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Neurocognitive deficits and functional outcome in bipolar disorder

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NEUROCOGNITIVE DEFICITS AND FUNCTIONAL OUTCOME
IN BIPOLAR DISORDER

by

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ABSTRACT

Neurocognitive Deficits and Functional Outcome in Bipolar Disorder

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Bipolar disorder affects approximately 1% of the population. It is a severe and debilitating illness, causing serious impairment of interpersonal, occupational and social functioning. The disorder is characterized by marked mood swings as well significant neurocognitive deficits. Based on work with other psychiatric and neurological disorders, neurocognitive deficits in bipolar disorder are expected to be strong predictors of functional capacity. However, few studies have evaluated the consequences of neurocognitive deficits in this disorder. Most available studies have focused on the clinical correlates of functional outcome, such as number of hospitalizations, age of disorder onset, and severity of symptoms. While useful, these studies provide only limited information regarding more complex functional domains, and their associations with neurocognitive functioning. To address this limitation, the current study examined the relationship between neurocognitive deficits and the psychosocial and occupational functioning of individuals with bipolar disorder. Forty-seven individuals with bipolar disorder received a standard battery of neuropsychological and functional outcome measures. Functional outcome measures were designed to assess presence and quality of activities, as well as patient satisfaction in various domains of functioning. These measures are both self-report format and performance-based in order to provide a

comprehensive view of the patients' functioning. Results indicated that functional outcome as measured by a performance-based assessment was significantly predicted by a global neurocognitive impairment rating ($R^2 = .160$, $F = 8.59$, $df = 1,45$, $p = .005$). Significant correlations were found between areas of functioning and neurocognitive domains. There were significant relationships between finance ability and the working memory and visual constructional/spatial domains, between communication ability and the verbal memory and learning domain, and between household skills and the attention/psychomotor speed and working memory domains. However, subhypotheses examining the prediction of specific areas of functional outcome by specific neurocognitive domains based on the literature in schizophrenia were not supported by the current study. Furthermore, mediator-moderator analyses examining the role of neurocognitive impairment as a mediator or moderator between chronicity and functional outcome as well as between mood symptoms and functional outcome were not supported by the current study. The current study adds additional support that neurocognitive deficits were related to functional outcome in bipolar disorder. Further, neurocognitive deficits are a significant predictor of functioning as measured by the ability to perform functional activities. Specific areas of functioning were related to neurocognitive domains, which can serve as a basis for future research.

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CHAPTER 1

INTRODUCTION

The purpose of the present study was to investigate the association between neurocognitive deficits and functional outcome in bipolar disorder. Bipolar disorder is a severe psychiatric disorder characterized by fluctuations in mood. People diagnosed with bipolar disorder experience mood episodes of mania, depression, or mixed, consisting of a combination of manic and depressive symptoms (American Psychological Association, 2000). They can also experience periods of time where they are free of mood symptoms or euthymic. The lifetime prevalence of bipolar disorder is estimated between 1.0 to 1.6% in the adult population (Leverich et al., 2001), and has been estimated as high as 5% (Akiskal et al., 2000). Originally it was thought that while in a euthymic mood state, the patient was essentially unimpaired and experienced a return to normal functioning (Olley et al., 2005). This view has been challenged as it has been found that patients with bipolar disorder in a euthymic state experience difficulties in various domains of social and occupational functioning (Gitlin, Swendsen, Heller, & Hammen, 1995). In fact, bipolar disorder has been reported as being the sixth leading cause of disability worldwide in terms of global health burden (Murray & Lopez, 1996). Some studies have shown that while mood state improves and patients achieve symptom recovery, functional recovery continues to be impaired and many patients don't return to premorbid levels of functioning (Dion, Tohen, Anthony, & Waternaux, 1988; Tohen et al., 2000).

In addition to impairments in functional outcome, research evidence has shown neurocognitive deficits in bipolar disorder. Neurocognitive deficits are impairments in cognitive ability that are closely linked to the functioning of specific brain areas, neural

pathways, or cortical networks. There has been a large focus in determining the presence of these deficits in severe mental illness. Research in this area has found that neurocognitive deficits are characteristic of many psychiatric disorders, and that they are present in addition to the more typical symptoms of a disorder (Bearden, Hoffman, & Cannon, 2001; Green, 1996). Neurocognitive deficits have been substantially documented in patients with bipolar disorder, and exist in the areas of executive functioning, verbal and visual memory, attention, and visuospatial ability (Bearden et al., 2001; Robinson & Ferrier, 2006). Some of these deficits seem to be impacted by the mood state the patient is experiencing, while others continue through periods where the patient is generally asymptomatic or euthymic (Bearden et al., 2001; Murphy & Sahakian, 2001). During euthymic mood states, patients with bipolar disorder continue to show deficits in executive functioning, verbal and visual memory, and sustained attention (Olley et al., 2005; Quraishi & Frangou, 2002). These deficits, which are present during asymptomatic states, may be trait-like characteristics of the disorder. To achieve the main objective of the study, neuropsychological assessments were grouped into seven cognitive domains: executive function, attention/psychomotor speed, verbal learning and memory, visual learning and memory, working memory, visuoconstructional/spatial organization, and motor ability. Performance in these domains was assessed to determine areas of neuropsychological deficits.

Research in bipolar disorder has consistently shown impairments in occupational and psychosocial functioning and neurocognitive abilities. The literature examining the association between these two areas is minimal and complicated by methodological issues. Small sample sizes, limited neuropsychological test batteries and poor

measurement of functional outcome weaken the conclusions in these few studies. Some of the main findings of this research have shown a relationship between neuropsychological domains and functioning, specifically that executive functioning, verbal memory, and sustained attention, among other neuropsychological domains, are associated with psychosocial and occupational functioning (Atre-Vaidya et al., 1998; Dickerson et al., 2004; Laes & Sponheim, 2006; Martínez-Arán et al., 2002; Martínez-Arán, Vieta, Colom, et al., 2004; Martínez-Arán, Vieta, Reinares, et al., 2004; Zubieta, Huguelet, O'Neil, & Giordani, 2001).

The current study seeks to examine this relationship while also avoiding some of the limits of previous studies. First there are many challenges in the measurement of functional outcome, which make an accurate assessment of functioning difficult to obtain. There are a number of ways to measure functional outcome which include patient self-report, collateral reports, clinician ratings, direct observation of a behavior in the actual setting it occurs, and performance-based measures in clinical settings (Patterson, Goldman, McKibbin, Hughs, & Jeste, 2001). All of these measures have certain limitations. Patient self-report measures may be unreliable and in psychiatric patients may be influenced by their psychopathology, while collateral reports may also be unreliable and may be difficult to employ, as some patients do not have a person that can report on them (Patterson et al., 2001). Clinician ratings are not as extensive as may be needed and do not contain domains useful to assess real-world functioning (Patterson et al., 2001). Direct observation of behavior over time in real-world settings is an extensive and costly procedure and while performance-based assessments occurring in a clinical environment are similar to direct observation and easier to accomplish, they may be

contrived and have questionable validity (Patterson et al., 2001). The existing studies of the association between neurocognitive deficits and functional outcome in bipolar disorder rely on self-report or clinician ratings as the determination of outcome, which are hampered by the prior mentioned limitations. In addition, when reliable and valid measures of psychosocial functioning were utilized (Atre-Vaidya et al., 1998; Laes & Sponheim, 2006), authors used an overall score from these measures to compare to neurocognitive domains and failed to examine specific functional domains and their relationship to neurocognitive domains. No study of bipolar disorder to date has examined functional outcome using a performance-based assessment. The current study utilized a combination of patient self-report and performance-based assessments, in order to obtain different measures for functioning. Both types of measures were used when determining the relationship between functioning and neurocognitive deficits.

As previously mentioned, limited research of neurocognitive deficits and functional outcome in bipolar disorder has been promising and has demonstrated a significant relationship between these two domains, so the current study represents a significant advance in this area. Additionally this study attempted to link specific neurocognitive deficits to impairment in specific functional domains. There is little attention to specific relationships in the bipolar literature thus far, although such information has the potential to inform both clinical and theoretical perspectives. As mentioned previously, the comprehensive measurement of functioning through self-report and performance-based measures represents a methodological strength of the current study and can help to discern associations in specific areas of functioning, and move away from results examining global functioning.

Findings of neurocognitive deficits that predict functional outcome could provide guidance to the clinical field and support the addition of neuropsychological measures to assess future outcomes of patients with bipolar disorder, which could also increase awareness in the field that mood symptoms are not the only factor impacting functional recovery. Assessing for these neurocognitive deficits could guide the treatment and future life goals direction of each patient. Treatments could also begin to include cognitive remediation, as has been seen in schizophrenia, to improve the cognitive functioning of select patients diagnosed with bipolar disorder, in order to increase likelihood of functional recovery.

In the following sections, research relevant to the current proposal was reviewed. Specifically, the available research on neurocognitive deficits in various mood states, functional impairments in bipolar disorder, clinical variables associated with functional impairments and neurocognitive deficits associated with functional impairments were reviewed to provide a background. Research with other populations, such as those with schizophrenia, was also included to serve as one basis for hypothesizing associations between the neurocognitive domains and specific functional domains. Based on this review, a number of specific hypotheses were proposed that served as the basis for the present study.

CHAPTER 2

LITERATURE REVIEW

Neurocognitive Function in Bipolar Disorder

As early as 1951, there was evidence for cognitive deficits in bipolar disorder. Early theories, influenced by differential performance on verbal versus performance scores on intelligence tests, focused on right hemispheric brain dysfunction in patients with affective disorders (Waldfogel & Guy, 1951). Some early evidence of this verbal-performance IQ split directed the hypothesis first formulated by Flor-Henry that affective disorder is primarily associated with right hemisphere dysfunction (Flor-Henry, 1976; Flor-Henry, 1983). This hypothesis led to additional studies examining cognition in affective disorders. Some early findings have consistently shown a relationship between cognitive deficits and the right hemisphere in unipolar and bipolar affective disorders (Taylor, Redfield, & Abrams, 1981; Waldfogel & Guy, 1951; Wexler, 1980). In addition to findings of better Verbal IQ relative to Performance IQ in bipolar disorder, support for the right-hemisphere dysfunction hypothesis was provided by impaired performance in tests of visuospatial ability (Dalby and Wereiams, 1986; Waldfogel & Guy, 1951). In contrast, some studies did not find support for abnormal hemispheric laterality. In a study examining verbal and nonverbal memory functioning in patients with bipolar disorder in euthymic and depressed states and patients with major depression, both the euthymic group and the depressed groups had no significant differences between their verbal and non-verbal recall (Calev, Korin, Shapira, Kugelmass, & Lerer, 1986). Further, Newman and Silverstein (1987) found no lateralizing differences between bipolar and unipolar affective disorder groups. More current research evidences deficits in visuospatial

memory in bipolar disorder, but the variation in results among studies is not supportive of a stable right hemispheric dysfunction (Bearden, Hoffman & Cannon, 2001). However, the right hemispheric dysfunction hypothesis has influenced recent research and increased the use of both simple and complex visuospatial and visuoconstructional tests in order to more specifically determine the neuroanatomical systems involved in bipolar disorder (Bearden et al., 2001).

Another vein of early research focused on using neuropsychological test performance to differentiate among the various affective disorders and control groups. Results were equivocal, but did reveal neurocognitive deficits in bipolar disorder. Some studies have highlighted deficits that are present for patients with bipolar disorder in depressed states that are not seen in manic state bipolar or depressed unipolar patients. For example, Savard, Rey and Post (1980) found that a depressed bipolar group had more errors on the Halstead Category Test than a depressed unipolar group and a control group. Also, 87% of subjects with bipolar disorder scored in the abnormal range on the test, while the unipolar group had 64% scoring in this range. A recovered older bipolar group (>40 years), defined as having mild residual depression after hospital discharge, had more errors than recovered younger bipolar and unipolar groups who performed in the normal range, suggesting that age is a factor associated with neuropsychological performance, and that deficits persist even during asymptomatic periods (Savard et al., 1980).

Blackburn (1975) found that patients with bipolar disorder in a depressed state performed more slowly on tests of mental and motor speed than those with unipolar depression or those in manic states. Interestingly, Blackburn also compared patients that were currently experiencing depressed or manic mood symptoms to those with asymptomatic bipolar

disorder and found that the current manic group performed at the same level to the asymptomatic group in mental and psychomotor speed. Calev and colleagues also found that patients with euthymic state bipolar disorder did not exhibit impaired performance relative to normal controls in a test of verbal and nonverbal learning, yet those with unipolar depression and depressed state bipolar disorder performed worse than controls (Calev, Korin, Shapira, Kugelmass, & Lerer, 1986).

Though these studies support problem-solving deficits, psychomotor slowing and memory difficulties in the depressed state of bipolar disorder, there has also been evidence of deficits during manic phases. In an early study, Waldfogel and Guy (1951) compared patients with depressed or manic states, and found that those in manic states had lower full scale IQ, which the authors attributed to deficiencies in attention and concentration, as digit span and arithmetic subtest scores were lower.

Conversely the few early studies that examined the same patients during both manic and depressed states found higher IQ's in hypomanic or euthymic states than in depressed states (Donnelly, Murphy, Goodwin, & Waldman, 1982; Henry, Weingartner, & Murphy, 1973). It was also found that in manic states, complex verbal memory processes were impaired relative to euthymic state performance (Donnelly et al., 1982).

One of the limitations of these early studies was the failure to differentiate patients with bipolar and unipolar affective disorder. This precluded an unequivocal determination of neuropsychological deficits unique to the phasic mood shifts that characterize bipolar disorder. Additionally, many of the studies only used intelligence tests as assessment measures, thus reducing sensitivity to brain dysfunction, which can be better assessed through neuropsychological tests (Reitan & Wolfson, 1985). Despite these

limitations, these early studies provided a basis for more recent studies of the neurocognitive deficits in bipolar disorder, which in turn have provided emerging evidence to suggest that deficits are present in symptomatic, as well as euthymic states.

The etiological basis of neurocognitive dysfunction in bipolar disorder is not yet fully understood, though some theories have been proposed. The temporal evolution of these deficits is unclear. Some evidence suggests that there is greater neurocognitive impairment in patients who have a more severe course of illness. In fact patients with higher rates of hospitalization, higher number of mood episodes, and presence of psychotic features have greater impairment in executive functioning, verbal memory, and attention and concentration than patients without these more severe clinical characteristics (Cavanagh, vanBeck, Muir, & Blackwood, 2002; Clark, Iversen, & Goodwin, 2002; MacQueen, Young, Galway, & Joffe, 2001; Martínez-Arán, Vieta, Reinares et al., 2004; Zubieta, Huguelet, O'Neil, & Giordani, 2001). These findings have lead to the proposal that increasing neurocognitive deficits result from repeated episodes of illness, which cause increasing damage to brain tissue thereby affecting cognitive processes (Altshuler, 1993). In turn this has resulted in hypotheses that suggest a progressive disease process that is accompanied by increasing neurocognitive deficits (Chowdhury, Ferrier, & Thompson, 2003).

Studies have also found neurocognitive impairment in the premorbid phase and early in the course of illness (Nasrallah, 1991; Sigurdsson, Fombonne, Sayal, & Checkley, 1999). More recent studies examining groups with a higher genetic risk for bipolar disorder have found worse performance IQ than verbal IQ, and deficits in verbal recall (Frantom, Allen & Knatz, 2005; Keri, Keleman, Benedek, & Janka, 2001; McDonough-

Ryan et al., 2002). These studies have provided support for hypotheses that neurocognitive deficits are present early in the course of illness, are not merely the product of affective symptoms and may represent phenotypes of the disorder that arise from neurodevelopmental or genetic processes (Savitz, Solms, & Ramesar, 2005). Further longitudinal and high-risk group studies may increase our understanding of the etiology of neurocognitive deficits in bipolar disorder.

As previously mentioned, there have been some limitations in the early research of the neuropsychological deficits in bipolar disorder. More recent studies have attempted to correct the limitations of the early research by improving the assessment batteries used and examining deficits specific to bipolar disorder, while controlling for mood state. In the following sections more recent findings of neuropsychological deficits in bipolar disorder related to each illness phase: manic, depressed or mixed, and euthymic will be reviewed. Additionally, the relationship between neuropsychological performance and clinical variables will be discussed.

Neurocognitive Deficits in Manic States

Mania is characterized by abnormally increased motor behavior, elated mood, irritability, and rapid and excessive thought processes (APA, 2000). Few studies have examined the specific neuropsychological deficits associated with the manic phase of bipolar illness. This may be due to the difficulty in obtaining reliable and valid assessment for patients who are experiencing manic episodes. Early studies of patients in a manic phase evidenced impairment in attention, visuospatial function and memory (Bunney & Hartmann, 1965; Taylor, Redfield, & Abrams, 1981). More recent findings replicate these results and also note the existence of executive functioning deficits. Deficits in

executive functioning, specifically planning, problem solving, concept formation and set shifting, have been consistently reported (McGrath, Scheldt, Welham, & Clair, 1997; Morice, 1990; Murphy & Sahakian, 2001; Sweeney, Kmiec, & Kupfer, 2000). Deficits have also been identified in vigilance or sustained attention (Clark, Iverson, & Goodwin, 2002; Sax, Strakowski, & Zimmerman, 1999). Sax et al. (1999) found that although patients in manic episodes were able to sustain attention, they had impulsive responding resulting in errors of commission. Finally deficits in pattern and spatial recognition memory have also been found (Murphy & Sahakian, 2001). A study of a mixed or manic state bipolar group found deficits in spatial working and short-term memory and delayed visual design recognition, as compared to a control group (Sweeney, Kmiec, & Kupfer, 2000).

Studies have compared patients with bipolar disorder in a manic state to those with schizophrenia and are helpful in understanding the type and severity of neuropsychological deficits in mania. Generally patients with bipolar disorder in acutely manic states perform similarly to patients with schizophrenia exhibiting deficits in executive functioning, attention, and visuospatial tasks (Hoff et al., 1990; McGrath et al., 1997; Morice, 1990; Oltmanns, 1978; Strauss, Bohannon, Stephens, & Pauker, 1984). This is noteworthy, as it has been generally held that schizophrenia is a more severe disorder with more serious neuropsychological deficits. Morice (1990) also found no differences in neuropsychological performance between manic bipolar and schizophrenia groups, with impairments in Wisconsin Card Sorting Test performance as compared to controls. Another study comparing schizophrenia and manic bipolar disorder found both groups to have impairments on measures of visual organization, visuospatial functioning,

attention, memory, verbal learning, and fine motor coordination, with no differences between the two groups (Hoff et al., 1990). In addition to executive functioning deficits, deficits in selective attention (Oltmanns, 1978) and perceptual span (Strauss et al., 1984) were found in manic bipolar disorder and were comparable to those found in schizophrenia. There is also support that during acute phase of mania, patients with bipolar disorder perform with similar executive functioning impairments to schizophrenia, but some evidence that they have different patterns of cognitive recovery as they move from mania to euthymia (McGrath et al., 1997). In this study, they found that as they move from manic to euthymic states, patients improved on the Wisconsin Card Sorting Test, but not on Trails A and B, whereas patients with schizophrenia had the opposite pattern such that as they recovered from acute illness, with performance improved on Trails A and B, but not on the Wisconsin Card Sorting Test (McGrath et al., 1997).

Manic state cognitive deficits have been replicated for the domains of executive functioning, attention and visuospatial memory and functioning. However, since these conclusions are based on a few studies, further research is needed to understand the exact nature of these impairments during mania.

Neurocognitive Deficits in Depressed States

It has become apparent that depression is the predominant affective state of bipolar disorder and therefore efforts to understand the deficits associated with this state have been undertaken (Judd et al., 2002). The depressed state of bipolar disorder has been differentiated from major depression as characterized by more psychomotor retardation, diurnal mood variation, and derealization (Mitchell & Malhi, 2004). Studies of

neuropsychological deficits in the depressed state of bipolar disorder also have found impairments in attention, memory and executive functioning.

Many studies examining the cognitive deficits associated with depressive episodes have focused on comparisons between major depressive disorder and depressed state bipolar disorder. Studies in this area have found poorer performance for the bipolar group in executive functioning and verbal fluency (Borkowska & Rybakowski, 2001; Savard et al., 1980; Wolfe et al., 1987). In a study comparing patients with bipolar disorder in a depressed state to those with major depression, Borkowska and Rybakowski (2001) found worse performance for the bipolar group on the Stroop Color-Word test, Trails B, Controlled Oral Word Association Test (COWAT/FAS), and the WAIS-R performance IQ scores. Patients with bipolar disorder in a depressed episode also had poor immediate and delayed verbal recall as compared to both controls and patients with major depression (Ilsley, Moffoot, & O'Carroll, 1995). In a study examining verbal memory performance of depressed bipolar, major depression, and Huntington's disease groups, the bipolar group had more impaired recall and recognition on the Rey Auditory Verbal Learning Task, a verbal list learning task, than the major depression group and the control group (Wolfe et al., 1987). This same study found that the bipolar group was impaired on executive functioning and performed worse than patients with major depression and more similar to patients with Huntington's disease (Wolfe et al., 1987). Other studies have not found differences in the neuropsychological profiles of patients with major depression and bipolar disorder in a depressed episode (Abrams & Taylor, 1980; Sweeney, Kmiec, & Kupfer, 2000). Some authors have come to the conclusion that the pattern of neuropsychological deficits between unipolar and bipolar depressed groups is similar but

generally more severe in bipolar disorder (Mitchell & Malhi, 2004; Murphy & Sahakian, 2001; Olley et al., 2005). Caution is suggested as the differences in severity may be due to a more severe clinical course found in bipolar disorder (Murphy & Sahakian, 2001). For example Kessing (1998) did not find significant differences between unipolar and bipolar groups but did find that patients with recurrent episodes had more impairment than patients with a single-episode.

Few studies have compared patients with bipolar disorder during depressive episodes to controls. Most studies either group patients with major depression and bipolar disorder into one “affective disorder” category or group all patients with bipolar disorder together, regardless of mood state. The few control studies on the depressed state of bipolar disorder suggest deficits in sustained attention, verbal fluency, verbal memory, and visual design recognition (Brand & Jolles, 1987; Calev et al., 1989; Sweeney, Kmiec, & Kupfer, 2000). In tasks of sustained attention, patients with bipolar disorder in a depressive episode have more errors of omission as compared to controls (Brand & Jolles, 1987). Tests of executive functioning, specifically in the areas of problem solving, concept formation and decision-making, have also been found to be impaired in the depressive phase of bipolar disorder, when compared to control groups (Martinez-Aran, Vieta, Reinares, et al., 2004; Murphy & Sahakian, 2001; Sweeney, Kmiec, & Kupfer, 2000). In a study comparing patients across mood states, no differences in the neuropsychological performance among manic, mixed-episode, and depressed groups were found, and all groups were impaired in verbal memory, verbal fluency, executive functioning and motor ability (Basso, Lowery, Neel, Purdie, & Bornstein, 2002), suggesting that deficits in these neurocognitive domains may be unaffected by changes in mood states.

Much of the research cited for mood state dependent neuropsychological impairments has not been substantially replicated and is complicated by methodological issues such as heterogeneous patient groups, where researchers neglect to indicate the mood state at the time of the assessment. Further research is needed to determine the cognitive profiles of mania and depression in bipolar disorder. Until then, it is accepted that impairments in memory, attention and executive functioning have been evidenced for both depressive and manic mood states and additionally visuospatial memory and functioning deficits have been found for manic mood states.

Neurocognitive Deficits in Euthymic States

The literature has provided support for the idea that patients with bipolar disorder suffer cognitive dysfunction in symptomatic phases of the illness. Recent studies have investigated cognitive impairments in asymptomatic or euthymic phases of bipolar disorder and have demonstrated deficits in executive functioning and verbal memory (Cavanagh, vanBeck, Muir, & Blackwood, 2002; Deckersbach, Savage, et al., 2004; Ferrier, Stanton, Kelly & Scott, 1999; Frangou, Donaldson, Hadjulis, Landau, & Goldstein, 2005; Frantom et al., 2005; Goswami et al., 2006; Martínez-Arán, Vieta, Colom, et al., 2004; Smith, Muir, & Blackwood, 2006; Zubieta et al., 2001). To a lesser extent, impairments in visual memory (Ferrier et al., 1999; Rubinsztein, Michael, Paykel, & Sahakian, 2000) and sustained attention (Clark et al., 2002; Deckersbach, McMurrich et al., 2004; Ferrier et al., 1999; Fleck, Shear, & Strakowski, 2005) have also been demonstrated.

Zubieta and colleagues (2001) found cognitive deficits in patients diagnosed with bipolar I disorder during a euthymic state. They noted more impaired performance as

compared to control subjects in neuropsychological domains of verbal learning, executive function, motor speed, coordination and sequential memory. Atre-Vaidya et al., (1998) also found impaired performance in a sample of 36 patients with asymptomatic bipolar disorder. The patients were more impaired on verbal memory and learning, oral fluency, and visuospatial ability, as compared to age-matched controls. Ferrier and colleagues (1999), found impairment in executive functioning in patients in euthymic states, even after controlling for premorbid IQ and depressive symptoms. Another study also found executive dysfunction in patients in a euthymic state, as measured by the Wisconsin Card Sorting Test, the Controlled Oral Word Association Test and the Stroop Color-Word Test (Frangou et al., 2005). A study examining history of alcohol dependence in euthymic bipolar disorder, found verbal memory impairment in patients with and without alcohol dependence, but executive function deficits only in patients with a history of alcohol dependence (van Gorp, Altshuler, Theberge, Wilkins, & Dixon, 1998). In contrast to these studies noting deficits in executive functioning, unimpaired accuracy in executive functioning tasks was found for patients experiencing a euthymic state, but instead these patients had slower reaction times to make their decisions, than controls (Rubinsztein et al., 2000).

There is some limited evidence for the presence of visual learning and sustained attention deficits in euthymic bipolar disorder. Ferrier et al. (1999) found impairments in visual learning and recall, visuomotor speed and sustained attention. In another study of bipolar disorder in clinical remission, patients had impairment on tests of visuospatial recognition memory as compared to controls, even though they had good social adaptation (Rubinsztein et al., 2000). Impairments in visual memory have also been noted

in another study, specifically that immediate recall of the Rey-Osterrieth Complex Figure Test was impaired due to poor use organizational strategies during encoding (Deckersbach, McMurrich, et al., 2004). Clark, Iversen, and Goodwin (2002) found impairments in sustained attention in a euthymic group as compared to a control group. Interestingly, in a study comparing manic and euthymic states, patients in manic states had poor performance on measures of sustained attention, while patients in euthymic states had slower reaction times but performance similar to controls when reaction time is controlled for (Fleck et al., 2005). Authors suggest that sustained attention deficits in euthymic state bipolar disorder differ from those found in manic state, and may reflect more complex cognitive processes that are difficult to capture using error measurement (Fleck et al., 2005).

A few studies have compared neuropsychological deficits in patients with bipolar disorder across mood episodes. In one study, three groups of patients with mood states of depressed, manic or hypomanic, and euthymic, and a group of normal controls were compared on neuropsychological measures (Martínez-Arán, Vieta, Reinares, et al., 2004). Authors found that performance was not significantly different between the patient groups, lending further support to the idea that neurocognitive deficits of bipolar disorder continue past the acute stage and remain during euthymic periods. Generally, the bipolar groups performed more poorly than the control groups on measures of verbal memory, as measured by the California Verbal Learning Test and the Wechsler Memory Scale – Revised logical memory subtest. Acutely ill patients, either depressed or manic, performed significantly lower than controls on verbal recognition tasks. Another neuropsychological domain affected was executive functioning, as measured by the

Wisconsin Card Sorting Test, Wechsler Adult Intelligence Scale digit span backward subtest and the Stroop Test. For this domain all patient groups performed significantly worse than the control group. Executive functioning and verbal memory deficits, though found in manic and depressed phases, persist through euthymic periods.

Another study comparing bipolar groups of manic, depressed and euthymic, found that all groups were impaired as compared to controls on the executive functioning components of strategic thinking, inhibitory control and response initiation, whereas the manic group had the most widespread impairment in executive functioning (Dixon, Kravariti, Frith, Murray, & McGuire, 2004). In a comparison of manic and euthymic states of bipolar disorder, patients in both states were found to have deficits in inhibitory control or self-regulation, as compared to controls (Larson, Shear, Krikorian, Welge, & Strakowski, 2005).

From the above reviewed research studies, it is clear that neurocognitive deficits are present in all phases of bipolar disorder, including euthymic periods. The persistence of these cognitive deficits has been found in as many as 32% of patients (Goodwin & Jamison, 1990). The deficits appear to be premorbid in nature reflecting genetic heritability and they do not appear to be explained by differences in gender, education level, premorbid IQ or economic status. Although it has been shown that cognitive deficits fluctuate with symptom severity, some such as executive functioning, verbal memory, and sustained attention deficits are present in euthymic states. Because of this, it is apparent that neurocognitive deficits are core features of bipolar disorder and are not simply state dependent.

Neuropsychological Deficits Related to Clinical Variables

The performance on neuropsychological tests has been associated with clinical features. Some of these reflect symptom severity, while others refer to illness course and chronicity. Evidence has been found for a relationship between clinical symptoms and neuropsychological test performance, such that worse symptoms are associated with poorer performance. The neuropsychological domains most impacted are verbal memory and executive functioning, the two main neurocognitive deficits found most frequently in euthymic state bipolar disorder. Subsyndromal mood symptoms found in euthymic bipolar disorder were shown as a factor in a reduction in verbal memory (Goswami et al., 2006). Another study of euthymic bipolar disorder also found that residual mood symptoms negatively impacted cognition, specifically attentional interference tasks (Frangou et al., 2005). Residual symptoms have been found to be related to executive function, specifically preservative errors, verbal fluency, and planning ability (Quraishi & Frangou, 2002). Atre-Vaidya and colleagues (1998) found that the most significant predictor of memory impairment was the degree of patient self-reported anhedonia, though the development of this relationship has not yet been determined. Psychotic features present in during the manic state of bipolar disorder were related to impairment on tasks of sustained attention, such as the Continuous Performance Test (CPT) or Span of Apprehension Test (SPAN); it is notable that patients were first-episode cases (Albus et al., 1996). Interestingly, treatment with antipsychotic medications has shown to negatively impact patients' performance on executive functioning tasks (Frangou et al., 2005), though longitudinal studies are needed to determine the process of interaction.

Various neuropsychological functions have been found to be related to chronicity of the disorder. Chronicity has been measured in numerous ways but most frequently as number and duration of mood episodes, onset of the disorder and number of hospitalizations. The main findings are that executive function and verbal memory are most commonly associated with chronicity. Other neuropsychological domains such as attention and concentration have also been linked to chronicity, but to a lesser extent. In a study of patients with bipolar disorder in a euthymic state, level of impairment on the California Verbal Learning Test was positively associated with the lifetime number of months depressed or manic (van Gorp et al., 1998). These authors also found that performance on tasks of executive functioning, as measured by the Wisconsin Card Sorting Test (WCST) and Trails B, were significantly negative correlated with number and duration of manic episodes (van Gorp et al., 1998). Verbal learning and memory performance was found to be negatively associated with number of manic episodes in a sample of patients with bipolar disorder in euthymic states (Cavanagh, vanBeck, Muir, & Blackwood, 2002). Another study examining the course of illness and neuropsychological functioning in bipolar disorder found poorer performance on abstraction, attention and memory tasks for patients with longer duration of illness, earlier illness onset and higher number of mood episodes and hospitalizations (Denicoff et al., 1999). In contrast, Ferrier and colleagues (1999) examined potential differences in arbitrarily created good and poor outcome bipolar groups, and found that there were no significant differences between the groups on any of the neuropsychological tests. The distinction of good and poor outcome was determined based on the number of mood episodes in the past three to five years, with two or less episodes in the last five years

reflecting good outcome and three or more episodes in the last three years reflecting poor outcome. In a study of patients in different mood episodes, verbal memory impairment was positively associated with duration of illness, number of manic episodes, number of hospitalizations, and number of suicide attempts regardless of mood state (Martínez-Arán, Vieta, Reinares et al., 2004). WCST and Trails A performance were negatively correlated with duration of illness for all mood phases (Martínez-Arán, Vieta, Reinares et al., 2004). Zubieta and colleagues (2001) also found negative correlations between WCST performance and number of manic episodes, major depressive episodes and number of hospitalizations. In addition to performance on executive functioning and verbal memory tests, performance on attention, concentration and general intelligence tests has been found to be negatively associated with duration of illness, years of exposure to antipsychotic medications and earlier age at onset (Clark et al., 2002; Denicoff et al., 1999). Duration of illness has also been found to predict loss of inhibitory control (Frangou et al., 2005).

As has already been discussed, bipolar disorder is characterized not only by mood symptoms but also by cognitive deficits that are present in the various mood episodes. Some symptomatic features, psychosis and residual mood symptoms during euthymia, as well as chronicity, have been found to be related to executive functioning, verbal memory and attention, such that a poorer course of disorder with more severe clinical features is associated with poorer performance on neuropsychological measures. Research has not delineated whether disorder severity results in brain insults leading to irreversible damage. The following section will briefly review the neuroanatomical and neuroimaging findings

in bipolar disorder and discuss the brain functional and structural abnormalities that have been discovered thus far.

Neuroanatomical and Neuroimaging Findings in Bipolar Disorder

The assertion that neurocognitive deficits are central to bipolar disorder is further supported by neuroanatomical and neuroimaging findings that evidence structural and functional abnormalities in specific brain regions. Brain structural abnormalities have been examined using a variety of neuroimaging techniques, including computerized tomography (CT) and magnetic resonance imaging (MRI). Structural abnormalities have consistently been reported in the ventricles, prefrontal cortex, subcortical structures, and temporolimbic structures (Bearden et al., 2001; Strakowski, DelBello & Adler, 2005).

Generally CT studies have found that the ventricle to brain ratio is higher in patients with affective disorders than controls indicating abnormally large ventricles (Bearden et al., 2001). The MRI findings of third and lateral ventricle enlargement in bipolar disorder have also evidenced larger ventricles in patients with bipolar disorder than controls (Bearden et al., 2001). Ventricular volume in bipolar disorder has been related to number of affective episodes and specifically number of manic episodes (Brambilla et al., 2001; Strakowski et al., 2005). In fact patients with multiple episodes had greater ventricle volumes than patients with just one episode, and the ventricle size of the first episode group did not differ from controls (Strakowski et al., 2005). Cognitively, ventricular enlargement in bipolar disorder was related to poor performance on the Halstead Reitan Neuropsychological Battery (Dewan et al., 1988).

Studies examining whole brain volumetric differences in bipolar disorder have been varied. Some CT studies have reported sulcal widening and cortical or cerebellar atrophy in bipolar disorder as compared to controls (Bearden et al., 2001), while more recent reviews suggest there is little evidence for this assertion (Strakowski et al., 2005).

Overall volumetric differences in the prefrontal cortex between patients with bipolar disorder and controls have not been consistently observed (Strakowski et al., 2005). However, more specific differences in this brain region have been found. Patients with bipolar disorder had smaller gray matter volumes in the left superior and middle and right prefrontal regions as compared to controls (Lopez-Larson, DelBello, Zimmerman, Schwiers, & Strakowski, 2002). Some evidence suggests that smaller gray matter volumes are associated with increasing age in individuals with bipolar disorder (Brambilla et al., 2001; Lopez-Larson et al., 2002). Another area of the prefrontal cortex, the left subgenual prefrontal cortex, a part of the anterior cingulate, was smaller in patients with bipolar disorder who had a family history of affective disorder (Drevets et al., 1997; Hirayasu et al., 1999). These studies suggest that specific prefrontal volumetric reductions exist in bipolar disorder.

There have also been reports of increased striatal size in bipolar disorder. Studies have shown both increased caudate and putamen volume in patients relative to controls (Bearden et al., 2001; Strakowski et al., 2005). These increases have been observed in adolescents with bipolar disorder and in affected and unaffected monozygotic twins suggesting a neurodevelopmental vulnerability factor (DelBello, Zimmerman, Millis, Getz, & Strakowski, 2004; Noga et al., 2001). Structural differences between patients and

controls in the thalamus have not been consistently reported (Bearden et al., 2001; Strakowski et al., 2005).

There also exists evidence of volumetric increases in the amygdala of patients with bipolar disorder relative to controls, yet there is no difference between these groups in hippocampal volume (Bearden et al., 2001; Strakowski et al., 2005). Interestingly smaller amygdala volumes were reported for adolescents with bipolar disorder (DelBello et al., 2004). It is unclear how to interpret these findings, but there is sufficient evidence to suggest structural abnormalities in this brain area.

MRI studies have led to the examination of hyperintensities in the brain. These signal intensities reflect tissue abnormalities that are typically not found in healthy people younger than 45 years old. In bipolar disorder, researchers have found hyperintensities in periventricular white matter, subcortical gray matter, and deep white matter brain regions (Bearden et al., 2001). Hyperintensities, though found in all lobes, occurred more frequently in the frontal lobes and frontal/parietal junction. A few studies indicated that the occurrence of white matter hyperintensities is related to increasing age (Altshuler et al., 1995; Aylward et al., 1994; Hickie et al., 1995). White matter hyperintensities have also been associated with cognitive impairment related to speeded performance and complex processing, as well as behavioral disturbances in depressed patients with vascular risk factors and in elderly patients with probable Alzheimer's disease (Appel, Moens, & Lowenthal, 1988; Bondareff, Raval, Woo, Hauser, & Colletti, 1990; Mangone, Gorelick, Hier, & Ganellen, 1990). White matter hyperintensities were also related to slowed performance on psychomotor speeded tasks in patients in the depressed state of bipolar (Hickie et al., 1995) and to poor verbal fluency and verbal recall in these patients

(Dupont, Jernigan, Heindel, & Butters, 1995). These hyperintensities may be related to the cognitive impairments found in bipolar disorder.

Brain functional impairments in bipolar disorder have been investigated during resting state and during cognitive task performance through the use of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Many of the early functional neuroimaging studies of bipolar disorder were performed during resting state and utilized PET imaging. These studies have mainly examined patients in depressed states and found reduced blood flow globally, as well as in the temporal lobe, frontal lobe, anterior cingulate, antero-lateral prefrontal cortex, basal ganglia and caudate (Baxter, 1985; Baxter et al., 1989; Buchsbaum, 1984; Buchsbaum, 1986; Martinot et al., 1990). Some of these areas have been mentioned above to be structurally abnormal, though the link between functional and structural brain abnormalities is still being investigated. A few studies examined glucose metabolism in patients in different mood states and found that patients with bipolar disorder in depressed states had lower global metabolism and that metabolism increases in euthymic state; in manic state metabolism was found to be higher than that of controls (Baxter et al., 1989; Drevets et al., 1997; Kishimoto et al., 1987). However, this has not always been observed and some investigators found increases in certain brain regions, e.g. anterior cingulate, and decreases in other areas, e.g. inferior frontal gyrus and right fronto-polar cortex (Blumberg et al., 2000; Rubinsztein et al., 2001). Thus far findings demonstrate lower temporal lobe blood flow (Migliorelli et al., 1993), decreased glucose metabolism in frontal lobe and left amygdala and increased right temporal lobe metabolism (al-Mousawi & Dunstan, 1996). It is difficult to make definitive conclusions from these few studies of brain functioning during resting state.

There is some support that glucose metabolism may be related to mood state, and that in depressed mood state glucose metabolism is decreased in the prefrontal cortex, anterior cingulate and caudate (Bearden et al., 2001).

Functional imaging that utilizes a cognitive task to activate a specific part of the brain has generally found mixed results. Brain activation differences between patients with bipolar disorder and controls seem to vary by both cognitive task performed and brain area examined. The wide range of cognitive tasks makes it difficult to compare studies (Strakowski et al., 2005). Additionally, as mentioned above, it has been found that mood state affects brain metabolism. Many of the imaging studies using a cognitive task do not delineate mood state, thus possibly confounding the results (Strakowski et al., 2005). When controlling for mood state, one study found more activation in emotional brain regions, such as the parahippocampus, amygdala and ventrolateral prefrontal cortex, during a non-emotional task as compared to controls (Strakowski et al., 2005). A recent study found low activation in the orbitofrontal region in people diagnosed with bipolar disorder currently in the manic phase as compared to controls (Altshuler et al., 2005). Participants performed a Go-NoGo task that requires behavioral inhibition and engages the orbitofrontal region. Authors propose the low activation of this region may partially explain disinhibition present during a manic episode. They also found that patients with longer current episode durations showed the least activity in the frontal lobe. Though patients with bipolar disorder had significant activation in the left cingulate, this activation was lower as compared to controls. Also a reduced activation was noted in the right hippocampus. These reductions may be related to attention and memory.

Both structural and functional neuroimaging provide evidence for abnormalities in the prefrontal regions, including the anterior cingulate, and in limbic areas (Bearden et al., 2001; Strakowski et al., 2005). It has also been consistently found that mood state impacts activation patterns and few functional imaging studies have examined patients in the euthymic phase of bipolar disorder to determine more trait abnormalities (Strakowski et al., 2005). Finally there is also some suggestion that abnormalities in these frontal limbic areas may disrupt cognitive functioning that occurs in the prefrontal regions (Mayberg et al., 1999; Strakowski et al., 2005).

Functional Impairments in Bipolar Disorder

Significant evidence exists demonstrating cognitive deficits and brain structural and functional abnormalities in bipolar disorder. There is also literature to suggest that people with bipolar disorder suffer poor outcomes, however, one difficulty in interpreting the results of functional outcome studies stems from the fact that outcomes are measured in a variety of ways. When examining bipolar disorder, outcomes can be assessed through symptomatic recovery and clinical variables such as number of episodes, number of hospitalizations, and length of episodes. Outcomes have also been measured by observing psychosocial and functional capacity. In terms of measurement of these outcomes, some studies have used more general measures such as a Global Assessment of Functioning (GAF) rating, whereas others have examined functioning more specifically as it relates to interpersonal, occupational and self-care abilities. Still in other studies, a functional recovery is a return to baseline functioning prior to hospitalization or first mood episode. An additional constraint in the research related to psychosocial/functional outcome in

bipolar disorder is the variability of functional domains assessed. Some researchers will only assess one or two domains, thus providing a limited picture of the person's functioning (Zarate, Tohen, Land, & Cavanagh, 2000).

Although outcome is measured in all different manners, the most important finding is that many patients with bipolar disorder do not exhibit a high level of functioning after onset of the disorder as compared to normal controls, non-affected first degree relatives, as well as to the patients' own baseline level of functioning (Zarate et al., 2000). Instead they have difficulties in the areas of occupational and interpersonal domains.

Interestingly, early in the study of bipolar disorder there was little evidence that functional impairments experienced during the symptomatic episodes extended into euthymic phases of the disorder. Some even suggested that the person returns to full functioning after the mood episode (Rennie, 1942). This characterization has recently been shown to be inaccurate, as more evidence suggests that functional impairment is a serious problem in bipolar disorder and many people diagnosed fail to return to full premorbid levels of functioning.

In an early study of the functional impairments in bipolar disorder, only 41% of patients returned to former work and responsibilities after mean follow-up period of 3.2 years post-hospital discharge (Carlson, Kotim, Davenport, & Adland, 1974). Social function and family interaction were unimpaired in 45% of patients, while symptomatically 57% of patients were well since hospital discharge and 10% had mood episodes but were well in between episodes.

A second study examined symptomatic and functional recovery in 44 patients diagnosed with bipolar disorder at hospitalization and at 6 months post discharge (Dion,

Tohen, Anthony, & Wateraux, 1988). In terms of occupational functioning, 36% of patients were unable to work competitively and 30% were unable to work at all at 6-month follow-up. Though the rest of the participants were working at some level of competitive employment, only 19% were working at a level consistent with their previous work, educational, and socioeconomic status. Residential status was also assessed in this study and 34% of patients were unable to live independently at 6-month follow-up and required assistance from others. Interestingly, at follow-up 78% of patients were asymptomatic or mildly symptomatic, and 97% experienced little or no manic symptomatology. Authors reported outcomes for this same sample at 2-year follow-up and found symptomatic recovery for 98.6% of patients with bipolar disorder but found that only 40.4% of patients recovered functionally, based on occupational and residential status (Tohen et al., 2000). In another 2-year longitudinal study examining work functioning of 52 people diagnosed with bipolar I disorder, 44% of the group had only fair or poor work functioning (Hammen, Gitlin, & Altshuler, 2000).

Strakowski et al. (1998) found similar results in that syndromic recovery, or resolution of groups of symptoms such that disorder criteria is no longer met, was found for 61% ($n = 39$ out of 64) of patients with bipolar disorder 12 months after first hospitalization for affective episode with psychosis. Only 36% of patients experienced a functional recovery as measured by a return to premorbid levels of psychosocial activity (Strakowski et al., 1998). Keck et al. (1998) found functional recovery in 25 of 106 patients diagnosed with bipolar disorder (24%) during a 12-month follow-up period post-hospitalization. While symptomatic recovery in bipolar disorder, even in severe psychotic

forms, seems to occur for many patients, functional recovery is more difficult to obtain. Thus while mood symptoms may resolve, functional impairment continues.

Some studies of euthymic bipolar disorder or bipolar disorder in remission lend support to this conclusion. Bauwens, Tracy, Pardoen, Elst and Mendlewicz (1991) found impairments in social interactions and overall adjustment for a remitted bipolar group as compared to a control group. More specifically they found that patients had less contact with friends in the two months preceding the interview. Similarly, a more recent study of patients in the euthymic phase of bipolar disorder, revealed 31% of patients were below an adequate level in community functioning, which encompasses involvement in work/school and in other life roles (Kusznir, Cooke, & Young, 2000).

Another recent study of patients with bipolar disorder in remission also supports functional impairments. The bipolar group obtained a mean score in the significant functional impairment range on the Work and Social Adjustment Scale, a self-report measure of work abilities, home management abilities, social leisure activities, private leisure activities and relationships with others (Fagiolini et al., 2005). These studies taken together support the idea that despite significant improvement in symptoms for most patients, far fewer experience recovery of function.

As noted previously, functional recovery is not the only difficulty in bipolar disorder outcome. Research suggests symptomatic recovery doesn't occur for a substantial minority of people diagnosed with bipolar disorder. In a 2-year follow up study, results indicated poor overall long-term outcome for 16.8% of patients and fair outcome for 35.6% as determined through the use of the LKP scale of impairment rating which considers symptom frequency and severity (Tsai et al., 2001). Similarly, Coryell et al.

(1998) found 20% of patients with bipolar disorder had poor long-term outcome in a 15-year follow-up study, as defined by the presence of a manic or major depressive disorder in the final follow-up year. In a 12-month follow up study of 106 patients with bipolar disorder, only 26% obtained symptomatic recovery during the follow-up period post-hospitalization (Keck et al., 1998). Additionally, authors found that only 48% had sustained syndromic recovery, or recovery from groups of symptoms such that disorder criteria are no longer met (Keck et al., 1998). Some authors (Keck et al, 1998; Strakowski et al., 1998) suggest a possible relationship between symptomatic, syndromic and functional recovery, in that symptomatic recovery is necessary for syndromic recovery, by definition. But more importantly, syndromic recovery may be necessary for functional recovery, as evidenced by research results in which all patients having functional recovery achieved syndromic recovery, and many achieved it prior to becoming functionally recovered (Keck et al, 1998; Strakowski et al., 1998).

As more and more research supports the idea that functional impairments in bipolar disorder are significant and persist through euthymic asymptomatic phases of the disorder, associations with and predictors of these impairments have been investigated. There is a large amount of research that suggests certain clinical variables are associated with functional impairment. However, little research exists regarding the neurocognitive variables that are related to functional impairment. The literature on both types of variables will be reviewed in the following two sections.

Clinical Correlates of Functional Outcome in Bipolar Disorder

Research studies have shown that the functional status in people with bipolar disorder relates to clinical variables and therefore some of these variables can help to predict good versus poor outcome in bipolar disorder. Depressive symptomatology, number and severity of affective episodes and symptoms, and treatment compliance are clinical variables related to outcome in bipolar disorder (Fagiolini 2005; Coryell 1998; Hammen et al., 2000; Gitlin, Swendsen, Heller, & Hammen, 1995; Dion et al., 1988; Dickerson et al., 2004; Vocisano, Klein, Keefe, Dienst, & Kincaid, 1996; Vocisano, Klein, & Keefe, 1997; Bauwens et al., 1991; Tsai et al., 2001; Morriss, 2002; Altshuler, Gitlin, Mintz, Leight, & Frye, 2002). Other variables, such as age at onset, social support, comorbid personality disorders, and premorbid functioning have also received some support as factors related to outcome in the disorder (Carlson et al., 2002; Carter, Mundo, Parikh, & Kennedy, 2003; Tohen et al., 2000; Hammen et al., 2000; O'Connell, Mayo, Flatow, Cuthbertson, & O'Brien, 1991; Goldberg & Ernst, 2004; Strakowski et al., 1998; Vocisano, Klein, & Keefe, 1997).

As mentioned previously, a limitation of the literature is the various definitions and measurement of outcome. Some studies examine outcome as it relates to symptom recovery, while others refer to outcome as occupational and psychosocial functioning. Additionally some research studies combine both types of factors into a single outcome measure that looks at overall impairment level. This makes it difficult to compare the clinical correlates of outcome and to determine what clinical factors influence a functional outcome, encompassing various occupational and psychosocial factors. Some

of the studies reviewed will examine clinical variables related to symptomatic outcome and others will focus on functional outcome.

Mood Symptoms

Much literature exists on the relationship between mood symptoms and outcome in bipolar disorder. This is expected given that mood symptoms are core features in bipolar disorder. Generally it has been found that depressive symptoms and depressive episodes are related to occupational and psychosocial functioning, such that the more depressive symptomatology a bipolar patient exhibits, the poorer their functioning (Coryell et al., 1998; Fagiolini, 2005; Hammen et al., 2000; Dion et al., 1988; Gitlin et al., 1995). Specifically, higher numbers of major depressive episodes have been related to greater family dysfunction and social maladjustment (Gitlin et al., 1995). Depressive symptoms assessed on hospital admission through the use of the Hamilton Depression Rating Scale were found to be related to dependent living environment at 6-months follow-up post discharge, such that more depressive symptoms were related to a more supervised living environment, for example a hospital, with family under high supervision or a halfway house (Dion et al., 1998). Coryell et al. (1998), in a 15-year multi-site follow-up study of severe bipolar disorder, found that poor symptomatic outcome in year 15 was related to healthiest level of functioning in the 5 years before initial baseline assessment and to depression symptomatology in years 1 and 2 of the study. Depression symptomatology in the first 2 years was correlated with depressive symptoms in year 15, yet no similar relationship was found for manic symptoms. In fact Hammen, Gitlin, and Altshuler (2000) found that depressive episodes, but not manic or hypomanic episodes, were related to poor job functioning. However, hypomanic, manic and other clinical symptoms

have also been found to be related to functioning (Kusznir, Cooke, & Young, 2000; Fagiolini et al., 2005; Coryell et al., 1998). The presence of mixed/rapid cycling episodes and increased numbers of manic or depressive symptoms in the most recent mood episode are related to functional deterioration, as measured by living dependently on others for basic necessities or hospitalization, increased unemployment, and decreased symptom remission (Vocisano et al., 1996; Vocisano et al., 1997). There is also some evidence that anxiety symptoms, as well as traditional manic and depressive symptoms, are related to negative outcomes in both occupation and psychosocial functioning (Kusznir, Cooke, & Young, 2000; Fagiolini et al., 2005). In a group of people diagnosed with bipolar I disorder in remission status, scores on a measure of occupational and psychosocial functioning, the Work and Social Adjustment Scale (WSAS) were significantly correlated with depressive, manic and panic-agoraphobic spectrum symptoms (Fagiolini et al., 2005). When authors regressed the WSAS scores on these variables, they found that there was a highly significant positive effect of depressive spectrum symptoms and a significant negative effect of duration of remission. Increasing severity of symptoms is also associated with poor psychosocial outcomes and poor employment status (Gitlin et al., 1995; Dickerson et al., 2004). The number of lifetime mood episodes has been positively correlated with occupational and psychosocial impairment (Bauwens et al., 1991).

Interestingly, there has also been some attention devoted to subsyndromal symptoms and their impact on functioning. Subsyndromal symptoms are affective symptoms that are not severe enough to meet the diagnostic criteria of a mood episode. Altshuler et al. (2002) found that for 25 patients with bipolar disorder who hadn't experienced mood

episodes for 3 months prior to the study, subsyndromal depressive symptoms were related to impairment on the Global Assessment of Functioning (GAF). Authors report that no participant obtained scores in the clinically depressed range, though even the mild depressive scores seem to impair functioning. In a literature review by Morriss (2002), the relationship between inter-episode symptoms and functioning in euthymic states is highlighted. Current residual symptoms were also found to be related to maladjustment in occupational, leisure and relationship functioning (Bauwens et al., 1991).

Hospitalization and Treatment Compliance

As might be expected, although not a direct measure of symptomatology, the number of psychiatric hospitalizations has been found to be associated with vocational outcome, functional recovery and psychosocial functioning (Dion et al., 1988; Tohen et al., 2000; Vocisano et al., 1996; O'Connell et al., 1991). Mean number of previous hospitalizations was higher for a poor outcome group than the good or fair outcome groups in a study of 248 patients with bipolar disorder (O'Connell et al., 1991). Shorter hospitalization was associated with functional recovery (Tohen et al., 2000), while a rapid re-hospitalization after discharge was related to functional deterioration (Vocisano et al., 1996). The relationship between hospitalization and outcome may be influenced by the underlying severity of the disorder, potentially with poorer outcome cases needing more care.

The relationship between outcome and treatment compliance in bipolar disorder has received some attention and it is generally held that treatment compliance is related to symptomatic recovery (Vocisano et al., 1996; Tsai et al., 2001; Strakowski et al., 1998). In a 15-year outcome study of 101 patients with bipolar disorder, full medication compliance was the strongest predictor of favorable long term outcome in terms of

symptoms and re-hospitalizations (Tsai et al., 2001). Strakowski et al. (1998) also found that full treatment compliance was related to syndromic recovery, or recovery such that disorder criteria are no longer met. Medication non-compliance was associated with functional deterioration in living situation, employment status and symptom remission (Vocisano et al., 1996). Treatment compliance has also been used as an outcome measure. One study found that about 39.5% of 200 patients diagnosed with bipolar I or bipolar II disorder were classified as mildly and poorly compliant (Colom et al., 2000). Compliance was measured through patient interviews, collateral interviews, and plasma concentrations of mood stabilizers. Good compliance was defined as all three criteria suggesting good compliance, while poor compliance was noted when none of the criteria suggested it, and medium compliance was considered when two of the three criteria suggested it. In this study, poor compliance was associated with personality disorder comorbidity and higher number of hospitalizations. The type of pharmacological treatment was not significantly related to compliance and no significant differences were found between bipolar I and bipolar II patients.

Premorbid Function and Personality Variables

There is research to support the idea that early clinical variables such as age at onset and childhood psychopathology is related to future functioning (Carlson et al., 2002; Carter et al., 2003; Tohen et al., 2000) though not all studies evidence this (Coryell et al., 1998; Kuznir et al., 2000). Carlson et al. (2002) examined clinical course and outcome in 123 people aged 15 to 60 diagnosed with bipolar I disorder first presenting with psychosis. Authors found that people with childhood psychopathology, either behavioral disorders or other clinically significant symptoms, had poorer course and outcome than

those individuals without childhood psychopathology. Poorer course and outcome were also related to first affect disorder prior to age 19, also referred to by the authors as early age at onset. Another study also found that people with early age at onset for either Bipolar I or II, had poorer clinical outcomes including more frequent suicidal ideation and attempts, rapid cycling course, comorbid AXIS I disorders, and substance use disorders (Carter et al., 2003). Early age at onset was defined as meeting the criteria for a mood disorder based on DSM-IV at age 18 years or younger (Carter et al., 2003). Finally Tohen et al. (2000) found that age of onset after 30 years was related to better functional recovery from hospitalization. An explanation for these results could be that early age at onset is more detrimental because neurocognitive developmental processes are interrupted by an earlier appearance of the disorder. These processes may be protective factors for later onset patients.

Premorbid functioning is a clinical variable that has been associated with functional outcome in other disorders such as schizophrenia (Allen, Kelley, Miyatake, Gurklis, & van Kammen, 2001). The evidence of its relationship to outcome in bipolar disorder is still not clear due to the minimal research in this area. The few available studies suggest that, as in schizophrenia, poor premorbid adjustment in bipolar disorder is related to more severe clinical outcomes such as substance abuse comorbidity, suicidality, and rapid cycling (Goldberg & Ernst, 2004), and lower frequency of a return to premorbid levels of functioning (Strakowski et al., 1998).

Personality disorder pathology has been linked to poor occupational functioning and functional deterioration (Vocisano et al., 1997; Hammen et al., 2000). Similarly, amount of relationship support the patient receives has also been found to be associated with

work and psychosocial functioning (Hammen et al., 2000; O'Connell et al., 1991).

Hammen, Gitlin, and Altshuler (2000) found that work functioning was associated with symptomatology and personality disorder pathology and was strongly associated with marital/relationship functioning. In fact, personality functioning and marital/close relationships were stronger predictors of work functioning than psychiatric factors of hospitalization and recent symptomatology (Hammen et al., 2000). Additionally it is probable that these two variables themselves, personality disorder features and relationship support, are inversely related.

Functional outcome in bipolar disorder is related to a number of clinical variables including symptom severity, number of symptoms or episodes, and treatment compliance. Even the functional status of patients in remission seems to be impacted by these clinical factors. Yet clinical variables are not solely accountable for the outcomes in bipolar disorder. As has been seen in other psychiatric disorders, such as schizophrenia and alcoholism, neurocognitive factors play a role in the functioning of a person with bipolar disorder.

Neurocognitive Deficits and Functional Outcome in Psychiatric Disorders

The search for neurocognitive deficits that are predictive of functional outcome has been undertaken for various psychiatric disorders. Neurocognitive deficits hinder a person's ability to learn treatment relevant information, initiate appropriate behaviors, and maintain skills to navigate real-world problems. In a sense, these deficits exert an upper limit on the potential abilities of an individual. It is useful to examine the literature of neurocognitive deficits associated with functioning in other psychiatric disorders, as a

way of guiding the research questions and hypotheses of the current study, especially as few studies exist examining this relationship in bipolar disorder.

Schizophrenia

Neurocognitive deficits have been found to be predictive of functional outcome in schizophrenia. In a seminal article, Green (1996) reviewed studies of neurocognitive correlates of functional outcome in schizophrenia and found that verbal memory was associated with all functional outcomes including social and vocational functioning, social problem solving, and psychosocial skill acquisition. Vigilance, or the ability to use attentional processes to discriminate stimuli, was significantly associated with acquisition of social skills and social problem solving. Interestingly, psychotic symptoms typically thought to be debilitating to a person with a diagnosis of schizophrenia were not significantly correlated with functional outcome measures. Green's review of this topic has led to a burgeoning research area that has consistently found a relationship between neurocognitive deficits and functional outcome in schizophrenia.

One of the main findings has been that global or composite measures of neurocognition account for 20 to 60 percent of the variance in outcome (Green, Kern, Braff, & Mintz, 2000). Velligan et al. (1997) found that for two patient samples, global measure of cognition accounted for 48 percent and 42 percent of the variance, respectively, in the activities of daily living. In another study of three groups of older schizophrenia patients differing in adaptive functioning levels, a composite measure of cognition accounted for 40 to 50 percent of the variance in each group (Harvey et al., 1998). Evans et al. (2003) found that in older outpatients diagnosed with schizophrenia, a global neuropsychological score accounted for 59% of the variance in daily living

abilities, which included communication, finance, shopping, transportation, and time orientation. When compared to disorder symptoms, cognitive measures accounted for more variance in functional abilities than psychiatric symptom ratings.

Green et al. (2000) in a more recent meta-analytical review, replicated results for more specific neurocognitive domains. Secondary verbal memory, or the ability to acquire and store verbal information over time, was related to community outcomes, social skill performance and psychosocial skill acquisition, which were all of the outcome types examined in the reviewed studies. Immediate memory was related to psychosocial skill acquisition, while vigilance, or sustained attention, was related to skill performance. Card sorting and verbal fluency were related to community outcomes. In their meta-analysis, Green and colleagues found that all of these relationships were highly significant and effect sizes ranged from small-medium to medium-large. More recently, longitudinal studies have become important in testing the predictive value of this relationship. Milev, Ho, Arndt, and Andreasen (2005), in a 7 year follow-up of first-episode schizophrenia, found that verbal memory and processing speed at initial intake were related to future outcome. They also found that verbal memory significantly predicted impairment in recreational activities, while negative symptoms and memory predicted impairment in relationships. Work performance was predicted by attention and negative symptoms. Fujii and Wylie (2003) also found that verbal memory predicted functioning, accounting for 44.5% of the variance.

Mediator-Moderator Models

One of the more recent developments in the neurocognitive/functional outcome literature for schizophrenia is a focus on mediator-moderator models to explain

associations. A mediator has been defined as a variable “that accounts for the relation between a predictor and a criterion”, whereas a moderator is a variable that “affects the strength and/or direction of the relation between a predictor and a criterion” (Baron & Kenny, 1986, p. 1174). The pursuit of mediators and moderators of the relationship of neurocognition and functional outcome has several benefits. They can provide more theoretical guidance for the research into this relationship. The schizophrenia literature in this area has been mainly atheoretical and would benefit from a more structured understanding. Mediators and moderators, once established, can become intervention targets and can influence assessments of adaptive functioning. Interestingly, researchers in the area of alcohol use disorders have also been examining the relationship between neurocognitive deficits and outcome but with inconsistent results (Bates et al., 2002). It has been suggested that just examining the direct effects of neurocognitive impairment on outcomes, may be the cause of the limited results and that other mediator-moderator pathways may be more applicable to understanding the relationship (Bates et al., 2002).

Thus far a few variables have been proposed as mediating the relationship between neurocognition and functional outcome in schizophrenia. Learning potential, or what an individual is capable of learning, may be a mediator (Green et al., 2000). Although most neurocognitive measures are not able to assess learning potential, list learning tasks do allow for examination of learning by repeatedly presenting the same list of words. Examination of the number of words recalled after each presentation allows for the evaluation of learning across trials. As already mentioned, Green et al.’s (2000) literature review demonstrates the importance of secondary verbal memory to outcome, and secondary verbal memory is measured through list learning tasks as well as passage/prose

memory. Green et al. (2000) separated out list learning studies from passage/prose memory studies and although both were significantly associated with functional outcome, there was a higher strength of association for list learning. This could be support for learning potential as a mediator variable. Additionally, social cognition has been proposed as a mediator between neurocognition and social competence (Green & Nuechterlein, 1999). Though much research has been completed, the mechanisms of association between neurocognitive variables and functional outcome in schizophrenia are not yet understood.

The schizophrenia literature is helpful in developing a framework to examine the relationship between cognitive deficits and functional outcome as similar neuropsychological deficits have been found for both clinical populations (Hoff et al., 1990; Martínez-Arán et al., 2002; Morice, 1990; Zihl, Grön, & Brunauer, 1998). These deficits were generally less severe in bipolar disorder as reviewed in prior sections. In terms of functional status, patients with bipolar disorder have been shown to have better psychosocial and occupational functioning than those with schizophrenia (Martínez-Arán et al., 2002). Although the severity of both neurocognitive deficits and functional outcome may be different between the two diagnoses, the neurocognitive domains related to functional outcome in the schizophrenia literature deserve attention in the current study, as they may also have predictive value in bipolar disorder.

Neurocognitive Deficits and Functional Outcome in Bipolar Disorder

Few studies have investigated neurocognitive functioning and its relationship to functional outcome in bipolar disorder. The studies that have examined this relationship

have generally found that neurocognitive deficits do influence functional outcome. The main findings have been that executive functioning, verbal memory, and verbal fluency are most strongly associated with a patient's psychosocial functioning (Atre-Vaidya et al., 1998; Dickerson et al., 2004; Laes & Sponheim, 2006; Martínez-Arán et al., 2002; Martínez-Arán, Vieta, Colom, et al., 2004; Martínez-Arán, Vieta, Reinares, et al., 2004; Zubietta, Huguelet, O'Neil, & Giordani, 2001). The earliest study examined 54 participants who had Structured Clinical Interview for DSM-III-R (SCID) diagnoses of major depression or bipolar disorder and found more attention and calculation impairment in deteriorated affective patients as compared to non-deteriorated patients (Vocisano, Klein, & Keefe, 1997). The Mini-Mental State Examination (MMSE) was used to assess cognitive functioning and functional status was determined by grouping participants into deteriorated and non-deteriorated groups. Deteriorated patients met the criteria of continuous hospitalization or complete dependence on others for necessities, no useful work or employment, and no symptom remission. Though there were significant differences between the groups on the attention and calculation items of the MMSE, total MMSE scores were not significantly different. Unfortunately authors did not separate the depression and bipolar diagnoses so it is difficult to make conclusions specifically about bipolar disorder. Also, the MMSE is a screening tool rather than a comprehensive measure of cognitive functioning. However, this early study provided tentative evidence for an association between functional status and cognition in affective disorders and likely bipolar disorder.

Atre-Vaidya et al. (1998) more specifically examined cognition and psychosocial functioning in 36 patients with bipolar disorder. Diagnoses were made by two

psychiatrists using DSM-III-R criteria. Authors assessed for mood symptoms using the structured interview Schedule for Affective Disorder and Schizophrenia (SADS-L) and most patients had 3 or fewer mood symptoms in the 6 weeks prior to the assessment and thus were considered asymptomatic. Atre-Vaidya and colleagues' neuropsychological test battery included standardized measures that assessed dementia, general intelligence and language, verbal fluency, verbal memory and visuospatial ability. Domains of executive function and attention were not assessed. Different methods were used for the VA and community samples, therefore making it impossible to combine the two groups for analyses. The community participants ($n = 13$) were administered the Structured and Scaled Interview for Maladjustment (SSAIM). The VA participants ($n = 23$) were rated based on a chart review by a psychiatrist on an impairment rating scale that is used in the VA clinic. Both rating methods examined various domains of functioning such as employment, social life, family, marriage, and clinical variables (hospitalizations and symptoms). In both groups poor memory, as measured by the California Verbal Learning Test variables, was associated with poor psychosocial functioning. In the community sample, verbal fluency was also associated with poor psychosocial functioning. Total score for psychosocial functioning on the SSAIM was utilized in the analyses, though it may have been beneficial to examine psychosocial domain scores to see if there were relationships between specific cognitive factors and these domains. Overall this study supports the general finding that verbal memory deficits are associated with poor psychosocial functioning in asymptomatic bipolar disorder. A main limitation of this study is the assessment of psychosocial functioning. Though a structured interview was utilized, a summary score was used in the analyses rather than domain scores that would

have been more descriptive. The neuropsychological measures did not include assessments of visual memory, executive function and attention, domains found to be impaired in bipolar disorder. A final limitation in this study is the small sample size.

Zubieta et al. (2001) also examined cognitive and social functioning during the euthymic phase of bipolar I disorder. Patients ($n = 15$) were diagnosed using SCID-IV and euthymic state was confirmed by using cutoff criteria on the Hamilton Depression Rating Scale and the Young Mania Rating Scale. Patients had more severe form of illness, as a criterion for study entry was psychosis during manic episodes. Social functioning was assessed using the Social and Occupational Functional Assessment Scale (SOFAS), which is a clinician rated scale ranging from 0 to 100. The SOFAS is similar to the DSM-IV General Assessment of Functioning score (GAF; APA, 2000). However, unlike the GAF, it does not include severity of psychological symptoms. In this study, Zubieta and colleagues found a mean functional rating of 69, which according to the SOFAS scale reflects some difficulty in social, occupational or school functioning but generally functioning well. The neuropsychological battery included assessments that examined the cognitive domains of memory, verbal fluency, executive functioning, sustained attention and concentration, and psychomotor functioning. Intellectual functioning was also assessed. The battery was comprehensive even though it didn't include tests of visuospatial ability. Authors found that the SOFAS scores significantly correlated with Wechsler Memory Scale Paired Associates subtest immediate recall scores and with the Stroop Color/Word T-scores. Similar to the results in the Atre-Vaidya 1998 study, verbal memory was associated with social/occupational functioning in the euthymic phase of bipolar disorder. Conclusions can be drawn from the Zubieta et al. study that this

association is present for bipolar I disorder specifically. Additionally Zubieta et al. found an association between social/occupational functioning and executive functioning. A strength of this study was the use of reliable rating scales for diagnosing bipolar I disorder, however, significant limitations exist. One limitation is the use of the SOFAS for determining functional status. Though perhaps better to use than the GAF score as it is not confounded with the psychological symptomatology that is reflected in a GAF score, the SOFAS is a non-standardized rating scale and may likely be unreliable. The small sample size was a major limitation of this study because it did not allow for a rigorous test of the study hypotheses. Also, using patients with psychotic features (a small percentage of the bipolar population), further limits generalizability of the results.

Martínez-Arán et al. (2002) directly assessed executive functioning and functional outcome. These authors examined patients diagnosed with either schizophrenia or bipolar disorder. There were 49 patients with bipolar disorder as diagnosed by DSM-IV, though no distinction was mentioned about bipolar I or II disorder. Patients were euthymic as assessed by the Hamilton Depression Rating Scale and the Young Mania Rating Scale and had at least 6-month remission. Social and occupational functioning was measured by a psychiatrist using the DSM-IV GAF. The neuropsychological assessments only included tests measuring executive functioning, though these assessments have been shown to be valid and reliable. Psychosocial functioning could be predicted by clinical variables, as measured by the Positive and Negative Syndrome Scale general psychopathology subscale (PANSS; Kay, Fiszbein, & Opfer, 1987), but not by neuropsychological variables. There was a trend toward significance for verbal fluency being related to functioning, and patients who performed poorly on the Controlled Oral

Word Association Test (COWAT/FAS) also showed poor functional outcome. What is interesting about the results in this study is that the instrument used to assess psychopathology (PANSS) also includes behavioral ratings for neurocognitive abilities of attention and motor retardation. Therefore it is difficult to determine if symptom ratings, neurocognitive ratings or both influence the predictability of psychosocial functioning by the PANSSG. Though this study only found a trend of verbal fluency associated with social and occupational functioning, and didn't find any relationship between executive abilities and functioning, the methodological limitations reduce the strength of these conclusions. The diagnosis of bipolar disorder was not performed with a valid and reliable rating instrument. Authors did not describe whether the diagnosis of the sample was bipolar I disorder, bipolar II disorder or a mixture of both diagnoses. Though the sample size was adequate and the neuropsychological assessments were appropriate, the measure of social and occupational functioning by the use of the GAF was a significant limitation.

This same research group published another study examining cognitive functioning in bipolar disorder across mood states (Martínez-Arán, Vieta, Reinares, et al., 2004). Diagnoses were made using DSM-IV criteria and again authors did not mention whether patients were diagnosed with bipolar I or bipolar II disorder, yet they did use the Hamilton Depression Rating Scale and the Young Mania Rating Scale to determine mood state. There were 30 patients in a depressed phase, 34 in manic or hypomanic phase, and 44 in euthymic phase with 6-month remission. Authors used the GAF to rate psychosocial functioning. They used a dichotomous rating scale for occupational functioning, such that good functioning meant the person was working at a good or

acceptable level and poor functioning meant that the person was not working or had poor occupational functioning during the last 3 years before evaluation. A comprehensive neuropsychological battery was administered examining cognitive areas of premorbid IQ, executive function, attention and concentration, verbal learning and memory and nonverbal learning and memory. Martínez-Arán, Vieta, Reinares, et al. found that psychosocial functioning was associated with neuropsychological measures of executive functioning, verbal fluency, attention and concentration, verbal memory, and nonverbal memory, instead of clinical variables. Occupational functioning was found to be associated with verbal fluency and all measures of verbal memory. Unlike the 2002 study by these authors, the current study suggests that neurocognitive factors are related to psychosocial and occupational functioning. Similar methodological weaknesses are present in the 2004 study as in the 2002 study. Patients were not described as either bipolar I or bipolar II and were not diagnosed using a standardized instrument. Again the use of the GAF as a measure of psychosocial functioning is limited and prone to variability, and the dichotomous rating of occupational functioning is based on clinician determination of good, acceptable and poor occupational functioning, which is likely unreliable if not adequately defined. Finally, though the authors determined mood state, when examining the relationship between psychosocial and neuropsychological functioning, all patients were grouped together. This makes it difficult to determine the effect of mood state on the association between functioning and neuropsychological deficits.

Martínez-Arán, Vieta, Colom, et al. (2004) in a similar study, examined cognitive impairments and their relationship to functional outcome in 40 patients with euthymia

and SCID-IV diagnosed bipolar disorder. Authors did not specify whether patients had a diagnosis of bipolar I or bipolar II disorder. The Hamilton Depression Rating Scale and the Young Mania Rating Scale were used to determine euthymic mood state.

Psychosocial functioning was assessed through the use of the GAF, and limitations of this instrument have already been noted. The neuropsychological battery assessed the domains of executive function, attention and concentration, and verbal learning and memory. Neuropsychological assessments chosen had appropriate validity and reliability. Authors found that verbal memory tasks, as measured by the California Verbal Learning Test, correlated with psychosocial functioning. Specifically measures of recognition and short- and long-delay recall. Additionally WAIS digit span backwards subtest, a measure of working memory, was also related to psychosocial functioning. Results suggest that in patients with bipolar disorder during asymptomatic periods, verbal memory is associated with psychosocial functioning, such that the better the memory performance, the higher the psychosocial functioning. Limitations of this study have already been mentioned in prior pages, but include limited test protocol, weak measure of psychosocial functioning, and lack of specificity in patient diagnosis.

In another study, Dickerson et al. (2004) examined employment status in 117 people with SCID-IV diagnosed bipolar I or bipolar II disorder. Employment status was determined by a categorization system with lowest functioning defined as being unemployed, to highest functioning as employed full time or full time student status. Though the authors did not report the reliability or validity for this rating scheme, it is valuable in that it doesn't include subjective ratings of poor or good work performance. It instead requires ratings of employment type: unemployed, volunteer, sheltered work,

part-time work (less than 20 hours per week), part-time student status, full-time work (at least 20 hours per week), full-time student status. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, Tierney, Mohr, & Chase, 1998) was administered and the test indexes include neuropsychological domains of immediate memory, visuospatial and constructional abilities, language, attention, and delayed memory. Authors also utilized the WAIS-III information and letter-number sequencing subtests and the Trail Making Test part A. They found that greater cognitive functioning was associated with better employment status for all neuropsychological assessments except the WAIS-III information subtest. The RBANS immediate memory subscale contributed independently to employment status in a regression model. This subscale includes a test of list learning and of story memory. In another regression model, a combination of RBANS total score and clinical variables, such as previous psychiatric hospitalizations, maternal education, and Brief Psychiatric Rating Scale total score, predicted employment status. It appears from this study that verbal memory is associated with employment status in addition to psychosocial functioning. Also better cognitive functioning in many domains is related to higher employment status. One of the limitations of this study is the differentiation of the patient group. Although authors assessed for mood symptoms using the Brief Psychiatric Rating Scale, the Hamilton Depression Rating Scale, and the Young Mania Rating Scale, they did not separate out the participants in different mood states for the statistical analyses, making it difficult to determine the relationship between mood state and employment status and how this relationship impacts the association of employment status and cognitive functioning. The scale for determining employment status was appropriate, yet it was lacking in

information about vocational adjustment and the individual's performance in a position. Finally the authors specified that the patient group consisted of bipolar I and bipolar II diagnoses, but they did not examine these diagnoses separately, making it impossible to determine if there were differences in the cognitive functioning for each group.

In a more recent article, Laes and Sponheim (2006) found weak results for the association between cognitive functioning and social functioning. Authors assessed a group of 27 outpatient participants diagnosed with bipolar disorder based on the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al., 1994). Social functioning was assessed using the Social Adjustment Scale II (SAS-II; Weissman, Prusoff, Thompson, Harding, & Myers, 1978). This scale is administered in interview-format and covers the domains of community functioning, family functioning, interpersonal relations, household adjustment and work adjustment, where higher scores reflect poorer functioning. This scale has adequate validity and reliability and has been used on psychiatric populations (Weissman & Bothwell, 1976). Another scale, the Quality of Life Interview (QOLI; Lehman, 1983) was administered to determine amount of social support in participants' living situations with levels ranging from non-social living type to heavy social living type, where heavy social living would be indicative of 24 hour supervised care. A neuropsychological battery was administered to assess cognitive functioning. This battery assessed the domains of intelligence, memory, motor functioning, verbal fluency, attention, vigilance or sustained attention, and executive functioning. Assessments selected have been shown to have acceptable reliability and validity in the neuropsychological literature. Laes and Sponheim found that problem solving ability or executive functioning (as measured by the Tower of London task) was

related to social functioning. There was a trend toward significance for the association between immediate and secondary verbal memory of the CVLT and social functioning. The limitations of this study include diagnostic and measurement issues. Though diagnoses were obtained reliably through the use of the DIGS, authors did not state whether diagnoses were bipolar I or bipolar II disorder or a mixture of both diagnoses. More importantly, mood state was not assessed so it is unclear what phase, manic, hypomanic, depressed, or euthymic, the patients were experiencing. Variations in mood state have been shown to affect neuropsychological functioning, thus confounding the results of this study. The use of the SAS-II was a strength, but unfortunately while the SAS-II scale covers various domains, the means of these domains were used to calculate an overall average score. This overall average was used in all analyses. The authors also used a quality of life scale, QOLI scale, and though ratings on this scale are likely an important factor in assessing functional status, authors did not consider their relationship to cognitive functioning.

Another study on the association between functional outcome and neurocognitive functioning in bipolar disorder is limited as it doesn't directly study this relationship but implies one (Goswami et al., 2006). Goswami et al. found a correlation between social dysfunction and soft neurological signs. They also found a correlation between soft neurological signs and tests of executive function. Authors imply that there is a link between these 3 domains. The study included 37 patients with bipolar I in a euthymic state diagnosed by a clinician using DSM-IV criteria. Euthymic mood state was determined by cutoff criteria of the Hamilton Depression Rating Scale and the Manic State Rating Scale. Social functioning was assessed using the Schedule for Assessment of

Psychiatric Disability, a test specifically developed for use in India. Domains rated included behavioral, social role, occupational and overall disability. Neurological soft signs were assessed using a modification of the Kolakowska battery (Kolakowska et al., 1985). Neuropsychological assessment focused on the domains of attention, executive function, non-verbal fluency, verbal fluency, short-term verbal memory, verbal memory and visuomotor speed. All assessments were established neuropsychological tests with adequate reliability and validity. The findings of an indirect association between executive function and social dysfunction are similar to previous results, which found a more direct association between these two variables (Martínez-Arán, Vieta, Reinares, et al., 2004; Laes & Sponheim, 2006).

The prediction of functional outcome, as measured by the GAF and level of work functioning, was examined by the Martínez-Arán group (2007) and they found that verbal delayed memory best predicted functioning. There were 77 participants with either bipolar I or bipolar II disorder in a euthymic state. Euthymic mood state was determined by cutoff criteria of the Hamilton Depression Rating Scale and the Manic State Rating Scale. This study represented an improvement in past studies in that the measure of functioning, GAF, was limited to only rating of psychosocial function and not symptoms and functioning. A GAF cutoff score of 60 was used to distinguish those with good and low psychosocial functioning. Good occupational functioning was defined as working at a good or acceptable level of functioning and poor occupational functioning was defined as not working at all or showing moderate to severe difficulties in their jobs. This information was obtained through clinical interview with the participant and confirmed by first-degree relative or partner and referred to the last 3 years prior to evaluation.

However, the study did not give specifics on the subjective measurement of moderate or severe job difficulties. Neuropsychological assessments included WAIS vocabulary test, Wisconsin Card Sorting Test, Stroop Color-word Test, FAS, Digit Span, Trail Making Test, and California Verbal Learning Test (CVLT). Authors found correlations between GAF functional rating and neuropsychological variables of Trails B, FAS, and all CVLT measures. Patients with lower psychosocial functioning showed even more impaired performance on CVLT free short and long delay recall, CVLT recognition, Stroop interference, and Trails B. The study did not find statistically significant differences in clinical variables, including age at onset, chronicity, hospitalizations, suicide attempts, and symptom rating measures, between high and low psychosocial functioning patients. In a regression equation, GAF scores were best predicted by CVLT free delayed recall and number of medications. In terms of occupational functioning, better neuropsychological performance was found in the good occupational group compared with the low occupational group on CVLT measures, FAS, and Trails B.

Malhi and colleagues (2007) examined the association between psychosocial functioning and neuropsychological deficits in the mood states of bipolar depression, hypomania, and euthymia. Twenty-five patients with bipolar I disorder were assessed in various mood states over a 30 month period. Mood state was determined through the use of the HDRS and YMRS rating scales. Similar to previous studies, psychosocial functioning was measured by the GAF score, and limitations of this rating scale as a measure of functioning have already been noted previously. Neuropsychological measures included tests of attention, working memory, learning and memory, executive functioning, and psychomotor speed. Authors found that in depressed patients poor

psychosocial functioning was associated with poor performance on tests of processing speed and reaction time. In hypomanic patients, poor psychosocial function was associated with poor working memory and poor new learning. However, there were no significant associations between neuropsychological test performance and psychosocial functioning in euthymic patients. Results are consistent with the findings that neuropsychological deficits vary depending on mood state; however, they are inconsistent with other findings that demonstrate neuropsychological performance is related to psychosocial functioning in euthymic mood states.

Though these studies help to shed light on the interaction between neurocognitive deficits and functioning, there are numerous methodological issues that prevent definitive conclusions. One of the most significant limitations is the inadequate measurement of functioning. Some studies use non-standardized ratings of a patient's psychosocial functioning and employment status (Vocisano et al., 1997; Atre-Vaidya et al., 1998; Martinez-Aran, Vieta, Reinares, et al., 2004; Dickerson et al., 2004), while others based social and occupational functioning on the DSM-IV General Assessment of Functioning score (GAF) (Martinez-Aran et al., 2002; Martinez-Aran, Vieta, Colom, et al., 2004). The use of the GAF in these studies is a significant limitation. The GAF has poor reliability, particularly when rated in clinical settings by practitioners, and no attempts are made to maintain reliability through rater meetings and training. Another problem with the GAF is that it combines both symptoms and functioning in an "either, or" fashion, therefore a person could obtain a GAF score of 30 reflecting primarily symptom severity and little impairment in function, while another person could have the same score for the opposite pattern of results. These studies using the GAF scores as a measure of functioning did not

specify the GAF criteria utilized, thus making it impossible to determine whether the significant correlations between the GAF and neurocognitive measures are accounted for by severity of symptoms or severity of functional impairments, or more likely a combination of both.

Though there are various ways to measure functional outcome, all have limitations. Self-report and clinician-rated methods may be inaccurate and lack validity (Patterson et al., 2001). Performance-based measures, where real-world tasks of daily living are simulated in a laboratory or clinic, may feel contrived to participants, while naturalistic observation of these tasks in real world settings is more authentic, it is especially difficult and expensive to conduct (Patterson et al., 2001). Although there are limitations to these various methods, utilizing a variety of methods would help increase reliability and validity. Additionally it is optimal to use measures that have been validated and tested for psychiatric populations. Judging from the most recent two studies, the trend seems to be moving in the direction of standardized scales that examine the patient's functioning in a variety of domains (Laes & Sponheim, 2006; Goswami et al., 2006). However in the existing studies, when reliable and valid measures of psychosocial functioning were utilized, the various domains of psychosocial functioning were collapsed into a single overall score, thus making it impossible to examine how neurocognitive domains were related to specific psychosocial domains (Atre-Vaidya et al., 1998; Laes & Sponheim, 2006).

Another methodological concern in these studies is the limited neuropsychological test protocols that only focus on a few domains of cognitive functioning. Though short test batteries tend to limit fatigue and burden on the participants, this is to the detriment

of a more comprehensive evaluation of neurocognitive function. The focus on neuropsychological domains of functioning is a way to ensure key processes are assessed. Yet many of the published studies on neurocognitive functioning and functional outcome in bipolar disorder leave out key cognitive domains that have been found to be impaired in bipolar disorder. Both sustained attention (Clark et al., 2001; Sax et al., 1995; Zubieta et al., 2001) and visual-spatial memory (Atre-Vaidya et al., 1998; Ferrier et al., 1999; Rubinsztein et al., 2000) appear to be impaired in people diagnosed with bipolar disorder as compared to control subjects. It seems likely that these domains may impact functional outcome, yet only four studies include only one of these domains (Atre-Vaidya et al., 1998; Zubieta et al., 2001; Dickerson et al., 2004; Laes & Sponheim, 2006).

The heterogeneity among clinical samples limits the conclusions that can be drawn from results. This heterogeneity could be due to lack of comprehensive rigorous diagnostic assessment or samples of convenience. Seven of the nine studies either failed to differentiate bipolar I disorder from bipolar II disorder and grouped patients together into a mixed Bipolar Disorder group or did not even specify what types of bipolar disorders composed the clinical group (Vocisano et al., 1997; Atre-Vaidya et al., 1998; Martinez-Aran et al., 2002; Martinez-Aran, Vieta, Reinares et al., 2004; Martinez-Aran, Vieta, Colom, et al., 2004; Dickerson et al., 2004; Laes & Sponheim, 2006). While recent literature reviews comparing bipolar I to bipolar II suggest there are few if any neurological or neurocognitive differences between the two disorders (Hauser et al., 2000), some researchers have found differences in the areas of symptom severity and symptom presentation (Berk & Dodd, 2005; Vieta, Gastó, Otero, & Nieto, 1997). It is too soon to tell whether these differences translate into difference in functional outcome.

There also may be some suggestion that Bipolar I disorder has a more severe functional course than Bipolar II disorder, and if true this likely impacts the conclusions of the above studies. Finally a related issue involves not assessing or incorporating the current mood state of the patient into the analyses (Vocisano et al., 1997; Dickerson et al., 2004; Laes & Sponheim, 2006). The neuropsychological literature on bipolar disorder has demonstrated that cognitive performance varies by mood state (Bearden et al., 2001; Olley et al., 2005). By not examining current mood state of the patients, it is difficult to determine the influence of mood state on the relationship between neurocognitive deficits and functional outcome.

Given these limitations, results should be interpreted with caution, yet it is clear that there is a relationship between functional status and neurocognitive variables. Executive functioning as assessed by the Tower of London task, Stroop Color/Word Test, and Wisconsin Card Sorting Test, was related to psychosocial and occupational functioning, such that people who performed better on these tasks had better functioning. Different measures of verbal memory were associated with functional status. These tests included the California Verbal Learning Test, Wechsler Memory Scale paired associates and logical memory subtests, and the RBANS list learning and story memory subtests. Finally verbal fluency as assessed by the Controlled Oral Word Association Test or FAS test, was related to functional outcome. Planning abilities and verbal fluency and memory abilities appear to be skills that may influence success in social and occupational domains for people with bipolar disorder.

Hypotheses

Based on the current literature review of patients with schizophrenia and bipolar disorder, along with expected associations between discrete neurocognitive abilities and real world behaviors, the following hypotheses were proposed.

- 1) It was hypothesized that generalized neurocognitive impairment will predict functional outcome such that on a general index of cognitive functioning, patients with greater generalized impairment will have lower W-QLI, UPSA, and LFQ scores.
- 2) It was hypothesized that there will also be associations between specific neurocognitive domains and specific functional outcomes. These are delineated in the following subhypotheses:

2.1 Based on prior research in schizophrenia and psychotic disorders demonstrating a relationship between the verbal learning and memory, executive function, and recreational planning and activities, as measured by performance based assessments (Twamley et al., 2002), it was hypothesized that the domain scores on verbal learning and memory and executive functioning will predict performance on the UPSA recreational planning domain. Specifically that poor neurocognitive performance will predict poor functional outcome performance.

2.2 Based on research with schizophrenia demonstrating a relationship between verbal and visual memory and quality of life (Buchanan, Holstein, & Breier, 1994), was is hypothesized that the two neurocognitive domains

verbal learning and memory, and visual learning and memory will be significantly associated with overall W-QLI score.

2.3 It was hypothesized that scores on the UPSA Finance domain will be predicted by the neurocognitive variables attention/psychomotor speed, verbal learning and memory, and executive functioning. This relationship has been shown in patients with psychotic disorders (Twamley et al., 2002) and in those with schizophrenia and schizoaffective disorder (Evans, Heaton, Paulsen, Palmer, Patterson, & Jeste, 2003) through the use of performance-based assessment measures.

2.4 Finally it was hypothesized that the level of occupation as measured by an item on the LFQ will be predicted by the neurocognitive variables verbal memory and learning, executive functioning and attention/psychomotor speed. Studies of bipolar disorder (Dickerson et al., 2004; Martinez-Aran, Vieta, Reinares, et al., 2004) and schizophrenia (for review see Green, 1996; Green et al., 2000) have found these neurocognitive domains to be associated with occupational level and functioning.

3) When chronicity (as measured by the number of mood episodes and number of hospitalizations) is included as a proxy for neurodegeneration, it is expected that neuropsychological variables will exhibit a mediating influence on the relation between chronicity and functional outcome (Model A). Chronicity has been shown to be related to functional outcome in both the schizophrenia and bipolar literature, with a more chronic course of the disorder being associated with more impairments in outcome (Bauwens et al., 1991; Dion et al., 1988; Tohen et al.,

2000; Vocisano et al., 1996; O'Connell et al., 1991). Additionally it has been suggested that mood episodes cause damage to the brain, resulting in neuropsychological deficits (Altshuler, 1993). Therefore it is also hypothesized that neurocognitive impairment will exhibit a mediating influence on the relation between depressive and manic symptoms (as measured by scores on the Hamilton Depression Rating Scale and the Young Mania Scale) and functional outcome (Model C). See Figure 1 in Appendix IV for model diagrams.

Due to the lack of information in this area, in addition to these a priori hypotheses, a number of exploratory analyses will be performed with neurocognitive and functional outcome variables, to provide direction for future research. For example, there is limited research support for an association between motor ability and household chores. The current study will investigate this relationship. The current study will also seek to understand whether there is a relationship between social and familiar relationship satisfaction and the neurocognitive variables executive functioning and verbal memory and learning. An examination of the relationship between executive functioning and verbal memory and learning and living situation (level of dependent/independent living) as measured by the LFQ, will be conducted. There is some suggestion in the schizophrenia research that these relationships may be significant (Green et al., 2000), though such specific research has not been performed for bipolar disorder and therefore is considered exploratory.

CHAPTER 3

METHOD

Participants

Participants in the study included 47 individuals (17 male and 30 female) diagnosed with Bipolar I or Bipolar II disorder. There were 34 individuals diagnosed with Bipolar I disorder and 13 diagnosed with Bipolar II. The age range of participants was 18 to 59 years. Individuals were selected for inclusion in the study if they met DSM-IV (American Psychiatric Association, 2000) criteria for Bipolar I or Bipolar II disorder as identified by a psychiatrist or psychologist, and confirmed using the Structured Clinical Interview for DSM-IV-TR (SCID-DSM-IV; First et al, 1996). Participants were included if they were not in a current mood episode as defined by DSM-IV. Exclusionary criteria were: 1) English as a second language; 2) history of traumatic brain injury or any other medical condition or neurological disease/damage that could cause cognitive deficits; 3) history of alcohol or substance abuse or dependence within the last six months; 4) diagnosis of mental retardation or any diagnosis of cognitive dysfunction; 5) current use of prescription or over-the-counter medications that could produce significant cognitive effects, other than those medications used to treat bipolar disorder.

Recruitment of participants was conducted from three sites including: 1) University of Nevada, Las Vegas, 2) Mojave Mental Health Center a community outpatient treatment facility, and 3) the community at large. Participants recruited through the University of Nevada, Las Vegas were recruited through the Psychology Department Subject Pool and through posted advertisements on campus using procedures approved by the University Institutional Review Board. The subject pool participants 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. All other participants were compensated monetarily at a rate of \$5.00 per hour, and \$30.00 bonus for completing the entire study (total of \$60.00 per participant). Participants who did not complete the entire study were compensated for the actual time spent participating on a pro-rated basis. All participants were required to read and sign an informed consent form prior to the initiation of any study procedures.

Sample size for the current study was determined using power analyses. For these analyses, correlation coefficients reported in studies of schizophrenia and bipolar disorder were considered. Based on these considerations, the current study was powered to detect medium to large effects sizes, so that significant differences could be detected with correlations ranging from .35 to .58. At the lower end of this range ($r = .35$), a sample size of 40 results in a power estimate of .72 ($\alpha = .05$; one tailed), while at the upper end of range ($r = .50$) a sample size of 40 results in a power estimate of greater than .90 ($\alpha = .05$; one tailed). The sample size of 47 provided adequate power to test the main hypotheses of the current investigation.

Procedure

Participants interested in completing the study were administered a brief phone or in-person screening to determine if they met study criteria. Participants who met the selection criteria were scheduled to complete the testing procedure in two testing sessions. Additional exclusionary criteria were evaluated during the experimental testing session. The first session included reviewing and obtaining informed consent and the

administration of a structured clinical interview, demographic and medical history questionnaires, clinical symptom scales, and three measures of functional status. This session lasted approximately 3 hours. The second session included the neuropsychological assessment and lasted approximately 3 hours. If the neuropsychological assessment was not complete by the close of the second session, the session was either continued for an extended period of time or was rescheduled for a third testing session.

All assessments and testing procedures are described below in the measures section. During the first testing session, the measures were administered in the following order: 1) informed consent, 2) demographic questionnaire (See Appendix I), 3) Structured Clinical Interview for DSM-IV, 4) Hamilton Depression Rating Scale, 5) Young Mania Rating Scale, 6) Life Functioning Questionnaire, 7) UCSD Performance-Based Skills Assessment, and 8) Wisconsin Quality of Life Index.

The second testing session included administration of the neuropsychological assessments in a fixed order as follows: 1) Lateral Dominance Examination, 2) California Verbal Learning Test, 3) Wisconsin Card Sorting Test, 4) Judgment of Line Orientation, 5) California Verbal Learning Test Delayed, 6) Controlled Oral Word Association Test (letter fluency), 7) Biber Figure Learning Test, 8) WAIS-III Vocabulary, 9) Trail Making Test A and B, 10) Biber Delayed, 11) Stroop Color-Word Test, 12) Continuous Performance Test, 13) WMS-III Logical Memory I, 14) WAIS-III Block Design, 15) Grip Strength, 16) Fingertapping Test, 17) WAIS-III Digit Span, 18) WMS-III Spatial Span, 19) WMS-III Logical Memory II (delayed), 20) Rey-Osterrith Complex Figure (copy), 21) Controlled Oral Word Association Test (category fluency), 22) Rey-Osterrith

Complex Figure (3 minute delay), 23) Purdue Pegboard, 24) WAIS-III Information, 25) Rey-Osterrith Complex Figure (30 minute delay).

Attempts were made to schedule the two evaluation sessions on the same day with the diagnostic portion completed in the morning and neuropsychological testing in the afternoon, with a break for lunch. When necessary participants were scheduled for more than one testing day. Also to minimize fatigue within each of the testing sessions, one scheduled mandatory break was taken. Breaks were also taken as needed, at the request of the participant, or in cases where the examiner deemed such a break necessary to decrease fatigue.

All testing was conducted by the primary author or other trained graduate students, and occurred in a quiet private setting (laboratory office) at the UNLV Neuropsychology Research Program Laboratory or at Mojave Mental Health Center. Time was allotted for questions after the examination, and the participant was given a debriefing form containing experimenter contact information and information regarding the nature of the study.

Measures

Measures used in the current study assessed 4 domains of psychological and psychosocial functioning: 1) clinical symptomatology, 2) psychosocial and occupational functioning, 3) neuropsychological functioning, and 4) estimated current and premorbid intellectual ability. Description of the format of each test and its procedures is provided below. Psychometric properties of all tests are also provided where relevant. Client demographic information was obtained from two sources. First, the Wisconsin Quality of

Life Index (W-QLI; Becker, Diamond, Douglas, & Thornton, 2000), further described below, contains a background information form that includes the following information: highest education level obtained, marital status, ethnicity, income, disability status, residential status, and residential inhabitants. Second, a separate demographic form (See Appendix I) was used to record the additional demographic and clinical information including medical and developmental history and family history.

Diagnostic and Clinical Symptom Measures

Several measures were included to assess clinical symptomatology relevant to bipolar disorder. Measures include the Structured Clinical Interview for DSM-IV-TR (SCID-I for DSM-IV; First, Gibbon, Spitzer, & Wewers, 1996), the Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978), and the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960, 1967). The SCID was used to verify DSM-IV Axis-I diagnosis of bipolar disorder and to determine that participants were not in a current mood episode. The Young Mania Rating Scale and Hamilton Depression Rating Scale were included to assess symptoms of mania and depression, respectively.

The Structured Clinical Interview for DSM-IV-TR Axis I Disorders- Research version (SCID-I for DSM-IV; First, Gibbon, Spitzer, & Wewers, 1996) is a semi-structured interview designed to allow the reliable and valid diagnosis of DSM-IV Axis I disorders. The SCID-I is appropriate for psychiatric and general medical patients, as well as for 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. The SCID-I is most widely used with adults 18 years or older with at least an eighth grade education. There are separate forms for the assessment

of inpatient (SCID-P), outpatient (SCID-OP), and non-patient groups (SCID-NP). The research version of the SCID-P was administered in the current study. This version is the most extensive of the SCID versions, and is designed specifically for research applications. It consists of a background and history section, a screening module, as well as 10 diagnostic modules that allow for the evaluation of 1) mood episodes, 2) psychotic symptoms, 3) psychotic disorders, 4) mood disorders, 5) substance use disorders, 6) anxiety disorders, 7) somatoform disorders, 8) eating disorders, 9) adjustment disorders, and 10) optional disorders. Modules 1-9 were administered in the current study, including the background and history section, and the screening module. The optional disorders module was not administered as it contains research criteria for further study of proposed disorders such as minor depressive disorder. The screening module of the SCID-P consists of 12 questions that are used to elicit information used in the diagnoses of disorder that occur later in the SCID interview. Diagnostic ratings for the SCID modules are based on an extensive structured clinical interview with the client that is conducted by a clinician trained in the DSM-IV diagnostic system (APA, 1994) and SCID procedures. Completing the SCID involves rating each DSM-IV diagnostic criteria either as 1 (symptom is absent), 2 (subthreshold symptom) or 3 (symptom is present). In terms of psychometrics, the SCID has been shown to have excellent inter-rater reliability ($\kappa = .85$, range = .71 to .97), and very good diagnostic accuracy, as compared to consensus diagnosis (82%) (Ventura, Liberman, Green, Shaner, & Mintz, 1998).

The Young Mania Rating scale (YMRS; 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 is rated based on the individual's subjective report over

the previous forty-eight hours, as well as on the behavioral observations of the clinician. The rating of each item is on a scale of 0 to 4 (absent to overtly present), except for four of the items, which receive double the weighting and are rated on a scale of 0 to 8. As an example, item 1 is elevated mood, which is rated from 0 (absent) to 4 (euphoric; inappropriate laughter; singing). This rating scale was used to assess for presence of manic symptoms and the total score was used in the analyses. 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 may demonstrate subthreshold symptoms or hypomania. Patients who were experiencing a current manic or mixed episode, as identified by the SCID-P, were excluded from the study.

The Hamilton Depression Rating Scale (HDRS; Hamilton, 1960, 1967) is extensively used in treatment outcome studies of depression. It is a clinician-administered scale that assesses the severity of depression, but it is not a diagnostic instrument. The version of the Hamilton Depression Rating Scale used in the current study consisted of 21-items. Each item was 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 considered to reflect an asymptomatic state, with an increasing continuum of symptom severity as scores increase 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). The HDRS total score was used in the analyses. Participants who were experiencing a current major depressive episode, as determined by the SCID-P, were excluded from the study.

Psychosocial and Occupational Functioning

Three measures were included to determine functioning in occupational and psychosocial domains, as well as the patient's subjective satisfaction with his/her life. These measures were selected because they provided a broad coverage of different functional domains, and are a mixture of self-report, interview, and performance-based formats. Also, they were specifically developed for use with psychiatric populations and been found to be related to cognitive variables. Finally, although many measures are available to assess functioning, the current study attempted to balance comprehensiveness with practicality and time constraints. Measures included the Wisconsin Quality of Life Index (W-QLI; Becker, Diamond, Douglas, & Thornton, 2000), the UCSD Performance-Based Skills Assessment (UPSA; Patterson et al., 2001), and the Life Functioning Questionnaire (LFQ; Altshuler, Mintz, & Leight, 2002).

The Wisconsin Quality of Life Index (W-QLI; Becker, Diamond, Douglas, & Thornton, 2000) is a patient self-report measure that assesses a participant's satisfaction in nine life domains including: life satisfaction, occupational activities, psychological well being, physical health, social relations, economics, activities and instrumental activities of daily living (ADL/IADL), symptoms, and goals. For example the life satisfaction domain contains the question: How satisfied are you with the way you spend your time? Very dissatisfied, moderately dissatisfied, a little dissatisfied, neither satisfied nor dissatisfied, a little satisfied, moderately satisfied, or very satisfied. Similarly, the

social relations domain contains the question: How satisfied or dissatisfied are you with how you get along with your friends? Very dissatisfied, moderately dissatisfied, a little dissatisfied, neither satisfied nor dissatisfied, a little satisfied, moderately satisfied, or very satisfied. The goal domain contains six open-ended response indicators asking the participant to write their treatment goals and to rate how important the goal is and whether the goal has been achieved. The scores for each of the nine domains range from -3 (the worst things could be) to +3 (the best things could be). A score of 0 is considered an average score. A domain score is obtained by averaging all the individual item scores. An overall W-QLI score is obtained by averaging the domain scores. The W-QLI has been developed specifically to evaluate quality of life in people with mental illnesses and has been found reliable and valid (Becker et al., 2000; Becker, Diamond, & Sainfort, 1993). It has been used in various patient populations including schizophrenia, mood disorders, borderline personality disorder and schizoaffective disorder (Becker et al., 2000; Becker, Diamond, & Sainfort, 1993; Caron et al., 2003). For the current study, the overall W-QLI score was used in the main analyses.

The UCSD Performance-Based Skills Assessment (UPSA; Patterson et al., 2001) is a performance-based measure of everyday functioning. Participants are asked to complete a number of tasks to determine skills in the areas of household chores, communication, finance, transportation, and planning recreational activities. As an example of household chores, participants are given a recipe for rice pudding and asked to write a shopping list of the items to buy based on the items they already have in a mock kitchen pantry. In the communication domain, participants are required to make several telephone calls using various instructions. The finance domain includes tasks related to counting change and

paying a bill by check. The transportation domain involves being able to use a bus schedule to determine information, for example the cost of a ride and which bus lines to travel. The area of planning recreational activities asks the participants to read two story scenarios and plan accordingly. For example in one scenario they are to read a story about a recreational area (e.g., beach, public park) and to pretend they are going on the outing and make plans for the trip (e.g., how to travel there, what they were do once there, what to bring). Each of the five subscales yields total raw scores; these are transformed into a 0-to-10 scale and then multiplied by 2. Therefore each of the five subscale scores range from 1 to 20. A summary score is calculated by summing the five subscale scores, giving a total score range from 0 to 100. The summary score, recreational planning domain score, and finance domain score were used in the analyses for the current study.

The UPSA was developed for use with psychiatric patients and performance on this measure has been found to be more impaired in schizophrenia patients as compared to normal controls (Patterson et al., 2001). In this study the mean total score for the patient group was 58.8 compared with the normal control group mean of 92.6. The UPSA was also found to be strongly correlated with the Direct Assessment of Functional Status (DAFS; Lowenstein et al., 1989) another performance-based measure developed for patients with dementia. In schizophrenia patient samples, worse performance on the UPSA was significantly related to negative symptoms and poor cognitive functioning as measured by brief cognitive assessment batteries, the Mattis Dementia Rating Scale and the Wisconsin Card Sorting Test (Keefe, Poe, Walker, & Harvey, 2006; Kurtz & Wexler, 2006; Patterson et al., 2001; Twamley et al., 2002). Although the UPSA has not been used with bipolar disorder, it is thought to be an appropriate measure for this disorder due

to its use with schizophrenia and its focus on community-dwelling patients and problems typically encountered by these individuals (Patterson et al., 2001).

The Life Functioning Questionnaire (LFQ; Altshuler, Mintz, & Leight, 2002) is a self-report measure of psychosocial and occupational functioning consisting of two parts. In part I, role functioning over the previous month is assessed in four domains: workplace (4 items), duties at home (4 items), leisure time with family (3 items), and leisure time with friends (3 items). Time spent in activity (Time), ability to get along with others (Conflict) and enjoyment obtained from spending time or working with others (Enjoyment) are assessed for each domain, and additionally quality of work performed (Performance) is assessed for the duties at home and workplace domains. The participant rates each question based on degree of difficulty functioning on a 4-point scale: 1 = no problems, 2 = mild problems, 3 = moderate problems, and 4 = severe problems. Impairment is defined as a mean score of 2 or more in any domain.

In part II of the LFQ, the participant is required to answer five multiple-choice questions on the topics of: 1) work situation this month, 2) number of days per week scheduled to attend work, school, day hospital, and activity center, 3) living situation over the last 6 months, 4) financial situation over the last six months, and 5) when and for how long the participant last worked full-time and reason for stopping full-time work. In addition to the scores on the 4 primary domains, these questions were be utilized as outcome measures.

Reliability and validity information was collected based on 3 samples of patients with bipolar disorder. Test-retest reliability for all four sections was found to be high ($r = .70$ to $.77$) (Altshuler, Mintz, & Leight, 2002). The LFQ was also shown to have high internal

consistency (above $r = .84$ for each section) (Altshuler, Mintz, & Leight, 2002). This measure significantly correlated with another self-report psychosocial rating instrument, the Social Adjustment Scale (SAS-SR).

Neuropsychological Functioning

The measures used to assess neuropsychological functioning were grouped broadly into 7 neurocognitive domains: 1) executive functioning, 2) verbal learning and memory, 3) visual learning and memory, 4) attention/psychomotor speed, 5) working memory, 6) visuoconstructional/spatial organization, and 7) motor ability. The measures selected are widely used in both clinical and research settings, have been used in previous studies assessing the neurocognitive functioning in patients with bipolar disorder, and have been found to be associated with occupational and psychosocial functioning. These assessments were also selected to collectively measure broad domains of cognitive functions that would be inclusive in a comprehensive neuropsychological battery. Refer to table 1, Appendix III for neuropsychological assessments organized by neurocognitive domain and including the scores of each assessment that were utilized for creating domain composite scores.

Measures of Executive Functioning

In the Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993), 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 et al., 1993). For the current study, number of categories achieved and percent perseverative errors were used to calculate the composite score.

The Controlled Oral Word Association Test, (COWAT; Sumerall, Timmons, James, Wing, & Oehlert, 1997) 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 were 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 et al., 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.

The Trail Making Test B or Trails B (Reitan & Wolfson, 1985) 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 in an alternating fashion from number to letter, with the circles numbered from 1 to 13 and the letters from A to L. The Trail Making test consists of parts A and B, which have a correlation of .49 (Spreeen & 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 Trails B was used as the measure of performance.

Measures of Verbal Learning and Memory

The California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) is 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 distractor 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 scores for this measure include 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. Scores included in the analyses to assess the verbal learning and memory domain included total words recalled on trials 1 to 5 and words recalled on List A after a delay.

The Logical Memory Subtest of the Wechsler Memory Scale – Third Edition (WMS-III; Wechsler, 1997 b) is a test of immediate and delayed memory for story passages. The test consists of an immediate memory portion, Logical Memory I, and a delayed memory condition, Logical Memory II. Both were administered in the current study. In Logical

Memory I, two stories are presented orally to the participant. Immediately after each story presentation, the participant is asked to retell the story from memory. The second story is presented twice sequentially and the participant is required to retell the story after both presentations. After a 25-35 minute delay period, the participant is asked to retell both stories without any cues. This is followed by yes/no questions about the stories. Raw scores can be converted to age-normed scaled scores for Logical Memory I and Logical Memory II. The raw score for immediate recall of the stories and the raw score for delayed recall of the stories were used to create the verbal memory domain.

Measures of Visual Learning and Memory

The Biber Figure Learning Test-Extended (BFLT-E; Glosser et al., 2002) is 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 combined 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. For the current study, the following variables were used to measure the nonverbal learning and memory domain: learning trials 1-5 and delayed recall.

The Rey-Osterrieth Complex Figure (ROCF; Rey, 1941; Osterrieth, 1944) is a commonly used test to assess visuo-perceptual and visuo-constructional 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 was administered with a copy condition, a 3-minute delayed recall trial, and a 30-minute delayed recall 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 ROCF was scored using the system developed by Meyers and Meyers (1995). The 3-minute and 30-minute delayed recall scores were used

to evaluate the visual memory domain. The copy condition was used as a visuoconstructional/spatial organization task discussed below.

Measures of Attention and Psychomotor Speed

The Degraded Stimulus Continuous Performance Test (DS-CPT) is a computerized vigilance test. Vigilance tests measure the ability to focus and sustain attention in itself. The current study utilized the degraded stimulus CPT (Nuechterlein & Asarnow, 1992), as this version is extensively used in investigations of clinical population, particularly in individuals with schizophrenia (Nuechterlein, 1991). Administration time is approximately 15 - 20 minutes. The task requires the examinee to press a key-board response button each time a predesignated target stimulus appears on the screen (target number = 0) within a field of distracter targets. Stimuli are degraded by 50% and presented at irregular lengths (mean = 1000 ms), with a stimulus duration of 200 ms. Targets compose 25% of the 480 total trials. The most common indices calculated for the CPT, and those used in the current study, include sensitivity (CPT d') and response criterion (CPT b). Sensitivity (CPT d') refers to the ability to discriminate target (signal) stimuli from nontarget (noise) stimuli. CPT d' is obtained by evaluating the hit rate and false alarm rate, where a CPTd' of 0.0 represents a chance discrimination level. Response criterion (CPT b) measures the amount of perceptual evidence that the person requires to decide that a stimulus is a target. The Continuous Performance Test has been used extensively to differentiate individuals with schizophrenia from normal controls and other patient groups (Albus et al., 1996; Addington & Addington, 1998; Liu et al., 2002).

A computerized version of the Stroop Color-Word Test was administered to participants. This is considered a test of selective attention and inhibition. This version of

the Stroop test was designed for studies in the neuropsychology research laboratory by Gregory Strauss, Ph.D. Participants are presented words printed in four ink colors (red, yellow, green, blue). The stimuli appear on a computer screen as color words presented against a black background for a duration of 5 s or until a verbal response is given. Participants are required to say the color of the ink that the words are printed in. Verbal response is measured by a voice-operated microphone. To ensure that stimuli were presented at the appropriate inter-stimulus-interval (ISI) of 250 ms for all stimuli, a refresh rate detector was connected to the computer. After each response, the experimenter determines the accuracy of the participant's response. There are two types of stimuli, congruent and incongruent. For the congruent condition, the color of the ink and the word itself were the same. For example the word "red" was printed in red ink. The required response is "red." For the incongruent condition, the word and color of the ink were different. The participant must ignore the printed word and say the color of the ink the word is printed in. As an example the word "red" may be written in blue ink. The participant is required to say "blue" instead of "red". Participants are shown a total of 50 congruent and 50 incongruent stimuli. Stimuli were presented in a fixed semirandom order with the restriction that no two colors could appear in consecutive trials. All stimuli appeared in uppercase Arial font, size 18 points. The variable used for the current study is the Stroop difference score, which is the average reaction time for congruent condition minus the average reaction time for the incongruent condition.

The Trailmaking Test Part A or Trails A (Reitan & 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 the performance measure for this task.

Measures of Working Memory

Auditory working memory was assessed using the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997a) Digit Span Forward and Backward subtest. For the Digit Span 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. Raw scores can be converted to scaled scores based on age-normative data. The raw scores of Digits forward and Digits backwards were used in the analyses.

Visuospatial working memory was assessed using the Wechsler Memory Scale Third Edition (WMS-III; Wechsler, 1997b) Spatial Span subtest. The Spatial Span subtest is considered to be a visual analog of the Digit Span subtest, with Forward and Backward tapping components. 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 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 per 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 condition. Scores are the sum of the number of trials successfully completed in both conditions. Raw scores can be converted to scaled scores based on age-normed data. Raw scores for Forward and Backward Span conditions were used in the current study.

Measures of Visuoconstructional / Spatial Organization

Visuospatial and visuoconstructional abilities were assessed using three tests including the Rey Complex Figure, WAIS-III Block Design subtest, and the Benton Judgment of Line Orientation subtest.

The Rey-Osterrieth Complex Figure (Osterrieth, 1944; Rey, 1941) was described previously. The copy condition was used as a measure of visuospatial and constructional abilities. The participant is shown the 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 3 and 30 minute delayed conditions.

The Block Design subtest of the WAIS-III (Wechsler, 1997a) 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. Raw scores can be converted to scaled scores based on age normative data. For the current study, raw scores were used to create the Visuoconstructional/Spatial Organization domain.

Judgment of Line Orientation (JOL; Benton et al., 1978) has been found to be predominantly a right hemisphere task (Lezak, 1995), which 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. Scores are based on the total correct out of 30.

Measures of Motor Ability

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. Lateral dominance is not a formal measure of motor function, but is included in this section as it was used to provide information on the participant's handedness in order to guide administration of the following motor tasks.

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 (Spreeen & 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 (Spreeen & 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.

In the Grip strength assessment 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. Measures of grip strength were recorded for the dominant and non-dominant hand.

The Purdue Pegboard Test (Tiffin, 1948) is a measure of motor speed as well as 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 (Spreeen & 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. 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 pegs (one at a time) 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 pegs 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 pegs 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 pegs inserted is calculated. Raw scores in terms of number of pegs placed within the 30-second time period were used for the dominant and non-dominant hands.

Intellectual Functioning

The Vocabulary and Information subtests from the WAIS-III were used to calculate an estimated premorbid IQ or measure of premorbid intelligence. The Information and Vocabulary subtests have the highest reliabilities among the WAIS-III verbal 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 mean of the Vocabulary and Information age-corrected scaled scores were used as the estimate of premorbid IQ (Bilder et al., 1992).

Current IQ was estimated using a dyadic short form of the WAIS-III that is based on the Vocabulary and Block Design subtests. Scores from these subtests are entered into a regression equation in order to estimate the Full Scale IQ score (Ringe, Saine, Lacritz, Hynan, & Cullum, 2002). The equation to be used in the current study is Vocabulary (2.727) + Block Design (2.727) + 42.535 = Estimated Full Scale IQ (Ringe et al., 2002).

This regression equation was normed on a mixed neurological/psychiatric sample and was found to estimate Full Scale IQ within 10 points in 81% to 93% of the sample (Ringe et al., 2002).

The Vocabulary subtest of the WAIS-III 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-III 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 "On what continent is Poland?" No credit is given for guesses or partial answers. The test is discontinued after consecutive errors.

Data Entry and Analyses

Data Entry and Screening

All tests were scored according to standardized procedures by two trained individuals. In cases where disagreement occurred, a third opinion (Daniel Allen, Ph.D.) was used to resolve discrepancies. Data was entered twice into Microsoft Access and SPSS version 14.0 was used to analyze the data.

Prior to conducting the analyses to examine the main hypotheses, functional outcome and neuropsychological test data were inspected for outliers. Skewness and kurtosis were examined to ensure that all variables are normally distributed. Descriptive statistics and

box plots were used to evaluate the presence of outliers. In cases where variables were not normally distributed, transformations were used to increase the normality of the distribution. Transformations were selected in accordance with the recommendations of Tabachnick and Fidell (2001). Outliers were defined as scores that are 2.0 standard deviations above the mean. In cases where outliers were detected, the individual data point was examined first to verify that it did not result from a data entry error and represented a valid case. For outliers deemed to be valid cases, the data point was retained but the score was converted to decrease its influence on measure of central tendency and the regression analyses.

For all regression analyses, appropriate diagnostic tests were run before building the final model. Residuals were examined for issues of non-constant variance and non-error variance.

Descriptive statistics of the group were calculated for the demographic variables of age, education, estimated IQ, ethnicity, and gender. Clinical variables were also reported, including the variables length of illness, age of onset, current symptomology (as measured by scores on the Young Mania Rating Scale and Hamilton Depression Rating scales), medication type, and number of hospitalizations using descriptive statistics.

Prior to performing the main analyses, seven composite scores were derived to reflect each of the seven neurocognitive domains. To accomplish this, raw scores were first converted to standard scores for each of the neuropsychological test score using the mean and standard deviation of the current sample. Then, the seven composite scores were derived by averaging the z scores from the respective tests that are included in each neurocognitive domain. Table 1 in Appendix III provides the list of scores comprising

each neurocognitive domain that were used to calculate the composite scores. Two principles were used to guide the selection of test scores used to calculate the composites, including 1) scores were selected that have demonstrated sensitivity to brain dysfunction, and 2) scores were selected that were most representative of the cognitive construct being assessed by that domain. A global neurocognitive composite score was also created by averaging the seven domain composite scores.

The summary scores for the W-QLI and UPSA were calculated according to the instructions in the respective manuals, including the domains of life satisfaction, occupational activities, psychological well being, physical health, social relations, economics, activities and instrumental activities of daily living (ADL/IADL), symptoms, goals and overall score. The UPSA domains are household chores, communication, finance, transportation, planning recreational activities and overall score. An overall score for the LFQ was created by averaging the summary scores of the four domains. The summary score for each domain was calculated by averaging scores within a domain, per manual instructions. The domains are workplace, duties at home, leisure time with family, and leisure time with friends.

Evaluation of Main Hypotheses

Hypothesis 1:

In order to determine whether neurocognitive impairment predicts functioning, the global neurocognitive composite score was used as a predictor in three linear regression equations. The dependent variables for the equations were the overall scores on the W-QLI , UPSA, and the LFQ. In each of these analyses, it was anticipated that

neurocognitive function would significantly predict functioning, with greater neurocognitive impairment associated with poorer functional outcome.

Hypothesis 2:

It was hypothesized that specific neurocognitive domains were associated with specific functional outcomes. Standard multiple regression analyses were used to test subhypotheses 2.1, 2.2., 2.3., and 2.4. For Hypothesis 2.1, the verbal learning and memory, and executive functioning composite scores were the independent variables and were entered into a standard multiple regression equation to predict the dependent variable UPSA recreational planning. Hypotheses 2.2, 2.3 and 2.4 were evaluated in a similar manner. However, for hypothesis 2.2 the independent variables was the composite scores of neurocognitive domains verbal learning and memory and visual learning and memory, with the dependent variable of overall W-QLI score. For, Hypothesis 2.3, the UPSA finance domain score served as the dependent variable, and the neurocognitive composite scores for attention/psychomotor speed, verbal learning and memory, and executive function, were the predictor variables. Finally hypothesis 2.4 utilized the “work situation this month” item in Part II of the LFQ to create a dependent variable “work functioning” which reflects the level of occupational functioning. This item on the LFQ ranges from competitive full-time employment to not working in job, school or home. This work functioning variable was predicted by the composite scores for the neurocognitive domains of verbal memory and learning, executive functioning, and attention.

Hypothesis 3:

Mediational analyses were conducted to determine the effects that mediating variables had on functional outcomes (Baron & Kenny, 1986). Four separate models were tested (See Figure 1 in Appendix IV). It was hypothesized that model A and model C would be significant, such that neurocognitive impairment functioned as a mediator between clinical characteristics and functional outcome. In model A, it was hypothesized that the relation between chronicity and functional outcome was mediated by neurocognitive impairment. Chronicity was assessed by first correlating the *z* scores of the number of mood episodes and number of hospitalizations. It was expected that these scores were positively correlated, as each hospitalization is likely to be associated with a mood episode. If the two indeed were correlated, only number of mood episodes was used as assessed by the SCID structured interview. If they did not significantly correlate with each other, then they were averaged, as it is then suggestive that they measure different types of chronicity. In order to evidence a mediation effect, four conditions must be met as tested by regression analyses, which include: 1) chronicity must be significantly related to neurocognitive impairment, 2) chronicity must be significantly related to functional outcome, 3) neurocognitive impairment must be significantly related to functional outcome, and 4) the impact of chronicity on functional outcome must be less after neurocognitive impairment is controlled for.

Model B examined the condition that neurocognitive impairment is a moderator of the relationship between chronicity and functional outcome. Consistent with Baron and Kenny (1986), as both the mediator and independent variables are continuous variables, functional outcome were regressed on chronicity, neurocognitive impairment, and the

product of chronicity and neurocognitive impairment. A moderator would be indicated by a significant effect of the product of chronicity and neurocognitive impairment, while the effects of chronicity and neurocognitive impairment were controlled.

In model C, it was hypothesized that the relation between symptoms and functional outcome was mediated by neurocognitive impairment. Symptoms of depression and mania were examined separately in the analyses, with depression being measured by the total scores on the HDRS, and mania by the total score on the YMRS. Therefore, the analyses for models C and D were conducted twice with depressive symptoms and manic symptoms as separate independent variables. In order to evidence a mediation effect, the four conditions for this model include: 1) symptoms must be significantly related to neurocognitive impairment, 2) symptoms must be significantly related to functional outcome, 3) neurocognitive impairment must be significantly related to functional outcome, and 4) the impact of symptoms on functional outcome must be less after neurocognitive impairment is controlled for.

Model D was a moderator model which examined the hypothesis that neurocognitive impairment was a moderator of the relationship between symptoms and functional outcome. Again as both the mediator and independent variables are continuous variables, functional outcome were regressed on symptoms, neurocognitive impairment, and the product of symptoms and neurocognitive impairment (Baron and Kenny, 1986). A moderator would be indicated by a significant effect of the product of symptoms and neurocognitive impairment, while symptoms and neurocognitive impairment are controlled.

The dependent variable, functional outcome, for all four models was measured by the overall scores on the Wisconsin Quality of Life Index, the UCSD Performance-Based Skills Assessment, and the Life Functioning Questionnaire, thus resulting in 3 separate analyses for each model.

Exploratory Analyses:

A number of exploratory analyses were also performed to determine relationships between neuropsychological domains and functional outcome domains. As an example, linear regression was used to determine if the composite score on the motor ability domain predicts the dependent variable UPSA household chores. Additionally standard multiple regression were used with independent variables of executive function and verbal memory and language domain composite scores, predicting social and familiar relationship satisfaction summary score from the W-QLI. In another exploratory analysis using standard multiple regression, the living situation score from the LFQ was the dependent variable, which is predicted by neurocognitive domain composite scores executive functioning and verbal memory and learning.

CHAPTER 4

RESULTS

Preliminary Analyses

The descriptive statistics for each neuropsychological variable and each functional outcome variable are presented in Table 2 and 3. Examination of the individual test scores using frequency statistics indicated that there were no out-of-range variables. Variables with skewness and kurtosis estimates within ± 1.0 were considered to be in the range acceptable for use of parametric statistical tests and procedures. In addition to skewness and kurtosis estimates, the Shapiro-Wilk test of normality was used to identify variables that were not normally distributed. Finally, box plot analysis was used to identify outliers, defined as data points greater than 2.0 standard deviations above or below the group mean. In most cases, variables that had skewness and kurtosis estimates greater than ± 1.0 also had a significant Shapiro-Wilk test as well as outliers. These variables were adjusted as described in the following section. Only two variables, Benton JOL and Logical Memory I recall total score, had a significant Shapiro-Wilk's test but no outliers and acceptable skewness and kurtosis. In these two instances the variables were not adjusted.

As can be seen from the Table 2, a number of the neuropsychological variables (10/29) exceeded the skewness and/or kurtosis criteria of $> \pm 1.0$, most markedly Biber Long Delay Recall and Stroop Difference Score. Box plots indicated that outliers were present for several variables, including WCST percent perseverative errors, WCST number of categories completed, Category Fluency, Trails A, Trails B, CVLT Long Delay Recall, Logical Memory II recall total score, Biber Long Delay Recall, Rey Copy,

CPT summary d', CPT summary b', Stroop difference score, Finger Tapping dominant hand, Purdue Pegboard (dominant, nondominant, and both hands), and Grip Strength (dominant and nondominant). In cases where outliers were identified, the data were rechecked to ensure that these values were all valid cases. All values identified as outliers were found to be valid cases. For extreme outliers, defined as greater than 2.5 standard deviations from the mean, each score was transformed to decrease its influence on the regression analysis. Transformation was done by adjusting the score to be ± 1 score point from the next lowest or highest score, respectively. After performing this adjustment for outliers, skewness and kurtosis estimates were within acceptable limits for Category Fluency, Trails A, Trails B, CVLT Long Delay Recall, CPT summary b', Stroop difference score, Finger Tapping dominant hand, Purdue Pegboard nondominant, and Grip Strength (dominant and nondominant) scores. Also, skewness and kurtosis were within acceptable limits for WCST percent perseverative errors, Logical Memory II recall total score Biber Long Delay Recall Rey Copy, CPT summary d', and Purdue Pegboard dominant, although outliers persisted. It was thus determined that further adjustment would not be necessary for these variables.

One variable, WCST number of categories, required a different approach. WCST number of categories had 9 outliers due to nature of this variable where most examinees obtain the maximum number of categories (6) and few scored below that. In this instance, the participants scoring less than 6 categories were outliers. It was determined that this variable should be transformed to reduce skewness and kurtosis (skewness = -1.83, kurtosis = 2.06). Initially Log 10 transformation was performed with an increase in skewness and kurtosis (skewness = -2.51, kurtosis = 6.59). Then Cosine transformation

was performed with some improvement (skewness = -1.75, kurtosis = 1.40). This Cosine transformed variable was used in the analyses to create the Executive Function composite.

In terms of the functional outcome measures a number of these variables (10/22) exceeded the skewness and/or kurtosis criteria of $> \pm 1.0$, most markedly LFQ Average problem rating (table 3). Box plots indicated that outliers were present for several variables, including LFQ average problem rating, LFQ family domain, LFQ home chores domain, WQLI Activities of daily living, UPSA total score, UPSA comprehension/planning subscale, UPSA finance subscale, UPSA transportation subscale, and UPSA household skills subscale. Again, conversion was performed by adjusting the score to be ± 1 score point from the next lowest or highest score, respectively. After the adjustment for outliers, skewness and kurtosis was adequate and there were no more outliers for the variables LFQ family domain, LFQ home chores domain, UPSA total score, UPSA transportation subscale, and UPSA household skills subscale. For variables the LFQ average problem rating, UPSA comprehension/planning subscale, UPSA finance subscale, and WQLI Activities of daily living, outliers persisted but skewness and kurtosis was at an acceptable level. It was determined that further adjustment would not be necessary.

Standardized scores were created for each neuropsychological assessment variable by converting the raw scores into z scores using the mean and standard deviation of the sample. Seven neurocognitive composite scores were created by averaging the z scores from the respective tests in each domain (Table 1). Finally a global neurocognitive composite score was created by averaging the seven domain composite scores.

Evaluation of Study Hypotheses/Main Analyses

Following the preliminary analyses, regression analyses were utilized to evaluate hypotheses one, two, and three, which addressed the use of the global neurocognitive composite score and the neurocognitive domain scores to predict performance on the functional outcome measures. Tables 4 and 5 contain descriptive statistics of the sample. Bipolar diagnoses, bipolar I and bipolar II, were combined into a single group for the analyses. Prior to combining, ANOVAs were performed to determine whether the groups differed significantly on neurocognitive domains and functional outcome measures. There were no significant differences between the bipolar I and bipolar II groups on age, education, number of hospitalizations and mood episodes, and current mood symptoms. The groups did not differ significantly on the functional outcome measure scores used in the analyses (Table 6). There were no significant differences between the bipolar I and bipolar II groups on the global neurocognitive composite score (Table 7). Additionally, there were no significant differences ($p > .05$) on the specific neurocognitive composites except for the motor domain. On the motor domain, the bipolar I group mean was significantly lower than the bipolar II group mean ($F = 7.02$, $df = 1, 45$, $p = .01$). Because the motor domain was not used in the main analyses, it was determined that the groups were similar and could be combined.

Overall, participants performed within normal limits on the neurocognitive measures. As can be seen in table 2, there was some variability in performance for the measures Biber total, Trails B, Phonemic Fluency, and Block Design. On the UPSA Communication measure, the mean score of 16.91 was lower than the mean score found in a sample of normal subjects ($M=18.6$) (Patterson et al., 2001). However the overall

UPSA total of 89.73 was similar to that obtained by a sample of normal control subjects (Patterson et al., 2001). On the self-report measures of functioning, the sample had an LFQ Average Problem score of 1.84 which is indicative of mild problems. Individual domains scores on the LFQ were also consistent with a report of no problems to mild problems. WQLI scores were consistent with reports of either satisfaction in domains or neither satisfaction or dissatisfaction, with the exception of the WQLI Money domain. The mean score on this domain was slightly below average indicating that participants endorsed some dissatisfaction with their finances.

None of the participants in the current study met criteria for a current DSM-IV mood episode and so they were considered euthymic. Furthermore, examination of descriptive statistics for the mood rating of depression and mania revealed Hamilton Depression Rating Scale (HDRS) mean of 7.77 ($sd = 5.21$) and Young Mania Rating Scale (YMRS) mean of 3.64 ($sd = 2.78$), which are within the euthymic range based on standard cutoffs reported in the literature for the HDRS (≤ 8) and YMRS (≤ 6) (Hamilton, 1960, 1967; Young, Biggs, Ziegler, & Meyer, 1978). However there were 19 participants with an HDRS score greater than 8 and 7 participants with a YMRS score greater than 6. It was determined to keep these participants in the study because criteria for euthymia in the current study was defined as not being in a current mood episode rather than HDRS and YMRS scores in order to have sufficient variability in subclinical mood symptoms to fully examine the main hypotheses.

Hypothesis One

Generalized neurocognitive impairment will predict functional outcome such that on a general index of cognitive functioning, patients with greater generalized impairment will have lower W-QLI, UPSA, and LFQ scores.

Results of the regression analyses provided partial support for the first hypothesis (table 11). The global neurocognitive composite significantly predicted UPSA total score ($R^2 = .16$, $F = 8.59$, $df = 1,45$, $p = .005$). However, the global neurocognitive composite score did not significantly predict Wisconsin Quality of Life weighted total score ($R^2 = .004$, $F = .18$, $df = 1,45$, $p = .68$) or the LFQ average problems index score ($R^2 = .04$, $F = 1.79$, $df = 1,45$, $p = .19$). Plots of residual scores on the ordinate and estimated y-values on the abscissa displayed a random pattern, suggesting that the assumptions of linear form, constant error variance and independence of errors were not violated.

Hypothesis Two

There will be associations between specific neurocognitive domains and specific functional outcomes. These are delineated in the following subhypotheses:

2.1 The domain scores on verbal learning and memory and executive functioning will predict performance on the UPSA recreational planning domain. Specifically that poor neurocognitive performance will predict poor functional outcome performance.

Hypothesis 2.1 was not supported. The executive function and verbal learning and memory composite scores did not significantly predict UPSA comprehension and planning subscale score ($R^2 = .08$, $F = 1.84$, $df = 2, 44$, $p = .17$).

2.2 The two neurocognitive domains verbal learning and memory, and visual learning and memory will be significantly associated with overall W-QLI score.

Hypothesis 2.2 was also not supported. The verbal learning and memory and visual learning and memory composite scores did not significantly predict WQLI weighted total score ($R^2 = .04$, $F = .99$, $df = 2, 44$, $p = .38$).

2.3 It is hypothesized that scores on the UPSA Finance domain will be predicted by the neurocognitive variables attention/psychomotor speed, verbal learning and memory, and executive functioning.

Hypothesis 2.3 was not supported. The executive function, verbal learning and memory, and attention/psychomotor speed composite scores did not significantly predict UPSA finance subscale score ($R^2 = .03$, $F = .36$, $df = 3,43$, $p = .78$).

2.4 The level of occupation as measured by an item on the LFQ will be predicted by the neurocognitive variables verbal memory and learning, executive functioning and attention/psychomotor speed.

The variable “work functioning” was created by examining the “work situation this month” item in Part II of the LFQ to determine an individual’s level of occupational functioning, which ranges from competitive full-time employment to not working in job, school or home. Three categories were created to classify subjects into good work functioning, moderate work functioning, and poor work functioning. An individual was determined to have good work functioning if they were 1) working full-time, 2) working part-time and attending school part-time, or 3) attending school full-time. An individual

was determined to have moderate work functioning if they were 1) working part-time, or 2) attending school part-time. An individual was determined to have poor work functioning if they were 1) not working in a job or attending school. This last category included individuals who were between jobs and those receiving disability.

Polytomous ordinal logistic regression was used to predict work functioning by the domains verbal memory and learning, executive functioning, and attention/psychomotor speed. Ordinal logistic regression is used for analyzing data where the dependent variable is ordinal and is modeled as a function of a vector of interval scale covariates. This form of regression allows a categorical variable to be characterized into more than two categories.

Results of the regression analysis did not support hypothesis 2.4. Work performance level was not significantly predicted by the cognitive domains of verbal learning and memory, executive functioning, and attention/psychomotor speed (Chi-Square = 2.856, $p = .41$).

Hypothesis Three

When chronicity (as measured by the number of mood episodes and number of hospitalizations) is included as a proxy for neurodegeneration, it is expected that neuropsychological variables will exhibit a mediating influence on the relation between chronicity and functional outcome (Model A). It is also hypothesized that neurocognitive impairment will exhibit a mediating influence on the relation between depressive and manic symptoms (as measured by scores on the Hamilton Depression Rating Scale and the Young Mania Rating Scale) and functional outcome (Model C).

Hypothesis three was not supported in the analyses and no mediating or moderating effect of global neurocognitive impairment rating was demonstrated.

Model A, which hypothesized that neuropsychological functioning would have a mediating influence on the relationship between chronicity and functional outcome, was not supported by the analyses. Chronicity, as defined by the average of the number of hospitalizations and number of mood episodes, was not significantly related to the global neurocognitive impairment rating ($r = .16, p = .29$). Further analyses were not performed as the first condition for a mediational effect was not met. As per the criteria set forth by Baron and Kenny (1986) to test for a mediational effect, the independent variable, chronicity, must be significantly related to the mediator, neurocognitive impairment.

Model B, which tested a moderator effect of neurocognitive impairment on the relationship between chronicity and functional outcome, was not supported for all three dependent variables. Firstly, chronicity was not a significant predictor of Wisconsin Quality of Life Index weighted total ($R^2 = .001, F = .06, df = 1, 45, p = .82$). Global neurocognitive impairment rating also did not significantly predict WQLI weighted total ($R^2 = .005, F = .15, df = 1, 44, p = .71$). Further analyses were not performed as the conditions for a moderator effect were not met since neither the independent variable (chronicity) nor the proposed moderator (global neurocognitive impairment rating) significantly predicted the dependent variable (WQLI weighted total).

Next chronicity was not a significant predictor of UPSA total score ($R^2 = .043, F = 2.01, df = 1, 45, p = .16$). Global neurocognitive impairment rating did significantly predict UPSA total score ($R^2 = .160, F = 8.59, df = 1, 45, p = .005$). Results support a

direct prediction of UPSA total score by neurocognitive impairment rather than a moderator effect.

Finally, chronicity was not a significant predictor of Life Functioning Questionnaire average problems index ($R^2 = .003$, $F = .15$, $df = 1, 45$, $p = .70$). Global neurocognitive impairment rating also did not significantly predict LFQ average problem index ($R^2 = .046$, $F = 1.99$, $df = 1, 44$, $p = .17$). Further analyses were not performed as the conditions for a moderator effect were not met.

Model C, which hypothesized that neurocognitive impairment exerts a mediating influence on the relationship between symptoms and functional outcome, was not supported for either depressive symptoms or manic symptoms. Depressive symptoms as measured by the total score on the Hamilton Depression Rating Scale were not significantly related to the global neurocognitive impairment rating ($r = -.09$, $p = .56$). Further analyses were not performed as one of the conditions for a meditational effect was not met. Symptoms, the independent variable, must be significantly related to neurocognitive impairment, the mediator (Baron & Kenny, 1986).

Manic symptoms as measured by the total score on the Young Mania Rating Scale were not significantly related to the global neurocognitive impairment rating ($r = -.07$, $p = .64$). Further analyses were not performed one of the conditions for a meditational effect was not met; the independent variable must be significantly related to the mediator variable.

Model D, which tested a moderator effect of neurocognitive impairment on the relationship between symptoms and functional outcome, was not supported. Depressive symptoms were a significant predictor of Wisconsin Quality of Life Index weighted total

($R^2 = .34$, $F = 23.12$, $df = 1, 45$, $p = .0001$). However, global neurocognitive impairment rating did not significantly predict WQLI weighted total ($R^2 = .004$, $F = .18$, $df = 1,45$, $p = .68$). The product of depressive symptoms and neurocognitive impairment did not contribute significantly to the prediction of WQLI weighted total beyond that of the depressive symptoms alone ($R^2 = .35$, F Change = $.22$, $df = 1,43$, $p = .64$, R^2 Change = $.003$). Results are consistent with a direct relationship between depressive symptoms and quality of life, rather than a moderator effect of neurocognitive impairment.

Depressive symptoms were not a significant predictor of UPSA total score ($R^2 = .02$, $F = .93$, $df = 1, 45$, $p = .34$), although the global neurocognitive impairment rating did significantly predict UPSA total score ($R^2 = .16$, $F = 8.59$, $df = 1,45$, $p = .005$). Results support a direct prediction of UPSA total score by neurocognitive impairment rather than a moderator effect.

Depressive symptoms were a significant predictor of Life Functioning Questionnaire average problems index ($R^2 = .20$, $F = 10.93$, $df = 1, 45$, $p = .002$). However, global neurocognitive impairment rating did not significantly predict LFQ average problem index ($R^2 = .04$, $F = 1.79$, $df = 1,45$, $p = .19$). Also, the product of depressive symptoms and neurocognitive impairment did not contribute significantly to the prediction of LFQ average problem index beyond that of the depressive symptoms alone ($R^2 = .23$, $df = 1,43$, $p = .41$, R^2 Change = $.01$). These results indicate a direct relationship between depressive symptoms and LFQ average problems index, rather than a moderator effect of neurocognitive impairment.

Manic symptoms were not a significant predictor of Wisconsin Quality of Life Index weighted total ($R^2 = .001$, $F = 0.001$, $df = 1, 45$, $p = .997$). The global neurocognitive

impairment rating also did not significantly predict WQLI weighted total ($R^2 = .004$, $F = .18$, $df = 1,45$, $p = .68$). Further analyses were not performed as the conditions for a moderator effect were not met.

Manic symptoms were not a significant predictor of UPSA total score ($R^2 = .04$, $F = 1.17$, $df = 1, 45$, $p = .20$). The global neurocognitive impairment rating did significantly predict UPSA total score ($R^2 = .16$, $F = 8.59$, $df = 1,45$, $p = .005$). Results support a direct prediction of UPSA total score by neurocognitive impairment rather than a moderator effect.

Manic symptoms were not a significant predictor of Life Functioning Questionnaire average problems index ($R^2 = .01$, $F = .62$, $df = 1, 45$, $p = .44$). The global neurocognitive impairment rating did not significantly predict LFQ average problem index ($R^2 = .04$, $F = 1.79$, $df = 1,45$, $p = .19$). Further analyses were not performed as the conditions for a moderator effect were not met.

Exploratory Analyses

Exploratory analyses were conducted to examine associations with limited previous investigation in the literature. It was thought that subtle impairments in motor ability would predict functioning in the area of household skills which requires some manual tasks. The motor composite scores did not significantly predict UPSA household skills subscale score ($R^2 = .002$, $F = .09$, $df = 1, 44$, $p = .77$). Results suggest that perhaps the motor impairments in bipolar disorder are not severe enough to significantly impact a person's ability to complete household tasks. Based on some of the schizophrenia research showing a relationship between verbal learning and memory and executive

function and social skills, it was suggested that these neurocognitive domains would predict WQLI social domains. The verbal memory and executive function composite scores did not significantly predict WQLI social relations and support domain score ($R^2 = .009$, $F = .20$, $df = 2, 44$, $p = .82$).

An exploratory analysis predicting work functioning was performed. Refer to hypothesis 2.4 for description of the work functioning variable. Stepwise multiple regression was used to predict work functioning by all seven neurocognitive domains. It was found that the visual memory domain was the only significant predictor of work functioning, such that better work functioning was related to better performance on the visual memory domain ($R^2 = .12$, $F = 6.01$, $df = 1,45$, $p = .02$).

CHAPTER 5

DISCUSSION

This study examined the relationship between neurocognitive impairment and functional outcomes in individuals with bipolar disorders, in order to determine the impact of neurocognitive deficits on functioning across a number of domains. The study also attempted to further clarify whether there was a direct relationship between neurocognitive impairment and functional outcome, or whether neurocognitive impairment acted as a mediator or moderator on the relationships between chronicity and functional outcome, and mood symptoms and functional outcome. Three specific hypotheses were explored to answer these questions. Hypothesis one was partially supported by the data, but hypotheses two and three were not supported by the data. The specific findings and implications of each hypothesis will be discussed individually in the following sections.

Hypothesis One

The first hypothesis addressed whether global neurocognitive impairment would predict overall functional outcome in individuals with bipolar disorder. The premise of this hypothesis was based on several lines of evidence, including a substantive body of research in schizophrenia that has demonstrated that neurocognitive deficits are predictors of outcomes across a number of domains. Additionally, individuals with bipolar disorder have cognitive impairments that extend beyond acute episode states and into euthymic periods (Bearden et al., 2001; Murphy & Sahakian, 2001) and should therefore impact functioning even in the absence of significant affective

symptomatology. Research has also found that those with bipolar disorder have impairments in their work and psychosocial functioning and many do not return to premorbid levels of functioning (Dion et al., 1988; Strakowski et al., 1998; Tohen et al., 2000; Zarate et al., 2000). Despite these considerations, there has been only limited research on the association between functioning and neurocognitive ability in bipolar disorder, but the main findings have shown a significant association between a person's functional outcome and their neurocognitive deficits (Atre-Vaidya et al., 1998; Dickerson et al., 2004; Laes & Sponheim, 2006; Martínez-Arán, Vieta, Reinares, et al., 2004; Zubieta et al., 2001). In the current study it was hypothesized that a global neurocognitive impairment rating would significantly predict functional outcome as measured by the overall scores on three separate functional outcome measures, such that patients with greater generalized neurocognitive impairment score lower on these three outcome measures.

The results of regression analyses revealed that functional outcome as measured by the total score on the UCSD Performance-based Skills Assessment (UPSA) was significantly predicted by the global neurocognitive impairment score and that lower global neurocognitive scores were associated with more impaired functional performance. The global neurocognitive impairment score did not significantly predict performance on a self-report life satisfaction measure (Wisconsin Quality of Life Inventory) or a self-report measure of psychosocial and occupational functioning (Life Functioning Questionnaire). There are a number of implications of these results. First, results lend further support to the idea that neurocognitive deficits impact functional abilities in individuals with bipolar disorder. These results are consistent with prior

studies reporting that neurocognitive abilities are predictive of psychosocial and occupational functioning. They also lend support for the use of a global neurocognitive summary score that encompasses performance across domains of cognitive functioning in predicting these outcomes.

This is the first study of functional outcome in bipolar disorder to utilize a performance-based measure for functioning. The UPSA requires individuals to perform various tasks, such as writing a check, reading bus maps, and planning a recipe. Performance on these tasks is used to derive domain and global scores. The UPSA has been used in schizophrenia patient samples and in these studies worse performance was significantly associated with negative symptoms and poor cognitive functioning (Keefe, Poe, Walker, & Harvey, 2006; Kurtz & Wexler, 2006; Patterson et al., 2001; Twamley et al., 2002). Previous research of functional outcome in bipolar disorder has utilized self-report and clinician ratings to measure functional outcome. Inherent in these measures are limitations including social desirability and low insight influencing patient self-report, non-standardized clinician ratings of a patient's psychosocial functioning and employment status (Vocisano, Klein, & Keefe, 1997; Atre-Vaidya, Taylor, Seidenberg, Reed, Perrine, et al., 1998; Martinez-Aran, Vieta, Reinares, Colom, Torrent, et al., 2004; Dickerson, Boronow, Stallings, Origoni, Cole, et al., 2004), and use of the DSM-IV General Assessment of Functioning score (GAF) which has poor reliability and combines both symptoms and functioning in one rating (Martinez-Aran, Penades, Vieta, Colom, Reinares, et al., 2002; Martinez-Aran, Vieta, Reinares et al., 2004; Martinez-Aran, Vieta, Colom, et al., 2004). Although performance-based measures of functional outcome also have limitations, including having a contrived feel when performed in a laboratory setting

and being difficult to administer, scores are standardized and not subject to bias of a rater or patient (Patterson et al., 2001).

Interestingly, in the current study, only the performance-based measure of functioning was significantly predicted by the global neurocognitive impairment rating. This result has implications beyond bipolar research. It suggests that the type of functional measure is variably related to neurocognitive ability. In the current study patient self-report measures of functioning were not associated with neurocognitive deficits, yet the patient's ability to perform real world tasks was associated with these deficits. Perhaps direct measures of functioning are more sensitive to the functional impairments of individuals with bipolar and other disorders. When clinically evaluating patients to determine their strengths and weakness in psychosocial and occupational functioning, it may be beneficial to ask them to demonstrate tasks or administer a performance-based assessment, rather than simply rely on their self-report of their abilities or the ratings of a clinician based on an interview and examination. However, replication of this finding using performance-based measures of functioning is needed in order to determine whether this type of measurement is more sensitive to the effects of neurocognitive impairment. Indeed, it appears that the trend is moving toward the use of standardized scales to assess patient functioning in various domains rather than non-standardized clinician or patient ratings (Laes & Sponheim, 2006; Goswami et al., 2006).

Hypothesis Two

The second hypothesis examined specific associations between neurocognitive performance and functional outcome domains. Prior research has shown that the

cognitive domains of executive functioning, verbal memory, and verbal fluency are most strongly associated with a patient's psychosocial functioning (Atre-Vaidya et al., 1998; Dickerson et al., 2004; Laes & Sponheim, 2006; Martínez-Arán et al., 2002; Martínez-Arán, Vieta, Colom, et al., 2004; Martínez-Arán, Vieta, Reinares, et al., 2004; Zubieta et al., 2001). However, the current results did not find that these abilities were predictive of functional outcomes. Specifically, the prediction that the UPSA recreational planning domain would be predicted by verbal learning and memory and executive function was not supported (Hypothesis 2.1). In fact, there were no significant correlations between any neurocognitive domain and the UPSA recreational planning domain score. Similarly, expected associations were not present between verbal learning and memory and visual learning and memory with overall quality of life as measured by the Wisconsin Quality of Life Inventory (WQLI) (Hypothesis 2.2). Furthermore, there were no significant correlations between any neurocognitive domain and the WQLI total score. However, with regard to financial skills, there was a significant association with some neurocognitive domains (Hypothesis 2.3). Specifically, correlations revealed a significant relationship between UPSA finance domain score and working memory and visual spatial domain scores. Finally, contrary to predictions, occupational functioning was not predicted by neurocognitive domains of verbal memory and learning, executive functioning, and attention/psychomotor speed (Hypothesis 2.4). However, correlational analyses revealed that occupational functioning was significantly associated with only one neurocognitive domain, visual learning and memory, such that those with good work functioning performed best on the neurocognitive domain.

The aforementioned hypotheses were formulated based on research in schizophrenia and psychotic disorders that have shown specific relationships between neurocognitive abilities and functional domains (Buchanan, Holstein, & Breier, 1994; Evans et al., 2003; Twamley et al., 2002). However, for bipolar disorder, there have been no studies that attempt to correlate or predict specific functional abilities by neurocognitive domains. A few studies of bipolar disorder have examined various neurocognitive domains as they relate to a global functional rating or outcome, such as a GAF rating, total score on a psychosocial impairment rating scale, or employment level (Atre-Vaidya et al., 1998; Dickerson et al., 2004; Laes & Sponheim, 2006; Martínez-Arán et al., 2002; Martínez-Arán, Vieta, Colom, et al., 2004; Martínez-Arán, Vieta, Reinares, et al., 2004; Zubieta et al., 2001). One study that did utilize a scale to examine different domains in functioning (SAS-II) used an overall average score of the domains in the analyses (Laes & Sponheim, 2006). For the current study, the more advanced schizophrenia literature in this area was used to guide hypotheses, with the assumption that those with bipolar disorder would have similar patterns of relationships between neurocognitive domains and functional outcome domains as those with schizophrenia. However, it may be that key differences exist between patients with bipolar disorder and schizophrenia with regard to factors that facilitate or impair adequate adjustment, so that neurocognitive deficits play a different role in functional outcomes in the two disorders.

One obvious difference between the disorders is that although a similar pattern of neurocognitive deficits is found in bipolar disorder and schizophrenia, the deficits are generally less severe in bipolar disorder (Hoff et al., 1990; Martínez-Arán et al., 2002; Morice, 1990; Zihl, Grön & Brunbauer, 1998). Therefore, the contribution of

neurocognitive deficits to functional outcomes is expected to be less substantive in bipolar disorder than in schizophrenia. It may be that more sensitive measures are necessary to identify associations between neurocognition and functional outcomes in bipolar disorder. Similarly, functional abilities are less impaired in bipolar disorder than in schizophrenia (Martínez-Arán et al., 2002), which is consistent with findings from the current study. For example, on the UPSA, patients in this study exhibited good performance overall, with many obtaining perfect scores on the test. Not only does this limit variability which may have artificially attenuated association between the neurocognitive domains and the functional measures, but it may further suggest that as functioning more closely approximates that observed in the normal population, the less impact neurocognitive abilities have on predicting this outcome. It may be that for individuals in the normal population, social support, financial solvency, satisfaction with current occupation, and other factors may have a greater influence on social adaptation and adjustment. If this is the case, then one might consider these factors in models that attempt to predict functional outcomes in individuals with bipolar disorder, particularly those who exhibit normal or near normal neurocognitive abilities and functioning. In any case, the results of the current study suggest that the relationships found in schizophrenia between neurocognitive domains and functional abilities are different than those in bipolar disorder. These associations may be mediated by the differences in deficit severity between these two groups. Additional research in bipolar disorder examining specific functional abilities is necessary to further elucidate their relationship with neurocognitive impairments.

It is interesting to note that some significant correlations were observed between work functioning and the neurocognitive domains (Hypothesis 2.4), which was hypothesized based on studies of bipolar disorder and schizophrenia that demonstrated impaired work functioning in individuals with neurocognitive deficits (Dickerson et al., 2004; Martínez-Arán, Vieta, Reinares, et al., 2004; Green et al., 2000). However, additional research is needed to determine which neurocognitive abilities relate to a patient's occupational ability. Only two studies examined occupational level and neurocognitive abilities in bipolar disorder. One study showed that occupational functioning was related to verbal fluency and verbal memory (Martínez-Arán, Vieta, Reinares, et al., 2004) and the other also found verbal memory to be related to occupational level (Dickerson et al., 2004). The current study suggests that visual memory was most significantly related to level of occupational functioning, such that those working or attending school full-time had the better visual memory performance, and those not working or attending school had more impaired visual memory performance.

Hypothesis Three

The third hypothesis examined neurocognitive abilities as both mediator and moderators of functional outcomes, with the general finding that global neurocognitive functioning was not a significant mediator or moderator in any of the models that were examined.

The first two models (A and B) examined whether neuropsychological variables would exhibit a mediating or moderating influence on the relation between chronicity and functional outcome. Research has examined chronicity of bipolar disorder and its

relationship to a functional ability, with more mood episodes and more hospitalizations being related to poorer outcomes in functioning (Coryell et al., 1998; Fagiolini, 2005; Hammen, Gitlin, & Altshuler, 2000; Gitlin et al., 1995; Dion et al., 1988; Tohen et al., 2000; Vocisano et al., 1996; O'Connell et al., 1991). In the current study, chronicity was examined both in terms of number of manic and depressive episodes and number of psychiatric hospitalizations. Chronicity served as a proxy for neurodegeneration in that a more unremitting course of bipolar disorder is related to structural and functional changes in the brain. With neurodegeneration in a chronic disorder, it is expected that cognitive abilities will decrease. Indeed it has been reported that those with higher rates of hospitalization, high number of mood episodes, and presence of psychotic features have greater neurocognitive impairment than those without these more severe clinical characteristics (Cavanagh et al., 2002; Clark, Iversen, & Goodwin, 2002; MacQueen et al., 2001; Zubieta et al., 2001). Some have even proposed that repeated affective episodes result in increased neuropathology which is evidence by more severe neurocognitive deficits (Altshuler, 1993). Models A and B were not supported by the current study. Chronicity measures were not significantly related to the global neurocognitive rating score or to measures of functional outcome. The chronicity measures were both based on patient estimation of how many mood episodes they had and how many psychiatric hospitalizations which may have led to inaccuracy in these variables. For many patients, estimating the number of hospitalizations was performed in a systematic way by identifying dates and locations related to each hospitalization. However some patients were hospitalized frequently over the course of many years and they were unable to report specifics about each incident. Further, number of mood episodes was also based on

patient self-report and this variable was more problematic to measure in that patients had difficulty identifying specific information such as dates surrounding each episode especially if episodes occurred early in the course of their disorder and perhaps prior to treatment. Methods of examining chronicity in the literature focus on patient self-report of given events (i.e. hospitalizations, episodes, age of first mood episode) or a review of medical records to obtain objective information about these events. In one study of outcomes in bipolar disorder, mood episodes were measured over the past three to five years, with those with two or less episodes having good outcomes and those with three or more having poorer outcomes (Ferrier et al., 1999). This method likely reduced some of the problems of inaccurate reporting by limiting the time frame to the past five years instead of the person's entire life. It also examined chronicity on a more recent basis, which may better relate to a person's current level of functional outcome. Additionally, in the current study, chronicity was used as a proxy for neurodegeneration to quantify the potential changes in a person's brain. It was thought that by using the number of mood episodes and number of hospitalizations, a more reliable estimate of chronicity could be obtained that would, in turn, provide a more valid estimate of the neuropathophysiology resulting from these affective episodes. However, it is recognized that chronicity is not the most sensitive proxy for neurodegeneration and that given additional resources, brain functional and structural imaging data would have been better able to estimate abnormalities in brain structure and function in our patients. It may also be that disease chronicity is not associated with increased neuropathology, a suggestion which is also consistent with the current findings as well as with some reports in the literature (DelBello et al., 2004).

Past research has also demonstrated that there is a relationship between mood symptoms and neuropsychological performance, such that worse symptoms are associated with poorer performance. Additionally, worse mood symptoms are related to poorer psychosocial and functional outcome (Coryell et al., 1998; Dion et al., 1988; Fagiolini, 2005; Gitlin et al., 1995; Hammen, Gitlin, & Altshuler, 2000; Keck et al., 1998; Strakowski et al., 1998). The current study sought to understand whether neurocognitive impairment impacted the relationship between mood symptoms and functional outcome. The global neurocognitive impairment score was used as both a mediator and moderator in the prediction of functional outcome by depressive symptoms and manic symptoms. Neither of these two models (C and D) was supported in the current study. In fact there was no relationship between mood symptoms and neurocognitive impairment, and mood symptoms and functional outcome measures with the exception of a direct relationship between depressive symptoms and self-reported quality of life and self-report of problems in domains. The lack of a relationship between mood symptoms and neurocognitive impairment rating may be due to inadequate sensitivity of the mood rating forms. However, this is unlikely as mood symptoms were measured by the Hamilton Depression Rating Scale for depressive symptoms and the Young Mania Rating Scale for manic symptoms. Both are clinician rating scales based on information obtained through a clinical interview. These measures are used frequently in studies of bipolar disorder and major depressive disorder to determine whether participants are in a current mood episode. It is more likely that because participants in the current study were euthymic and did not meet DSM-IV diagnostic criteria for a current depressive, manic, or hypomanic episode, there was little variability in symptoms

and so associations between symptoms and neurocognitive deficits were not observed. From a statistical standpoint, limited variability may have attenuated correlations, but it is also relevant to note that outside of statistical considerations, euthymia, by its very nature, reflects a stability in underlying neurobiological function that is not present when patients are in acute affective episodes. In fact, research has demonstrated that during mania there is increased severity of impairment in sustained attention and impulsivity, executive functioning, and visuospatial abilities (Clark, Iverson, & Goodwin, 2001; Sax, Strakowski, McElroy, Keck, & West., 1995; Hoff et al., 1990; McGrath, Scheldt, Welhelm, & Clair, 1997; Morice, 1990; Oltmanns, 1978; Strauss, Bohannon, Stephens, & Pauker, 1984), while depressive episodes are accompanied by impairments in memory and executive functioning (Ilsley, Moffoot, & O'Carroll, 1995; Borkowska & Rybakowski, 2001; Martinez-Aran et al., 2004; Murphy et al., 2001; Murphy & Sahakian, 2001; Sweeney, Kmiec, & Kupfer, 2000). Thus, the absence of findings regarding symptoms is, in retrospect, not surprising but would be expected to be more apparent in patients who were in the midst of depressed, manic, or mixed episodes.

It may also be that the use of a global neurocognitive impairment rating rather than specific domain scores obfuscated relationships that would have otherwise been apparent between specific neurocognitive abilities and specific functional outcome domains. The use of a global score does have the advantage of providing a more reliable estimate of overall severity of neurocognitive impairment, which is why it was used in this study. However, prior research has demonstrated the strongest associations have been between psychosocial functioning and executive functioning and verbal memory (Atre-Vaidya et al., 1998; Dickerson et al., 2004; Laes & Sponheim, 2006; Martínez-Arán, Vieta,

Reinares, et al., 2004; Zubieta et al., 2001). Analyses using mediator moderator models and substituting the individual domain scores of executive functioning and verbal learning and memory for the global neurocognitive score resulted in nonsignificant findings for the executive functioning domain and similar results for the verbal memory domain to that seen with the global neurocognitive impairment rating. Verbal memory directly predicted the outcome measure UPSA total score ($p = .012$) and all mediator and moderator models were not supported. Results further suggest that the prediction of functional outcome requires further study to determine other potential mediators and moderators. The current research lends support for a direct prediction of functional outcome by neurocognitive deficits, rather than neurocognitive deficits serving as mediators or moderators. Future research may focus on the use of chronicity variables and subsyndromal mood variables as mediating or moderating the direct relationship between neurocognitive deficits and outcome.

Limitations of the Study

The current study has a number of limitations. First, forty-seven subjects in the study was comparable to those seen in the literature of bipolar disorder and functional outcome, ranging from 15 – 117 participants, with the mean number of participants equal to 53 (Atre-Vaidya et al., 1998; Dickerson et al., 2004; Laes & Sponheim, 2006; Martínez-Arán et al., 2002; Martínez-Arán, Vieta, Colom, et al., 2004; Martínez-Arán, Vieta, Reinares, et al., 2004; Vocisano et al., 1997; Zubieta et al., 2001). However, additional subjects would have increased the power in the study and may have resulted in more significant findings. Additionally, in the current study bipolar I and bipolar II diagnoses

were combined to form one bipolar group. This was done because there were no significant differences between the groups on any of the neurocognitive, symptom, or functional outcome measures. Additionally, regression analyses were run for both groups separately and there were no differences in the direction of the regression results. Therefore groups were combined to increase the sample size and this is a common strategy in the literature (Martínez-Arán et al., 2002; Martínez-Arán, Vieta, Reinares, et al., 2004; Vocisano et al., 1997). The lack of significant differences between these two diagnoses suggest that the bipolar I group was at the high range of functioning for this disorder, as diagnostically bipolar I is a more severe disorder clinically than bipolar II, with some preliminary reports of more severe neurocognitive deficits in bipolar I disorder (Simonsen et al., 2008). Exclusion criteria of no current substance use or abuse diagnoses may have also resulted in exclusion of lower functioning bipolar patients and lead to a preference for higher functioning individuals who are working and/or attending college on at least a half-time basis (72.4% of sample). Also, recruitment of a community dwelling sample, including students attending a local university, produced a higher functioning sample than what might have been obtained from outpatient or inpatient mental health facilities that provide services to individuals who are disabled due to the severity of their mental illnesses. Further, the neurocognitive and functional outcome mean scores for the sample were generally within normal limits providing evidence that the current sample is functioning well compared to those of other studies of bipolar disorder. This has implications for results in that restricted range of functioning for the bipolar group may have reduced the strength of the correlations and therefore may not

accurately reflect the relationship between neurocognitive deficits and functional outcome in the more severe forms of the disorder.

Implications and Future Directions

This study advanced the research literature examining the relationship between neurocognitive ability and functional outcomes in bipolar disorder. Understanding the nature of this relationship continues to be of paramount importance as neurocognitive deficits may be a target for remediation thus leading to improved functional status. The literature examining this association is minimal and has been complicated by methodological issues such as small sample sizes, limited neuropsychological test batteries and poor measurement of functional outcome. The current study examined specific neurocognitive domains as they relate to specific functional ability areas. There is little to no focus on specific relationships in the bipolar literature thus far and such information has the potential to inform both clinical and theoretical perspectives.

Additionally, no study of bipolar disorder to date has examined functional outcome using a performance-based assessment. The current study used a combination of patient self-report and performance-based assessments, in order to obtain different sources for functioning. The significant results of the current study showing a relationship between neurocognitive ability and performance on a skills-based assessment instrument highlight the usefulness of these types of measures. In this study, only the performance-based measure, UCSD Performance-based Skills Assessment (UPSA; Patterson et al., 2001), was significantly predicted by a global neurocognitive rating. Future research examining

functional outcome in bipolar disorder and other psychiatric disorders should utilize performance-based measures in addition to the traditional methods.

The results of the current study suggest that adding neuropsychological measures to the evaluation of patients with bipolar disorder can help determine future outcomes. Results suggest that those with better neuropsychological test performance should perform better on daily functioning tasks. This will increase awareness in the field that mood symptoms are not the only factor in functional recovery. Assessing for these neurocognitive deficits can guide the treatment and future goal direction of each patient. Treatments may also begin to include cognitive remediation, as has been seen in schizophrenia, to improve the cognitive functioning of select patients diagnosed with bipolar disorder, in order to increase likelihood of functional recovery.

APPENDIX I
DEMOGRAPHIC SHEET

Demographic Questionnaire

Please answer the following questions completely and honestly. All of your responses were remain confidential.

1. Birth Date _____ / _____ / _____
Month Day Year
2. Gender **Male** **Female**
3. Ethnicity/Race: _____ Asian American _____ American Indian/Alaska Native
_____ African American _____ Hawaiian/Pacific Islander
_____ Hispanic/Latino _____ Biracial
_____ Caucasian _____ Other
4. Highest Level of Education Completed _____ (Years) _____ (Months)
5. Marital Status: _____ Married _____ Widowed _____ Divorced
_____ Remarried _____ Separated _____ Never married
6. Current Occupation _____
7. Usual living arrangements (past 3 yr.):
_____ With partner and children _____ With partner alone
_____ With children alone _____ With parents
_____ With family _____ With friends
_____ Alone _____ Controlled environment
_____ No stable arrangements _____ Other _____
8. How many children do you have? _____
9. Have you ever been homeless? **Yes** **No**
10. Do you have a twin? **Yes** **No**
11. Are you left handed, right handed, or ambidextrous? **Left** **Right** **Ambidextrous**

HEALTH-RELATED QUESTIONS

12. Are you color-blind? **Yes** **No**
13. Do you have diabetes? **Yes** **No**
14. Is your vision corrected (glasses/contacts)? **Yes** **No**
Are you wearing them now? **Yes** **No**
15. Do you have severe visual impairments, such as cataracts or glaucoma? **Yes** **No**
16. Do you have any hearing loss (hearing aid)? **Yes** **No**
17. Have you ever or do you now have seizures? **Yes** **No**
18. Have you ever had a head injury (e.g., automobile accident, fall, sports injury)? **Yes** **No**

19. Have you ever been unconscious? **Yes No** If so, for how long? _____
20. Do you have any medical conditions? **Yes No** (please describe) _____
21. Do you have any neurological disorders? **Yes No**
22. Do you have a learning disability? **Yes No**
 Has this been formally diagnosed? **Yes No** Diagnosis: _____
23. Have you ever received ECT treatment? **Yes No**
24. Have you ever received psychosurgery? **Yes No**
25. How many times have you been hospitalized for a psychiatric reason:
26. How many months since your last mood episode:
27. Do you smoke? **Yes No**
- a. Cigarettes? **Yes No**
- b. Cigars / Pipes? **Yes No**
- c. Chewing tobacco? **Yes No**
- d. How many do you smoke per day? _____
28. When were you were born:
- a. Were you born full term? **Yes No Don't Know**
- i. If premature, how many months was the pregnancy? _____
- b. Were there any obstetric complications? **Yes No Don't Know**
- c. Was your mother exposed to anything during her pregnancy (e.g., disease, toxins, alcohol, etc.)? **Yes No Don't Know**
- d. Was your birth normal (e.g., head first, natural birth)? **Yes No Don't Know**
- e. Did your mother smoke when she was pregnant? **Yes No Don't Know**

FAMILY HISTORY QUESTIONS

*Please complete these questions concerning your family. Please **DO NOT** list any specific names or identify any specific person in your answers.*

29. Does anyone in your family have a mental disorder? **Yes No**
30. Do you have any first degree relatives (e.g., mother, father, brother, child) with a mental disorder? **Yes No**
- a. What is the disorder?
- i. Schizophrenia **Yes No**
- ii. Affective disorder **Yes No**
- iii. Alcoholism **Yes No**
- iv. Parkinsonism **Yes No**
- v. Movement disorder **Yes No**
- vi. Schizophrenia spectrum disorder **Yes No**
- vii. Other _____

31. Do you have any second degree relatives (e.g., aunt, uncle, grandmother, grandfather) with a mental disorder? **Yes No**

a. What is the disorder?

i. Schizophrenia **Yes No**

ii. Affective disorder **Yes No**

iii. Alcoholism **Yes No**

iv. Parkinsonism **Yes No**

v. Movement disorder **Yes No**

vi. Schizophrenia spectrum disorder **Yes No**

vii. Other _____

32. Please list any medications you are currently taking

Current Medications

Dosage

Date Started

Current Medications	Dosage	Date Started
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
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APPENDIX II
HUMAN SUBJECTS APPROVAL FORM



Social/Behavioral IRB – Full Board Review Approval Notice

NOTICE TO ALL RESEARCHERS:

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

DATE: January 12, 2006
TO: Dr. Daniel Allen, Psychology
FROM: Office for the Protection of Research Subjects
RE: Notification of IRB Action
Protocol Title: **Neuropsychological and Emotion Processing Deficits in Adults with Bipolar Disorder**
Protocol #: 0510-1779

This memorandum is notification that the project referenced above has been reviewed by the UNLV Social/Behavioral Institutional Review Board (IRB) as indicated in Federal regulatory statutes 45CFR46. The protocol has been reviewed and approved.

The protocol is approved for a period of one year from the date of IRB approval. The expiration date of this protocol is November 17, 2006. Work on the project may begin as soon as you receive written notification from the Office for the Protection of Research Subjects (OPRS).

PLEASE NOTE:

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

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

Should the use of human subjects described in this protocol continue beyond November 17, 2006, it would be necessary to submit a **Continuing Review Request Form** 60 days before the expiration date.

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



Social/Behavioral IRB – Expedited Review Modification Approved

NOTICE TO ALL RESEARCHERS:

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

DATE: November 9, 2006
TO: Dr. Daniel Allen, Psychology
FROM: Office for the Protection of Research Subjects
RE: Notification of IRB Action by Dr. J. Michael Stitt, Chair *JMS ICE*
Protocol Title: **Neuropsychological and Emotion Processing Deficits in Adults with Bipolar Disorder**
Protocol #: 0510-1779

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

Modifications reviewed for this action include:

- The title of the study will change to "Neuropsychological, Emotional, and Functional Deficits in Adults with Bipolar Disorder.
- The addition of Daniell Knatz, Carol Randall, and Brian Leany to the research team.
- The addition of Mojave Adult, Child and Family Services to the research sites.
- The expected amount of completion time will change to 6 hours.
- The removal of the Minnesota Multiphasic Personality Inventory -II from the protocol and the addition of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders as a measure.
- An increase in the number of subjects from 50 to 150.
- Advertisements will now be released to the UNLV Public Relations Department.
- Contact letters will now be sent to local psychiatrists, psychologists, and psychotherapists.
- Participants will now be compensated monetarily at a rate of \$5.00 per hour and \$2.50 per half hour and will be given a \$30.00 bonus in addition to the \$5.00 per hour upon completion of the entire study. Research credits will now increase to 6 to participants from the subject pool.
- Participants who may contact by phone will now be screened as well as verbally consented for the screening.
- An additional Informed Consent will be added for individuals diagnosed with Bipolar Disorder from the subject pool.
- The inclusion of a demographic form, functional outcome measure and additional symptom and neuropsychological assessments.
- Three functional outcome measures will be added to the assessment battery.

Office for the Protection of Research Subjects
4505 Maryland Parkway • Box 451047 • Las Vegas, Nevada 89154-1047
(702) 895-2794 • FAX: (702) 895-0805



Social/Behavioral IRB – Full Board Review
Continuing Review Approved



NOTICE TO ALL RESEARCHERS:

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

DATE: September 10, 2007
TO: Dr. Daniel Allen, Psychology
FROM: Office for the Protection of Research Subjects
RE: Notification of IRB Action
Protocol Title: Neuropsychological and Emotion Processing Deficits in Adults with Bipolar Disorder
Protocol #: 0510-1779

Continuing review of the protocol named above has been reviewed and approved.

This IRB action will reset your expiration date for this protocol. The protocol is approved for a period of one year from the date of IRB approval. The new expiration date for this protocol is September 5, 2008.

PLEASE NOTE:

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

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

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

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

Office for the Protection of Research Subjects
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APPENDIX III

TABLES

Table 1

Neuropsychological Assessments by Neurocognitive Domain

Cognitive Domain	Test	Scores used to create domain composite scores
Executive Function	Wisconsin Card Sorting Test	% perseverative errors, number of categories achieved
	Controlled Oral Word Association Test	total number of words
	Trail Making Test Part B	time in seconds to complete
Verbal Memory and Learning	California Verbal Learning Test	total words recalled on trials 1-5, words recalled on list A after delay
	WMS-III Logical Memory Subtest	raw score for immediate (LMI) and delayed recall (LMII)
Visual Memory and Learning	Biber Figure Learning Test	scores on trials 1-5, score on delayed recall
	Rey-Osterrith Complex Figure	scores on 3 minute and 30 minute delayed recall
Attention and Psychomotor Speed	Continuous Performance Test	sensitivity (CPT d') and response criterion (CPT b)
	Stroop Color-Word Test	Difference score avg RT for congruent minus avg RT for incongruent
	Trail Making Test Part A	time in seconds to complete
Working Memory	WAIS-III Digit Span Subtest	raw score of sum of digit span forwards and backwards
	WMS-III Spatial Span Subtest	raw score of sum of spatial span forwards and backwards
Visuoconstructional / Spatial Organization	Rey-Osterrith Complex Figure	score on copy condition
	WAIS-III Block Design Subtest	raw score
	Benton Judgment of Line Orientation	total correct
Motor Ability	Fingertapping Test	mean number of taps for 5 trials
	Grip Strength	mean number of kilograms for 2 trials
	Purdue Pegboard	number of pegs for right hand and left hand

Table 2

Descriptive Statistics for Neuropsychological Variables

Variable <i>N</i> = 47	<i>M</i>	<i>SD</i>	Skewness	Kurtosis	Normality (Shapiro- Wilk)	<i>p</i>
Biber total	148.2	35.71	-.55	-.23	.95	.063
Biber delayed	35.38	8.14	-1.61	4.10	.86	.000
Benton JOL	24.85	4.30	-.88	.66	.91	.001
Trails A	26.23	7.61	1.19	3.89	.93	.006
Trails B	58.51	23.17	1.18	1.58	.91	.002
Digit Span	17.96	3.68	.18	-.799	.97	.225
Spatial Span	16.17	3.102	-.27	-.35	.97	.327
CPT Beta	.34	.396	-.899	.65	.93	.011
CPT D'	2.54	.95	.082	.865	.97	.299
Rey copy	30.66	4.97	-1.21	.69	.86	.000
Rey 3-min Delay	18.74	6.78	-.17	-.82	.96	.161
Rey long delay	18.37	6.55	-.28	-.92	.96	.072
Category fluency	22.53	4.73	.74	.68	.96	.070
Phonemic Fluency	44.23	10.61	.21	.06	.99	.918
Stroop diff score	-19.12	82.06	-2.22	7.73	.81	.000
WCST categories	5.32	1.37	-1.83	2.06	.56	.000
WCST % persever errors	12.23	6.92	1.52	1.72	.82	.000
Purdue DOM	13.76	2.58	-.78	1.77	.94	.023
Purdue ND	13.21	2.38	-1.13	2.48	.93	.007

Table 2 (Continued)

Descriptives of Neuropsychological Variables

Variable <i>N</i> = 47	<i>M</i>	<i>SD</i>	Skewness	Kurtosis	Normality (Shapiro- Wilk)	<i>P</i>
Grip Dom	31.67	12.24	.92	.797	.92	.005
Grip ND	26.71	10.91	.84	.87	.95	.047
Finger Tap Dom	46.27	9.45	-.63	.64	.97	.160
Finger Tap ND	43.13	7.68	-.19	.41	.98	.750
Block Design	42.00	13.42	-.35	-.38	.97	.340
CVLT Trials 1-5	56.66	9.33	-.46	-.59	.96	.116
CVLT long free	12.45	2.47	-.55	-.43	.94	.020
LM I recall	45.09	9.38	-.56	-.43	.95	.032
LM II recall	28.28	6.93	-.80	.97	.94	.030

Table 3

Descriptives of Functional Outcome Variables

Variable	<i>M</i>	<i>SD</i>	Skewness	Kurtosis	Normality (Shapiro- Wilk)	<i>P</i>
<i>N</i> = 47						
UPSA Comp	18.41	1.25	-1.02	1.21	.89	.004
UPSA Finance	18.30	1.54	-.80	.37	.84	.000
UPSA Commun	16.91	2.56	-.51	-.58	.90	.004
UPSA Transport	17.59	2.84	-1.46	2.12	.71	.000
UPSA Household	18.51	2.74	-1.71	2.14	.60	.000
UPSA Total	89.73	6.60	-1.09	1.47	.92	.023
LFQ Friends	4.36	1.10	.53	-.65	.83	.000
LFQ Family	5.51	2.14	1.10	1.12	.89	.003
LFQ Home Chores	7.17	2.60	.97	.39	.88	.002
LFQ Work/School	6.22	2.13	.92	.17	.90	.005
LFQ Avg Prob	1.84	.91	3.85	17.94	.92	.020
WQLI Gen Satisf	.53	1.22	.04	-.83	.95	.148
WQLI Occup	.14	1.59	.38	-1.15	.92	.024
WQLI Psych	.03	1.29	.48	-.46	.94	.058
WQLI Physical	-.20	1.41	.25	-.62	.95	.129
WQLI Soc Support	1.22	1.22	-.01	-.96	.96	.204
WQLI Money	-.62	1.63	.46	-.99	.92	.013
WQLI ADLs	2.45	.61	-1.08	.16	.84	.000
WQLI Symptoms	1.65	.85	-.08	-1.13	.92	.022
WQLI Total	.68	.84	.25	-.43	.97	.500

Table 4

Demographic Characteristics of the Sample

Variable	Bipolar Group (<i>N</i> = 47)	
	<i>M</i>	<i>SD</i>
Age	34.68	13.48
Years of Education	14.55	2.51
Premorbid IQ Estimate	12.29	1.91
Current IQ Estimate	106.59	11.64
	<i>N</i>	%
Bipolar Diagnosis		
Bipolar I	34.00	72.30
Bipolar II	13.00	27.70
Sex		
Male	17.00	36.20
Female	30.00	63.80
Ethnicity		
Caucasian	35.00	74.50
Asian American	4.00	8.50
Biracial	3.00	6.40
Hispanic/Latino	1.00	2.10
American Indian/Alaska Native	1.00	2.10
Other	3.00	6.40

Table 5

Clinical Characteristics of the Sample

Variable	Bipolar Group (<i>N</i> = 47)	
	<i>M</i>	<i>SD</i>
Age at onset (years)	14.74	8.22
Number of hospitalizations	1.74	2.10
Length of illness duration (years)	19.94	12.91
Hamilton Rating Scale of Depression	7.77	5.21
Young Mania Rating Scale	3.64	2.78
Medication status		
Mood stabilizers (% of subjects)	55.30	
Antipsychotic (% of subjects)	40.40	
Antidepressants (% of subjects)	46.80	
	<i>N</i>	%
Work Functioning		
Full time work or college	28.00	59.60
Part time work or college	6.00	12.80
Not working or in college	13.00	27.70

Table 6
Comparison between Bipolar I and Bipolar II Groups on Demographic Variables and Functional Outcome Measures

	Groups				Univariate <i>F</i> Tests	
	BPI		BPII			
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>F</i> (1,45)	<i>p</i>
Age	35.62	14.65	32.23	9.88	.588	.447
Education	14.32	2.58	15.15	2.30	1.030	.315
Psychiatric Hosp	2.03	2.18	1.00	1.73	2.324	.134
HDRS	8.35	5.59	6.23	3.86	1.578	.216
YMRS	3.74	2.94	3.38	2.40	.147	.703
W-QLI Total	.63	.85	.80	.85	.412	.524
UPSA Total	88.93	6.53	92.42	4.09	3.204	.080
LFQ Average	1.73	.46	1.68	.37	.124	.726

Table 7
Comparison between Bipolar I and Bipolar II Groups on Neurocognitive Domains

	Groups				Univariate <i>F</i> Tests	
	BPI		BPII			
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>F</i> (1,45)	<i>p</i>
Global Composite	-.49	.375	.127	.456	1.833	.183
Verbal Memory	-.116	.799	.302	.751	2.655	.110
Visual Memory	-.017	.833	.044	.867	.048	.827
Attention/Psychomotor speed	-.015	.500	.039	.366	.122	.728
Working Memory	-.051	.781	.134	.745	.122	.728
Visuospatial	-.030	.837	.079	.943	.148	.703
Motor	-.156	.702	.407	.482	7.020	.011
Executive Function	.043	.304	-.113	.306	2.490	.122

Table 8

Correlations between Neurocognitive Domains and UPSA Domains

	Global	Executive Functioning	Verbal Memory	Visual Memory	Attention Psychomotor Speed	Working Memory	Visual construct. spatial	Motor
UPSA								
Comprehension Planning	.199	.168	.215	-.014	.075	.126	.208	.056
Finance	.315*	-.004	.156	.216	-.045	.310*	.371*	.069
Communication	.161	-.227	.368*	.285	-.133	.002	-.045	.130
Transportation	.288*	.008	.107	.241	-.062	.226	.191	.305*
Household Skills	.173	-.159	.207	.281	-.288*	.324*	.060	-.044
Total	.400**	-.117	.362*	.395**	-.201	.340*	.264	.214

* $p < .05$. ** $p < .01$.

Table 9

Correlations between Neurocognitive Domains and Life Functioning Questionnaire (LFQ) Domains

	Global	Executive Functioning	Verbal Memory	Visual Memory	Attention Psychomotor Speed	Working Memory	Visual construct. spatial	Motor
LFQ Problems								
Friends	.041	.049	.286	.054	-.169	.079	-.045	-.142
Family	-.133	-.056	-.061	-.290	.140	-.125	-.017	-.025
Home Chores	-.110	-.033	.052	-.220	.143	-.094	-.017	-.200
Work/School	.126	-.037	.042	.007	.291	.085	.120	.035
Average Domain	-.196	-.158	-.027	-.289*	.205	-.212	-.062	-.170
Work Situation	.189	.004	.189	.343*	-.222	.145	.041	.070

* $p < .05$.

Table 10

Correlations between Neurocognitive Domains and Wisconsin Quality of Life (WQLI) Domains

	Global	Executive Functioning	Verbal Memory	Visual Memory	Attention Psychomotor Speed	Working Memory	Visual construct. spatial	Motor
WQLI Domains								
General Satisfaction	.037	-.070	-.014	.013	-.066	.135	-.060	.152
Occupational Activities	-.121	.063	-.017	.077	-.345*	-.017	-.167	-.134
Psychological Wellbeing	-.055	.006	-.092	-.029	-.179	-.019	-.026	.088
Physical Health	-.092	-.098	-.149	.000	-.067	-.074	-.053	.036
Social Relations/Support	-.047	-.068	-.063	.030	-.133	.096	-.116	.001
Money/Economics	-.086	-.089	-.193	-.067	-.025	.125	-.068	-.046
ADLs	.063	.004	-.242	.062	-.153	.144	.175	.185
Symptoms	.050	.047	-.124	.140	-.272	.050	.076	.187
Total	-.062	-.068	-.154	.039	-.207	.055	-.066	.069

* $p < .05$.

Table 11

Summary of Regression Analysis Predicting Functional Outcome by Global Neurocognitive Score

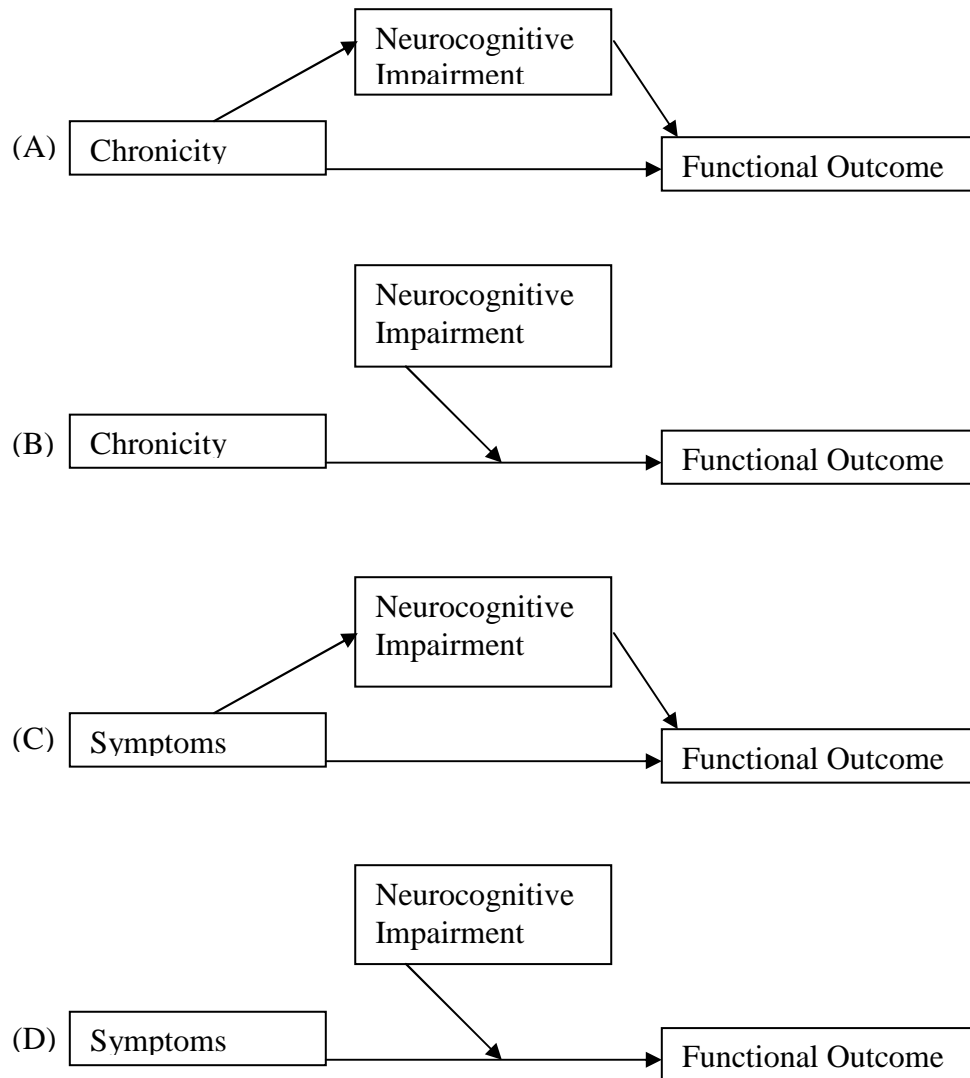
Outcome Measure	R ²	B	SE B	β	F
WQLI Weighted Total Score	.004	-.131	.312	-.062	.175
UPSA Total Score	.160	6.099	2.081	.400	8.588**
LFQ Average Problems Index	.038	-.211	.157	-.196	1.792

*p < .05. **p < .01.

APPENDIX IV

FIGURES

Figure 1. Mediator-Moderator Analyses



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