue Pegboard in the BP group without evidence of strong lateralizing deficits in the non-dominant hand or right hemisphere. In contrast to the Caligiuri et al.

study (2004), no evidence was found in the current study for strong lateralizing motor deficits.

Although several prior studies have reported findings indicative of right hemisphere dysfunction, few studies have directly compared differences in right and left hemisphere tasks specifically. Miller et al. (1995) examined two psychometrically-matched tasks corresponding to right and left hemisphere functioning in a sample of affectively disorder patients with diagnoses of major depression, schizoaffective disorder, and bipolar disorder. These researchers found support for hemispheric asymmetry of function in the participants with diagnoses of major depression only, with these individuals demonstrating poorer performance on the visuospatial (right hemisphere) task relative to the verbal (left hemisphere) task. Similar trends were noted but did not reach significance for the bipolar group. The researchers reported preliminary support for right hemisphere dysfunction in affectively disordered (unipolar) patients and proposed that future studies utilize more measures to examine these effects. On the other hand, Calev et al. (1986) failed to find differential effects using psychometrically matched right and left hemisphere tasks in a mixed group of affectively disordered patients.

In this study, several measures were used to represent right and left hemisphere functioning. Efforts were made to utilize comparable tasks or analogs for left and right hemisphere functioning (e.g., CVLT and Biber Figure Learning, Digit Span and Spatial Span), to assess a broad range of right and left hemisphere functions, and to use the same number of tests for the right and left composites, thereby giving equal weight across all measures. It has been proposed that right hemisphere dysfunction is typically more

apparent in symptomatic states, especially mania (Savitz et al., 2005). Given this assumption, the aforementioned findings on hemispheric deficits are perhaps more salient, because of the fact that the BP group in this study was relatively euthymic at the time of testing.

Several of the tasks that were found to be impaired in the BP and FDR groups, and which demonstrated intermediate patterns (or trends thereof) consistent with the criteria of cognitive endophenotypes, were primarily right hemisphere visual tasks, including Judgment of Line Orientation, Rey Copy, Block Design, and Biber Figure Learning tasks. Interestingly, a recent neuroimaging study by Lyoo and colleagues (2004) documented degreased gray matter density in the right inferior frontal gyrus, a region known to process visual information. These findings lend additional support to the hypothesis of right hemisphere dysfunction in bipolar affective disorder as proposed by Flor-Henry (1976, 1983).

There is other converging evidence from electrophysiological, neuroanatomic, and neuroimaging studies that suggests that bipolar disorder may be a right hemisphere dysfunction. El Badri and colleagues (2001) found visuospatial deficits on neurocognitive tasks and corresponding resting EEG abnormalities in the right hemisphere involving areas of visuospatial processing. These abnormalities were observed in relatively young and euthymic individuals with bipolar disorder. In one of the few at-risk studies, Jouvent and colleagues (2000) documented event-related potential abnormalities suggesting right hemispheric information processing deficits in first-degree relative of patients with bipolar disorder. This investigation is one of the few studies

documenting electrophysiological abnormalities of the right hemisphere in unaffected relatives. Another investigation (Oluboka, Stewart, Sharma, Mazmanian, & Persad, 2002) demonstrated preliminary evidence of right hemisphere dysfunction using quantitative EEG. These researchers reported that patients with bipolar disorder demonstrated less organization (or coherence) in the right hemisphere during quantified EEG compared to patients with schizophrenia, although no comparisons were made to a normal control group.

Using functional magnetic resonance imaging, Caliquiri et al. (2004) also detected right hemisphere abnormalities during reaction time tasks. The patients with bipolar disorder exhibited abnormal activation patterns in both the primary motor area and supplementary motor areas, with manic bipolar patients exhibiting increased right hemispheric activity in the supplementary motor area

In summary, this investigation found support for right hemisphere dysfunction in bipolar disorder with the BP group demonstrating a differential deficit in right versus left hemisphere tasks relative to the NC and FDR group. When comparing right and left composite scores, the BP performed significantly worse than the NC group on both composites but not significantly different than their unaffected relatives. Additional studies with both bipolar probands and first-degree relatives combining cognitive tasks and neuroimaging techniques would be most useful to further clarify the functional differences in hemispheric functioning.

Strengths of the Study

This investigation addressed some of the limitations inherent in prior neurocognitive research conducted on individuals at risk for bipolar disorder. One of the major limitations identified in the literature was the relative lack of studies using comprehensive neuropsychological batteries to examine broad domains of neuropsychological functioning. Several at-risk studies (Duffy et al. 2001; Gilvarry et al. 2001; Keri et al. 2001; McIntosh et al. 2005; Pierson et al. 2000; Zalla et al. 2004) utilized a few selective measures to address specific domains and research questions, whereas others (Ferrier et al., 2004; Gourovitch et al., 1999; Kremen et al., 1998) utilized a more comprehensive battery similar to the one used in this study, although those studies using more extensive batteries had a number of other limitations. For example, the Kremen et al. (1998) study compared only female relatives in their sample and noted that replication was necessary with male relatives. As such, the use of a comprehensive neuropsychological test battery, such as the one used in this study, allows for more direct comparison to previous studies as well as a more effective means of exploring potential indicators of risk for developing bipolar disorder from a wide variety of measures.

The current study also specifically explored the premise of right hemisphere functioning, a concept that has been discussed in the literature by various researchers (Abrams & Taylor, 1981; Gruzelier & Flor-Henry, 1979; Flor-Henry 1976, 1983), but that has met with equivocal support. Most researchers have discussed significant findings of individual neurocognitive tests with respect to implications for right hemisphere dysfunction. However, few prior studies have directly examined right versus

left hemisphere tasks comparatively to determine whether this finding holds true with a broad domain of cognitive measures. Additionally, this study utilized a relatively new measure to assess visual learning and memory, the Biber Figure Learning Test, which has been utilized primarily in studies of patients with temporal lobe pathology (Glosser et al., 1997). Because verbal declarative memory has been found to be the most consistent deficit in bipolar disorder, it is reasonable to propose that declarative visual learning and memory might likewise be impaired, in accordance with the theory of right hemisphere dysfunction. Some preliminary findings were demonstrated in this investigation in terms of deficits in visual learning and memory. Several measures were found to be impaired in both the BP and FDR group in the domain of visual memory prior to adjustment for mood symptomology. Additional studies using the Biber Figure Learning Test or similar measures will be beneficial to clarify cognitive functioning in visual learning and memory and to make comparisons with verbal learning and memory.

This investigation also attempted to match participants in terms of gender, age, education, premorbid IQ, current estimated IQ, and mood symptoms. No differences were found among the groups on all the variables except for mood symptomology and current estimated IQ. Mood symptoms were assessed with standardized measures of depression (Hamilton Depression Rating Scale) and mania (Young Mania Scale). Ferrier and Thompson (2002) discuss the difficulties inherent in cross-comparison studies of cognitive function in bipolar disorder due to the failure to control for residual affective symptoms and stress the importance of accounting for residual mood symptoms in neurocognitive studies. Although as a whole the group means represented clinically

euthymic levels, there were a few individuals in the BP group that demonstrated clinically elevated symptom scores. Analyses of covariance were therefore performed to account for residual mood symptomology, and results were discussed in terms of these analyses as well as the main analyses. It has been suggested that mood symptoms must be adequately controlled for in order to make appropriate cross comparison across studies (Ferrier and Thompson, 2002).

An additional strength of the current study was that all participants were assessed with the Structured Clinical Interview for DSM-IV (SCID-for DSM-IV, research version). This methodology was used to ensure a homogenous group of participants in the BP group and to rule out diagnoses of bipolar disorder or psychotic disorders in the relatives and the normal controls. Normal controls and first-degree relatives were excluded if they demonstrated current mood episodes or met criteria for bipolar I or II disorder. A few of the first-degree relatives demonstrated subthreshold criteria, as expected, but they did not meet full criteria for bipolar I disorder or other mood disorders such as bipolar II, cyclothymia, major depressive disorder, or dysthymia. Additionally, the SCID was used to rule out significant alcohol or substance abuse in the last six months for all groups, as substance and alcohol abuse has been shown to potentially impact performance on neurocognitive testing, creating potential confounds with the obtained results.

Limitations of the Study

Several limitations were identified in the current investigation. The primary limitation, which has been problematic across most of the at-risk literature, was the

relatively small sample size. Although this study examined 57 individuals (n = 19 in each group), the overall sample size was still limited, contributing to potentially decreased statistical power to detect differences among the groups. Most at-risk studies have examined sample sizes of 15 to 20 bipolar probands and relatives (or fewer), due in part to the strict selection criteria and the difficulty inherent in recruiting subject-pairs to participate. Despite the limited sample size, significant differences were found in the current study among the three groups on several neurocognitive measures. Future studies, however, should attempt to include larger sample sizes to optimize the findings and inferences.

Another potential limitation of this study was the use of a mixed sample of first-degree relatives, which included parents, siblings, or offspring of bipolar probands. Although similar sampling frames of first-degree relatives have been used in several high-risk studies, there may be inherent problems with using parents of bipolar probands as individuals at risk. When including either parent of bipolar probands, it is uncertain which lineage, paternal, maternal, or both may have contributed to the genetic predisposition or risk factor. The pattern of transmission (maternal of paternal) may be an important factor in terms of applicability to genetic linkage and pedigree studies. Thus far, it has not been shown that bipolar I disorder has a specific pattern of transmission, although some studies suggest that bipolar II may involve preferential transmission through the maternal line (McMahan, Stine, Meyers, Simpson, & DePaulo, 1995; Stine, 1995). Although not all manifestations of bipolar disorder are familial, it might be methodologically more accurate to utilize only siblings or offspring in at-risk studies or

to include parents if line of familial transmission is evident. Only two at-risk studies of adult relatives (Ferrier et al., 2004; Jouvent et al., 2000) utilized siblings and adult offspring only, although they did not provide a specific rationale for this selection. The majority of studies in the literature appeared to use similar criteria as this current study or did not specifically delineate the characteristics of the first-degree relative group. The issue or selection of which first-degree relatives to include could affect the strength of inferences to be formulated from the results.

In the current investigation, parents comprised 8/19 or 42% of the first-degree relative sample. The remainder of the relatives consisted of five siblings and six offspring. Of those eight individuals, three of these unaffected relatives reported a family history of bipolar disorder, four individuals reported a family history of major depressive disorder, and only one of the first-degree relatives denied a history of familial bipolar disorder or depression. This pattern is relatively consistent with the fact that family history of major depression is a major risk factor for the development of bipolar disorder (Duffy, 2001). It appears that at least seven of the eight relatives may have had potential genetic vulnerability or risk of transmission in their familial lines. Caution must be noted, however, because this information was gathered strictly from self-report, as extensive interviews to verify these familial diagnoses were not conducted. Further studies might consider more extensive and verifiable review of the first degree relatives in terms of psychopathology. Nonetheless, it appears that the majority of the parents utilized in this study had probable transmission of risk on their side of the family, which lends validity to their inclusion.

In addition to the inclusion of all first-degree relatives, the selection process in itself may have posed a threat to internal validity. The participants in this study were recruited through the University of Nevada, Las Vegas, as well as from the community at large via advertisements and presentations at various support group meetings and mental health centers. In general, the bipolar probands were relatively high functioning, with a few attending the university or working in the community. None of the bipolar probands had recently been hospitalized and the number of total lifetime hospitalizations was relatively low. There may also have been a selection bias in the first-degree relatives and bipolar probands who chose to participate from those that did not, but data are not available on these potential differences. Several at-risk studies recruited bipolar probands through hospital settings (Gilvarry et al., 2001; Kremen et al., 1998; McIntosh et al., 2005; Pierson et al., 2000; Zalla et al., 2004), although some investigations did recruit participants directly from the community (Keri et al. 2001). Other researchers did not specify their method of recruitment (Ferrier et al., 2004). In general, the use of high functioning samples of BP patients would serve to decrease the observed differences in comparison to normal controls, as neurocognitive deficits have been shown to be associated with a more severe disease course and poorer outcomes. While a limitation, the inclusion of high functioning probands only strengthens the between groups differences noted in this study. These differences are expected to be even greater when more individuals with more severe and chronic bipolar disorder are evaluated.

Lastly, another potential limitation of this investigation was the failure to use strict cut-off criteria to include only bipolar probands in euthymic states. Several studies have

used standardized cut-off scores of 8 on the Hamilton Depressing Rating Scale and of 6 on the Young Mania scale, although not all studies choose to exclude participants with residual affective symptoms. Similar to the current study, several investigations have merely assessed and controlled for residual mood symptoms through the use of covariates, which appears to be acceptable practice. It might have been more beneficial, however, to include only euthymic individuals with bipolar disorder considering the underlying interest in this study was to identify trait-specific cognitive markers. As such, it is necessary to document neurocognitive deficits that exist in euthymic states. Additionally, it would have been helpful to assess for number of lifetime affective episodes and to examine the influence of this variable on overall neurocognitive function in the BP group, although this factor is more crucial when comparing across clinical populations. Future studies assessing neurocognitive function will best be served by strictly controlling the state of illness at time of testing (euthymic, depressed, or manic) and by verifying the total number of affective episodes in order to achieve better standardization for cross-comparison purposes. However, the fact that neurocognitive deficits were found in this relatively high functioning and euthymic group of bipolar probands lends further support to the possibility of the observed cognitive deficits as potential trait rather than state markers.

Significance of the Study/ Conclusions

This study extended the findings in the literature addressing neurocognitive function in individuals with bipolar disorder and examined the neuropsychological performance in

a group of individuals at risk for developing bipolar disorder. Clarification of neurocognitive functioning in individuals with bipolar disorder continues to be of paramount importance because of the increasing evidence linking cognitive and neuropsychological variables to functional outcomes (Zarate et al., 2000). Studies have demonstrated that quality of life and occupational impairment continues to be significantly impaired even during periods of relative euthymia, suggesting that factors beyond clinical symptoms contribute to poor functional outcomes and occupational functioning (Dean, Gerner, and Gerner, 2004; Dion et al., 1988). Future studies should examine the role of specific cognitive impairments on functional outcomes in order to address treatment implications. Similar strategies are being used to address the role of cognition and functional outcomes in individuals with schizophrenia (Green, Kern, and Heaton, 2004) and may prove useful to the treatment and management of bipolar affective disorder.

Second, but of no lesser importance, is the issue of identifying the processes mediating between the genetic manifestation of bipolar disorder, the genotype, and the behavioral manifestations of the illness, or the phenotype. Studies addressing these potential mediating variables are crucial to assist in the identification of genetic loci for the illness and to facilitate more accurate classification of family members in pedigree and genetic linkage studies. Because bipolar affective disorder is a complex, polygenetic illness and demonstrates imperfect penetrance, it is important to identify variables that are associated with the genotype but that are easier to observe and quantify. Several types of endophenotypes are being considered, including neurocognitive, neuroimaging,

molecular genetic, and neurophysiological variables (Savitz et al., 2005). Behavioral traits or temperaments are also being investigated in the bipolar spectrum (Evans et al., 2005). Neurocognitive variables, however, are demonstrating increasing value and promise as endophenotypes for bipolar affective disorder (Glahn et al., 2004; MacQueen, Hajek, & Alda; Savitz et al., 2005). Cognitive endophenotypes could assist in the identification of potential candidate genes, which implicate these cognitive vulnerabilities and contribute to the genotypic expression of bipolar disorder.

In order for neurocognitive variables to be considered valid endophenotypes, the variables must be shown to be highly heritable, associated with the illness, independent of clinical state, and must co-segregate within the family of probands (i.e., show an intermediate pattern of deficit such that NC > FDR > BP). In their review of cognitive endophenotypes, Glahn et al. (2004) propose that the domains of executive function/working memory and verbal learning memory have met all four criteria, with sustained attention meeting three of the four criteria. More research is necessary with respect to the visual learning and memory, visuospatial, as well as information processing speed/psychomotor domains. Ferrier et al. (2004) reported deficits in visuospatial recognition in a recent investigation with first-degree relatives (N=17) in comparison to a normal control group. Interestingly, the current investigation found some preliminary support for the visuospatial and executive function domains to be considered as endophenotypes. Judgment of Line, Block Design, and Rey Figure-copy, three of the four visuospatial tasks examined in this study, demonstrated significant differences between the three groups and trends towards an intermediate pattern of performance (NC

> FDR > BP) indicative of an endophenotype. Additionally, Digit Symbol and Trails B, tasks of psychomotor speed and executive function, were also found to demonstrate similar patterns of impairment in both the first-degree relatives and normal controls.

Although overall differences were found between the three groups on visual learning and memory, these differences did not remain significant when residual mood symptoms were controlled. Nonetheless, several findings were found to be significant in the visual learning and memory domain prior to the more stringent analyses, and it is believed that this domain necessitates further investigation. Because visual learning and memory tasks are predominantly right hemisphere functions and because verbal declarative memory has demonstrated consistent evidence of impairment (Glahn et al., 2004), it is believed that visual declarative memory tasks, such as the Biber Figure Learning Test, warrant further investigation. Studies with larger sample sizes and thus greater power to detect differences will be necessary to bear out additional findings in the visual learning domain.

This study replicated previous findings of cognitive deficits in individuals with bipolar disorder, most notably in the domains of visuoconstructional/spatial abilities, visual learning and memory and executive function. Reduced power secondary to small sample size may have contributed to the lack of significant findings in the domain of verbal learning and memory, which has been consistently documented in the literature. Of interest was the fact that this sample of bipolar probands was relatively euthymic and high-functioning, supporting the notion of cognitive dysfunction as a trait-like feature in bipolar affective disorder and lending further support to the phenotypic concept.

Additionally, this study found results consistent with the theory of right hemisphere dysfunction in bipolar disorder, which is receiving ever increasing support from neuroanatomic and neuroimaging studies and which further differentiates bipolar disorder from schizophrenia, a disorder implicating more left hemisphere dysfunction.

In general, further studies with bipolar probands and at-risk individuals, particularly first-degree relatives, are needed to further clarify the role of neurocognitive variables as endophenotypes as well as the theory of right hemisphere function. Ideally, longitudinal studies examining cognitive variables in high-risk individuals during childhood and functional and diagnostic outcomes in adulthood would be beneficial in terms of predictive and criterion validity. Studies differentiating cognitive function across manic, depressed, and euthymic states will further clarify state versus trait cognitive markers, the latter of which are believed to typify cognitive endophenotypes. In addition, few studies have examined whether neurocognitive deficits show progressive decline with age and course of illness or whether these deficits are static, although preliminary findings suggest that deficits are more pronounced in elderly bipolar samples (McKay et al., 1995; Savard et al., 1980). Lastly, future directions in research on neurocognitive endophenotypes should incorporate behavioral/cognitive tasks with neuroimaging techniques to more accurately identify these potential markers and to further examine hemispheric functioning in bipolar affective disorder.

APPENDIX I

PARTICIPANT INFORMATION AND DEMOGRAPHIC SHEETS

INFORMATIONAL FLYER

UNLV RESEARCH STUDY ON COGNITIVE ABILITIES

- Hello, my name is Linda Frantom, and I am conducting research as a doctoral student in the psychology department at UNLV under the guidance of Dr. Daniel Allen, Ph.D., Assistant Professor.
- My research examines cognitive abilities (memory, learning, and abstract thinking skills) in individuals in the community.
- To be eligible, you must be between the ages of 18 and 55, be primarily English speaking, and be able to provide informed consent and participate. If you participate, you will be asked to do various tests which will take 3 to 4 hours. UNLV psychology students will be given 3 credit hours of participation. Community individuals will be given monetary compensation.
- For additional information, please contact the investigator at 339-6890

UNLV DEPARTMENT OF PSYCHOLOGY

Information Sheet on Research Study of Cognitive Abilities in Bipolar Disorder

You are being asked to participate in a study being conducted by Linda Frantom, M.A., and Daniel N. Allen, Ph.D., from the Psychology Department at the University of Nevada-Las Vegas. You are being asked to consider participating in this study as an individual with bipolar disorder or as the first-degree relative of someone who has bipolar disorder. The study will look at different areas of thinking such as memory, attention, and planning. It is hoped that information from this study will help us to better understand bipolar disorder.

If you agree to participate in this study, you will be given a variety of tests that measure mood and the abilities of learning, memory, attention, and motor coordination. Most of these tests are paper-and-pencil tests and two tests are administered on the computer. Most of these tests are quite easy while others may seem more difficult. Some have time limits while others do not. For the attention and problem-solving tests, you will be asked to do things such as identify a target stimulus on a computer screen, sort cards into different categories, or connect letters and numbers in sequence. Tests of learning and memory will ask you to learn and remember words, faces or designs. This study will take approximately four hours to complete. You will be provided with rest breaks as needed. You will not receive individual feedback after the testing, but you will be given information on how to contact the researchers when the project is completed to receive the general results of the project.

You will receive $5.00 for every half hour completed or $40.00 for completion of the entire study. Also, by participating in this study, you will be adding to the understanding of specific cognitive abilities and bipolar disorder. This could lead to improvement in the detection and treatment of bipolar disorder and a greater understanding of the causes of the disorder.

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

All material gathered in this study will be kept private and confidential. No reference will be made in written or oral materials that could link you personally to this study at any time. All records will be stored in a locked facility at UNLV for at least 3 years after completion of this study.

Participant Consent to be contacted:

I have read or have had read to me the above information. I give consent to be contacted by the study investigator. I am at least 18 years of age. If you have any further questions, you may contact the investigator, Linda Frantom, at 339-6890.

_____ _____

Signature of participant Date

_____ _____

Participant Name Phone number

DEMOGRAPHIC QUESTIONNAIRE

Name _____

Participant (I.D. No.) _____

Age: _____ Gender _____

Race: _____

Years of Education (last year completed) _____ GED :_____

Marital Status: _____

Current Medications: _____

_____

History of any of the following:

___ Head trauma/Neurosurgery

___ Neurological diseases such as M.S.

___ Mental retardation

___ Seizure Disorder

___ Loss of consciousness, if yes, how long _____

___Stroke

___ Family history of bipolar disorder

___ Family history of Major depression

___ Family history of Schizophrenia

___ History of substance abuse in the last 6 months; 0= never 1= recreational/episodic use; 2= regular use; 3=abuse (6 mo. to 5 years); 4= sustained abuse/dependence (> 5 years)

___ History of alcohol abuse in the last 6 months (same scale as above)

___ Treatment for substance/alcohol abuse

For bipolar patients only: _____ age of onset (yrs) _____ no. of hospitalizations

_____Total length of illness (yrs)

Current medications:

_____

APPENDIX II

INFORMED CONSENTS

DEPARTMENT OF PSYCHOLOGY

INFORMED CONSENT FORM A

Introduction: You are being asked to participate in a study being conducted by Linda Frantom, M.A., and Daniel N. Allen, Ph.D., from the Psychology Department at the University of Nevada-Las Vegas. The study will look at different areas of thinking such as memory, attention, and planning.

Procedure: If you agree to participate in this study, you will be given a variety of tests that measure mood and the abilities of learning, memory, attention, and motor coordination. Most of these tests are paper-and-pencil tests and one test is administered on the computer. Most of these tests are quite easy while others may seem more difficult. Some have time limits while others do not. For the attention and problem-solving tests, you will be asked to do things such as identify a target stimulus on a computer screen, sort cards into different categories, or connect letters and numbers in sequence. Tests of learning and memory will ask you to learn and remember words, faces or designs. This study will take approximately four hours to complete. You will be provided with rest breaks as needed. You will not receive individual feedback after the testing, but you will be given information on how to contact the researchers when the project is completed to receive the general results of the project.

Benefits of Participation: You will receive $5.00 for every half hour completed or $40.00 for completion of the entire study.

Risks of Participation: There are minimal risks to you from participating in this study, apart from possible fatigue and/or boredom. You may experience some test anxiety, but the tests will not be administered in a stressful manner. You are encouraged to inform me of any discomfort or anxiety that may occur as a result of the testing procedures. I will try to answer any questions you have regarding the tests without invalidating the procedures.

Contact Information: If you have any further questions about the study or if you experience any harmful effects as a result of participation in this study, you may contact me at 339- 6890 or Dr. Daniel Allen at the UNLV Psychology Department at 895-0121. For questions regarding the rights of research subjects, you may contact the **UNLV Office for the Protection of Human Subjects at 895-2794.**

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

Confidentiality: All material gathered in this study will be kept private and confidential. No reference will be made in written or oral materials that could link you personally to this study at any time. All records will be stored in a locked facility at UNLV for at least 3 years after completion of this study.

Participant Consent: I have read or have had read to me all of the above information. I agree to participate in the study. I am at least 18 years of age. A copy of this form has been given to me. _____ _____

Signature of participant Date

_____ _____

Participant Name Witness

DEPARTMENT OF PSYCHOLOGY

INFORMED CONSENT FORM B

Introduction: You are being asked to participate in a study being conducted by Linda Frantom, M.A., and Daniel N. Allen, Ph.D., from the Psychology Department at the University of Nevada-Las Vegas. You are being asked to participate in this study as an individual with bipolar disorder or as the first-degree relative of someone who has bipolar disorder. The study will look at different areas of thinking such as memory, attention, and planning. It is hoped that information from this study will help us to better understand bipolar disorder.

Procedure: If you agree to participate in this study, you will be given a variety of tests that measure mood and the abilities of learning, memory, attention, and motor coordination. Most of these tests are paper-and-pencil tests and one test is administered on the computer. Most of these tests are quite easy while others may seem more difficult. Some have time limits while others do not. For the attention and problem-solving tests, you will be asked to do things such as identify a target stimulus on a computer screen, sort cards into different categories, or connect letters and numbers in sequence. Tests of learning and memory will ask you to learn and remember words, faces or designs. This study will take approximately four hours to complete. You will be provided with rest breaks as needed. You will not receive individual feedback after the testing, but you will be given information on how to contact the researchers when the project is completed to receive the general results of the project.

Benefits of Participation: You will receive $5.00 for every half hour completed or $40.00 for completion of the entire study. Also, by participating in this study, you will be adding to the understanding of specific cognitive abilities and bipolar disorder. This could lead to improvement in the detection and treatment of bipolar disorder and a greater understanding of the causes of the disorder.

Risks of Participation: There are minimal risks to you from participating in this study, apart from possible fatigue and/or boredom. You may experience some test anxiety, but the tests will not be administered in a stressful manner. You are encouraged to inform me of any discomfort or anxiety that may occur as a result of the testing procedures. I will try to answer any questions you have regarding the tests without invalidating the procedures.

Contact Information: If you have any further questions about the study or if you experience any harmful effects as a result of participation in this study, you may contact me at 339- 6890 or Dr. Daniel Allen at the UNLV Psychology Department at 895-0121. For questions regarding the rights of research subjects, you may contact the **UNLV Office for the Protection of Human Subjects at 895-2794.**

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

DEPARTMENT OF PSYCHOLOGY

INFORMED CONSENT FORM C

Introduction: You are being asked to participate in a study being conducted by Linda Frantom, M.A., and Daniel N. Allen, Ph.D., from the Psychology Department at the University of Nevada-Las Vegas. You are being asked to participate in this study as an individual with bipolar disorder or as the first-degree relative of someone who has bipolar disorder. The study will look at different areas of thinking such as memory, attention, and planning. It is hoped that information from this study will help us to better understand bipolar disorder.

Procedure: If you agree to participate in this study, you will be given a variety of tests that measure mood and the abilities of learning, memory, attention, and motor coordination. Most of these tests are paper-and-pencil tests and one test is administered on the computer. Most of these tests are quite easy while others may seem more difficult. Some have time limits while others do not. For the attention and problem-solving tests, you will be asked to do things such as identify a target stimulus on a computer screen, sort cards into different categories, or connect letters and numbers in sequence. Tests of learning and memory will ask you to learn and remember words, faces or designs. This study will take approximately four hours to complete. You will be provided with rest breaks as needed. You will not receive individual feedback after the testing, but you will be given information on how to contact the researchers when the project is completed to receive the general results of the project.

Benefits of Participation: You will receive one hour or research participation credit for each hour you participate in this study. Also, by participating in this study, you will be adding to the understanding of specific cognitive abilities and bipolar disorder. This could lead to improvement in the detection and treatment of bipolar disorder and a greater understanding of the causes of the disorder.

Risks of Participation: There are minimal risks to you from participating in this study, apart from possible fatigue and/or boredom. You may experience some test anxiety, but the tests will not be administered in a stressful manner. You are encouraged to inform me of any discomfort or anxiety that may occur as a result of the testing procedures. I will try to answer any questions you have regarding the tests without invalidating the procedures.

Contact Information: If you have any further questions about the study or if you experience any harmful effects as a result of participation in this study, you may contact me at 339- 6890 or Dr. Daniel Allen at the UNLV Psychology Department at 895-0121. For questions regarding the rights of research subjects, you may contact the **UNLV Office for the Protection of Human Subjects at 895-2794.**

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

Confidentiality: All material gathered in this study will be kept private and confidential. No reference will be made in written or oral materials that could link you personally to

this study at any time. All records will be stored in a locked facility at UNLV for at least 3 years after completion of this study.

Participant Consent:

I have read or have had read to me all of the above information. I agree to participate in the study. I am at least 18 years of age. A copy of this form has been given to me.

_____	_____
Signature of participant	Date
_____	_____
Participant Name	Witness

DEPARTMENT OF PSYCHOLOGY

INFORMED CONSENT FORM D

Introduction: You are being asked to participate in a study being conducted by Linda Frantom, M.A., and Daniel N. Allen, Ph.D., from the Psychology Department at the University of Nevada-Las Vegas. The study will look at different areas of thinking such as memory, attention, and planning.

Procedure: If you agree to participate in this study, you will be given a variety of tests that measure mood and the abilities of learning, memory, attention, and motor coordination. Most of these tests are paper-and-pencil tests and two tests are administered on the computer. Most of these tests are quite easy while others may seem more difficult. Some have time limits while others do not. For the attention and problem-solving tests, you will be asked to do things such as identify a target stimulus on a computer screen, sort cards into different categories, or connect letters and numbers in sequence. Tests of learning and memory will ask you to learn and remember words, faces or designs. This study will take approximately 3.5-4.0 hours to complete. You will be provided with rest breaks as needed. You will not receive individual feedback after the testing, but you will be given information on how to contact the researchers when the project is completed to receive the general results of the project.

Benefits of Participation: You will receive one hour or research participation credit for each hour you participate in this study. Also, by participating in this study, you will be adding to the understanding of specific cognitive abilities and bipolar disorder. This

could lead to improvement in the detection and treatment of bipolar disorder and a greater understanding of the causes of the disorder.

Risks of Participation: There are minimal risks to you from participating in this study, apart from possible fatigue and/or boredom. You may experience some test anxiety, but the tests will not be administered in a stressful manner. You are encouraged to inform me of any discomfort or anxiety that may occur as a result of the testing procedures. I will try to answer any questions you have regarding the tests without invalidating the procedures.

Contact Information: If you have any further questions about the study or if you experience any harmful effects as a result of participation in this study, you may contact me at 339- 6890 or Dr. Daniel Allen at the UNLV Psychology Department at 895-0121. For questions regarding the rights of research subjects, you may contact the **UNLV Office for the Protection of Human Subjects at 895-2794.**

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

Confidentiality: All material gathered in this study will be kept private and confidential. No reference will be made in written or oral materials that could link you personally to this study at any time. All records will be stored in a locked facility at UNLV for at least 3 years after completion of this study.

Participant Consent:

I have read or have had read to me all of the above information. I agree to participate in the study. I am at least 18 years of age. A copy of this form has been given to me.

Signature of participant	Date
Participant Name	Witness

APPENDIX III

TABLES

Table 1

Descriptives of Neuropsychological Variables

Variable $N = 57$	*M*	*SD*	Skewness	Kurtosis	Normality (Shapiro-Wilk)	*p*
Vocabulary	11.56	2.28	-.53	.66	.94	.02
Block Design	10.32	2.60	.59	-.49	.94	.01
CVLT Trials 1-5	51.60	9.02	.26	-.68	.973	.29
CVLT short free	10.93	2.58	-.13	-.72	.953	.04
CVLT short cued	11.86	2.32	-.12	-.71	.97	.62
CVLT long free	11.61	2.46	.05	-.46	.97	.16
CVLT long cued	12.00	2.34	.01	-.66	.96	.12
CVLT hits	14.72	1.49	-.99	-.51	.78	.00
CVLT discrim.	95.07	3.99	-.53	-.34	.90	.00
CVLT response	-.04	.44	.66	1.31	.85	.00
Faces I	10.89	2.53	.21	-.09	.96	.11
Faces II	11.25	2.36	.25	.39	.96	.06
Face Recognition	46.09	3.84	-3.40	19.13	.71	.00
Judgment of Line	24.18	3.88	-.75	.05	.71	.00
Finger Tap Dom	47.09	6.51	.15	-.20	.99	.79
Finger Tap ND	42.08	5.32	-.31	-.82	.97	.30
Grip Dom	28.41	13.0	1.78	5.40	.87	.00
Grip ND	26.74	12.0	1.23	2.31	.91	.001

Table 1 (Continued)

Descriptives of Neuropsychological Variables

Variable $N = 57$	*M*	*SD*	Skewness	Kurtosis	Normality (Shapiro-Wilk)	*p*
Purdue DOM	26.74	12.06	1.23	2.31	.91	.001
Purdue ND	14.04	1.92	.46	-.03	.96	.10
Grip ND	12.89	1.61	.41	.22	.98	.44
Purdue DOM	41.21	9.91	.15	-.79	.97	.33
Purdue ND	141.6	32.50	-.80	.49	.95	.03
Verbal Fluency	33.26	8.60	-.85	.45	.94	.001
Biber total	34.09	8.50	-1.06	1.07	.91	.001
Biber short recall	14.39	1.13	-2.52	8.60	.66	.001
Biber delayed	1.35	1.88	1.71	2.28	.72	.001
Biber hits	.93	.07	-2.62	8.63	.60	.001
Biber false alarms	.96	.11	-1.90	4.36	.75	.001
Biber hit rate	29.60	9.23	.10	2.11	.92	.001
Biber discrim.	71.84	25.41	1.60	3.29	.86	.01
Trails A	10.41	2.59	.02	-.77	.97	.15
Trails B	9.82	2.89	.08	.17	.97	.22
Digit Span	.74	.16	-.51	-.77	.95	.02
Spatial Span	.90	.05	-.52	-.62	.96	.06
CPT hit rate	.45	.31	-1.11	.73	.89	.001

Table 1 (continued)

Descriptives of Neuropsychological Variables

Variable $N = 57$	*M*	*SD*	Skewness	Kurtosis	Normality (Shapiro-Wilk)	*p*
CPT sensitivity	.90	.05	-.52	-.62	.96	.06
CPT Beta	.45	.31	-1.11	.73	.89	.001
CPT D'	2.46	.76	.36	-.64	.96	.08
Rey copy	33.86	4.38	-2.97	8.97	.92	.001
Rey 3-minute	43.78	14.35	-.32	-.90	.94	.001
Delay						
Rey long delay	42.64	14.45	-.15	-.95	.94	.001
Category fluency	20.56	4.15	.27	-.214	.98	.43
Stroop words	45.95	9.51	-.03	.266	.97	.31
Stroop color	43.02	10.51	.47	.63	.97	.15
Stroop interference	49.28	6.51	.60	.93	.98	.34
WCST	4.91	2.02	-1.60	.99	.61	.001
categories						
WCST persev.	15.55	12.35	1.41	1.21	.80	.001
Digit Symbol	9.70	2.69	-.21	-.79	.96	.11

Table 2

Comparison of Parametric and Nonparametric Multivariate and Univariate Tests

	Parametric Tests				Nonparametric Tests			
	Pillai's Trace		Univariate Tests		Pillai's Trace		Univariate Tests	
Domains and Tests	$F(2, 53)$	p	$F(2, 53)$	p	$F(2, 53)$	p	$F(2, 53)$	p
Visuoconstructional/ Spatial Domain	3.01	.01			3.50	.01		
Rey Figure Copy			0.63	.54			6.09	.001
Block Design			11.0	.01			12.97	.001
Judgment of Line			5.63	.01			5.88	.01
Face Recognition			.05	.95			1.69	.19
Verbal Learning and Memory (CVLT)	1.12	.34			1.38	.20		
Trials 1-5			3.67	.03			3.28	.05
Short Delay Free			2.07	.14			0.47	.63
Short Delay Cued			1.18	.32			0.84	.44
Long Delay Free			0.64	.53			1.99	.15
Long Delay Cued			2.64	.08			2.52	.09
Recognition Hits			0.25	.12			3.05	.06
Discriminability			4.32	.02			5.34	.01
Response bias			0.06	.94			0.23	.80
Working Memory Domain	1.26	.29			1.58	.20		
Digit Span			0.73	.49			1.43	.25
Spatial Span			1.00	.38			2.49	.09

Table 2 (continued)

Comparison of Parametric and Nonparametric Multivariate and Univariate Tests

	Parametric Tests				Nonparametric Tests			
	Pillai's Trace		Univariate Tests		Pillai's Trace		Univariate Tests	
Domains and Tests	$F(2, 53)$	p	$F(2, 53)$	p	$F(2, 53)$	p	$F(2, 53)$	p
Executive Function Domain	2.62	.01			2.42	.01		
FAS Verbal Fluency			1.49	.24			1.09	.34
WCST categories			1.65	.20			1.95	.15
WCST errors			4.93	.01			2.51	.09
WCST failure to maintain			2.26	.11			3.27	.05
Category fluency			0.76	.47			1.11	.34
Digit Symbol			10.3	.01			10.31	.001
Trails B			5.52	.01			5.27	.01
Attention/ Psychomotor	1.08	.39			1.03	.43		
Stroop Test-Words			3.51	.04			6.90	.001
Stroop Test-Colors			3.30	.05			2.77	.07
Stroop Interference			2.58	.09			2.65	.08
Trails A			0.63	.54			0.42	.66
CPT hit rate			0.73	.49			0.63	.54
CPT sensitivity			0.15	.86			0.09	.91
CPT D'			0.18	.83			0.15	.86
CPT response bias			0.70	.50			0.67	.52

Table 2 (continued)

Comparison of Parametric and Nonparametric Multivariate and Univariate Tests

	Parametric Tests				Nonparametric Tests			
	Pillai's Trace		Univariate Tests		Pillai's Trace		Univariate Tests	
Domains and Tests	$F(2, 53)$	p	$F(2, 53)$	p	$F(2, 53)$	p	$F(2, 53)$	p
Visual Learning / Memory Domain	1.90	.02			1.72	.04		
Trials 1-5			4.34	.02			5.17	.01
Short Delay Free			2.31	.11			2.08	.14
Long Delay Free			6.78	.01			7.96	.001
Immediate Memory			2.80	.07			2.91	.06
Discriminability			4.22	.02			3.40	.04
Hit rate			2.97	.06			2.99	.06
False alarm rate			3.86	.03			6.39	.001
Rey 3-minute			4.81	.01			3.98	.02
Rey Delayed			2.54	.16			2.78	.07
Faces I			6.23	.01			6.90	.001
Faces II			4.32	.02			5.34	.01
Motor Domain	1.96	.04			1.47	.15		
Grip Strength Dom			3.31	.04			1.90	.16
Grip Strength ND			2.36	.10			1.28	.29
Finger Tap Dom			1.71	.19			1.70	.19
Finger Tap ND			0.13	.88			0.72	.93
Purdue Dominant			5.23	.01			5.22	.01
Purdue Non-Dom			4.68	.01			4.22	.02

Table 3

Demographic Characteristics of Normal Control, First-Degree Relative, and Bipolar Groups

Variable	Group								
	NC		FDR		BP				
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*(2,54)	*p*	Scheffé
Age	33.95	10.88	38.26	15.67	35.47	12.98	.51	.60	NS
Education	14.74	1.15	13.53	1.92	13.37	2.75	2.53	.08	NS
Premorbid IQ	15.86	2.91	13.45	3.61	14.71	2.65	2.93	.06	NS
Current Estimated IQ	108.73	9.90	99.57	10.42	97.63	8.61	7.14	.00	*NC>FDR=BP

*$p < .05$; Premorbid IQ based on Bilder Index; Current Estimated IQ based on regression equations using Vocabulary and Block Design subtests.

Table 3 (continued)

Demographic Characteristics of Bipolar, First-Degree Relative, and Normal Control Groups

Variable	Group								
	NC		FDR		BP		Chi-Square $\chi(2, N=57)$	p	
Sex	*N* (males)	% (males)	*N* (males)	% (males)	*N* (males)	% (males)	4.17	.12	NS
	7	37	4	21	10	53	Chi-Square $\chi(10, N=57)$		
Ethnicity	*N*	%	*N*	%	*N*	%	10.43	.40	NS
Caucasian	13	68	15	79	14	74			
African American	2	11	2	11	3	16			
Hispanic	3	16	0	0	0	0			
Native American	1	5	1	5	1	5			
Asian	1	5	1	5	1	5			

Table 4

Clinical Characteristics of the Bipolar Group

Variable	Bipolar Group (N=19)	
	M	SD
Age at onset	24.21	9.11
Number of hospitalizations	2.89	3.71
Length of illness duration	11.32	11.20
Hamilton Rating Scale of Depression	6.89	5.24
Young Mania Scale	6.16	5.54
Medication status		
Mood stabilizers (% of subjects)	74.00	
Antipsychotic (% of subjects)	37.00	
Antidepressants (% of subjects)	42.00	
Family history of bipolar disorder (%)	58.00	
Family history of depression (%)	68.00	

Table 5

Comparisons among Normal Control (NC), First-Degree Relatives (FDR), and Bipolar (BP) Groups on Visuoconstructional / Spatial Domain

Visuoconstructional / Spatial Variables	Groups						Univariate		Post Hoc Tests
	NC		FDR		BP				
	N=19		N=19		N=19		F tests		
	M	*SD*	*M*	*SD*	*M*	*SD*	$F(2, 54)$	p	$p < .05$, $*p < .10$
Rey Figure Copy	34.68	4.78	33.82	4.84	33.07	3.46	6.09	.00	NC>BP, *FDR>BP
Block Design	12.16	2.21	10.05	2.26	8.79	2.23	12.97	.00	NC>FDR, BP, *FDR>BP
Judgment of Line	26.42	2.06	23.26	4.58	22.84	3.67	5.88	.00	NC>FDR, BP
Face Recognition	46.32	5.76	45.95	2.68	46.00	2.31	1.69	.19	

Table 6

Comparisons among Normal Control (NC), First-Degree Relatives (FDR), and Bipolar (BP) Groups on Visual Learning and Memory

Visual Learning and Memory Variables	Groups						Univariate		Post Hoc Tests
	NC $N=19$		FDR $N=19$		BP $N=19$		F tests		
	M	*SD*	*M*	*SD*	*M*	*SD*	$F(2, 54)$	*p*	$p < .05$, $^{*}p < .10$
Biber Trials 1-5	157.2	23.58	135.84	32.15	130.79	35.56	5.16	.01	NC >BP, NC > FDR
Short Delay Free Recall	36.33	6.91	32.58	8.97	30.74	9.27	2.07	.14	
Long Delay Free Recall	39.17	5.10	33.16	8.91	30.00	8.71	7.96	.00	NC >BP, NC > FDR
Immediate memory	44.42	1.64	44.05	1.96	42.74	3.07	2.91	.06	*NC > BP
Discriminability	.92	.04	.86	.11	.82	.15	3.39	.04	NC > BP

Table 6 (continued)

Comparisons among Normal Control (NC), First-Degree Relatives (FDR), and Bipolar (BP) Groups on Visual Learning and Memory

Visual Learning and Memory Variables	Groups						Univariate		Post Hoc Tests
	NC $N=19$		FDR $N=19$		BP $N=19$		F tests		
	M	*SD*	*M*	*SD*	*M*	*SD*	$F(2, 54)$	*p*	$p < .05$, $^{*}p < .10$
Hit rate	.96	.02	.93	.06	.91	.10	2.99	.06	
False alarm rate	.04	.03	.07	.07	.09	.06	6.39	.00	NC > BP
Rey 3-minute	23.16	3.93	16.61	8.44	18.55	6.86	3.98	.02	NC > FDR, * NC > BP
Rey Delayed	22.13	4.21	17.03	9.58	18.29	6.98	2.78	.07	
Faces I	12.42	2.12	10.26	2.47	10.00	2.27	6.89	.00	NC > BP, FDR
Faces II	12.47	2.12	10.68	2.29	10.57	2.29	5.33	.01	NC > BP, *NC > FDR

Table 7

Comparisons among Normal Control (NC), First-Degree Relatives (FDR), and Bipolar (BP) Groups on Executive Function Domain

Executive Function Variables	Groups NC N=19		FDR N=19		BP N=19		Univariate F tests		Post Hoc Tests
	M	*SD*	*M*	*SD*	*M*	*SD*	$F(2, 53)$	p	$p < .05$, $^{*}p < .10$
WCST categories	5.58	1.43	4.66	2.06	4.47	2.39	1.94	.15	
WCST perseverative errors	8.84	5.18	17.17	14.73	20.74	13.80	6.07	.01	NC > BP
WCST failure to maintain	.53	.77	.83	1.24	1.26	1.15	3.27	.05	*NC > BP
Letter Fluency (FAS)	44.53	6.92	39.44	10.63	40.11	11.36	1.09	.34	
Category Fluency	21.11	3.00	20.72	4.90	19.53	4.27	1.11	.34	
Digit Symbol	11.00	2.03	10.50	2.66	7.84	2.20	10.31	.01	NC > BP, FDR > BP
Trails B	58.53	11.54	73.17	21.13	86.12	34.05	5.27	.01	NC > BP, * NC > FDR

Table 8

Comparisons among Normal Control (NC), First-Degree Relatives (FDR), and Bipolar (BP) Groups on Verbal Learning and Memory Domain

Verbal Learning and Memory (CVLT scores)	Groups						Univariate		Post Hoc Tests
	NC		FDR		BP				
	N=19		N=19		N=19		F tests		
	M	*SD*	*M*	*SD*	*M*	*SD*	$F(2, 54)$	*p*	$p < .05$, $^{*}p < .10$
Trials 1-5	55.37	7.76	47.79	8.67	51.60	9.02	3.28	.05	
Short-delay free recall	11.37	2.52	10.42	2.98	11.00	2.24	0.47	.63	
Short-delay cued recall	12.32	2.00	11.21	2.70	12.05	2.20	0.84	.44	
Long-delay free recall	12.53	1.98	11.05	3.03	11.26	2.10	1.99	.14	
Long-delay cued recall	12.89	1.91	11.21	2.66	11.89	2.18	2.52	.09	
Recognition	15.21	1.32	14.21	1.51	14.74	1.52	3.05	.07	
Discriminability	96.79	3.65	93.53	3.82	94.89	3.99	4.28	.02	
Response Bias	-.03	.46	-.07	.49	-.03	.39	0.23	.80	

Table 9

Comparisons among Normal Control (NC), First-Degree Relatives (FDR), and Bipolar (BP) Groups on Attention/Psychomotor Domain

Attention / Psychomotor Variables	Groups						Univariate		Post Hoc Tests
	NC		FDR		BP				
	N=19		N=19		N=19		F tests		
	M	*SD*	*M*	*SD*	*M*	*SD*	$F(2, 50)$	*p*	
Stroop-Words	104.20	12.97	96.53	15.00	92.82	11.69	3.41	.04	
Stroop-Colors	74.79	10.96	70.53	14.03	63.88	13.20	2.77	.07	
Stroop Test-Interference	43.79	9.52	38.41	10.88	36.94	8.17	2.65	.08	
Trails A	28.21	6.07	29.00	12.56	31.65	.14	.42	.66	
CPT hit rate	.78	.14	.72	.20	.72	.05	0.15	.86	
CPT sensitivity	.91	.05	.90	.06	.90	.66	0.09	.91	
CPT D'	2.53	.72	2.46	.92	2.38	.49	0.15	.86	

Table 10

Comparisons among Normal Control (NC), First-Degree Relatives (FDR), and Bipolar (BP) Groups on Working Memory Domain

Working Memory Variables	Groups						Univariate		Post Hoc Tests
	NC		FDR		BP				
	$N=19$		$N=19$		$N=19$		F tests		
	M	SD	M	SD	M	SD	$F(2, 54)$	p	$p < .05$, $^{*}p < .10$
Digit Span	11.00	2.40	10.63	2.69	9.95	3.03	1.43	.25	
Spatial Span	10.68	2.88	9.84	3.04	9.32	3.11	2.49	.10	

Table 11

Comparisons among Normal Control (NC), First-Degree Relatives (FDR), and Bipolar (BP) Groups on Motor Domain

Motor Variables	Groups						Univariate		Post Hoc Tests
	NC		FDR		BP				
	N=19		*N*=19		*N*=19		*F* tests		
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*(2, 53)	*p*	$p < .05$, $^{*}p < .10$
Grip Strength Dominant	34.34	17.39	24.42	7.58	26.26	10.37	1.91	.16	
Grip Strength Non-Dom	31.36	15.74	23.28	7.96	25.42	10.01	1.28	.29	
Finger Tapping Dominant	49.24	8.14	45.59	5.21	46.20	5.62	1.70	.19	
Finger Tapping Nondom	42.45	5.31	41.99	4.87	41.57	6.00	.72	.93	
Peg Board Dominant	14.75	1.71	14.22	2.11	12.96	1.36	5.22	.01	
Purdue Non-dominant	13.57	1.65	12.99	1.65	12.07	1.22	4.22	.02	

Table 12

Comparison of Adjusted and Unadjusted Means for Visual Learning and Memory Domain

Test	Group	Uncorrected Mean	Corrected for Mania	Corrected for Depression
Faces I scaled score	NC	12.42	12.44	12.52
	FDR	10.26	10.27	10.33
	BP	10.00	9.98	9.83
Faces II scaled score	NC	12.47	12.48	12.70
	FDR	10.68	10.69	10.85
	BP	10.58	10.57	10.19
Biber Trials 1-5	NC	158.37	155.79	155.92
	FDR	135.84	134.88	134.07
	BP	130.79	134.33	135.01
Biber immed. recall	NC	36.47	35.69	35.83
	FDR	32.58	32.29	32.12
	BP	30.74	31.82	31.84
Biber delayed recall	NC	39.11	38.16	38.34
	FDR	33.16	32.81	32.60
	BP	30.00	31.29	31.32

Table 12 (continued)

Comparison of Adjusted and Unadjusted Means for Visual Learning and Memory Domain

Test	Group	Uncorrected Mean	Corrected for Mania	Corrected for Depression
Biber hit rate	NC	0.96	0.96	0.96
	FDR	0.93	0.93	0.93
	BP	0.91	0.91	0.91
Biber false alarms	NC	0.58	0.74	0.49
	FDR	1.42	1.48	1.36
	BP	2.05	1.83	2.20
Biber discrimination	NC	0.92	0.91	0.92
	FDR	0.86	0.86	0.86
	BP	0.82	0.83	0.82
Rey 3'delay	NC	23.16	22.98	23.42
	FDR	16.61	16.54	16.79
	BP	18.55	18.80	18.10
Rey delayed	NC	22.13	22.02	22.58
	FDR	17.03	16.98	17.35
	BP	18.29	18.44	17.52

APPENDIX IV

FIGURES

Figure 1. Total Right and Left Composite Scores for NC, FDR, and BP groups

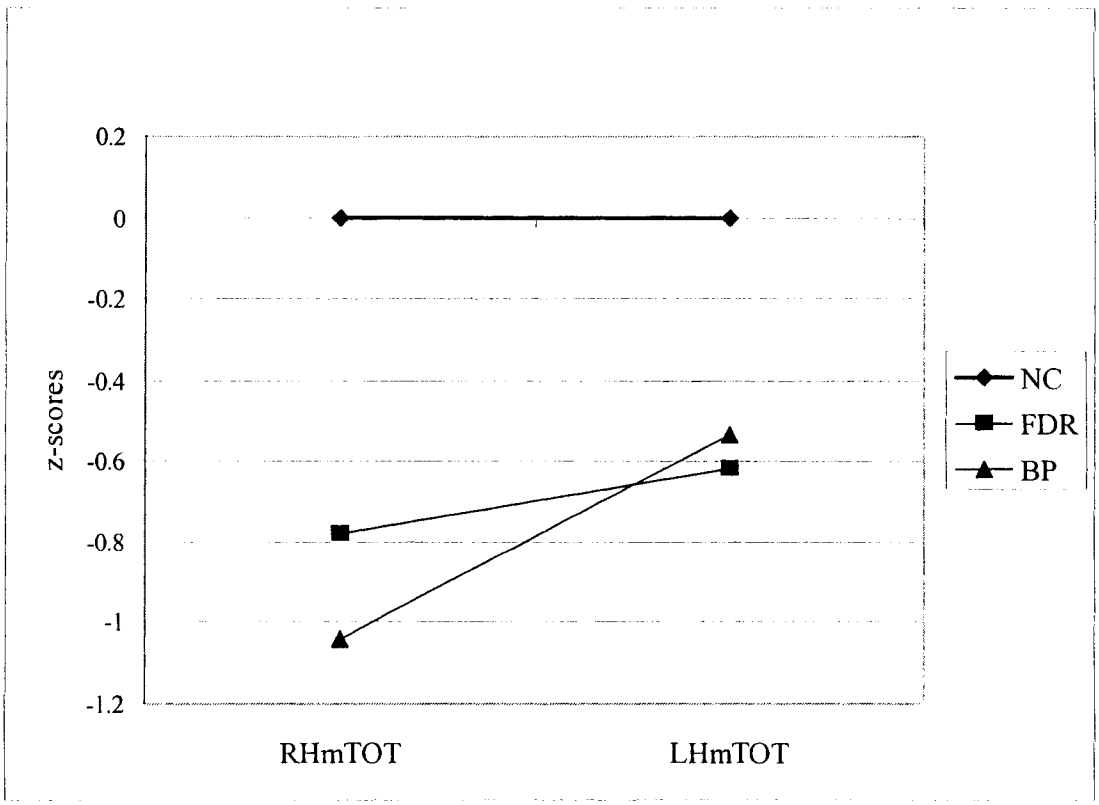


Figure 2. Right and Left Cognitive Composite Scores for NC, FDR, and BP groups.

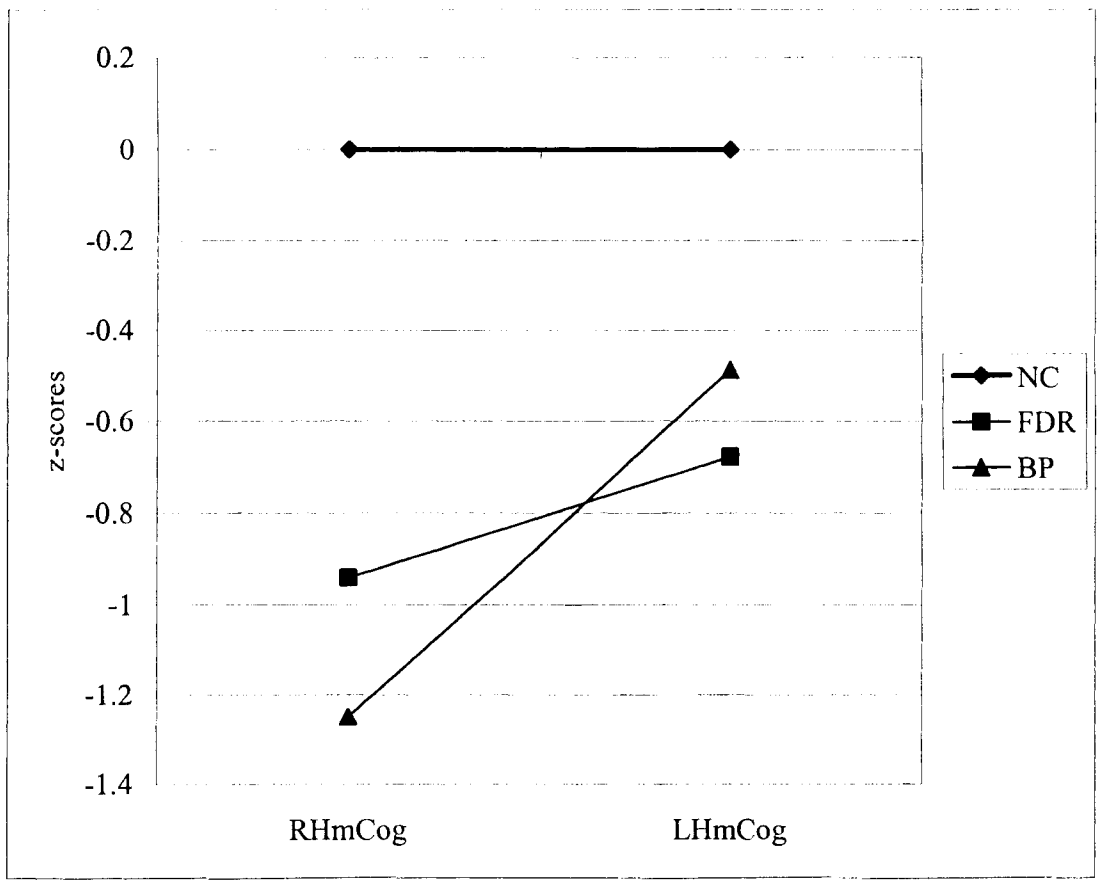


Figure 3. Right and Left Motor Composites for NC, FDR, and BP groups.

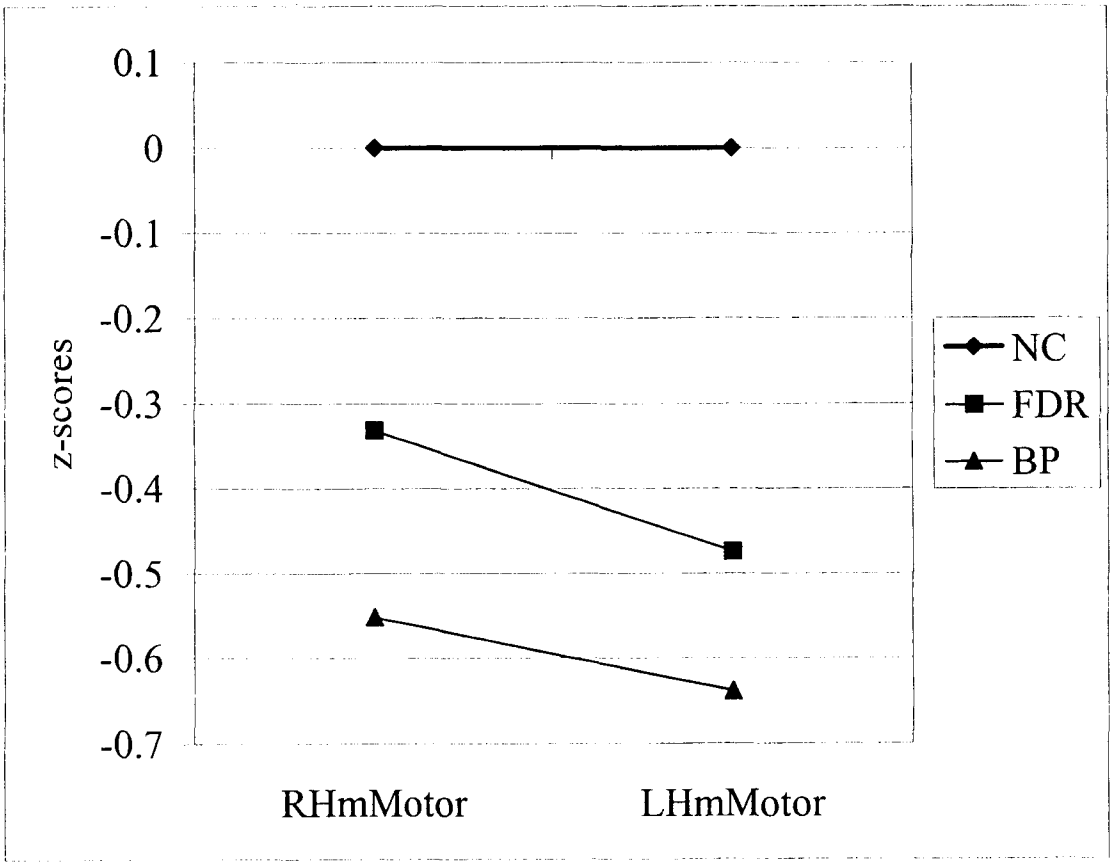
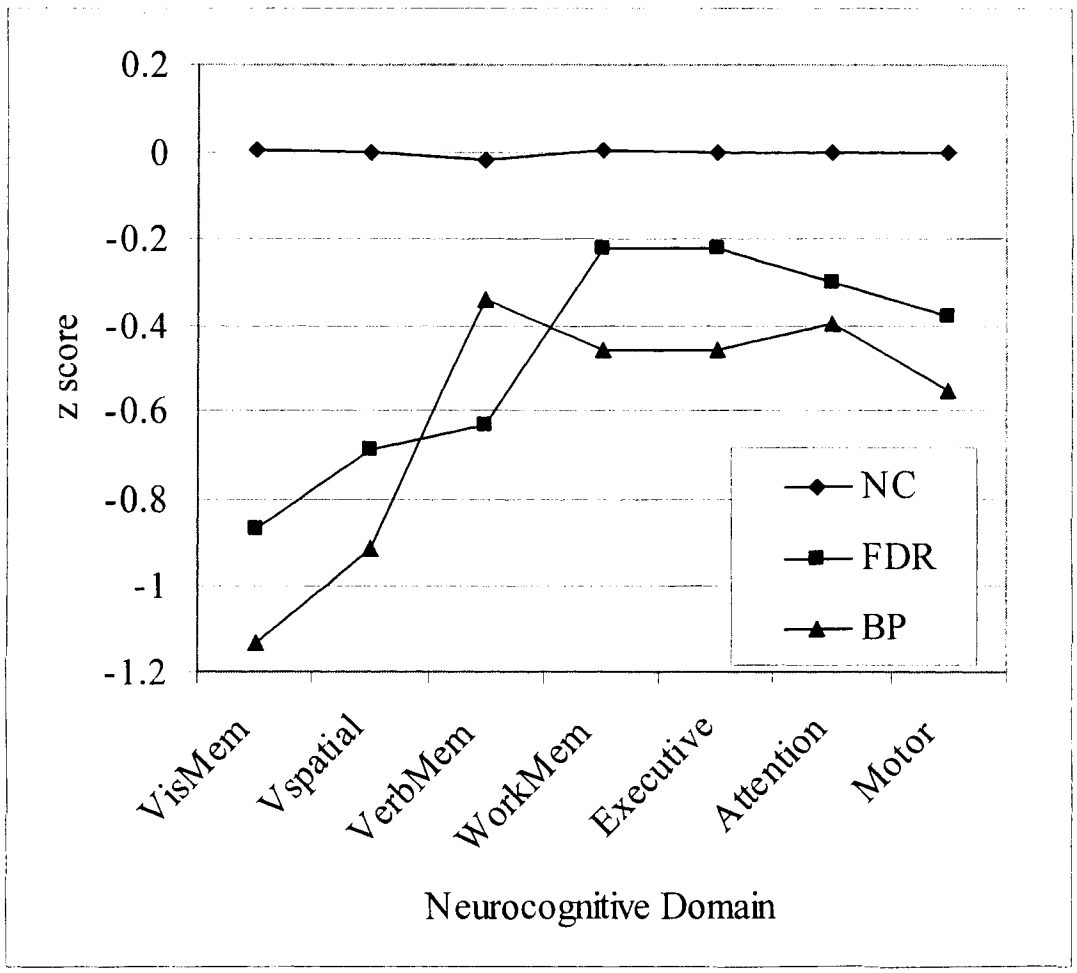


Figure 4. Neurocognitive Domain Performances of FDR and BP groups relative to NC group.



VisMem = Visual Learning and Memory Domain; Vspatial = Visuoconstructional/Spatial domain; VerbMem = Verbal Learning and Memory Domain; WorkMem= Working Memory Domain; Executive = Executive Function Domain; Attention = Attention/psychomotor speed Domain; Motor = Motor Domain.

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