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A Longitudinal study of neurocognitive deficits and functional outcome in bipolar disorder

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A LONGITUDINAL STUDY OF NEUROCOGNITIVE DEFICITS AND FUNCTIONAL OUTCOME IN BIPOLAR DISORDER

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ABSTRACT

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Bipolar disorder is an affective disorder that, in addition to being characterized by depressive and expansive mood symptoms, often presents with neuropsychological deficits. Bipolar disorder not only impairs an individual's cognitive abilities, but these cognitive impairments may also impact day-to-day activities causing functional impairment. In other psychiatric disorders such as schizophrenia, it has been shown that the neuropsychological deficits are predictive of poor, long term treatment outcome and functioning. However, while bipolar disorder affects nearly 1 - 2% of the U.S. population (Keck, McElroy, & Arnold, 2001), little is known about the extent that neurocognitive deficits may play in the functional deficits experienced by those with bipolar disorder. Further, the research that does exist to examine this relationship has a number of limitations, including that it does not address longitudinal changes in cognition and function. These investigations also lack a comprehensive measure of either neurocognitive functioning or functional outcome.

The current study employed a longitudinal design in which symptoms, functional outcomes and neurocognitive abilities were evaluated on two separate occasions separated by approximately 12 months from the first assessment (M = 11.86, SD = 4.47) . The primary goals of the study was to determine the extent to which neurocognitive

abilities can predict functional outcomes over the long term, with a secondary goal to examine the stability of neurcognitive deficits over time. Assessment of neurocognitive abilities emphasized the domains of verbal learning and memory, visual learning and memory, executive functioning and visioconstruction/spatial abilities measured through the application of standardized neuropsychological instruments. Further, evaluation of symptoms and functional outcomes were accomplished using psychometric measures. It was predicted that neurocognitive abilities measured at the first evaluation would predict functional outcomes at the second evaluation, such that impaired neurocognitive functioning would predict poorer performance in functional measures (i.e. self-report measures of life-functioning and quality of life, as well as demand based functional tasks) and vice-versa. Further, it is predicted that some neurocognitive abilities would evidence improvement from evaluation 1 to evaluation 2, while others will not. The ability to predict long-term functioning, based upon acute neurocognitive abilities has important implications for treatment planning and implementation.

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CHAPTER 1

INTRODUCTION

Bipolar disorder is characterized by affective instability and neuropsychological deficits. The impact of this illness on functioning can be severe with neurocognitive deficits as a potentially important contributing factor to a patient's impairment. In disorders such as schizophrenia, it is becoming increasingly apparent that the neuropsychological deficits are predictive of treatment outcome and functioning. However, while bipolar disorder affects nearly 1 - 2% of the U.S. population (Keck, McElroy, & Arnold, 2001); little research has been conducted that examines the role that neuropsychological deficits play in outcome and functioning for these patients. Available studies have typically examined associations among general measures of outcome (e.g., the global assessment of functioning scale from the DSM) and neuropsychological measures that are collected at the same point in time. While research assessing clinical variables, such as the number of episodes have been examined retrospectively, those comparisons have typically only compared these retrospective reports to current self report measures of life functioning (Coryell et al., 1998; Fagiolini, 2005; Hammen, Gitlin, & Altshuler, 2000; Dion et al., 1988; Gitlin et al., 1995). (Thus, it is unclear whether neuropsychological deficits can also predict long-term functioning over the long term and if so, the relationship of specific neurocognitive deficits to specific functional domains.) This is important as the current study used a longitudinal approach to examine whether neurocognitive deficits are predictive of poorer functional outcomes over time.

CHAPTER 2

LITERATURE REVIEW

Mood episodes, which are indicative of bipolar disorder can consist of experiences of depressive mood symptoms as well as manic mood episodes, or mixed mood episodes. Additionally, individuals may experience psychotic symptoms such as hallucinations or delusions (American Psychological Association, 2000). It has been estimated that the lifetime prevalence of bipolar disorder is between 1.0 to 1.6% in the adult population (Keck, McElroy, & Arnold, 2001), with some estimates as high as 5% (Akiskal et al., 2000).

Along with the typical mood symptoms that define the disorder, neurocognitive impairments are also present (Bearden, Hoffman, & Cannon, 2001; Green, 1996). These neurocognitive deficits have been demonstrated for verbal and visual memory, visuospatial skills as well as executive functioning and attention (Bearden et al., 2001; Robinson & Ferrier, 2006), and can be compounded when the individual is experiencing a mood episode (Bearden et al., 2001; Murphy & Sahakian, 2001). It is important to understand the relationship between these mood states, neurocognitive deficits and the resulting outcome, as they are all interrelated. That is to say, mood episodes may degrade neurocognitive performance, which could ultimately impair daily living skills (functional performance).

Neurocognitive Deficits in Bipolar Disorder

Most of the research examining the neurocognitive and psychosocial functioning of individuals with Bipolar disorder has focused on examining these domains at a single point in time (i.e., Atre-Vaidya et al., 1998; Laes & Sponheim, 2006). This approach of assessment has some potential weaknesses as research has suggested that individuals with Bipolar disorder may not return to premorbid levels of neurocognitive functioning despite mood state and symptoms improvement (Dion, Tohen, Anthony, & Waternaux, 1988; Tohen et al., 2000). The following sections review the literature examining neurocognitive deficits in bipolar disorder, as they occur in depressed, manic, and euthymic states.

Depressed States

Anhedonia, severe disruptions in sleep and appetite, as well as psychomotor retardation, are symptomatic of the depressive mood state of bipolar disorder (Mitchell & Malhi, 2004) 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). Naturally, the comparisons of individuals in a depressive state with those diagnosed with major depressive disorder have been conducted. While sharing common symptomology, their neurocognitive performances are distinctly different, with bipolar group performing significantly worse in the domains of verbal fluency and executive functioning than those with unipolar depression (Borkowska & Rybakowski, 2001; Savard, Rey, & Post, 1980; Wolfe et al., 1987). Further comparisons of these groups have shown a significant impairment for the bipolar group in Performance IQ of the WAIS-R as well as tests of verbal memory and cross-

hemisphere executive functioning (Wolfe et al., 1987; Ilsley, Moffoot, & O'Carroll, 1995).

While this research has been able to demonstrate neurocognitive differences between depressive mood disorder and the depressive mood state of bipolar disorder, other research has shown mixed results. These results range from a pattern of neuropsychological deficits between unipolar and bipolar depressed groups that are largely similar but generally more severe in bipolar disorder (Mitchell & Malhi, 2004; Murphy & Sahakian, 2001; Olley et al., 2005) to a complete lack of discrimination (Abrams & Taylor, 1980; Sweeney, Kmiec, & Kupfer, 2000). The variability in reported results may due to the clinical course of the disorder, as recurrent mood episodes tend to exacerbate neurocgnitive performance (Murphy & Sahakian, 2001; Kessing 1998).

Much of the research for depressive mood states is confounded due to its focus on comparisons to other disorders, and a lack of description over time. While the research has demonstrated a cumulative effect of recurrent mood episodes on the impairment of neurocognitive functioning in bipolar disorder, this research tends to rely on retrospective reports of heterogeneous patient groups and neglects a description of the course of the mood states for any group of disorders. However, it appears that certain cognitive deficits are worse during depressive mood states including decreased verbal memory performance and neurocognitive measures of executive functioning (i.e., Trails B).

Manic States

Rapid, excessive and expansive thought processes as well as extraordinary elevations of motor activity, mood and irritability are characteristic features of mania (APA, 2000). The majority of studies related to the presentation of deficits in mania are related to

symptomology or functional impairment, with little attention given to neurocognitive deficits, presumably because of the difficulty in obtaining accurate measures because of the symptomatic presentation. However, those studies that attempted to measure such impairment, demonstrate impairment in important domains of visuospatial abilities and attention (Bunney & Hartmann, 1965; Taylor & Abrams, 1981), as well as deficits in executive functioning, particularly in the areas of problem solving strategies (McGrath et al., 1997; Morice, 1990; Murphy et al., 1999; Sweeney, Kmiec, & Kupfer, 2000). Deficits for visuospatial performance have been shown for the areas of memory and recognition, both in short-term as well as delayed performance (Murphy et al., 1999; Sweeney, Kmiec, & Kupfer, 2000). The impairment in problem solving may be a result of impaired functioning in the areas of vigilance, sustained attention, and a tendency for impulsive responding, which intuitively increases the likelihood of errors (Clark, Iverson, & Goodwin, 2001; Sax, Strakowski, McElroy, Keck, & West., 1995).

While schizophrenia, has been considered a much more severe disorder, with greater neurocognitive deficits (Morice 1990), comparisons are often made for this disorder and individuals in manic episodes of bipolar disorder. The deficits observed for manic episodes are very similar to those seen in patients with schizophrenia during stable periods, particularly in the areas of executive functioning, and visuospatial tasks (Hoff et al., 1990; McGrath, Scheldt, Welhelm, & Clair, 1997; Morice, 1990; Oltmanns, 1978; Strauss, Bohannon, Stephens, & Pauker, 1984). One such example of these deficits can be seen for the Wisconsin Card Sorting Test performance. This similarity in impairment between Schizophrenia and Bipolar disorders has been shown to extend into the domains of verbal learning, perceptual span performance (Strauss et al., 1984) and fine motor

coordination, (Hoff et al., 1990). While there is a great deal of similarly in deficits, some research has suggested that individuals moving out of an episode of mania, do demonstrate some cognitive recovery, as they transition into a euthymic mood episode, as demonstrated by performance on the WCST (McGrath et al., 1997).

Overall, these findings demonstrate considerable neurocognitive deficits for the domains of visuospatial abilities as well as executive functioning and memory during manic episodes. While recovery of neurocognitive function is suggested when symptoms resolve, the research available is limited, the extent and stability of recovery should be examined over a larger time.

Euthymic States

For many years, it was thought that bipolar disorder was not characterized by severe neurocognitive deficits and that those deficits that were present were largely associated with mood episodes or the result of other factors, such as medication effects. However, recent endeavors in the exploration of neurocognitive performance in the euthymic phase of bipolar disorder have demonstrated a perseveration of neurocognitive impairment in a number of areas. Performance on cognitive tasks, during euthymic states has also demonstrated consistent impairment (Zubieta et al., 2001) in the domains of motor speed and coordination, as well as verbal learning, sequential memory and executive functioning (Atre-Vaidya et al., 1998). When compared to normal controls, asymptomatic patients have demonstrated impaired performance on verbal learning and memory, oral fluency, and visuospatial ability. Research has also demonstrated impairment in executive functioning as demonstrated by performance on the WCST (Frangou et al., 2005). Further, the impairment in executive functioning has been shown to exist during

euthymic periods, even after controlling for premorbid IQ levels, (Ferrier et al., 1999; Frangou et al., 2005).

Impairment has also been shown for visual memory (Ferrier et al, 1999) and visuospatial recognition tasks (Rubinsztein et al., 2000), even in the presence of functional recovery, during asymptomatic periods. It has been suggested that this impairment may be a direct result of the difficulties observed for sustained attention tasks (Fleck, Shear, & Strakowski, 2005).

Martínez-Arán, and colleagues (2004), found comparable performance for individuals in all phases of a bipolar mood disorder, patients were impaired on tasks of verbal memory and learning (CVLT) (WCST, Backwards Digit Span and Stroop). This would suggest that performance is degraded in mood states, yet continues to exist in asymptomatic (euthymic) mood states. Additional studies have shown that this impairment in executive functioning is more specific for depressed and euthymic groups, and more global for individuals in a manic episode (Kravariti, Frith, Murray, & McGuire, 2004). When specifically comparing manic and euthymic groups deficits in the tasks of self-regulation and inhibition have been equivocal (Larson, Shear, Krikorian, Welge, & Strakowski, 2005).

Thus, consistent impairment has been reported for the domains of verbal memory, executive functioning, and visuospatial abilities (Cavanagh, Muir, & Blackwood, 2002; Deckersbach, Savage et al., 2004; Ferrier, Stanton, Kelly & Scott, 1999; Frangou, Donaldson, Hadjulis, Landau, & Goldstein, 2005; Frantom et al., 2008; Goswami et al., 2006; Martínez-Arán, Vieta, Colom et al., 2004; Smith, Muir, & Blackwood, 2006; Zubieta, Huguelet, O'Neil, & Giordani, 2001). This impairment also extends, to a lesser

degree into the domains of sustained attention (Clark, Iversen, and Goodwin, 2002; Deckersbach, McMurrich et al., 2004; Ferrier et al., 1999; Fleck, Shear, & Strakowski, 2005) and visual memory (Ferrier et al., 1999; Rubinsztein, Michael, Paykel, & Sahakian, 2000).

The above research suggests that impairment in neurocognitive tasks is pervasive. While it can be most prominent during mood episodes, the neurocognitive deficits do not seem to remit with the mood symptoms. Further, the deficits seem to exist even when some aspects of functional performance return. This persistent impairment because of the large number (32%) of individuals that are affected outside of a mood episode (Goodwin & Jamison, 1990). Further, these impairments do not seem to be better accounted for by differences in demographic or socioeconomic variables.

Mood Symptoms and Functional Outcomes

Concerning the relationship among mood symptoms and functional outcomes, depressive symptomatology has been shown to be the most predictive of impairment in social and familial problems (Coryell et al., 1998; Fagiolini, 2005; Hammen, Gitlin, & Altshuler, 2000; Dion et al., 1988; Gitlin et al., 1995). These findings indicate there is a positive correlation between the number of episodes and impairment in psychosocial functioning as well as the number of depressive symptoms and impaired functioning. In addition, depressive symptoms are also predictive of impairment in occupational skills and success (Bauwens et al., 1991; Gitlin et al., 1995; Dickerson et al., 2004). Additionally, some research has also shown a relationship between mood symptoms and an inability to perform household and occupational tasks. However, these findings found only a relationship between depressive symptoms and outcome, and consisted of several

administrations of the functional assessments at 3-month intervals (Simon, et al., 2007). Further, the assessments of psychosocial functioning used were strictly questionnaires and were limited in their scope of assessment. This is not to say that mania is not predictive of psychosocial outcome. In fact manic symptom severity has been shown to predict a decrease in an individual's functioning as well as an increase in unemployment and a need for assisted supportive measures (Vocisano et al., 1996; Vocisano, Klein, & Keefe, 1997).

It was largely assumed that during the euthymic phase of bipolar disorder there was a lack significant impairment in functioning or at the very least, that most problems with functioning would resolve when mood symptoms abated (Olley et al., 2005). However, it is clear now that even in the euthymic state, significant impairment remain across the domains of social and occupational functioning (Gitlin et al., 1995). In fact, this impairment has been ranked as a major cause of worldwide disability (Murray, Lopez, & Jamison, 1994) with a lasting impact on functional abilities even after individuals have returned to a stable mood state (Dion, Tohen, Anthony, & Waternaux, 1988; Tohen et al., 2000). Given that functional deficits persist even after mood symptoms have resolved, it must be that other factors are contributing to these functional deficits. Since neurocognitive deficits are present even in euthymic states (Frantom et al., 2008) and such deficits have been shown to predict functional impairment, they may have a critical role in producing functional deficits even after symptoms have resolved.

Clinical Predictors of Functional Outcome of Individuals with Bipolar Disorder

DelBello and colleagues (2007) examined syndromal and functional recovery for first episode manic or mixed bipolar disorder. Their findings showed good syndromal recovery (particularly for males), but poor functional recovery. Predictors of poor recovery were the existence of comoorbid diagnoses of ADHD, anxiety disorders and disruptive behavior disorders. Recovery seemed to be further impacted by poor treatment adherence. This was a retrospective study, and was most notably limited by the paucity of information regarding the functional assessment measures. Others (Loftus & Jaeger, 2006) found a relationship between the presence of comorbid personality disorders and poor social/leisure outcomes. However, the differences were only significant while the individual was experiencing current mood symptoms. In addition to these first episode studies, cross-sectional research for bipolar patients has attempted to categorize specific groups of symptomatology with groups of behaviors on functional outcomes (Brieger, et al., 2007).However, the Brieger, et al. (2007) study seemed to attempt to develop this understanding of longitudinal outcome through a combination of symptom ratings and self-report questionnaires. The authors combined symptoms quality of life and self-reported depressive symptoms used to describe a “general subjective” dimension which seems to be indicative of a greater likelihood of neurotic features, personality disorders, and a lack of hospitalization for the past year. A second dimension was described as a “functional/disability” dimension, which consists of maladaptive symptoms and overall low functioning, and tends to be predicted by a greater number of serious mood episodes and poor premorbid adjustment. Finally, the third dimension labeled, “manic/psychotic” consisted purely of observer related positive symptoms and are usually predicted by poor

pharmacotherapy compliance. Thus the study did not address the potential role that neurocognitive functioning played in the outcomes of these patients.

Neurocognitive Deficits and Functional Outcomes

As previously suggested, while a large body of research has shown neurocognitive impairment while individuals are in the manic and depressed states, there is also strong evidence indicating that impairment persists during periods of euthymic mood. While the research focused on chronicity of bipolar disorder suggests that the number, duration, type and severity of the mood disorder all have a cumulative effect on neurocognitive impairment and psychosocial functioning (Gitlin et al., 1995; Bearden et al., 2001; Quraishi & Frangou, 2002; Murphy & Sahakian, 2001; Olley et al., 2005), few studies exist that actually examine how these factors may influence the relationships between neurocognitive deficits and functional outcomes from a longitudinal perspective. However, in order to more fully understand the need for a longitudinal study of bipolar mood disorder, one need only to look at the literature that exists for schizophrenia. This is because while there is a limited amount of research available for the impact of neurocognitive deficits on functional outcome in bipolar disorder, a much more extensive body of research exists for schizophrenia. The disparity between the schizophrenia and bipolar research in this area is more generally related to Kreapelin‘s original conceptualization of schizophrenia as a disorder characterized by cognitive deficits (dementia praecox) while bipolar disorder was primarily a disregulation of mood with intact cognitive function. Thus, while schizophrenia has been the focus of neuropsychological studies for more than 50 years, it has been only recently that

intensive efforts have been aimed at clearly delineating the neurocognitive profile of bipolar disorder.

Despite the limited research into functional outcomes in bipolar disorder, studies of patients with schizophrenia who also display neurocognitive deficits and mood symptoms may be used as a model for studies of bipolar disorder, and provide clear direction for hypothesis testing. With regard to neurocognition, schizophrenia may provide a model for bipolar disorder because research has been conducted that compares individuals with bipolar disorder, particularly the manic episodes, to schizophrenia. This research has shown that the level of impairment for bipolar disorder tends to be less severe than in schizophrenia (both in neurocognitive functioning and functional outcomes), but that there is overlap in the impairment of executive functioning tasks, verbal learning and memory as well as attentional abilities (Hoff et al., 1990; McGrath, Scheldt, Welhelm, & Clair, 1997; Morice, 1990; Oltmanns, 1978; Strauss, Bohannon, Stephens, & Pauker, 1984). It is also the case that although classified as a psychotic disorder, patients with schizophrenia exhibit a high degree of affective instability, with depressive episodes being very common. While mania symptoms occur to a much lesser degree in schizophrenia than do depressive symptoms, the presence of affective disturbance in schizophrenia also makes it an appropriate analog from studies of functional outcomes in bipolar disorder. Thus, the literature regarding association among neurocognitive deficits and functional outcomes in schizophrenia will be reviewed to help in the conceptualization and examination of these areas in bipolar disorder.

Neurocognitive Deficits and Functional Outcome in Schizophrenia

Neurocognitive deficits have been shown to be predictive of functional outcome, such as social skills attainment, in schizophrenia, such that those individuals with impaired neurocognitive abilities demonstrate impaired psychosocial functioning, and those with spared neuorcognitive abilities demonstrate relatively normal psychosocial functioning. This research has shown that increased performance on verbal learning and distractibility tasks was indicative of better attainment for social skills (Kern, Green & Satz, 1992). Additionally, from a longitudinal perspective, neurocgnitive performance was relatively stable across all domains, and thus relatively predictive of outcome measures for community skills, personal skills and social skills. Further, when examining specific domains of neurocognitive functioning in relationship to performance based functional assessments (UPSA; Patterson, et al., 2001), verbal memory seemed to be the best predictor of functional outcomes (Kurtz, et al., 2008). At time points as long as seven years out, verbal memory, attention, and processing speed have all been shown to be predictive of functional outcomes for psychosocial functioning in schizophrenia. However, this research emphasized a study of performance at onset as compared to performance at 7 years post-onset. It is less indicative of the degradation of performance and outcome for more chronic presentations of schizophrenia.

Neurocognitive Deficits and Functional Outcome in Bipolar Disorder

For the few studies investigating the relationship between neurocognitive deficits and functional outcome, verbal memory and verbal fluency have been shown to be the strongest predictors of psychosocial outcome performance (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), such that sparing in neurocognitive abilities predicted relatively normal psychosocial functioning, while impairment of neurocognitive abilities yielded corresponding impairment in functional measures.

One of the initial attempts of quantifying the relationship between neurocognitive deficits and functional outcome, tested individuals who had either a diagnosis for depression or bipolar disorder, and compared their performance on a neuropsychological screening instrument and classified them into functional performance groups of deteriorated or non-deteriorated based upon their abilities to obtain and maintain employment, number of hospitalizations, lack of symptom remission, or dependence on others for support (Vocisano, Klein, & Keefe, 1997). This study demonstrated impairment in working memory (via calculation) and attention for deteriorated patients more so than non-deteriorated patients. The generalizability of these findings are limited by the lack of distinction in analysis between depressed and bipolar diagnoses, and their use of a screening instrument, rather than a true neurocognitive measure.

Another study attempted to use a standardized neuropsychological test in a community sample, as well as a VA sample, using the CVLT as a measure of verbal learning and fluency. This was done in order to assess the relationship between impairment in this domain and functional performance as measured by either a psychiatric chart review or a structured clinical interview. This study again demonstrated the positive predictive relationship between verbal learning and memory and psychosocial outcome. However, this study had several methodological limitations (i.e.

using different functional assessments for each group), and did not include measures of executive functioning nor attention.

An evolution in the study of the relationship between neurocognitive abilities and functional outcomes can be seen in the study of Zubieta and colleagues (2001). This study also examined cognitive and social functioning during the euthymic phase of bipolar I disorder. This study consisted of 15 participants with a confirmed diagnoses of bipolar I disorder (using the SCID-IV), and the Hamilton Depression Rating Scale and the Young Mania Rating Scale. The participants in this study must have experienced psychosis as inclusionary criteria. Their social functioning was assessed using the Social and Occupational Functional Assessment Scale (SOFAS; APA, 2000; Goldman, 1992), which is a clinician rated scale ranging from 0 to 100. The SOFAS is analogous to the DSM-IV GAF score, without the inclusion of symptom severity included into the domain score (GAF; APA, 2000). Zubieta and colleagues (2001), found a mean functional rating of 69, which indicates generally well functioning, with some difficulty in social, occupational or school functioning. A neuropsychological battery comprised of assessments for the neurocognitive domains of memory, verbal fluency, executive functioning, sustained attention and concentration, and psychomotor functioning was administered, as well as an assessment of Intellectual functioning. SOFAS scores were significantly, positively correlated with Wechsler Memory Scale Paired Associates subtest immediate recall scores and with the Stroop Color/Word T-scores. A similar association between verbal memory scores and functional outcome was also demonstrated, even in the euthymic phase of the mood disorders. While this study allows us to make conclusions regarding the impairment in verbal abilities and its relationship to

functional outcomes, it included individuals who had all experienced psychotic symptoms, thus limiting its generalizability to the broader population of individuals with bipolar disorder who have not had a psychotic episode.

Additional studies have examined individuals outside of psychotic features (Martínez-Arán, Vieta, Reinares, et al., 2004). In this research, there were 30 patients in a depressed phase, 34 in manic or hypomanic phase (determined by DSM-IV criteria, HAM-D, and YMRS) and 44 in euthymic phase with 6-month remission. Psychosocial functioning was measured using the GAF. Occupational functioning was based upon the 3 years before evaluation, and was classified as either good or poor. The neuropsychological battery administered for this study examined the cognitive areas of premorbid IQ, executive function, attention and concentration, verbal learning and memory and nonverbal learning and memory. Martínez-Arán, et al. (2004), found executive functioning, verbal fluency, attention and concentration, verbal memory, and nonverbal memory, was positively predicted psychosocial functioning. The predictive ability of the neurocognitive measures was better than that of symptoms. Further, verbal fluency and all measures of verbal memory positively predicted occupational functioning. However, this study is limited in its lack of distinction for either bipolar I or bipolar II, and the use of the GAF as a measure of psychosocial functioning, is limited and prone to variability. Further, the categorization, by clinicians for occupational functioning leaves much to be desired, due to its high level of subjectivity.

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. The 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 with 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, were positively 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 similarly correlated 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, a weak measure of psychosocial functioning, and lack of specificity in patient diagnosis.

While the above studies do demonstrate a relationship between neurocognitive impairment and functional outcome, they are limited by their lack of measurement for the course of the disorder, with at best, a hypothesis about the impact of course and impairment and outcome, based on retrospective studies.

The majority of longitudinal studies for bipolar disorder are focused on predicting the severity and likelihood of remittance for clinical symptoms. Recently however, research has begun to shift focus towards functional performance and recovery. To that end, one study examined functional recovery for patients with pharmacological or social skills

training, at a 9-month post treatment time point. This study found that there was, with intensive social skills and CBT therapy, and improvement of social skills in the absence of recovery from depressive symptoms. However, this study was limited, because the assessment of functioning and symptoms was retrospective in nature. Further, the observed improvement did not extend to a recovery of occupational functioning, nor did this study attempt to address neurocognitive impairment, which may contribute to poorer functional outcomes (Miklowitz, et al., 2007).

Research examining executive functioning for bipolar disorder at a 5-year time-span demonstrated that for individuals with bipolar disorder, attentional measures of neurocognitive function were more stable and predictive of functional outcomes (Burdick, et al., 2006). This study examined 16 patients with schizophrenia and 16 patients with bipolar disorder at time points 5 years apart. They were reassessed six times over the subsequent 15 to 20 years, at ranges of 1.5 to 4 years apart. However, initial assessments consisted primarily of clinical variables. Neurocognitive batteries were not conducted until the latter assessments at years 14-15, and years 19-20, again with the comparisons being over a 5-year span. The neurocognitive test battery administered included measures of executive function (i.e., perseverative errors from the Wisconsin Card Sorting Test [WCST; Heaton et al., 1993]), attention (i.e., California Verbal Learning Test [CVLT], memory including short-term memory (i.e., List A Short Delay Free Recall from the CVLT), long-term memory (i.e., List A Long Delay Free Recall from the CVLT), and long-term recognition memory (i.e., Recognition Hits raw score from the CVLT), and learning (CVLT List A Trials 1-5 total raw score). Among the schizophrenia subjects, there was minor impairment in executive functioning. No

statistically significant changes over time were seen in any of the remaining neurocognitive domains. However, and most important for the premise of this study, among the bipolar subjects, significant or near-significant improvements were seen across assessments in two of three memory domains (i.e., short-term and long-term delayed free recall) and two of three executive function domains (WCST perseverative errors and verbal fluency). No significant changes were observed in attentional measures or in any other neurocognitive tests. Notably, as predicted, subjects' performance was impaired relative to normative data on the majority of measures at both time points and within both diagnostic groups. This study suggests that while there is some improvent (although only approaching statistical significance) for bipolar disorder, attentional processes may be *more* stable than those processes involved in executive or memory-based functioning. While this study does demonstrate a *good* degree of neurocognitive stability, the change observed is not discussed, and no implications are discussed for its impact on functional outcomes.

Only one, very recent study has begun to examine this relationship between neuropsychological performance and functional outcomes over a much shorter time span. To date, Tabarés-Seisdedos and colleagues (In Press b), have developed a paradigm which most closely approximates the desired goals of the current study. This study examined eight neurocognitive domains including: 1) Executive Functions/Reasoning and Problem Solving (i.e., WCST Categories and Perseverative Errors); 2) Verbal Working Memory (i.e., the backward part of the Digit Span Test); 3)Verbal Memory (the Babcock Story Recall Test); 4) Visual Memory (the Rey–Osterrieth Complex Figure Test); 5) Visual-Motor Processing/Speed of Processing (i.e., Trail Making Test, part and

Digit Symbol Substitution Test [DSST] from the WAIS-R); 6) Vigilance (from the Asarnow Continuous Performance Test); 7) Motor Speed (i.e., Finger-Tapping Test); and 8) Language or Vocabulary (i.e., the Vocabulary Subtest of the WAIS-R, which was also used as the premorbid IQ). The authors found that the executive functioning domain (specifically visual processing) was consistent with findings showing impaired attentional performance was more indicative of poor outcome (as measured by the psychosocial domain of the GAF, and the DAS, occupational adaptation level), than the symptoms themselves (Tabarés-Seisdedos, et al. in press). However, contrary to the findings of Martinez-Aran and colleagues (2007), they did not find verbal memory to be predictive of functional or prospective performance. While this study approximates the desired goals of this study, it is limited in a number of ways. First, the contrary findings for the predictive ability of verbal performance warrants further investigation. Additionally, as the authors suggest, the GAF score used was limited purely to the social functioning domain, and was based upon retrospective reports of functioning, rather than current functioning. Further, the functional measures did not encompass a broad enough spectrum of functional performance. Much research has been conducted in the area of functional outcomes for schizophrenia, which suggest that several domains must be assessed in order to establish an appropriately accurate representation of psychosocial functioning (Penn et al., 1995; Tohen et al., 2003; Green et al., 2004). Finally, this study included individuals with bipolar disorder; with assessments conducted during both symptomatic and asymptomatic periods being grouped into the same analysis. In order to truly understand the unique contribution of neurocognitive deficits to functional outcomes, it is imperative that patients be assessed when asymptomatic so that there is

not a strong influence of current symptoms on functioning. Further, research examining executive functioning for bipolar disorder at a 5-year time-span demonstrated that for individuals with bipolar disorder, attentional measures of neurocognitive function were more stable and predictive of functional outcomes (Burdick, et al., 2006).

This research has suggested that individuals with Bipolar disorder may not return to premorbid levels of Neurocognitive functioning despite mood state and symptoms improvement. In fact, it is more likely that a cumulative effect of impairment on neurocognitive functioning would thus extend to a cumulative reduction in performance for functional measures. In order to examine this relationship, assessment over time will enable one to explore the stability, or lack their of, for neurocognitive measures of performance, and the resulting outcome.

These studies make clear the need to further explore the associations between impaired neurocognitive performance and poor functional outcome for bipolar disorder as a positive predictive relationship clearly exists. While, current research continues to expand the resolution of what we know about the exact nature of this relationship, attention must now be shifted to the trajectory of these relationships over time. In addition, research in other psychiatric disorders has demonstrated the relationship between impairment of performance and impairment in functioning (as measured by the GAF and DAS occupational domain) for these domains over time. While it would be naïve to assume that these patterns will completely extend beyond the disorders for which they were examined, they are a natural impetus for the current study. Thus, the current study proposed to address the relationship between the domains of neurocgnitive impairment in individuals with bipolar disorder and their functional outcomes over time.

Assessment of Functioning in Bipolar Disorders

While it seems intuitive that an impairment in functional abilities would occur with the occurrence of a mood disorder, as well as demonstrated cognitive impairment, there is a difficulty in finding a universally applicable measure of this functioning. One difficulty lies in the ability to choose the appropriate domain of functional performance. Typical functional abilities are reported using a single score, such as the Global Assessment of Functioning (GAF) score. However, this score can be interpreted based upon a number of different domains of functional performance (i.e. social, occupational and self-care). In clinical practice, the choice of domain(s) to examine, or which domains to report are obvious. However, when researching predictive relationships between impairment, outcome and recovery, the choice becomes less obvious, and in fact is highly variable. Further, complicating the interpretability of this measure of functional performance is what establishes the individual's baseline, which can range from an individual's functioning prior to a first mood episode, or hospitalization (Zarate, Tohen, Land & Cavanagh, 2000).

Thus, the functional abilities for individuals with bipolar disorder that have been shown to be impaired are assessed in a number of ways. These may include self-report, clinician ratings, or collateral reports from those able make direct observations of the target behaviors in their natural environment (i.e. parent, spouse or primary caregiver; Patterson, Goldman, McKibbin, Hughs, & Jeste, 2001). However, these methods of measuring functional abilities have been shown to be limited.

Self-report measures alone, are inherently subject to response biases and their reliability is increasingly degraded in patients whose psychopathology may be further

distorted, and while clinician ratings may not be susceptible to response bias, in terms of their real world assessment capabilities, they are not always exhaustive in their assessment of day-to-day functioning. In-vivo observation of behavior can be costly, and while attempts have been made to create simulations in the clinical environment (i.e. the Performance-Based Skills Assessment; UPSA), their external validity has been criticized (Patterson et al., 2001). This is not to say that reliable and valid measures of psychosocial functioning do not exist, nor is there a lack of implementation in their use. However, research that has utilized these measures have yet to demonstrate that the scores obtained from the measures provide us with useful information regarding the relationship between more specific domains of functional skills or neurocognitive abilities/impairment (Atre-Vaidya et al., 1998; Laes & Sponheim, 2006).

Therefore, in order to elucidate the relationship between neurocognitive impairment and functional outcomes over time, this study examined previously assessed individuals on a reduced battery of specific neurocognitive tasks. This performance was then compared to performance on a functional assessment of life skills (UPSA) and responses to functional questionnaires (WQL-I and LFQ).

Summary and Hypotheses

The literature has demonstrated that bipolar disorder can impair several domains of neurocognitive functioning. Primarily these impairments tend to be in the areas of executive functioning, verbal learning and memory, visuospatial learning and memory, and visuospatial and visuoconstructional abilities. Further, it is apparent that the course of the mood disorder is crucial in understanding the relationship between these

neurocognitive variables and the day-to-day life of individuals who are diagnosed with bipolar disorder, particularly as they relate to functional outcomes. Based on these considerations, the primary goal of this study was to determine whether neurocognitive functioning was predictive of long-term outcomes in patients with bipolar disorders. A secondary goal was to examine the stability of neurocognitive function over time in these individuals. To accomplish these goals, a longitudinal design will be employed in which subjects were evaluated on two occasions. Both evaluations included assessments of symptoms, neurocognitive abilities, and functional outcomes. The first evaluation was completed as part of an ongoing research program evaluating bipolar disorders. The second evaluation was completed for this study and conducted approximately twelve months (M = 11.86, SD = 4.47) after the first evaluation. Neurocognitive abilities assessed at the first evaluation will be used to predict functional outcomes at the second evaluation to determine whether neurocognitive deficits have the capability to make long-term predictions regarding functions, such that neurocognitive impairment would predict poorer functional performance, and relative neurocognitive sparing would indicate relatively normal functioning. Because neurocognitive deficits are more stable than symptoms and may provide a more direct assessment of brain function, it is expected that they will in fact have predictive capabilities over the long term. As a secondary goal, in order to further evaluate the stability of neurocognitive deficits in bipolar disorder, neurocognitive test performance at first evaluation was compared to performance on the same tests at the second evaluation. Thus, this longitudinal design allows for determination of the predictive strength of neurocognitive variables over the long term

with regard to daily functioning, as well as provides valuable information regarding the stability of neurocognitive deficits in those affected with bipolar disorder.

Based on the review of the literature, the following hypotheses were proposed:

H1: Impairment in time two UPSA scores will be predicted by impaired neurocognitive functioning at time one on tests of Verbal Memory ability and Executive Functioning .

H2: Scores on Life Satisfaction and Wisconsin Quality of Life Inventories at time two will be predicted by verbal memory ability (i.e. CVLT-Trials 1 to 5 Total Correct, Short Delay Recall and Long Delay Recall) and Working Memory Performance tasks (i.e., digit span and spatial span) at time one, such that impairment in these domains should predict decreased quality of life and life satisfaction, or conversely high scores on these neurocognitive domains would predict greater quality of life and life satisfaction.

H3: Performance on the UCSD Performance-Based Skills Assessment is assessed by a much broader range of neurocognitive functioning. Therefore, it is expected that the speed of processing (measured for each of the subtasks of the UPSA in seconds) for this task, will be most likely be accounted for by the neurocognitive domains of executive functioning working memory, with impaired functioning at time one predicting poorer functional outcomes at time two.

H4: Performance from time one to time two will show improvement for measures of neurocognitive functioning, specifically in the areas of verbal and visual memory, with less improvement for visuoconstructional/spatial abilities and no improvement in attention.

CHAPTER 3

METHOD

Participants

Participants consisted of 29 individuals (19 males and 10 females) diagnosed with Bipolar disorder and ranging in age from 19 to 58 years (Mean = 29.17, SD = 10.96; Mean = 38.1, SD = 13.26; respectively). These individuals were clinically stable (months since last mood episode *M* = 20.41, *SD* = 30.41), with relatively few hospitalizations (*M* = 1.03 *SD* = 1.74), in a current euthymic mood state (YMRS: *M* = .86, *SD* = 1.87; HAM-D: *M* = 3.86, *SD* = 3.03), and were selected for inclusion from a pool of previously identified participants based upon their meeting DSM-IV (American Psychiatric Association, 2000) criteria for Bipolar 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, 1995). This follow-up was conducted at almost 12 months from the first assessment (*M* = 11.86, *SD* = 4.47) from the date of their first assessment (*M* = , *SD* =). Exclusionary criteria include: 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 substance use disorder within the last six months; 4) diagnosis of mental retardation; 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; 6) history of depressive, manic, mixed episode or psychosis within the past month.

Recruitment of participants was conducted based on a previously approved follow-up contact protocol in accordance with procedures approved by the University Institutional

Review Board. All participants were compensated monetarily at a rate of $10.00 per hour, for a total, that did not exceed 5 hours (total of $50.00 per participant). Participants who did not wish to complete the entire study were compensated for the actual time spent participating and this compensation was pro-rated based on time they spent participating. All participants were required to provide informed consent prior to the initiation of any study procedures.

Measures

Measures used in the study assessed four domains of psychological and psychosocial functioning: 1) diagnosis and 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. The Wisconsin Quality of Life Index (W-QLI; Becker, Diamond, Douglas, & Thornton, 2000), further described below, contains a background information form that was collect the following information: highest education level obtained, marital status, ethnicity, income, disability status, residential status, and residential inhabitants. A separate demographic form was be 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 be included to establish psychiatric diagnosis and assess clinical symptomatology relevant to bipolar disorder. The Structured Clinical Interview

for DSM-IV-TR (SCID-I for DSM-IV; First, Gibbon, Spitzer, & Williams, 1996) was administered to establish the diagnosis of Bipolar I or Bipolar II disorder, as well as rule out the presence of a current mood episode, or a substance use disorder within the past 6 months. To assess clinical symptomatology, the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) the Young Mania scale (Young, Biggs, Ziegler, & Meyer, 1978), and the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960, 1967) were included to assess manic and depressed symptoms, respectively.

Structured Clinical Interview for the DSM-IV-TR

The SCID-I for DSM-IV (First, Gibbon, Spitzer, & Williams, 1996) is a semi-structured interview developed for obtaining DSM-IV Axis I diagnoses. The SCID-I was designed to be administered by clinicians trained in the DSM-IV diagnostic system (APA, 1994) it has been determined to be appropriate for psychiatric and general medical patients, as well as with individuals in the community for the purpose of research and mental health. It is primarily 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 were administered in the current study. This is the most extensive version of the SCID and designed to be modified to address the unique needs of individual research programs, so that only particular modules can be administered to assess, for example, psychotic disorders or substance use disorders. The 10 modules include mood episodes, psychotic symptoms, psychotic disorders, mood disorders, substance use disorders, anxiety disorders, somatoform disorders, eating disorders, adjustment disorders, and optional disorders. All 10 modules were administered, including the screening module.

The screening module of the SCID-I consists of 12 questions that are used to elicit further evaluation in subsequent modules. Scoring or rating of all the SCID modules involves rating each response of diagnostic criteria either as 1 (symptom is absent), 2 (sub threshold symptom) or 3 (symptom is present). In terms of psychometrics, the SCID-I has been shown to have excellent inter-rater reliability (kappa = .85, range = .71 to .97), and very accurate diagnostic accuracy, as compared to consensus diagnosis (82%) (Ventura, Liberman, Green, Shaner, & Mintz, 1998).

Brief Psychiatric Rating Scale

The Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) was used to assess current psychiatric symptom severity and psychosocial functioning in patients with schizophrenia. The BPRS is a 16-item interview-based rating scale that assesses the severity of psychiatric symptoms, including psychotic symptoms, over the past week. The items are rated on a 7-point scale.

The Young Mania Scale

The Young Mania Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978) is an eleven-item clinician administered scale used to measure the severity of mania and as such, 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 to the patient group to assess for presence of manic symptoms. A score of 6 or less typically

characterizes an asymptomatic state. It is anticipated that the majority of community-dwelling patients would not be acutely manic at the time of testing, but may demonstrate sub threshold symptoms or hypomania. Patients who are in a current manic episode as identified by the SCID-I for DSM-IV, were excluded from the study.

The Hamilton Depression Rating Scale

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

Psychosocial and Occupational Functioning

Five 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 have been selected because they provide a broad coverage of different functional domains, and are a mixture of self-report, interview, and performance-based

format. They have been developed and used extensively with psychiatric populations, and have been found to be positively correlated with cognitive variables in studies of psychiatric disorders. Though many measures are available to assess functioning, the current study attempted to balance comprehensiveness with practicality and time constraints. The first measure is the Wisconsin Quality of Life Index (W-QLI; Becker, Diamond, Douglas, & Thornton, 2000) and a self-report measure. The second measure was the UCSD Performance-Based Skills Assessment (UPSA; Patterson et al., 2001), which is a performance-based assessment measure. The third measure of functional status was the Life Functioning Questionnaire (LFQ; Altshuler, Mintz, & Leight, 2002), which is a self-report measure of the time, conflict level, enjoyment and performance in role functioning. The fourth measure was the Hollingshead Index of Social Position (Hollingshead & Redlich, 1958), a scale that examines highest level of education and current occupation to obtain a two-factor index of social position ranging from I (Highest Level, i.e. Professional) to V (Lowest Level, i.e. middle school dropout). Finally, the Global Assessment of Functioning scale (GAF) were completed as part of the SCID administration and used to assess current level of functioning. For the present study, separate GAF's were assigned for symptom severity and for functional impairment, and an overall GAF were assigned as well.

Wisconsin Quality of Life Index

The Wisconsin Quality of Life Index (W-QLI; Becker, Diamond, Douglas, & Thornton, 2000) is a patient self-report measure used to assess a participant's own satisfaction in various life domains. There are nine domains: 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. 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, 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 for people with mental illness 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).

UCSD Performance-Based Skills Assessment

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. They then have to select the items from a mock grocery store. 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 will do once there, what to bring). Each of the five subscales yields total raw scores; these are transformed into a 0 to10 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. In addition to this score, we collected times (in seconds) for completion of each item as we have found that this is a more sensitive measure of functional outcome than the total score when used with high functioning patients. The UPSA takes approximately 30 minutes to complete.

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). 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 dementia patients. 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).

Life Functioning Questionnaire

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 6 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 utilized as outcome measures. The LFQ takes approximately 5 minutes to complete.

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 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) working memory, and 5) visuoconstructional/spatial organization. The measures selected are widely used research instruments and 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 have also been selected to collectively measure broad domains of cognitive functions that would be inclusive in a comprehensive neuropsychological battery. To be included in the current study, the measure had to demonstrate sensitivity to the neurocognitive deficits of bipolar disorder, schizophrenia, or other neurological disorders. They also were required to have been shown to assess the particular neurocognitive domain for which they were used in the current study (i.e., using the WCST to measure executive functioning and the CVLT to measure verbal

learning and memory) neuropsychological assessments organized by neurocognitive domain and including the scores of each assessment that will utilized for creating domain composite scores.

Measures of Executive Functioning

Wisconsin Card Sorting Test. In the Wisconsin Card Sorting Test (WCST, Grant & Berg, 1948; 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 problem solving, abstraction and concept formation and the ability to shift cognitive sets in response to feedback. The Wisconsin Card Sorting Test has been shown to be sensitive to dorsolateral prefrontal cortex dysfunction (Sullivan, Mathalon, Zipursky, Kersteen-

Tucker, Kight, & Pfeerbaum, 1993). The scores obtained for this measure are the number of categories achieved, number of perseverative errors, and trials to first set.

Measures of Verbal Learning and Memory

California Verbal Learning Test. 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 distracter list, and the participant is asked to recall items once again from list A. Following the recall trials, the participants are cued with the categories of fruit, clothing, tools, and spices (Cued recall) and are again asked to recall as many items as possible in each category. Following a 20-minute delay, in which non-verbal tasks are performed, the participants are asked to recall as many items from list A in both a free recall and cued situation. A recognition trial then follows in which participants select the words from List A that are presented with 16 distracter items. Therefore, the CVLT-I measures the basic component of learning and memory, including, encoding, storage, and retrieval of information, as well as the susceptibility of information to interference effects and deterioration of information over time. 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 will also be measured.

Measures of Visual Learning and Memory

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

The BFLT-E, a modification of the original Biber Figure Learning Test, (BFLT; Glosser et al., 1989), consists of 15 geometric designs constructed of simple shapes (circles, squares, and triangles) which are 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). This test is easy to administer, and in fact the inter-tester reliability for the BLFT-E has been found to be as high as .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. The variables of this measure include learning trials 1-5, immediate recall, delayed recall, immediate memory, hit rate, discriminability, and total false alarm rate.

Measures of Working Memory

WAIS-III Digit Span Subtest. In the Wechsler Adult Intelligence Scale – Third Edition (WAIS; Wechsler, 1997a) Digit Span Forward and Backward subtest, the examiner verbally presents a series of numbers and the participant is asked to repeat the numbers verbatim, first in a forward sequence (Digits forward) and then in a reverse order (Digits backward). The task begins with a string of two numbers and progresses to a string of eight numbers or until the participant fails two consecutive trials. The total number of correct trials is summed for both digits forward and backwards. Digit Span involves attentional processes of being able to hold sequences of strings of numbers in working memory and reiterate the sequences in the auditory channel. Raw scores can be converted to scaled scores based on age-normative data.

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

presented a three dimensional board of ten blue blocks in which the examiner points out a fixed sequence of patterns by touching 1 block per second. The sequences begin with touching two blocks and progresses to more difficult patterns. The participant is asked to mimic the presentation of the touching in the same order in the Forward Span condition, and to touch 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.

Measures of Visuoconstructional/Spatial Organization

Benton Judgment of Line Orientation. Judgment of Line Orientation (JOL; Benton et al., 1983) 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.

Block Design. The Block Design task of the WAIS-III (Wechsler, 1997a) has been shown to demonstrate right hemisphere processing for visual spatial organization and reproduction. It involves making a comparison of a prototypical design, and reproducing this design through the manipulation of a set of blocks. The participant is given the necessary amount of blocks, and then asked to reproduce, either the blocks set in front of them (for initial trials), or a picture representation of the blocks. The task is timed, and is scored based on, reproduction accuracy, and time to complete.

Intellectual Functioning

Current IQ was based upon estimates from the participants first testing session, which used a dyadic short form of the WAIS-III scaled scores on the Vocabulary and Block Design subtests, based on regression equations to estimate the Full Scale IQ score (Ringe, Saine, Lacritz, Hynan, & Cullum, 2002). The equation to be used in the current study is V(2.727) + BD(2.727) + 42.535 = Estimated Full Scale IQ (Ringe et al., 2002). This regression equation has been 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).

Data Entry and Screening

All tests were scored according to standardized procedures by two trained individuals. In cases where disagreement occurs, a third opinion (Daniel Allen, Ph.D.) was used to resolve discrepancies. Data was entered into Microsoft Access and SPSS version 18.0 was used to analyze the data, including calculating missing values and bootstrapping procedures.

Prior to performing the analyses to examine the main hypotheses, functional outcome and neuropsychological test data was inspected for outliers. Skewness and kurtosis was 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 are 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 or below the mean. It is expected, given the current sample size, that one or possibly two subjects will obtain scores ± 2 standard deviations. If such outliers are detected, the individual data was examined first to verify that it represents a valid case. If it is determined that the subjects who obtain extreme scores are members of the population under investigation, their data was retained but the score was converted to decrease its influence on the regression analyses.

Descriptive statistics of the group were calculated for the demographic variables of age, education, estimated IQ, ethnicity, gender, and Hollingshead SES category. Clinical variables reported, include the variables; length of illness, current symptomology (as measured by scores on the YMRS and HAM-D), number of mood episodes, and number of hospitalizations using descriptive statistics (See Table 3.1). This population was mostly medicated (See table 4 with only 33.4% of the population unmedicated at time one and only 17.2% of the population unmedicated at time two.

Prior to calculating the main analyses, standardized scores were created for each neuropsychological assessment by converting the raw scores for each measure into *z* scores using the mean and standard deviation of the current sample. Raw scores were used rather than age-corrected scaled scores, which are available for many of the measures, because of the potential confound of averaging across age-corrected and non-age-corrected scores. Then five composite scores, one for each of the five neurocognitive, domains, were created by averaging the *z* scores from the respective tests that are included in each domain. Table 1 in Appendix II provides the list of subtests 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 be created by averaging the five domain composite scores.

The summary scores for the W-QLI and UPSA were calculated according to the instructions in the respective manuals. The domain scores on these two measures were obtained per instructions in the manual for each of the domains mentioned here. The W-QLI domains are 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.

To test hypotheses 1, 2 and 3, separate regression analyses were conducted, one for each of the functional outcome measures (WQL-I, LFQ and UPSA). In these analyses, the neuropsychological composite scores based on the neuropsychological testing conducted at evaluation 1 served as the predictors and the functional outcome measures total scores served as the dependent variables. For all regression analyses, cross validation was performed on the entire sample using the bootstrapping method, where statistics are generated using random sampling with replacement from within the strata

(in this case the diagnoses of bipolar I and bipolar II) of the original data set (Tabachnick and Fidell, 2001).

To test hypothesis 4, separate repeated measures ANOVAs were conducted for each of the cognitive domains. In these analyses, the test scores that make up the domains served as dependent variables and the time of the evaluation will serve as a repeated measure. It was anticipated that a significant improvement in test performance from the first testing session would be present for the Verbal Memory and Visual Memory domains. It was further predicted that the Visuoconstructional/spatial domain would demonstrate an intermediate level of improvement, but less than the memory domains.

Procedure

Individuals with bipolar disorder who had previously participated in research studies at the Neuropsychology Research Program were contacted by phone and asked if they would be interested in participating in the current study. In order to be contacted, subjects needed to have been assessed with a battery of neuropsychological tests at least 120 days in the past. Those who agreed to participate were administered a brief phone or in-person screening to determine if they still meet study criteria (see phone screen form in Appendix II). Participants who met the study criteria were scheduled to complete the testing procedure. Further exclusionary criteria, including the presence of a mood episode and substance used disorder, were evaluated during the testing session. The session included reviewing and obtaining informed consent and the administration of a structured clinical interview, demographic and medical history questionnaires, clinical symptom

scales, neuropsychological assessment and three measures of functional status. The test sessions lasted for approximately 4 hours.

The measures were administered in the following order: 1) informed consent and demographic questionnaire 2) Brief Psychiatric Rating Scale, 3) Structured Clinical Interview for DSM-IV, 4) Hamilton Depression Rating Scale, 5) Young Mania Scale, 6) Biber Figure Learning Test, 7) WAIS-III Digit Span, 8)Life Functioning Questionnaire , 9) Wisconsin Quality of Life Index 10) Biber Delayed, 11) California Verbal Learning Test, 12) WMS-III Spatial Span, 13) Judgment of Line Orientation, 14) WAIS Block Design, 15) California Verbal Learning Test Delayed, 16)Wisconsin Card Sorting Test, and 17)UCSD Performance-Based Skills Assessment. All evaluation procedures were completed on the same day. In addition, after 2 hours of testing, 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 graduate students who were extensively trained to administer the assessments in a reliable and valid manner. Testing occurred in a quiet setting (laboratory office) at the UNLV Neuropsychology Research Program Laboratory. 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.

The five neurocognitive domains were assessed using the raw scores from the respective tests in each domain (see table 1). Global neurocognitive composite scores

were created by averaging z-scores calculated for each of the domain composites for time one and time two, respectively.

CHAPTER 4

RESULTS

Preliminary Analyses

The descriptive statistics for neurocognititve and functional variables are presented in tables 5-6 respectively. A preliminary examination of the individual test scores using frequency statistics indicated that there were no out-of-range variables. These data were further analyzed using standard procedures to assess skewness and kurtosis. Skewness and kurtosis estimates within ± 1.0 were generally considered to be acceptable for use of parametric statistical tests and procedures. The clinical nature of the research question and the expected mortality of a longitudinal study yielded a predictably less than robust sample size. Further, this sample is not a truly random sample, but due to the nature of the study is in fact a convenience sample and thus potentially subject to the biases inherent with such a population. In order to accommodate for this sample size, in particular potential error normally attributed to small sample size, a bootstrapping procedure was employed. Because the data are obviously stratified by diagnosis, the bootstrapping method of stratified sampling was employed. Further while an initially random Mersenne Twister seed set the start point for sampling, it was held consistent throughout all bootstrapping procedures, for the purpose of replicating results. The bootstrapping evaluations were used to evaluate the extent to which the existing neurocognitive data for both time one and time two are likely to be seen in the general population. The descriptive analysis of the data reveal that the sample data is in fact representative of what we would expect in the general population (at a 95% CI; See Tables 5-6)

Data Screening

Subsequent to the evaluation of skewness and kurtosis for the various domains, a secondary process of data screening was conducted to establish whether or not values were in fact observed values or a result of data entry. Although all data were entered using a double data entry process, the possibility exists that any scores which fell ± 2 standard deviations or more from the mean could be data entry errors, and thus were verified against the original data sheets. In order to further assess the normality of distribution of the variables of interest, the Shapiro-Wilk's test of normality was used. Finally, outliers, defined as data points greater than 2 standard deviations above or below the group mean, were identified via box plot analysis. When looking at time one neurocognitive variables, Block Design, Benton-JOL, CVLT-Short Delay and Biber Long Delay as well as the WCST Number of Trials Completed variables were all found to have skewness and kurtosis which was greater than ± 1 as well as contain individual outliers of greater than 2 standard deviations from the mean. These scores were adjusted by ± 1to the next highest or lowest score, respectively. For time two neurocognitive variables, the subtests of Spatial Span, Benton-JOL, CVLT Trials 1 to 5 Total Score, Biber Long Delay, as well as all three of the WCST Scores used for subsequent analyses, were all found to have skewness and kurtosis which was greater than ± 1 as well as contain individual outliers of greater than 2 standard deviations from the mean. These scores were similarly adjusted by ± 1to the next highest or lowest score, respectively. Upon the completion of these transformations, the data was reassessed and with the exception of a subset of time one and time two WCST variables, was found to demonstrate an

acceptable degree of normality as judged by skewness and kurtosis, as well as Shapiro-Wilk's test of normality.

Because of the nature and sensitivity of the WCST (rules for this test are either quickly discovered or result in dramatically poor performance), any impairment in performance typically creates outliers. It is likely due to this sensitivity that the normal transformations failed to correct the distribution normality. Therefore, an attempt to reduce kurtosis and skewness was made using a Log10 procedure for the raw scores of the WCST subtests of percent perseverative errors, number of trials completed and failure to maintain set of both time one and time two data. This initial transformation actually yielded an increase in the skewness and kurtosis. Next a cosine transformation was attempted for these variables. However, this transformation yielded either little or no change. Thus the initial transformations based upon ± 1 low and high scores were maintained.

Upon completion of the evaluation of the skewness and kurtosis for the neurocognitive variables, the same process was completed for the functional measures provided by the UPSA, LFQ and WQL-I, and all subsequent analyses were conducted using the normalized data established using the aforementioned and following procedures.

For the UPSA, the Transportation and Housing domains for time one and the Communication, Transportation, Housing and Companionship domains all exceeded ± 1 SD from the mean. Again, individual scores were checked to ensure that they were within the appropriate range as well as 2 SD of the mean for that domain. Those scores that fell more than 2 standard deviations from the mean for the above domains were transformed

to fall within ± 1 point of the next highest or lowest score, respectively. With the exception of Transportation and Housing from time one and Companionship from Time 2, this transformation provided acceptable normality, as measured by skewness, kurtosis and the Shapiro-Wilk's test. Because the distribution of the housing domain is flat (all scores are equal to 4), no further transformations were attempted. However, for Transportation at time one and Companionship at time two a Cosine transformation was performed for the variables, which provided acceptable skewness and kurtosis.

For the LFQ, the domains of Family Functioning for time one as well as Friends, Home and Work domains for time two, were identified as falling outside the aforementioned ± 1 SD, and the same screening and transformation process was carried out as was done for the previous neurocognitive and functional domains. This corrected skewness and kurtosis for all but the home domain for time two. For this domain a Cosine transformation was used to normalize the distribution.

Finally, this process was repeated for the WQL-I measure. An examination of the distribution for time one and time two variables showed only Occupational Activities and Activities of Daily Living (ADL) warranted further exploration. The data entries appeared to fall within the range of appropriate scores and for the Occupational Activities, did not demonstrate any extreme outliers (again those which are more than 2 SD from the mean). However, the ADL domain had two scores which warranted the ± 1 high/low score transformation discussed for the previous measures. Upon completion of this transformation, all domains for the WQL-I had acceptable skewness and kurtosis.

Because of the disparity in representation for the diagnoses of bipolar disorder (a

much larger proportion of bipolar I as compared to bipolar II), an initial comparison of the outcome variables (using ANOVA) was conducted.

Evaluation of Study Hypothesis

Hypothes 1: Predicting UPSA

Hyposthes 1 predicted that UPSA scores for time two will be predicted by a model containing Verbal Learning and Memory ability and Executive Functioning from time one, with impaired performance predicting lower UPSA scores. Individual regression analysis for the domain of Verbal Learning and Memory as well as Executive functioning were conducted in order to evaluate this relationship. While the overall model of Verbal Learning and Memory and Executive Functioning did not predict UPSA Total Scores (R^2 = 0.18, F = 2.86, df = 2, 26, p = 0.075), Verbal Learning and Memory was found to predict the UPSA Total score for time 2 (R^2 = 0.15, F = 4.76, df = 1, 27, p = 0.038). However, Executive Functioning did not predict UPSA Total score for time 2 (R^2 = 0.05, F = 1.40, df = 1, 27, p = 0.247). Because the initial hypothesis was not supported by the results, further analysis was conducted, examining a model including all of the time one neurocognitive domains. A stepwise regression was conducted using a stepwise method of entry of all neurocognitive domain composites. This model suggested that the best predictor of the UPSA Total score at time 2, was the domain of Visual Learning and Memory (R = 0.509, F = 9.44, df = 1, 27, p = .005). In addition to an assessment of time one neurocognitive functioning to predict longitudinal, an analyses of the relationship between acute neurocognitive functioning and Functional Life Performance (as measured by the UPSA Total Score at time two) was conducted. Using step-wise regression, the

neurocognitive domain of Visual Learning and Memory was indicated as the best predictor (*Adj*. R^2 = 0.276, *F* = 11.65, *df* = 5, 23, *p* = 0.002).

Hypothesis 2: Predicting Quality of Life and Life Satisfaction from Verbal Learning and Memory as well as Working Memory

In order to assess the ability of verbal memory ability and performance tasks to predict quality of life and life satisfaction, individual regression analyses were conducted.

To assess quality of life as reported by the WQL-I unweighted total score, a model containing Verbal Learning and Memory as well as Working Memory was used. However, this model did not predict WQL-I total scores (R^2 = 0.15, *F* = 0.20, *df* = 2, 26, *p* = 0.822).

In an attempt to identify a model of neurocognitive performance which predicts Quality of Life (as measured by the WQL-I), regression analysis were conducted using both a stepwise and forward entry methods, for which no variables were entered. This suggests that no single domain from time one impairment adequately predicts Quality of Life at time two, and thus all variables were entered into the model. However, this model also failed to predict Quality of Life (*Adj*. R^2 = -0.076, *F* = 0.60, *df* = 5, 23, *p* = 0.696). In an attempt to assess if current neurocognitive functioning is a better predictor of Quality of Life, similar analyses were conducted for which a similar inability to identify a model of neurocognitive functioning (albeit at time two) that predicts Quality of Life as measured buy the WQL-I (*Adj*. R^2 = 0.006, *F* = 1.04, *df* = 5, 23, *p* = 0.405).

To assess life satisfaction, the variable of Life Functioning total scores for time two was compared to a model containing Verbal Learning and Memory as well as Working

Memory was used. However, this model did not predict Life Functioning Total scores (R^2 = 0.15, F = 2.31, df = 2, 26, p = 0.120).

Again, in order to ascertain a model of neurocognitive domain impairment that might predict Life Satisfaction, regression analysis were conducted using both a stepwise and forward entry methods, for which no variables were entered. This suggests that no single domain adequately predicts Life Satisfaction as measured by the LFQ. Additionally regression analysis entering all neurocognitive domain scores from time one did not approach statistical significance (*Adj.* R^2 = 0.036, F = 1.21, df = 5, 23, p = 0.337) suggesting that the overall model is inadequate in its ability to predict Life Satisfaction as measured by the LFQ. As before, an attempt to predict current Life Satisfaction from acute nuerocognitve domain scores was evaluated using the same process of regression analyses, first using step-wise, then forward, and finally an enter-all method. Here too, entering all neurocognitive domains failed to generate a model which was able to predict Life Functioning at an acceptable level of statistical significance (*Adj.* R^2 = 0, F = 0.93, df = 5, 23, p = 0.479).

H3: Predicting UPSA Performance

Performance on the UCSD Performance-Based Skills Assessment is assessed by a much broader range of neurocognitive functioning. Therefore, it is expected that the speed of processing (measured in seconds) for this task, will be most likely accounted for by executive functioning and working memory domains, with impaired functioning predicting poorer functional outcomes and conversely spared or improved functioning predicting average to above average outcomes, respectively.

To assess speed of processing for the UPSA, composite times for each of the domains were accomplished by summing the individual subtask times within a domain (with the exception of household chores, which contains only one score). Once composite scores for each domain were created for time one and time two, a regression analysis was conducted to assess how well the overall model containing Working Memory and Executive Functioning at time one predicts the processing speed for the individual UPSA domains at time two. This analysis found that the overall model did not predict UPSA Processing Speed for any of its domains (See Table 7). Additionally, an repeated measures ANOVA was conducted to assess individual change in UPSA processing speed as a function of time one and time two. This analysis revealed no statistically significant change over time (see table 8), suggesting a relative stability of UPSA performance over time, even in the absence of a predictive model of neurocognitive domains for UPSA performance. Finally, individual regression analyses for an overall model containing all of the neurocognitive domains, was conducted to assess the ability of time one neurocognitive variables to predict UPSA processing speed at time two. With the exception of transportation processing speed there was no predictive ability of neurocognitive variables for UPSA processing speed (see table 9).

H4: Change in Neurocognitive Functioning

To examine the change in neurcognitive functioning from time one to time two multiple repeated measures ANOVA's were run for the raw scores (normalized using the aforementioned procedure) of each of the subtests that comprise the domains (Verbal Memory, Visual Memory, Visuoconstruction/spatial ability, Working memory, Executive functioning), as well as for the composite Neurocognitive Domains. Due to the large

degree of variability in the range of the raw scores used for each of the neurocognitive domains, a composite score created from z-scores for each of the subtests was used to create an averaged measure of global neurocognitive functioning. For the domains of Verbal Learning and Memory, Visual Learning and Memory, and Working Memory, no significant change from time one to time two was observed in neurocgnitive functioning. There was however a significant difference between time one and time two for the domains of Visioconstructional/spatial (F = 3.50, df = 2,27, p = 0.045 partial eta squared = 0.206) performance and Executive Functioning (F = 4.70, df = 3,26, p = 0.009 partial eta squared = 0.352). For the domain of Visioconstructional/spatial, Block Design for time one (M = 44.69, SD = 12.07) was significantly better than time two (M = 41.79, SD = 12.56). For the domain of Executive Functioning, there was a significant effect of time for Number of Categories (F = 4.83, df = 1,28, p = 0.036, partial eta squared = 0.147), with more categories being completed for time one (M = 5.79, SD = 0.412) as compared to time two (M = 5.48, SD = 1.056), and Percent Perseverative Errors (F = 6.93, df = 1,28, p = 0.014, partial eta squared = 0.198) being larger for time one (M = 10.34, SD = 4.98) as compared to time two (M = 13.79, SD = 8.79). Typically one would suspect any change in performance to be in the opposite direction, as a result of practice effects (Goldberg et al., 2007). Yet, the two domains, which demonstrated significant change, demonstrated a degradation of performance. This may be a result of symptom functioning and thus warrant further examination.

In order to better understand the change in neurocognitive functioning, an examination in the change of symptom ratings for the YMRS and HAM-D from time one to time two. This comparison was done via a repeated measures ANOVA. This analysis

revealed a significant effect of time for the YMRS (F = 27.59, df = 1,28, p = 0.021, partial eta squared = 0.176) and HAM-D (F = 26.26, df = 1,28, p = 0.0001, partial eta squared = 0.484) with performance being worse for both the YMRS at time 1 (M = 3.24, SD = 2.50) compared to time 2 (M = .86, SD = 1.87), as well as performance being worse for both the HAM-D at time 1 (M = 7.14, SD = 4.92) compared to time 2 (M = 3.86, SD = 3.03). This difference suggests a decrease in symptom severity. Additionally, a chi-square analysis was conducted to evaluate possible changes in medication status (medicated vs. unmedicated) from assessment one to assessment two. This analysis revealed no significant change in medication status (χ^2 = 0.80, df = 1,29 , p = 0.78). Thus, the decline for the neurocognitive domains cannot be explained by an increase in symptom severity, nor a change in medication status.

Overall, these results demonstrate the relative stability of neurocognitive functioning over time, thus suggesting that, with the exception of Executive Functioning and Visioconstructional/spatial abilities one could predict neurocognitive functioning and impairment should not significantly change over time, and that any changes seen for these domains would not be necessarily attributable to an increase in symptom severity. However, even in the case of Executive functioning, where we see statistical significance, we are most likely approaching a ceiling effect, as the overall mean of the sample for number of trials completed for both time one and time two is nearly the maximal value of 6 (recall categories completed M = 5.79, SD = 0.412 for time one as compared to time two (M = 5.48, SD = 1.056).

Because of the seemingly normal performance for our sample on the neurocognitive domains, it was decided to examine the cases with the poorest performance on the

functional outcome measures of the LFQ and WQL-I. The UPSA was considered for this type of analysis as well. However, the worst score on the UPSA was 79.6, which is not classified as impaired by the UPSA in comparison to the schizophrenia literature for which the above hypotheses were based, so it was not included in these analyses.

The poorest outcome for the LFQ total score was 7. An examination of the variables which comprise the neurocognitive domains of visual learning and memory as well as visual learning and memory fell one standard deviation below the sample mean (see Table 10). This would suggest that for this individual, their low level of life functioning was associated with poor performance on tests of verbal and visual learning and memory abilities.

The individual with the poorest outcome as measured by the WQL-I had a total score of -0.96 . This score falls more than one standard deviation below that normative mean and is classified by the WQL-I as impaired. Examination of the individual neurocognitive test scores indicated that there was markedly worse performance for the tests that comprised the visuoconstructional/spatial abilities and working memory domains. The scores for these domains fell at least one standard deviation below the sample mean (see table 11), suggesting that for this individual decreases in these neurocogntiive abilities was associated with impaired quality of life.

CHAPTER 5

DISCUSSION

This study was designed to explore the impact of neurocognitive functioning on various functional outcomes for individuals diagnosed with a bipolar mood disorder. More specifically, the study analyzed the longitudinal power of five neurocognitive domains to predict various measures of functional abilities, quality of life, and life satisfaction measures that were evaluated approximately 12 months from the first assessment (M = 11.86, SD = 4.47) after the neurocognitive domains were assessed. The impetus for this study was based on the now commonly reported associations between neurocognitive function and functional outcomes for individuals with other mental disorders, primarily schizophrenia. Furthermore, there is an increasing literature suggesting that, like schizohprenia, neurocogntive deficits are core features of bipolar disorder. Less information is available regarding the stability of neurocognitive deficits in bipolar disorder over time, but given that neurocognitive deficits are core features of the disorder, and these deficits have been demonstrated to be stable over time in schizophrenia, one would expect that neurocognitive deficits would be stable over time in bipolar disorder. Based on these considerations, neurocognitive deficits might be useful for longitudinal prediction of functional outcomes in bipolar disorder. Despite these observations, very little information is available regarding the ability of neurocognitive tests to predict functional outcomes in bipolar disorder. The few studies that have addressed this issue have employed either limited assessment of neurocognitive abilities, limited assessment of functional outcomes, or both (Atre-Vaidya et al., 1998; Burdick, et al., 2006; Dickerson et al., 2004; Laes & Sponheim, 2006; Martínez-Arán, Vieta, Colom,

et al., 2004; Miklowitz, et al., 2007; Vocisano, Klein, & Keefe, 1997; Zubieta et al., 2001). To our knowledge, there has been not been any study that examines these matters from a longitudinal perspective. Thus, the current study was designed to address these obvious gaps in the empirical literature with regard to the longitudinal predictive power of neurocognitive functioning in relation to functional outcomes in bipolar disorder, by applying a comprehensive assessment of both neurocognitive function and functional outcomes. A secondary goal of the study was to examine the longitudinal stability of neurocognitive deficits in these patients.

Four hypotheses were proposed to address these matters. Hypothesis 1, 2 and 3 all examined the relationship between time one neurocognitive abilities and functional as well as quality of life/life satisfaction outcomes, while hypothesis four specifically addressed stability of neurocognitive functioning. Hypothesis 1, 3 and 4 were partially supported by the data while hypothesis 2 was not supported by the data. The implications of these findings, potential limitations and future research will be discussed.

Neurocognitive Functioning and Functional Outcome

Neurocognitive impairment for individuals with bipolar mood disorder persists outside of mood episodes (Bearden et al., 2001; Kravariti, Frith, Murray, & McGuire, 2004; Martínez-Arán, et al., 2004; Murphy & Sahakian, 2001), and impairments are also apparent in psychosocial domains (i.e. school, work, social, etc,;Dion et al., 1988; Strakowski et al., 1998; Tohen et al., 2000; Zarate et al., 2000). Thus, it was expected that the domains of functioning would exhibit longitudinal stability, or possibly degrade over time in association with the chronic negative impact of bipolar disorder on functioning.

Additionally, because neurocognitive functioning is stable from a longitudinal standpoint in severe mental health disorders such as schizophrenia (Kurtz, et al., 2008), we also expected that temporal relationships between neurocognitive abilities and functional outcomes reported in other studies would persist over time, so that neurocognitive abilities might be useful in the longitudinal prediction of functional outcomes. While we expected self-report measure of functioning to not only reveal the chronic impact of mood episodes, it is expected that these are most amenable to describing acute states. Thus it was posited that an objective, ecologically valid performance based measure of daily functioning would be sensitive to the impact of disorder chronicity as it relates to neurocognitive functioning. In this vein the UPSA was chosen as a measure that would demonstrate this objective functioning in comparison to previously collected performance on a number of neurocognitive domains, including Verbal Learning and Memory and Executive functioning, and that these domains would be predictive of UPSA performance approximately twelve months later.

Contrary to our expectations, we found that the best predictor of UPSA performance was Visual Learning and Memory at time one with better performance for Visual Learning and Memory indicating better performance on the functional outcome measure of the UPSA. This finding is of interest, as most of the tasks for the UPSA are comprised of tasks that are typically represented by verbal abilities (Communication), Executive Functioning (Planning an activity, Household Chores, Transportation) and Working Memory (Planning an Activity, Communication) neurocognitive abilities (Patterson, et al., 2001), and verbal memory has been specifically identified as a predictor of functioning for this measure in patients with schizophrenia (Kurtz, et al., 2008). It may be

that while the UPSA is highly loaded toward verbal information, some of the tasks, such as reading bus routes rely more heavily on visuospatial processing, which may account for the relationship noted here. It may also be that the findings are attributable to more severe impairment of visuospatial memory relative to verbal memory, which has been reported by some (Frantom et al., 2008) although not by all who have examined this issue (Knatz et al., unpublished data). For the current sample, performance on the visual memory tasks was poorer than on the verbal memory tasks. Thus, it may be that visuospatial memory tasks were more sensitive predictors than verbal memory tasks, simply because the former abilities were impaired. In other words, in cases where neurocognitive deficits contribute to impaired functional outcomes, one would not expect that neurocognitive abilities in the average range would be very useful in predicting functioning.

With regard to the UPSA, it was also hypothesized that in addition to overall performance as reflected by a raw score, that the time to complete the UPSA would be predicted by neurocognitive variables, simply because time to complete the UPSA was reflective of processing speed for the individual domains. Executive functioning and Working Memory were identified as particularly important in this regard, simply because intactness of problem solving ability (Executive Functions) and the ability to hold and manipulate information on line (Working Memory) are critical for the efficient performance of novel tasks and decision making. While initial repeated measures analyses found relative stability for the UPSA processing times, only transportation processing time was predicted by an overall model of all of the five neurocognitive domains. Specifically, Verbal Learning and Memory as well as Visual Learning and

Memory. This suggests that neurocognitive functioning is indicative of one aspect of daily living skills performance. The transportation domain of the UPSA requires that individuals be able to use community transportation maps and timetables to plan a daily outing, which may explain its association with verbal learning and memory as well as visual learning and memory.

Neurocognitive function, Quality of Life and Life Satisfaction

As previously mentioned, a large body of research has suggested that psychosocial functioning is greatly impacted by impaired neurocognitive impairment in schizophrenia, and that this impairment is in fact, predictive for these psychosocial performance domains (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). Additionally, studies have demonstrated a limited relationship between neurocognitive impairment and broader measures of functioning, such as the global assessment of functioning (GAF) used in clinical settings to describe psychosocial functioning (APA, 2000; Atre-Vaidya et al., 1998; Dickerson et al., 2004; Martínez-Arán, Vieta, Colom, et al., 2004; Martínez-Arán, Vieta, Reinares, et al., 2004). Thus, Hypothesis two posited that neurocognitive abilities at time one should be predictive of time two ratings for life satisfaction and quality of life as measured by the LFQ and WQL-I, respectively. Specifically, it was hypothesized that the neurocognitive domains of Verbal Learning and Memory as well as Working Memory would be the best predictor of these outcomes measures. The results for this hypothesis suggest that there is no relationship between neurocognitive domains and life satisfaction or quality of life

ratings. This held true when looking at relationships of all neurocognitive domains at both time one and time two.

One implication for this finding could be the overall general health of the sample as reported by the HAM-D and YMRS (See table 3). Another implication suggests that while broad measures of functioning (e.g. GAF scores), may be predicted by neurocognitive functioning in bipolar disorder, more specific and subjective measures of functioning (e.g. quality of life and life satisfaction) are more influenced by environmental factors such as social support system, finances, and job satisfaction, as opposed to neurocognitive functioning. Additionally, much of the literature used to develop and support a hypotheses for the positive predictive relationship between neurocognitive performance and functional impairment are derived from the literature related to schizophrenia (Buchanan, Holstein, & Breier, 1994; Evans et al., 2003; Kern, Green & Satz, 1992; Twamley et al., 2002), which is a more severe and impairing mental disorder compared to bipolar disorder. Patients with schizophrenia not only demonstrate more severe neurocognitive deficits than those with bipolar disorder (Hoff et al., 1990; Martínez-Arán et al., 2002; Morice, 1990; Zihl, Grön & Brunnauer, 1998), have poorer levels of premorbid functioning (Uzelac, et al., 2006) and also have more severely impaired functioning and adjusted, as indicated by, for example, greater impairment of psychosocial function, increased rates of unemployment and homelessness, increased need for supportive housing and work environments, and fewer long-term significant relationships, among others (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). Furthermore, evidence suggesting

associations between neurocognitive function and functional outcomes for bipolar disorder is based largely on patient data comparing deteriorated patients to those which were not deteriorated (Vocisano, Klein, & Keefe, 1997). In contrast to these groups, most of the individuals in this study were not significantly impaired, and might be considered a high functioning bipolar group, as indicated by that fact that most were employed, they had on average more than a high-school education and many were involved in long-term relationships. Thus, the absence of association between neurocognitive function and life satisfaction in this study may be accounted for by the high functioning nature of the patients studied. This group of high functioning individuals with bipolar disorder is interesting in its own right, as the current findings do suggest that while neurocognitive deficits are core features of bipolar disorder, there are some patients with the disorder that exhibit relatively mild levels of cognitive impairment and little impairment of functioning. This spared neurocognitive functioning has been observed for individuals with schizophrenia and autism. For these individuals neurocognitive abilities are within the average range of performance, yet an examination of patterns of performance are consistent with those who have a diagnosis of schizophrenia (Allen, Goldstein, & Warnick, 2003). Studies of these patients have classified them as a neuropsychological normal subset of patients with schizophrenia, not unlike the classification of high functioning in autism (Goldstein, Allen, Minshew, Williams, Volkmar, Klin, & Schulz, 2008). There has been a demonstrated relationship among preserved neurocognitive functioning and decreases in nueroanatomical deterioration and severity of impairment as well as the improvement in prognosis for individuals with schizophrenia (Allen et al., 2000; Wexler et al., 2009). These studies in conjunction with the results of this current

study suggest that further study for the creation of a similar classification for bipolar disorder would be warranted.

Finally, it may be that this group of individuals may represent a generally normal level of neurocognitive functioning. Thus the self-report measures of quality of life and life functioning domains may represent a much more variable picture based upon subjective evaluations provided by self report measures of the LFQ and WQL-I, as compared to the much more objective performance based tasks for these domains provided by the UPSA. Examination of the individual cases with impaired functional outcomes, as measured by the LFQ and the WQL-I, indicated that there was impairment for these individuals in Verbal and Visual Learning and memory as well as Visuoconstructional/Spatial abilities and Working Memory, respectively. Additionally, when looking at the individual with the slowest overall times for task completion, there was high average performance on specific verbal memory tasks (CVLT trials 1 to 5 and CVLT short delay; see table 12), yet demonstrated impairment in the Executive Functioning domain (failure to maintain set and categories completed; see table 12). This suggests that the measures used to assess functional outcomes are indeed sensitive when used to assess patients with bipolar disorders, but that overall the current sample was high functioning and so that absence of associations between neurocognitive measures and functional outcomes may simply have resulted from a lack of variability in performance in our participants. Put another way, since the large majority of our patients experiences normal functioning and average to above average neurocognitive abilities, the association between the neurocognitive measures and functional outcomes could only account for variation that is observed in normal populations. However, the predicted

associations between neurocognitive abilities and functional outcomes might be present in patients who have a more severe course of bipolar disorder and who, as a result, also exhibit more severe functional impairment and neurocognitive deficits. The UPSA total score was not examined in these analyses because the individual who scores the lowest was still at a level of performance which suggested no impairment in the functional abilities assessed by the UPSA (Total Score = 79.6). This score is above that of the mean of individuals with schizophrenia who have shown the ability to function independently (*M* = 78.6) as compared to those who were institutionalized (*M* = 62.89; Mausbach et al., 2006).

Longitudinal Stability of Neurocognitive Functioning

Hypothesis four predicted an improvement in neurocognitive functioning from time one to time two, and that this improvement would be most evident for the domains of verbal and visual learning and memory. This prediction was based on well-established practice effects for measures of learning an memory that results from repeated exposure to the test stimuli, which causes an artificial improvement in these domains. However, the only significant changes in performance between time one and time two were found in the Executive Functioning and Visiocstruction/spatial domains. Furthermore, changes in these domains indicated a statistically significant (although clinically unremarkable) decline, rather than improvement. Subsequent analyses examined the potential impact of changes in symptom severity and medication status between the two assessment periods as possible explanatory factors in the decline in these scores, as well as the lack of expected improvement in the learning and memory measures. If playing a role, it was expected that symptom severity would have increased from the first to the second

assessment, as increased symptoms of mania and depression have been associated with increased impairment of some specific cognitive abilities (Abrams & Taylor, 1980; Bunney & Hartmann, 1965; Clark, Iverson, & Goodwin, 2001; Kmiec, & Kupfer, 2000; McGrath et al., 1997; Mitchell & Malhi, 2004; Morice, 1990; Murphy et al., 1999; Murphy & Sahakian, 2001; Olley et al., 2005; Sax, Strakowski, McElroy, Keck, & West., 1995; Sweeney, Kessing 1998; Taylor & Abrams, 1981). Also, if medication status was having an influence, it was anticipated that significantly fewer individuals would have been medicated at time second assessment compared to the first. Yet, these analyses revealed no significant change in medication status and an improvement in symptoms of mania and depression, as measured by the YMRS and HAM-D, which should have been associated with an increase in cognitive functioning from the first to the second assessment. While the reasons for this decline could not be directly determined based on the current data, it may be that the test retest interval of 12 months accounted for the lack of improvement in scores on the learning and memory measure, as well as some of the other measures. Additionally, practice effects tend to be attenuated in individuals with cognitive impairment simply because learning does not occur as efficiently in these individuals in comparison to normals. The decrease of performance on the Executive Functioning and Visiocstruction/spatial domains is not easily explained by these considerations. The most likely explanation is that the sample demonstrated a relatively normal level of functioning at time one and time two. The primary measure of Executive functioning tends to be more sensitive to impairment and thus ceiling effects are expected for healthy individuals, in which all categories of the task are typically completed. Thus, any change in performance would be an artifact of ceiling effects for the sample. Also, it

could be that other factors that were not included in the current evaluations might account for the decrements in performance noted here, but this scenario is much less likely than mere ceiling effects.

Limitations

The predominant limitation of this study was the relatively small sample size. While a limited availability of participants was predicted and the statistical procedure of bootstrapping was employed as a means of addressing this limitation, it is likely significant association would have been observed with a larger data set. The ability of this study to obtain a larger sample was limited by the prevalence of bipolar disorder in the general population, the attrition that typically occurs in most longitudinal samples, and the restrictive inclusion criteria that were employed in order to reduce the effect of confounding variables (i.e. prior participation, time since last assessment, period since substance abuse/dependence criteria and period since last mood episode). Additionally, as mentioned before, the current sample was one of convenience, and so it is unclear whether the current results would generalize to the population of individuals with bipolar disorder. This may be particularly relevant with regard to severity of disorder, as the current sample was relatively high functioning compared to the bipolar population in general.

Implications and Future Study

This study does provide important information for the understanding of the longitudinal course of bipolar disorder. Past research in this area has been largely limited

to studies of functional and neurocognitive performance in bipolar disorder, and did not extend much beyond most recent mood episode. Additionally, past research was limited in its retrospective approach to the question of longitudinal outcomes and prognosis in bipolar disorder. This study addressed both the issue of elucidating a more specific study of the relationship between neurocognitive domains and functional outcomes as well as a planned study of longitudinal outcomes rather than a retrospective approach. The latter is most important as retrospective studies rely largely on the ability of an individual to accurately assess historical information. However, research has shown that individuals with bipolar disorder are poor historians, and thus any such information is much more likely to be biased. These results suggest that there is a relative stability of neurocognitive abilities over time, particularly in the domains of verbal and visual learning and memory as well as visioconstruction/spatial abilities, even with the presence of a serious mood disorder such as bipolar disorder. The domains of Executive Functioning and Working Memory appear to be less stable, and in this study were actually worse from time one to time two, and thus tasks requiring one to attend to, maintain and utilize novel information are the most likely to be negatively impacted by bipolar disorder. Additionally, the current study provided a much more comprehensive evaluation of neurocognitive abilities and functional outcomes than has previously been accomplished.

Future research would benefit from obtaining a larger and more representative sample than the one investigated here. Such studies may employ more liberal inclusion and exclusion criteria, so that the obtained sample is more representative of the various comorbid issues of substance use, abuse and dependence as well as the consideration of including those either in or recently in a mood episode. Such a study would have the

potential to obtain data with a greater prognostic ability and broader generalizability would suggest that the endeavor is worthwhile. It may also be important to continue the study of high functioning individuals with bipolar disorder to determine whether they are differentiated from more severely affected patients not only in the areas of neurocognition and functional outcome, but also differences in neuroanatomical, genetic, and environmental factors are also apparent. Such factors may be useful in more clearly understanding protective factors associated with decreased symptom and disease severity, that might by extension be useful in develop preventative or intervention strategies to decrease the onset of the disorder in those at risk, or to more effectively treat those who have already developed the disorder.

TABLES

Table 1

Subtests Comprising Neurocognitive Domains used for the Analyses of Hypotheses.

Neurocognitive Domain	Subtest
Verbal Learning and Memory	
	CVLT Trials 1-5
	CVLT Short Delay
	CVLT Long Delay
Visual Learning and Memory	
	Biber Trials 1-5
	Biber Short Delay
	Biber Long Delay
Executive Functioning	
	WCST Perct. Persev. Errors
	WCST Failure to Maintain Set
	WCST Number Completed
Working Memory	
	WAIS-III Digit Span Forward
	WAIS-III Digit Span Backward
	WMS-Spatial Span Forwardly
	WMS-Spatial Span Backward
Visuoconstructional/Spatial Memory	
	Block Design
	Benton- JOL

Note: CVLT: California Verbal Learning and Memory Test; WCST: Wisconsin Card Sorting Test; WAIS: Wechsler Adult Intelligence Scales; WMS: Wechsler Memory Scale.

Table 2

Descriptive Statistics for the Demographic Characteristics of the Sample

Variable	(N = 29)	*M*	*SD*
	Age	36.10	13.07
	Education	14.10	1.45
	Current IQ	109.24	10.58
Sex		*N*	*%*
	Male	19.00	27.94
	Female	10.00	14.71
Ethnicity			
	American Indian/Alaska Native	2.00	2.94
	Asian American	2.00	2.94
	Caucasian	21.00	30.88
	Hispanic/Latino	2.00	2.94
	Other	2.00	2.94
Marital Status			
	Committed Relationship	3.00	4.41
	Divorced	4.00	5.88
	Married	5.00	7.35
	Never Married	12.00	17.65
	Separated	5.00	7.35

Table 3

Descriptive Statistics for the Clinical Characteristics of the Sample

Variable	*N*	*M*	*SD*
Months since last mood episode	27	20.41	30.9
Number of Suicide Attempts	28	1.5	2.03
Hospitalizations	29	1.03	1.74
Age of Onset	14	30.38	12.71
Hamilton Rating Scale Time 1	29	7.14	4.92
Hamilton Rating Scale Time 2	29	3.73	3.06
Young Mania Scale Time 1	29	3.24	2.5
Young Mania Scale Time 2	29	1.8	1.86

Table 4

Descriptive Statistics for Medications at Evaluation One and Evaluation Two

Drug Classification	Time 1 N	Time 1 Percentage	Time 2 N	Time 2 Percentage
Antidepressants	14	48.3	12	41.3
Mood Stabilizers	10	38.5	18	62.1
Antipsychotics	8	27.6	10	34.4
Benzodiazepine	5	17.2	7	24.1
Stimulant	1	3.4	1	3.4
Sedative	1	3.4	3	10.3
Narcotic	1	3.4	0	0
Unmedicated	10	38.4	3	10.3

Table 5

Descriptive Statistics and boot-strapping results for Neurocogntive Variables at Time 1

Variable						95% CI	
		Statistic	Std. Error	Bias[b]	Std. Error[b]	Lower[b]	Upper[b]
Spatial Span Total	N	29		0	0	29	29
	M	16.45		-0.04	0.63	15.14	17.59
	SD	3.40		-0.06	0.41	2.53	4.18
	Skewness	-0.42	0.43	0.07	0.37	-1.00	0.38
	Kurtosis	-0.23	0.85	-0.15	0.67	-1.43	1.09
Block Design Raw	N	29		0	0	29	29
	M	44.69		-0.15	2.10	40.41	48.69
	SD	12.07		-0.26	0.80	10.14	13.27
	Skewness	0.21	0.43	0.03	0.33	-0.40	0.94
	Kurtosis	-1.61	0.85	0.13	0.34	-1.84	-0.53
Benton-JOL	N	29		0	0	29	29
	M	25.14		-0.03	0.68	23.73	26.45
	SD	3.69		-0.06	0.33	2.93	4.26
	Skewness	-0.43	0.43	0.00	0.32	-1.06	0.21
	Kurtosis	-1.17	0.85	0.11	0.50	-1.65	0.23
Digit Span Total	N	29		0	0	29	29
	M	17.86		-0.02	0.61	16.66	19.10
	SD	3.39		-0.09	0.32	2.68	3.93
	Skewness	0.20	0.43	-0.04	0.31	-0.47	0.76
	Kurtosis	-0.83	0.85	0.01	0.42	-1.55	0.11
CVLT Trials 1to5 Total	N	29		0	0	29	29
	M	56.00		-0.05	1.63	52.73	59.10
	SD	9.51		-0.25	0.99	7.24	11.16
	Skewness	-0.22	0.43	0.02	0.29	-0.76	0.39
	Kurtosis	-0.74	0.85	0.06	0.44	-1.32	0.37
CVLT Short Delay	N	29		0	0	29	29
	M	12.41		-0.02	0.46	11.48	13.24
	SD	2.61		-0.06	0.22	2.13	2.97
	Skewness	-0.17	0.43	0.03	0.34	-0.83	0.52
	Kurtosis	-1.26	0.85	0.05	0.40	-1.81	-0.24
CVLT Long Delay	N	29		0	0	29	29
	M	12.55		-0.01	0.42	11.69	13.38
	SD	2.37		-0.06	0.23	1.82	2.77
	Skewness	-0.30	0.43	0.02	0.31	-0.91	0.33
	Kurtosis	-0.87	0.85	0.07	0.42	-1.44	0.25
Biber Trial 1-5 Total	N	29		0	0	29	29
	M	145.62		-0.39	6.03	133.32	156.59
	SD	33.96		-0.88	3.39	26.40	39.37
	Skewness	-0.05	0.43	0.04	0.31	-0.62	0.61
	Kurtosis	-0.80	0.85	0.00	0.40	-1.44	0.23

Table 5 *(cont.)*

Descriptive Statistics and boot strapping results for Neurocogntive Variables at Time 1

Biber Short Delay	N	29		0	0	29	29
	M	11.45		-0.02	0.36	10.66	12.10
	SD	2.05		-0.05	0.20	1.63	2.38
	Skewness	-0.10	0.43	0.01	0.26	-0.62	0.40
	Kurtosis	-0.79	0.85	0.07	0.42	-1.34	0.26
Biber Long Delay	N	29		0	0	29	29
	M	12.52		-0.02	0.38	11.66	13.17
	SD	2.06		-0.07	0.36	1.35	2.68
	Skewness	-1.13	0.43	0.29	0.57	-1.80	0.27
	Kurtosis	2.13	0.85	-1.05	1.82	-1.38	5.22
WCST Perct.Persev. Resp.	N	29		0	0	29	29
	M	11.07		0.11	1.40	8.62	14.17
	SD	7.70		-0.31	2.26	3.63	11.34
	Skewness	2.82	0.43	-0.68	0.82	0.71	3.52
	Kurtosis	10.16	0.85	-4.41	4.73	-0.89	14.90
WCST Number Comp.	N	29		0	0	29	29
	M	5.38		-0.02	0.22	4.90	5.79
	SD	1.24		-0.03	0.21	0.77	1.55
	Skewness	-1.77	0.43	-0.06	0.69	-3.59	-0.84
	Kurtosis	1.61	0.85	0.72	3.84	-1.15	11.70
WCST Failure	N	29		0	0	29	29
	M	17.14		0.00	1.87	13.73	21.13
	SD	10.74		-0.35	1.86	5.95	13.50
	Skewness	1.75	0.43	-0.02	0.53	0.81	2.92
	Kurtosis	2.20	0.85	0.15	2.54	-0.78	8.96

Note: CVLT: California Verbal Learning and Memory Test; WCST: Wisconsin Card Sorting Test; JOL: Benton Judgment of Line Orientation.

a. Unless otherwise noted, bootstrap results are based on 1000 stratified bootstrap samples

b. Bootstrapping variables

Table 6

Descriptive Statistics and boot strapping results for Neurocogntive Variables at Time 2

Variable						95% CI	
		Statistic	Std. Error	Bias[b]	Std. Error[b]	Lower[b]	Upper[b]
Spatial Span Total	*N*	29		0	0	29	29
	M	17.34		-0.02	0.66	15.93	18.62
	SD	3.58		-0.05	0.34	2.85	4.18
	Skewness	-0.25	0.43	0.02	0.32	-0.87	0.40
	Kurtosis	-1.05	0.85	0.04	0.40	-1.57	0.02
Block Design Raw	*N*	29		0	0	29	29
	M	41.79		-0.10	2.21	37.34	45.96
	SD	12.56		-0.34	1.32	9.56	14.80
	Skewness	-0.02	0.43	0.02	0.27	-0.52	0.57
	Kurtosis	-0.64	0.85	0.08	0.45	-1.29	0.57
Benton-JOL	*N*	29		0	0	29	29
	M	24.76		-0.03	0.72	23.28	26.14
	SD	4.02		-0.07	0.64	2.75	5.20
	Skewness	-1.08	0.43	0.13	0.43	-1.78	-0.14
	Kurtosis	1.24	0.85	-0.47	1.39	-1.23	4.12
Digit Span Total Raw	*N*	29		0	0	29	29
	M	18.14		-0.01	0.55	17.14	19.21
	SD	3.08		-0.07	0.34	2.28	3.61
	Skewness	0.65	0.43	-0.02	0.30	0.06	1.25
	Kurtosis	-0.36	0.85	0.06	0.72	-1.32	1.45
CVLT Trials 1 to 5	*N*	29		0	0	29	29
	M	59.79		-0.07	1.86	56.28	63.48
	SD	10.30		-0.17	0.88	8.44	11.93
	Skewness	-0.06	0.43	0.00	0.31	-0.70	0.54
	Kurtosis	-1.26	0.85	0.08	0.31	-1.63	-0.42
CVLT Short Delay	*N*	29		0	0	29	29
	M	12.66		-0.02	0.49	11.69	13.59
	SD	2.72		-0.06	0.27	2.15	3.18
	Skewness	-0.46	0.43	0.03	0.29	-1.02	0.13
	Kurtosis	-0.80	0.85	0.07	0.53	-1.45	0.77
CVLT Long Delay	*N*	29		0	0	29	29
	M	13.14		-0.02	0.39	12.31	13.86
	SD	2.25		-0.04	0.25	1.68	2.69
	Skewness	-0.69	0.43	0.02	0.30	-1.28	-0.12
	Kurtosis	-0.38	0.85	0.05	0.79	-1.35	1.68
Biber Trial 1-5 Total	*N*	29		0	0	29	29
	M	152.59		-0.13	7.40	138.21	166.96
	SD	41.52		-1.11	5.38	30.32	51.53
	Skewness	-0.75	0.43	0.08	0.35	-1.40	-0.02
	Kurtosis	0.26	0.85	-0.09	0.99	-1.07	2.64

Table 6 *(cont.)*

Descriptive Statistics and boot strapping results for Neurocogntive Variables at Time 2

Biber Short Delay	*N*	29		0	0	29	29
	M	12.00		-0.01	0.47	11.03	12.90
	SD	2.52		-0.07	0.34	1.88	3.10
	Skewness	-0.89	0.43	0.11	0.42	-1.66	-0.01
	Kurtosis	0.26	0.85	-0.41	1.18	-1.72	2.66
Biber Long Delay	*N*	29		0	0	29	29
	M	12.72		-0.01	0.42	11.86	13.48
	SD	2.23		-0.07	0.36	1.55	2.85
	Skewness	-1.07	0.43	0.22	0.47	-1.78	0.02
	Kurtosis	1.29	0.85	-0.80	1.49	-1.49	4.03
WCST Perct.Persev. Resp.	*N*	29		0	0	29	29
	M	12.52		0.01	0.71	11.38	14.00
	SD	3.84		-0.24	1.13	1.18	5.62
	Skewness	2.87	0.43	-0.19	0.77	1.31	4.53
	Kurtosis	8.28	0.85	-0.40	5.39	0.78	22.55
.	*N*	29		0	0	29	29
WCST Failure	*M*	13.79		0.10	1.64	10.90	17.21
	SD	8.79		-0.20	1.43	5.50	11.04
	Skewness	1.41	0.43	-0.06	0.41	0.61	2.28
	Kurtosis	1.34	0.85	0.09	1.90	-1.04	6.23
WCST Number Comp	*N*	29		0	0	29	29
	M	5.24		-0.02	0.26	4.66	5.69
	SD	1.46		-0.03	0.24	0.90	1.85
	Skewness	-1.72	0.43	0.01	0.61	-3.13	-0.76
	Kurtosis	1.80	0.85	0.19	2.91	-1.14	9.33

Note: CVLT: California Verbal Learning and Memory Test; WCST: Wisconsin Card Sorting Test; JOL: Benton Judgment of Line Orientation.

b. Unless otherwise noted, bootstrap results are based on 1000 stratified bootstrap samples

b. Bootstrapping variables

Table 7

Repeated Measures ANOVAs to Evaluate the Stability of Neurocognitive performance at Time One and Time Two

Neurocognitive Domain	F	df	p	partial eta squared
Verbal Learning and Memory	2.74	3,26	0.064	0.240
Visual Learning and Memory	1.16	3,26	0.342	0.118
Working Memory	1.39	4,25	0.267	0.182
Executive Functioning	4.70	3,26	0.009	0.352
Visioconstructional/spatial	3.50	2,27	0.045	0.206
Global Composite	0.0001	1,28	1.000	0.0001

For all comparisons N=29.

Table 8

Regression Analyses for Prediction of UPSA Processing Speed at Time Two from Time One Based on a Model Containg the Neurocognitive Variables of Executive Functioning and Working Memory

UPSA Domain	*R*	R^2	*Adj.* R^2	*F*	*p*
Finance	0.152	0.023	-0.052	0.309	0.737
Household Chores	0.222	0.049	-0.027	0.646	0.533
Communication	0.309	0.095	0.023	1.317	0.286
Planning and Recreation	0.076	0.006	-0.074	0.072	0.931
Transportation	0.395	0.156	0.088	2.310	0.120

df for all analyses = 2,27; N = 29

Table 9

Regression Analyses for Prediction of UPSA Processing Speed at Time Two, from Time One Based on a Model Containing all Neurocognitive Variables

UPSA Domain	*R*	R^2	*Adj.* R^2	*F*	*p*
Finance	0.504	0.254	0.091	1.563	0.210
Household Chores	0.448	0.201	0.020	1.107	0.385
Communication	0.517	0.267	0.101	1.604	0.201
Planning and Recreation	0.383	0.146	-0.048	0.754	0.592
Transportation	0.660	0.435	0.307	3.389	0.020

df for all analyses = 2,27; N = 29

Table 10

Scores at Time 1 for Individual with Lowest LFQ Total Score at Time 2

Test	Score	*M*	*SD*
Spatial Span Forward	8	8.66	1.76
Spatial Span Backward	6	7.76	1.99
Block Design Raw	37	44.69	12.07
Benton-JOL_Correct	21	25.14	3.69
Digit_Span Forward_	11	10.69	1.97
Digit_Span Backward	8	7.17	2.12
CVLT Trials 1to5_	46	56.00	9.51
CVLT Short Delay	10	12.41	2.61
CVLT Long Delay	10	12.55	2.37
Biber Trial 1-5	79	145.62	33.96
Biber Short Delay	8	11.45	2.05
Biber Long Delay	8	12.59	1.86
WCST Failureto Maintain Set	0	0.83	0.97
WCST Pct. Persev.	13	13.79	8.79
WCST Number of Categories	6	5.79	0.41

Note: CVLT: California Verbal Learning and Memory Test; WCST: Wisconsin Card Sorting Test; WAIS: Wechsler Adult Intelligence Scales; WMS: Wechsler Memory Scale

Table 11

Scores at Time 1 for Individual with Lowest WQL-I Total Score at Time 2

Test	Score	*M*	*SD*
Spatial Span Forward	5	8.66	1.76
Spatial Span Backward	3	7.76	1.99
Block Design Raw	30	44.69	12.07
Benton-JOL_Correct	18	25.14	3.69
Digit_Span Forward_	10	10.69	1.97
Digit_Span Backward	4	7.17	2.12
CVLT Trials 1to5_	49	56.00	9.51
CVLT Short Delay	11	12.41	2.61
CVLT Long Delay	11	12.55	2.37
Biber Trial 1-5	111	145.62	33.96
Biber Short Delay	10	11.45	2.05
Biber Long Delay	11	12.59	1.86
WCST Failure to Maintain Set	0	0.83	0.97
WCST Pct. Persev.	8	13.79	8.79
WCST Number of Categories	6	5.79	0.41

Note: CVLT: California Verbal Learning and Memory Test; WCST: Wisconsin Card Sorting Test; WAIS: Wechsler Adult Intelligence Scales; WMS: Wechsler Memory Scale

Table 12

Scores at Time 1 for Individual with Slowest UPSA Domain Performance Speeds at Time 2 (Measured in Seconds)

Test	Score	*M*	*SD*
Spatial Span Forward	8	8.66	1.76
Spatial Span Backward	6	7.76	1.99
Block Design Raw	38	44.69	12.07
Benton-JOL_Correct	25	25.14	3.69
Digit_Span Forward_	9	10.69	1.97
Digit_Span Backward	8	7.17	2.12
CVLT Trials 1to5_	66	56.00	9.51
CVLT Short Delay	15	12.41	2.61
CVLT Long Delay	14	12.55	2.37
Biber Trial 1-5	119	145.62	33.96
Biber Short Delay	12	11.45	2.05
Biber Long Delay	12	12.59	1.86
WCST Failure to Maintain Set	3	0.83	0.97
WCST Pct. Persev.	16	13.79	8.79
WCST Number of Categories	5	5.79	0.41

Note: CVLT: California Verbal Learning and Memory Test; WCST: Wisconsin Card Sorting Test; WAIS: Wechsler Adult Intelligence Scales; WMS: Wechsler Memory Scale

APPENDICES

APPENDIX I

HUMAN SUBJECTS APPROVAL

UNLV
UNIVERSITY OF NEVADA LAS VEGAS

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: July 2, 2008

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

FROM: Office for the Protection of Research Subjects

RE: Notification of IRB Action
Protocol Title: **Longitudinal Study of Neuropsychological, and Functional Deficits in Adults with Bipolar Disorder**
Protocol #: 0805-2748

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 June 11, 2009. 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 June 11, 2009, it would be necessary to submit a **Continuing Review Request Form** *60 days* before the expiration date.

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

UNLV
UNIVERSITY OF NEVADA LAS VEGAS

Social/Behavioral IRB – Expedited 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: June 15, 2009

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

FROM: Office for the Protection of Research Subjects

RE: Notification of IRB Action by Dr. J. Michael Stitt, Chair
Protocol Title: **Longitudinal Study of Neuropsychological, and Functional Deficits in Adults with Bipolar Disorder**
Protocol #: 0805-2748

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 June 10, 2010.

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 June 10, 2010, 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.

APPENDIX 2

PHONE CONTACT PROTOCOL

BIPOLAR RESEARCH STUDY - CONTACT PROTOCOL

Date_____ ID#: _____ Researcher: _____

Contact Protocol Instructions:

Dial participant's phone number. When someone answers the phone say:

"Hi, this is Daniel Allen from UNLV. Is (*participant name*) there?"

1. (NO) If participant is NOT there say: **"Could you please have (*participant name*) give me a call? Again, my name is Daniel Allen and my phone number is 895-1379."**

    a. NO MESSAGE: say **"Is there a better time I could call when (*participant name*) might be there?"** (Record date/time for return call here: _____)

    OR **"Is there another number I could use to try to reach (*participant* name)?"** (Record number here: _____)

    b. **"Thank you so much for your time and assistance. Have a good day."** **A follow up call will be provided in three days if there has not been a return call from the participant. **

    c. IF AN ANSWERING MACHINE PICKS UP: **"This is Daniel Allen from UNLV calling for (*participant* name). Please call me back at 895-1379 at your earliest convenience. Thank you."**

2. (YES) If participant IS there, wait for the participant to get on the phone.

    a. DISCUSS THE CURRENT RESEARCH STUDY: **"Hi (*participant name*), my name is Daniel Allen, and I run the Neuropsychology Research Lab at UNLV. I am calling you because you previously participated in a research study of ours and had indicated that you would be interested in participating in future research studies. Well, we are actually conducting a new research study now that you may find interesting and may want to participate in. Would you like for me to tell you a little bit about it to see if you are interested?"**

i. If YES, provide a few details about the current study. Then say, **"Does this sound like something you'd be interested in doing?"**

1. YES: **"Well, why don't we schedule a time for you to come in and we can talk about the research in a little more detail? And let me say that by coming in to discuss the research, you are in no way committing to participation. You will still be free to choose not to participate. With that said, what days are better for you to meet to discuss the research?"** Go on to schedule meeting time and record here: Date: _____ Time: _____ Then say, **"Well (*participant name*), I truly appreciate your time. I'll plan on seeing you on (*date scheduled*) at (*time scheduled*). If you need to cancel or reschedule for any reason, or if you have any questions, feel free to call me at 894-1379. Have a great day!"** End phone call.

2. If the answer is *"No"*, see 2.a.ii (just below). End phone call.

ii. If NO, say **"Well, I appreciate your time. Would you like to be contacted in the future regarding other research studies, or would you like to be taken off of our list?"**

1. Regardless of answer, say **"Well (*participant name*), thank you for your time. Again, my name is Daniel Allen. Please feel free to contact me any time at 895-1379 if you have any questions or to update your information. Have a great day!"** End the phone call and indicate on contact form whether or not the individual would like to be contacted for future studies.

b. UPDATE CONTACT INFORMATION: **"Hi, (*participant name*), my name is Daniel Allen, and I run the Neuropsychology Research Lab at UNLV. I am calling you because you previously participated in a research study of ours and had indicated that you would be interested in participating in future research studies. Well, we don't yet have any research programs going on for which you would qualify as a possible participant, but since it has been several months since we were last in contact with you, I am calling to make sure that our contact information for you stays current and accurate. But first off, are you still interested in being contacted for possible participation in future research studies here in our lab?"**

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