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Working memory deficits in psychotic bipolar disorder: Trait marker for psychosis

Carol Randall
University of Nevada, Las Vegas

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WORKING MEMORY DEFICITS IN PSYCHOTIC BIPOLAR DISORDER:

TRAIT MARKER FOR PSYCHOSIS

by

Carol Randall

Associate of Arts
Rancho Santiago College
1992

Bachelor of Arts
University of Nevada, Las Vegas
2004

A thesis submitted in partial fulfillment
Of the requirements for the

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Department of Psychology
College of Liberal Arts

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University of Nevada, Las Vegas
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University of Nevada, Las Vegas

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Carol Randall

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Examination Committee Chair

Dean of the Graduate College

Examination Committee Member

Examination Committee Member

Graduate College Faculty Representative
ABSTRACT

Working Memory Deficits in Psychotic Bipolar Disorder: Trait Markers for Psychosis

By

Carol Randall

Dr. Daniel N. Allen, Examination Committee Chair
Associate Professor of Psychology
University of Nevada, Las Vegas

There is significant overlap in the symptom presentation and cognitive impairment found in individuals with bipolar disorder with psychotic features and in those with some subtypes of schizophrenia. Due to this overlap, debate regarding the existence and nature of a relationship between these disorders has been an ongoing and complicated one. Some continue to view these disorders as they are conceptualized in the current psychiatric diagnostic manual, as distinct and categorical in nature. Others have proposed an “affective-psychotic spectrum” with schizophrenia lying at one end of this spectrum, non-psychotic affective disorders lying at the opposite end of the spectrum, and schizoaffective and psychotic bipolar disorders falling near the middle of the spectrum. To better understand the relationship between these disorders, some studies have compared the neurocognitive profiles of bipolar disorder and schizophrenia. Because neurocognitive abilities are highly heritable and under strong genetic influence, deficits in these abilities can serve as trait markers or endophenotypes for bipolar disorder, as well as for schizophrenia. An overlap in the
neurocognitive deficits found in these disorders may therefore implicate similar genetic vulnerabilities.

Relatively few studies have compared the neurocognitive deficits found in individuals with bipolar disorder with psychotic features with those found in individuals with bipolar disorder without psychotic features. These studies strongly suggest that among individuals with bipolar disorder, those with psychotic features experience greater working memory impairment than do those with no history of psychotic features. In that working memory deficits have repeatedly been found in schizophrenia and other psychotic disorders, working memory deficits may serve as endophenotypes for psychosis in general, and the identification of such markers could provide important insight into whether bipolar disorder and schizophrenia are discrete conditions or fall along a continuum of severity. Identification of working memory deficits in bipolar disorder with psychotic features would thus provide some support for a continuum of rather than discrete conceptualization of these disorders.

In this study, we will use Baddeley and Hitch’s working memory model to investigate and interpret differential deficits in working memory processes in bipolar disorder with psychotic features and bipolar disorder without psychotic features. Taking into account the results of previous research, it is hypothesized that a significantly greater amount of impairment will be found by way of lower performance scores in bipolar individuals with psychotic features as compared to bipolar individuals without psychotic features on measures designed to assess working memory systems. Largest group differences are expected to be found on measures of central executive and
visuospatial sketchpad function, with smaller differences expected on measures designed to assess phonological loop function.
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CHAPTER 1

INTRODUCTION

Bipolar affective disorder (BP) is a severe and debilitating mental disorder characterized by affective, cognitive, and motor impairment, as well as by behavioral and psychosocial dysfunction. Individuals with BP typically experience recurrent and fluctuating cycles of major depression and mania, with intermittent periods of recovery, referred to as euthymia. Due to the phenomenological variability of BP, with course and presentation differing widely between individuals and across time, the disorder is often misdiagnosed and inadequately treated (Hirschfeld, Lewis, & Vornik, 2003; Lish, Dime-Meenan, Whybrow et al., 1994). Perhaps at the root of this problem is confusion and controversy regarding the correct conceptualization and classification of BP. This issue continues to be the topic of strong debate, with some conceptualizing a “bipolar spectrum” with many sub-classifications (Akiskal, 2002). In that psychotic episodes can be present during active affective episodes of BP and that affective episodes are often present during active episodes of some psychotic disorders, an alternative conceptual model, in which affective and psychotic disorders are seen as lying on an “affective-psychotic spectrum”, has garnered interest and mounting empirical support. According to this model, which suggests the existence of a common genetic basis for BP and schizophrenia, schizophrenia comprises one end of this spectrum, BP without psychotic
features comprises the opposite end of the spectrum, and schizoaffective and BP with psychotic features fall near the middle of this spectrum (Welner, Welner, & Leonard, 1977; Berrettini, 2000; Glahn, Bearden, Cakir et al., 2006).

In this study, we focus specifically on working memory performance, as this neurocognitive deficit is a putative marker for psychosis and has been viewed as an endophenotype for primary psychotic disorders. The identification of working memory deficits in BP with psychotic features that are not present in BP without psychotic features would go a long way toward supporting the notion that it is an intermediate condition lying towards the middle, BP without psychotic features lying at one end, and schizophrenia lying at the other end of a spectrum.

The main purpose of this study is to add to the literature and further understanding of the relationship between affective and psychotic disorders. A further aim is to clarify the ways in which psychoses potentially impact the deficits found in bipolar disorder. It is hypothesized that a greater amount of impairment will be found in BP with psychotic features relative to BP without psychotic features on measures designed to assess working memory systems and that the largest group differences will be found on measures of central executive and visuospatial sketchpad working memory function.
CHAPTER 2

LITERATURE REVIEW

Many of the neurocognitive impairments found in BP are thought to be associated with the affective dysregulation that is considered to be a core feature of the disorder. This is not surprising when we consider that the neural networks and brain structures essential to normal cognition overlap and are intricately interconnected with those utilized in the production and maintenance of affect and mood (Cabeza & Nyberg, 2000; Phan, Wager, Taylor, & Liberzon, 2002). Due to these interconnections, disturbances in the affective system in individuals with BP are thought to contribute to the broad range of cognitive and neuropsychological deficits found in the disorder, some of which persist even in euthymic or remitted states. These persistent neurocognitive impairments include deficits in executive function, attention, verbal memory, visual memory, visuospatial perception, psychomotor function, and speed of information processing (Bearden, Hoffman, & Cannon, 2001; Basso, Neel, & Lowery, 2002; Gourovitch, Torrey, Gold et al., 1999; Van Gorp, Altshuler, Dixon, & Theberge, 1999; Zubieta, Huguelet, Ohl et al., 2001).

In addition to having an impact on general cognitive processes, mood and affect are known to significantly influence attention and working memory processes. There is mounting evidence in the literature, which suggests the existence of working memory
deficits in BP across clinical states of the disorder, including remitted states (Martínez-Arán, Vieta, Reinares et al., 2004; El-Badri, Ashton, Moore et al., 2001).

According to one of Baddeley and Hitch's working memory models (see Figure 1), working memory is conceptualized as a multi-component cognitive system, which consists of a central executive and two sub- or slave systems: the phonological loop and the visuospatial sketchpad.

Figure 1. Structure of working memory

The phonological loop is thought to deal with auditory or phonological information that enters the loop automatically. This loop consists of a short-term phonological store, where auditory memory traces decay quite rapidly, and a rehearsal component, that facilitates revitalization of auditory memory traces (Baddeley & Hitch, 1974). In contrast, the visuospatial sketchpad functions to briefly store, rehearse, and manipulate visual and spatial information. It is thought to hold information about what is obtained visually and temporarily store details of that information (shape, color, spatial location,

1 Figure 1 taken from http://www.rashmisinha.com/graphics_mt/workingmemory.gif
movement, etc.) in memory. The visuospatial sketchpad is thought to comprise 3 separate components: a visual component, a spatial component, and a kinaesthetic component. The central executive functions as the control station for decision making in working memory (Baddeley & Hitch, 1974). The central executive plans, recruits and performs operations necessary for task completion. This component further functions to integrate incoming information and allocate lower-level processing to the visuospatial sketchpad and the phonological loop slave systems.

Function of the working memory and attentional systems are intricately connected, and some theorists view working memory as no more than a combination of short-term memory and controlled attention (Kane & Engle, 2003). Various studies have investigated this overlap between attention and working memory and the way in which it is demonstrated in the deficits found in BP. One such study found significant impairment in BP individuals on tasks of attentional set shifting and sustained attention processes of working memory (Clark, Iverson, & Goodwin, 2002).

Integral to attention and working memory is the inhibition response, which gives one the ability regulate inhibition and suppress attendance to irrelevant or unintended stimuli. This ability to inhibit attention is also thought by some to play a part in the emotional dysregulation as well as some of the cognitive deficits found in BP. Whereas studies have demonstrated that individuals with normal affective regulation tend to exhibit biases for environmental stimuli with positive emotional content and have better recall memory for, and greater accuracy and efficiency in the processing of information with positive emotional content (Boucher & Osgood, 1968), individuals with affective
disorders appear to have attentional and memory biases for environmental stimuli with negative emotional content (Kerr, Scott, & Phillips, 2005).

These biases for information with negative emotional content found in BP are viewed by some as stemming from defective central executive function, which causes individuals with BP to experience difficulty in blocking or inhibiting attentional focus on undesired stimuli in the environment (Mur, Portella, Martínez-Arán et al., 2007; Giakoumaki, Roussos, Rogdaki et al., 2006). An inability to regulate inhibition and attendance to stimuli with negative emotional content may cause a chain-reaction of sorts, in which individuals with BP experience difficulty suppressing intrusive negative cognitions. This in turn could cause miscalculations with regard to interpreting and understanding the meaning of later incoming stimuli, as much of this newer information is filtered through a negative cognitive lens.

A related theory regarding the processes that underpin attentional biases in BP is that defective central executive function and an inability to regulate inhibition causes working memory processes to quickly become overtaxed. In that working memory is a system of limited capacity and available resources, the interjection of salient affective content into working memory processes (as frequently occurs in individuals with affective dysregulation) can overburden the system. This has been explained in terms of Processing Efficiency theory in which performance is modulated by emotional states. According to this theory, emotional states cause increases in cognitive arousal and interfere with working memory resources, draining slave systems and central executive resource pools in BP (Fleck, Shear, & Strakowski, 2005).
While some studies have provided evidence that the working memory failure leading to attentional biases in BP are due to a malfunction in the visuospatial sketchpad or visual scanning system, others have provided evidence that refutes this assertion. In a recent study in which visuospatial sketchpad and central executive function were investigated in individuals with BP, researchers found evidence that higher order central executive deficits may underpin the deficits that lead to impaired performance of the visuospatial sketchpad. In this study, the BP group demonstrated significant impairment on Corsi Blocks Test (Spatial Span) performance and other more specific measures of executive function relative to the normal control group. The BP group did not, however, show significant impairment on performance of a visual memory task designed to minimally tax central executive function (Thompson, Hamilton, Gray, & Quinn, 2006).

These and similar findings highlight the difficulty in attempting to isolate aspects of working memory into separate and distinct cognitive structures as these sub-systems can share significant common variance. This is particularly true with regard to the central executive in that a malfunction of this control system can be demonstrated behaviorally as performance impairment on tasks that assess working memory slave systems. Further, each of the sub-systems within working memory utilizes various sub-processes, which share much variability with the other sub-systems.

Although few dispute the existence of working memory deficits in BP, these overlapping domains make it difficult to clearly discern the etiology, nature, and extent of these deficits in BP. Identification of the ways in which psychotic symptoms may augment and/or compound working memory impairment in individuals with BP is even yet more complicated. For these and other reasons, the impact that psychotic features
may have on the working memory processes of individuals with BP is not well understood. Nonetheless, adding to the literature in this regard is an important venture in that 50% or more of individuals with BP experience psychotic features at some point over the course of illness (Goodwin & Jamison, 1990).

Impact of Psychosis

Psychosis, by its strictest definition, refers to a state in which one experiences “delusions or prominent hallucinations, with the hallucinations occurring in the absence of insight into their pathological nature” (DSM-IV, 1994, p. 297). The psychotic disorders are chronic and severe and are characterized by a history of psychotic episodes. In individuals with schizophrenia, which is the most common type of psychotic disorder, a broad range of cognitive deficits are exhibited. These deficits include impairment in overall IQ, executive function, attention, memory, visuospatial abilities, psychomotor function, and language function (Fioravanti, Carlone, Vitale et al., 2005).

Various studies have identified significant working memory deficits in individuals with schizophrenia, and these studies suggest the presence of deficits in all three components of working memory in psychotic illnesses. Individuals with schizophrenia have been found to have marked phonological loop impairment, even when generalized cognitive deficits inherent in the psychotic disorders are taken into account (Fleming, Goldberg, Gold, & Weinberger, 1995).

Of special significance is the fact that various studies have found evidence that phonological loop and other working memory impairments are not only present in individuals with schizophrenia, but are also present in the unaffected family members of
these individuals, although to a less severe degree. One such study, in which individuals with schizophrenia and their first-degree, non-psychotic relatives were given the WAIS-III Digit Span Forward and Backward, an intermediate degree of impairment was found in auditory working memory in the unaffected family members (Conklin, Curtis, Katsanis, & Iacono, 2000).

Various other studies have also found significant visuospatial sketchpad impairment in individuals with schizophrenia (Park & Holzman, 1992), and some have suggested that these deficits may be potent trait markers for psychosis in general (Warrick, Wood, Phillips et al., 2006). As with phonological loop impairment, various studies have found evidence of visuospatial sketchpad deficits in unaffected family members of schizophrenic populations. In one study, in which monozygotic and dizygotic twin pairs discordant for schizophrenia were administered a battery of short- and long-term memory tasks, both monozygotic and dizygotic twin pairs demonstrated an intermediate level of impairment between their affected twins and healthy controls, with the monozygotic unaffected twins demonstrating a greater degree of impairment than the dizygotic unaffected twins (Cannon, Huttunen, Lonnqvist et al., 2000).

Multiple studies have also implicated central executive impairment as a vulnerability for those with psychotic illness. In that executive function is central to general cognition, deficits in this domain of working memory are associated with poorer outcomes and may at least in part be responsible for the cognitive fragmentation characteristic of schizophrenia and the psychotic illnesses (Leiderman & Strejilevich, 2004; Bilder, Goldman, & Robinson et al., 2000).
Of more pertinence to this study, are findings that implicate working memory deficits in schizoaffective disorder. Schizoaffective disorder and bipolar disorder are often similar in presentation and phenomenology, and oftentimes the only differentiating factor is the presence of psychosis occurring exclusively within a period of mood disturbance, as would be seen in bipolar disorder, but not in schizoaffective disorder (DSM-IV, 1994, p. 322). These and similar findings support the notion that working memory impairments may be linked to genetic risk for psychotic illness.

Although little research has investigated the impact of psychotic features in BP, there is evidence that psychosis is associated with greater symptom severity, increased morbidity, and earlier illness onset in BP (Tohen, Waternaux, & Tsuang, 2000). Studying specific effects of psychosis in individuals with affective and psychotic disorders presents many obstacles, however. Numerous studies, for practical reasons, have utilized inpatient populations, which are primarily made up of individuals with long histories of psychosis. In that psychotic illnesses are associated with significant morbidity and that these populations often have extended and prolonged psychopharmacological medication use, it can be difficult to differentiate impairments that are due specifically to the affects of psychosis from those that are primarily due to the affects of illness progression and/or medication use.

A number of recent studies have approached this difficulty in novel ways. One such study, in which cognitive functioning in first-break, never-medicated adolescents with psychosis were investigated, researchers assessed attention (using the Trail Making Test-A and the WAIS-III Digit Span test), memory (using a Serial Verbal Learning Task based on the California Verbal Learning Test), language (using the Controlled Oral
Word Association Test and the Boston Naming Test), executive function (using Trail Making Test-B, the Wisconsin Card Sorting Test, and the Stroop Task), perceptual motor-processing (using the Rey-Osterreith Complex Figure and the WAIS-III Block Design), and motor speed function (using the Finger Tapping Test). Though working memory was not specifically investigated, results were consistent with working memory impairment with the largest group differences being found on measures of executive function, attention, and memory (Brickman, Buchsbaum, Bloom et al., 2004).

In a similar study, investigators assessed cognitive impairment in high-risk populations thought to be in prodromal or pre-psychosis onset phases of illness. Subjects, who were assessed on various cognitive measures, were found to be more impaired with regard to global cognitive performance, with the largest group differences found on measures of executive function, working memory, attention, and verbal memory. Of note is the fact that subjects who later developed psychosis demonstrated significant impairment on measures of verbal memory relative to those who remained non-psychotic, while visuospatial functioning in these individuals appeared to remain relatively intact (Lencz, Smith, McLaughlin et al., 2005).

In contrast, in a recent review of cognitive and neuropsychological findings from high-risk studies, retrospective studies, and birth cohort studies researchers found evidence of visuospatial memory deficits that existed prior to psychotic illness onset. Investigators in this review assert from these findings that visuospatial memory deficits may be viewed as trait markers for psychotic illness (Brewer, Wood, Phillips et al., 2006). This assertion was supported by findings of another study in which individuals with schizophrenia, schizoaffective disorder, BP with psychotic features, and BP without
psychotic features were compared on measures of working memory performance. Although researchers found that impairment of performance on the Digit Span Backward subtest of the WAIS-III, which involves phonological loop as well as central executive function, was comparable in all the affective and psychotic disorders, results of the study indicated that those with psychoses were mildly impaired on Digit Span Forward relative to those without psychoses and healthy controls. Further, only those with a lifetime history of psychotic features, regardless of diagnosis, exhibited impairment with regard to visuospatial working memory (Glahn et al., 2006).

Other studies have produced divergent findings. In a recent study in which euthymic BP individuals with a history of psychosis, BP without a history of psychosis, and healthy controls were compared on measures of attention, executive function, verbal fluency, verbal memory, and auditory memory, researchers found that the Wisconsin Card Sorting Test- Categories Completed was the only measure on which those with a history of psychosis performed significantly worse than those without a history of psychosis. Researchers suggested that these results indicate that deficits in cognitive flexibility are potential trait markers for psychosis in BP (Bora, Vahip, Akdeniz et al., 2007).

Recent studies in which sensory gating deficits were investigated in individuals with BP with psychosis have produced interesting findings, and some of the findings implicate central executive dysfunction. Sensory gating is measured by way of auditory evoked potentials as well as startle reflex responses that are elicited subsequent to the presentation of intense stimuli. Normally, auditory evoked potentials and startle reflexes are attenuated when another stimulus briefly precedes the stimulus evoking the response.
(P50 gating and prepulse inhibition). These studies have demonstrated that this gating/inhibition is reduced in individuals with schizophrenia, their healthy family members, and in BP individuals in acute manic phases of the illness, especially in those with a history of psychotic features (Cadenhead, Swedlow, & Shafer, 2000). This finding has led some to speculate that impaired sensory gating, which constitutes a failure of the central executive and inhibition dysfunction, might reflect a general vulnerability and endophenotype for psychosis (Maier, Zobel, & Wagner, 2006).

According to a recent retrospective study, psychotic BP individuals may experience not only more cognitive impairment after development of psychotic symptoms, but they may also experience more impairment in prodromal stages than do those who never go on to develop psychosis (Sigurdsson, Fombonne, Sayal, & Checkley, 1999). Associated with these pervasive and chronic effects of psychosis is a decline in overall cognitive function and IQ. In a study in which manic, depressed and euthymic BP individuals were compared on cognitive performance, it was found that in conjunction with the inpatient population included in the investigation, those with BP with psychotic features had the lowest overall IQs, regardless of clinical state (Basso et al., 2002). Investigators in another study found that on measures of cognitive functioning, individuals with affective disorders with psychotic features performed as poorly as first-episode individuals with schizophrenia, while first episode BP and unipolar individuals without psychotic features performed comparable to normal controls (Albus, Hubmann, Wahlheim et al., 1996). These results suggest that the cognitive profile of BP with psychotic features may be more similar to that found in schizophrenia than to that of BP without psychotic features and that the presence or absence of psychotic features in BP
may have more impact on cognitive functioning than does diagnosis (Albus et al., 1996; Bearden, Hoffman, & Cannon, 2001; Goldstein, Shemansky, & Allen, 2005).

Considering the reviewed literature, the following hypotheses are made regarding the effects of psychosis on the components of working memory in patients with bipolar disorder.

1) Participants with bipolar disorder and a history of psychotic features will not differ from those without a history of psychotic features on tasks that assess the phonological loop.

2) Compared to participants with bipolar disorder and no history psychotic features, those who have a history of psychotic features will evidence more impairment on tasks that assess the visuospatial sketchpad.

3) Compared to participants with Bipolar disorder and no history of psychotic features, those who have a history of psychotic features will evidence more impairment on tasks that assess central executive functioning.

Establishing the existence of and more fully understanding the relationship between the affective and the psychotic disorders, if one truly does exist, is essential to gaining insight into common genetic vulnerabilities for these disorders. With such an understanding, inroads may be made with regard to earlier detection and treatment, and possibly prevention. It is hoped that this investigation will serve to bring us closer to that end; to bring us closer to a correct conceptualization of the bipolar disorders, further our understanding of the relationship between the affective and psychotic disorders, and potentially enable us to identify endophenotypes for psychosis. Further, in that working memory deficits, most particularly verbal memory and executive function impairment
(Green, 1996), are associated with less favorable functional outcomes for individuals with severe mental illnesses, it is hoped that this increase in understanding will, in the not-too-distant future, have important implications with regard to earlier and more affective diagnoses and treatment options for individuals with these debilitating disorders.
CHAPTER 3

METHODS

Participants

Participants for this study were part of an ongoing research protocol examining neurocognitive functioning in bipolar disorder. All of the participants recruited into this protocol were from the University of Nevada, Las Vegas and the community at large. For the current study, three groups were compared. These groups consisted of:

1) Twenty four subjects diagnosed with BP with psychotic features (defined as the presence of hallucinations or delusions), constituted the BP with psychotic features group (BP+).

2) Twenty two subjects diagnosed with BP without psychotic features constituted the BP without psychotic features group (BP-).

3) Thirty one healthy individuals with no history of psychiatric or neurological disorders constituted the normal control group (NC).

All subjects were between 18 and 65 years of age. Reasonable attempts were made to have approximately equal representation of gender in this study. All participants were required to provide informed consent and were required to have English as their primary language. Exclusion criteria for participation included:

1) A diagnosis of a chronic medical condition with known effects on CNS function.
2) Traumatic brain injury or other neurological disorder as determined by self report.

3) English as a secondary language as determined by self-report.

4) A current or recent (within past six months) diagnosis of a substance use disorder.

5) Current medication use (within the past week) that has known CNS function effects (with the exception of medications prescribed specifically for the treatment of BP).

6) A hearing impairment as determined by self report, hearing aid use, and a brief screener.

Individuals who had neurological disorders, medical conditions with known CNS affects, or were taking medications (other than medications for BP) with known CNS affects were excluded from the study in that conditions and substances with CNS affects have the potential to confound results making it difficult if not impossible to determine if performance is due to the affects of BP or the affects of the condition or medication.

Aside from these inclusion-exclusion criteria, individuals with a first-degree relative diagnosed with BP, MDD, or schizophrenia were excluded from the healthy control group. This exclusionary criterion was based on empirical evidence that suggests first-degree family members of individuals with affective or psychotic disorders may experience an intermediate level of impairment as compared to individuals without first-degree family members with these disorders and individuals with affective or psychotic disorders (Frantom, Allen, & Cross, 2007; Conklin et al., 2000).
Measures

Following is a description of the individual tests that were administered in this study.

Screening and diagnostic measures

The Structured Clinical Interview for DSM-IV

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al., 1997) is a semi-structured interview for diagnoses of DSM-IV Axis I psychiatric disorders and was used to establish all psychiatric diagnoses in the current study. The SCID-I was administered by clinicians that were trained in the DSM-IV diagnostic system (APA, 1994).

This instrument has been utilized in the diagnosis of both psychiatric and general medical patients and individuals in the community for the purpose of mental health surveys and research. The inpatient version of the SCID-I was utilized in this study, and all 12 modules were administered, including the screening module. The screening module is composed of 12 questions that are used to guide or elicit further administration of subsequent modules. Each item is rated on a scale of 1 to 3 (1 = symptom is absent, 2 = sub-threshold symptom, or 3 = symptom is present). The SCID-I has demonstrated fair to good reliability, achieving Kappa values as high as .98 for some diagnoses. Too, it has shown high validity for the diagnosis of schizophrenia, with good sensitivity (.89), specificity (.96), and agreement (.86) when compared to best estimate diagnoses made by psychiatrists on first-admission psychotic patients (Fennig et al., 1994).
Experience and Symptom measures

Hamilton Depression Rating Scale

The HDRS (HDRS; Hamilton, 1960, 1967) is a commonly used symptom rating scale for the evaluation of depressed mood, vegetative and cognitive symptoms of depression, and comorbid anxiety symptoms. It provides ratings on current DSM-IV symptoms of depression, with the exceptions of hypersomnia, increased appetite, and concentration/indecision. The HDRS has exhibited high internal consistency, and support for its construct validity was demonstrated by its pattern of correlations with other measures of depression, anxiety, and depression-relevant cognition. Factor analyses of the full 23-item and 17-item versions of the HDRS each yielded 4 factors, which accounted for 49% and 53% of the variance in participants' responses, respectively (Dozois, 2003). These results provide strong support for the HDRS as a reliable and valid instrument for the assessment of depression severity.

There are various versions of the Hamilton Depression Rating Scale, but the version used in this study is the 21-item scale, which was administered by trained clinicians. In this version of the HDRS, 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 as follows: 0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme symptoms. The three-point rating scale is structured as follows: 0 = absent, 1 = mild, 2 = obvious, distinct, or severe. On this scale, asymptomatic is characterized by an overall score of 6 or less with a continuum of severity thereafter.
Young Mania Scale

The Young Mania Scale (YMS; Young, Biggs, Ziegler, & Meyer, 1978) is a commonly used 11-item clinician administered rating scale to aid in the evaluation of mania symptom severity in individuals diagnosed with bipolar disorder. The rating of each item in the scale is based on the subjective report of an individual’s condition over the previous forty-eight hours, as well as behavioral observations of the clinician. Each item is rated on a 0 to 4 scale, (absent to overtly present) with the exception four items, which receive double weighting and are rated from 0 to 8. This scale was administered by trained clinicians who assigned severity ratings for each of the items based on personal interview. On this scale, an asymptomatic state is generally characterized by a score of 4 or less.

Neurocognitive measures

The tests utilized in this study assessed the following domains of working memory: central executive, visuospatial sketchpad, and phonological loop function. Measures were also administered to estimate premorbid and current IQ levels. The measures used are widely utilized research instruments and have been effectively used on multiple occasions in previous studies attempting to assess neuropsychological function in individuals with BP. Collectively, these measures served as a comprehensive neurocognitive test battery and can therefore constitute a representative index of working memory ability in the domains assessed. All measures were administered and scored in the appropriate standardized fashion through use of the testing manuals. Psychometric data of all tests are available in standard neuropsychological texts (Lezak, 2004).
All participants underwent the same battery of neurocognitive tests and received the following measures:

1) Vocabulary Wechsler Adult Intelligence Scale-III Subtest
2) Information Wechsler Adult Intelligence Scale-III Subtest
3) Block Design Wechsler Adult Intelligence Scale-III Subtest
4) California Verbal Learning Test-II
5) Digit Span Wechsler Adult Intelligence Scale-III Subtest
6) The Biber Figure Learning Test-Expanded
7) Spatial Span Wechsler Memory Scale Subtest
8) The Trail Making Test A and B
9) The Wisconsin Card Sorting Task

Premorbid and current IQ Estimates

Vocabulary, Information, and Block Design Subtests

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

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

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

*Phonological Loop*

**The California Verbal Learning Test**

The California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) is a clinical instrument that was designed to measure the way in which auditory learning tasks are solved, (the processes involved in performance of the task, the different strategies utilized, the errors demonstrated by a participant, etc.). Not only does the CVLT assess auditory recall and recognition abilities in general, but this task also serves to quantify the separate processes and components of auditory memory, such as auditory working memory, learning rate across trials, strategies utilized in auditory learning, serial position effects, consistency of item recall across trials, affects of proactive and retroactive interference, retention of auditory information over delays of varying length, and recall and recognition learning errors in auditory recall (Delis, Freeland, Kramer, &
Kaplan, 1988). In this task, participants are asked to learn a list of 16 common shopping list items on 5 consecutive trials (learning) and are then asked to recall and recognize these items following a delayed interval (memory). Recall measures involve both cued and free recall. Participants are verbally administered a series of 16 words over five immediate-recall trials. List 1, which is administered over 5 consecutive trials, consists of 4 words from each of four semantic categories (fruits, spices and herbs, articles of clothing, and household tools). Participants are then given a distracter list (list 2), which consists of 16 words belonging to the same semantic categories as list 1, after which they are asked to recall words from the original list in short delay recall trial. A cued recall trial is then administered wherein participants are asked to recall words from each of the four semantic categories. Following a twenty minute waiting period in which a task not involving auditory working memory is administered, participants are given a delayed recall trial and a second cued recall trial. Finally, a recognition trial, wherein participants are asked to identify words from the original word list (list 1) among 40 semantically related words, is administered. The CVLT list 1- Trial 1 and List 2 raw scores were used as dependent variables to assess phonological loop function as these sub-measures of the CVLT are affective measures of phonological store and rehearsal aspects of phonological loop function.

Digit Span

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

Visuospatial Sketchpad

The Biber Figure Learning Test- Expanded

The Biber Figure Learning Test- Expanded (BFLT-E) is a modification of the original Biber Figure Learning Test, (BFLT; Glosser et al., 1989) and is a test of recognition and recall of visuospatial stimuli in the form of geometric shapes. It is composed of 15 various geometric designs made up of simple shapes, such as circles, triangles, and squares. These fifteen designs are presented sequentially at a rate of one every 3 seconds. After the designs are presented, participants are asked to draw as many of the designs as can be recalled in any order desired. A task of interference is then introduced which is composed of figures different from those included in the 15 original design stimuli. This interference task is then followed by an immediate free recall condition. An unrelated task is then administered for 20-30 minutes, after which a delayed learning recall trial is introduced wherein verbal, non-visuospatial tasks are interjected into the condition. A recognition task is then introduced in which the participant is asked to recognize the original designs which are intermixed with distracter items. The reproduced designs are each scored on a scale of 0 - 3 according to the accuracy of the drawing.
The BFLT-E is generally considered to be a visual analog of the California Verbal Learning Test (Glosser et al., 2002) as both tests involve a series of five learning trials, a distracter or interference task, an immediate recall condition, a delayed recall condition, and a cued recall condition. The List 1 and Distracter list scores were utilized as dependent variables for the assessment of visuospatial sketchpad function as they are affective measures of visual and spatial aspects of this slave system in working memory.

Spatial Span

The Spatial Span Wechsler Memory Scale subtest (Wechsler Memory Scale, Wechsler, 1997) has a forward and a backward component, both of which consist of spatial pattern sequences that are presented to participants. In Spatial Span Forward, the experimenter points to block sequences of increasing difficulty and length one at a time. After each sequence, the participant is asked to point to the same blocks in the same sequence. In Spatial Span Backward, the participant observes the examiner point to a series of blocks of increasing length and difficulty but is then asked to point to the blocks in the reverse order of presentation. A total overall score is derived by adding the Spatial Span Forward score to the Spatial Span Backward score. The Spatial Span total score of participants was used as a dependent variable measure of visuospatial sketchpad function in this study. This score was used as it is a visuospatial analog to the Digit Span subtest of the WAIS-III.
Central Executive

Trail Making Test A and B

The Trail Making Tests A and B (TMT; Reitan, 1958) were utilized as measures of central executive function as they are designed to assess, among other things, an individual's cognitive set shifting ability. In Trails A, the participant is asked to connect a series of circles containing the numbers from 1 to 25 with a pencil as quickly as possible in numerical order. Similarly, in Trails B, the participant is asked to connect circles but to alternate from number to letter, with the circles numbered from 1 to 13 and the letters from A to L.

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

The Wisconsin Card Sorting Test

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

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

Subjects for the study were recruited from the community through private mental health practitioners interested in involvement in the study, mental health clinics in the community with an established relationship with the Department of Psychology at the University of Nevada Las Vegas, and various support groups within the community such as the National Alliance for the Mentally Ill (NAMI) and the Depression and Bipolar Support Alliance of Southern Nevada (DBSA). An informational flyer that provided contact information and a brief overview of the study was posted at various places on the University of Nevada Las Vegas campus as well as at various agencies in the community. In that symptomatology varies according to the subtypes of the disorder, separate flyer were utilized for recruitment of individuals with bipolar I disorder and bipolar II disorder, with each flyer highlighting the predominant symptoms of the target subtype (see Appendix III). Direct recruiting by way of case managers and mental health personnel was also employed in conjunction with participating community mental health agencies. Participants from the University of Nevada Las Vegas were recruited through the Psychology Department’s Subject Pool, on-campus mental health service providers, and through posted recruitment advertisements placed at various locations. Table 1 below contains a breakdown of the referral source for each group.
UNLV subject pool students received compensation of extra credit points or partial fulfillment of their course requirements, equivalent to one credit hour for each hour of participation. Participants who did not complete the entire study were compensated for the actual time spent participating. All other participants were compensated at the rate of $5.00 per hour of participation in the study, with a $30.00 final compensation given to those who completed the study in its entirety. Recruiting participants in this manner helped to ensure equal participation opportunity with regard to gender and ethnicity.

Potential participants were initially screened by way of a phone interview, which was conducted by a trained doctoral level student, in order to identify exclusionary demographic characteristics. Subsequent to the phone screening interview, participants who were found eligible for participation in the study completed an informed consent form. Included in Appendix II are all consent forms for a) individuals with BP and healthy individuals recruited from the community b) healthy individuals and individuals with BP recruited from UNLV. Prior to participation a trained researcher met individually with each participant to explicate the consent form and to ensure understanding of the requirements involved in participation. All potential participants were instructed to read the consent form and were given the opportunity to ask

### Table 1. Subject Referral Source by Group

<table>
<thead>
<tr>
<th>Referral Source (%)</th>
<th>BP+</th>
<th>BP-</th>
<th>NC</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNLV Flyer/Subject Pool</td>
<td>33</td>
<td>36</td>
<td>35</td>
</tr>
<tr>
<td>Community College</td>
<td>29</td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td>BP Support Group</td>
<td>29</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Therapist Referral</td>
<td>4.5</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Community Flyer</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Other (Personal Referral, etc.)</td>
<td>4.5</td>
<td>9</td>
<td>65</td>
</tr>
</tbody>
</table>
questions. Two consent forms were signed. One consent form was given to the participant and one was kept in a locked filing cabinet in the Neuropsychology Research Laboratory at UNLV. This process served to ensure that the privacy of participants was maintained and that participation was voluntary and under complete informed conditions. All other information pertaining to participants was identified by way of alpha numeric code to ensure subject anonymity. Participants in the study, as was explicated in the informed consent form, were given no information or feedback regarding test scores or test results. Raw data is accessible only to study personnel, including Carol Randall and Daniel Allen, as well as research staff as is necessary.

Following informed consent, all participants orally completed a demographic interview (included in Appendix II) with a trained administrator, after which participants underwent diagnostic interview and symptom screening procedures. All diagnoses were based on the results of this screening and interview supplemented by available medical records (upon participant record release consent form signature).

Following the screening and diagnostic interview, all participants were given the same battery of neuropsychological tests in a fixed order by the principal investigator or a trained research assistant/technician. All measures and tests were administered individually in a quiet, private room at the UNLV Neuropsychological Laboratory or at the respective mental health agency when the individual was unable to come to UNLV. The total test administration time was between 6 and 8 hours.
CHAPTER 4

RESULTS

Data Screening

Preliminary analyses were conducted prior to performance of the main analyses, and raw data from the various neuropsychological tests were inspected to ensure that assumptions for MANOVA were met. Descriptive statistics and box plots were carried out for each of the neuropsychological variables. Skewness and kurtosis were examined to ensure the existence normal distribution of variables, and box plots were utilized for the evaluation of potential outliers. Outliers were defined as scores lying 3.0 standard deviations above or below the mean. Upon doing this data screening, a number of variables were found to exceed the skewness and/or kurtosis criteria of $>\pm 1.0$. These variables included BFLT-E Trial 1, TMT-A, TMT-B, WCST Perseverative Errors, WCST Categories Completed, and WCST Failure to Maintain Set.

In that multiple variables were non-normally distributed, parametric and nonparametric MANOVA were utilized in order to simultaneously control for the violations of homogeneity of variance and normality, without altering the raw data. The nonparametric analyses were performed by converting the non-normally distributed dependent variable into ranked scores (Conover, 1998). Standard MANOVA and univariate analyses were then performed using the ranked variable scores, and these
results were subsequently compared to the results of the MANOVA using unranked scores to discern the presence of differences.
Preliminary Analyses

Following data screening, preliminary analyses were conducted to determine the existence of significant differences among the three groups (BP+, BP-, and NC) on variables that are known to have an impact on neurocognitive test performance, including age, years of education, premorbid IQ, and current IQ. Differences among the groups for sex and race were also examined. Likelihood-ratios were utilized for analysis of categorical variables and analysis of variance (ANOVA) was used for continuous variables, and these analyses were followed by post-hoc contrasts when overall significant differences were identified. The demographic characteristics and results of these analyses are presented in Table 2, Appendix I.

In all, 224 potential participants were prescreened by way of phone interview. Of that number, 34 were found initially eligible and were administered a more extensive demographic screening and the SCID-I to ensure eligibility and BP diagnosis. As is delineated in Table 3 below, of those that passed the initial phone screening interview, but were subsequently excluded, 18% could not be contacted after the initial screening or partial participation in the study, 41% had a diagnosis other than BP (MDD, Schizoaffective, etc.), 18% had a concurrent exclusionary psychological diagnosis (substance use disorder, etc.), 9% were in a current BP mood episode, 3% had an exclusionary medical condition (thyroid condition), and 11% were excluded for reasons other than those listed (relocated, etc.).
Table 3. Number and Nature of Participant Exclusions

<table>
<thead>
<tr>
<th>Reason for Exclusion</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis Other than BP</td>
<td>41</td>
</tr>
<tr>
<td>Could Not Contact after Initial Screening</td>
<td>18</td>
</tr>
<tr>
<td>Concurrent Exclusionary Psych Diagnosis</td>
<td>18</td>
</tr>
<tr>
<td>Current BP Episode</td>
<td>9</td>
</tr>
<tr>
<td>Concurrent Exclusionary Medical Condition</td>
<td>3</td>
</tr>
<tr>
<td>Other (Relocated, etc.)</td>
<td>11</td>
</tr>
</tbody>
</table>

Among those included in the final study, no significant differences were found among the groups for age, $F(2, 74) = 1.31, p = .28$, education, $F(2, 74) = .72, p = .49$ or current IQ $F(2, 74) = 2.27, p = .11$ (current IQ was calculated based on the WAIS-III Vocabulary and Block Design subtests). Additionally, likelihood-ratio analyses indicated non-significant differences for sex, likelihood-ratio (2) = 1.00, $p = .61$, and race, likelihood-ratio (12) = 13.18, $p = .36$.

Significant differences were found among the groups with regard to symptom ratings, as measured by the Hamilton Depression Rating Scale $F(2, 74) = 18.20, p < .001$ and the Young Mania Scale $F(2, 74) = 20.15, p < .001$. For both depression and mania, post hoc analyses indicated that both bipolar groups reported significantly more manic and depressive symptomatology than the controls, although they did not differ from each other. This finding is expected when comparisons are made between the healthy controls and bipolar groups. It is important to note that participants were carefully and thoroughly screened by way of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al., 1997) so as to prevent evaluation during a current mood episode and/or active psychosis.
Significant differences among the groups were also found with regard to premorbid IQ, $F(2, 75) = 13.22, p < .01$, which was based on WAIS-III Information and Vocabulary subtest score averages. Post hoc analyses indicated that premorbid IQ was significantly higher in the NC group relative to both bipolar groups, and the bipolar groups did not differ from each other. Therefore, premorbid IQ was used as a covariate in the main analyses to determine its potential impact on differences among the groups for the working memory measures.

Additional clinical and demographic characteristics of the individuals in the bipolar groups are presented in Tables 4 and 5. Tables include duration of illness, number of hospitalizations, and medication status.

Table 4. Clinical characteristics for the bipolar disorder sample.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of hospitalizations</td>
<td>2.11</td>
<td>2.81</td>
</tr>
<tr>
<td>Length of illness duration</td>
<td>16.33</td>
<td>12.02</td>
</tr>
</tbody>
</table>

Table 5. Medication status by group.

<table>
<thead>
<tr>
<th>Medication</th>
<th>BP+</th>
<th>BP-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood Stabilizers</td>
<td>79</td>
<td>36</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>63</td>
<td>32</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>54</td>
<td>50</td>
</tr>
<tr>
<td>Mood Stabilizers/Antipsychotics</td>
<td>58</td>
<td>14</td>
</tr>
<tr>
<td>Mood Stabilizers/Antidepressants</td>
<td>50</td>
<td>23</td>
</tr>
<tr>
<td>Antidepressants/Antipsychotics</td>
<td>38</td>
<td>18</td>
</tr>
</tbody>
</table>
Although mean illness duration was 16.33 years, individuals with bipolar disorder reported an average of only 2.11 lifetime hospitalizations. This, taken with the fact that the mean years of education for the combined BP groups was 14.54 years, most were employed or attending university, and their mean current IQ was 104.69, it is apparent that the bipolar groups were composed of high functioning individuals in comparison to those who are more severely affected by the disorder.
Analyses of the Main Hypotheses

After preliminary analyses were completed, multivariate analyses of variance (MANOVA) was utilized to test each of the three main hypotheses and to examine differences between the groups on the various neurocognitive measures. Separate MANOVA were performed for each component of the working memory system, including the phonological loop, visuospatial sketchpad, and the central executive. Test scores used to assess these three components served as dependent variables in the MANOVA and group membership (BP+, BP-, and NC) served as the between subjects factor. When overall significant differences were found among the groups on the MANOVA, univariate F tests and contrasts were used to further examine group differences on individual measures. Table 6 (Appendix I), contains descriptive statistics for the neuropsychological tests as well as results of the multivariate and univariate analyses and post-hoc tests.

In order to directly compare the performance of the groups on each of the three components of working memory, the neuropsychological tests were used to compute three separate composite scores, one for the visuospatial sketchpad, another for the phonological loop, and a third for the central executive. Composite scores were calculated by first converting raw test scores into z-scores using the mean and SD of our control group. Then, the average of the z-scores for measures within each of the three working memory components were calculated, resulting in three composite scores that are all on the same scale and provide a summary score of the individual tests used to assess each domain. More specifically, the Phonological Loop Composite score was computed by summing and averaging the z-scores for the CVLT- List A, Trial 1, CVLT
List B, and WAIS-III Digit Span total. The Visuospatial Sketchpad Composite score was computed by averaging the z-scores for the BFLT-E Trial 1, BFLT-E Distracter List, and WMS Spatial Span total. The Central Executive Composite score was computed by averaging the z-scores for the TMT-A, TMT-B, the WCST Perseverative Errors, WCST Categories Completed, and the WCST Failure to Maintain Set.
Hypothesis 1: Phonological Loop.

Participants with bipolar disorder and a history of psychotic features will not differ from those without a history of psychotic features on tasks that assess the phonological loop.

MANOVA revealed no significant difference among the three groups, $F(3, 72) = 1.08, p = .38$, on tests assessing the phonological loop (see Table 6, Appendix I).

In that data from the Digit Span Backward was found to be abnormally distributed, nonparametric MANOVA were performed in which ranked data were analyzed. Ranked data MANOVA results were found to be similar to and the pattern of performance did not differ from results of parametric analyses (see Table 7, Appendix I).

In that in the post hoc preliminary analyses premorbid IQ was found to be significantly higher in the NC group than in the BP groups, MANCOVA was utilized. As can be seen from Table 7 (Appendix I), these analyses revealed that results of analyses wherein premorbid IQ was used as a covariate were similar to results of MANOVA.

Subsequent contrasts of unranked data, in which premorbid IQ was not used as a covariate, indicated that the BP+ group performed significantly worse than the NC group on CVLT List B (contrast, $p < .019$).

Figure 2 presents a comparison of the standard scores for each of the tests used to assess the integrity of the phonological loop of each group. As can be seen from Figure 2, the BP+ group demonstrated more impairment than the BP- group, and both BP groups performed worse than the NC group, but these differences did not reach statistical significance.
Figure 2. Phonological Loop Performance of BP+, BP−, and NC groups

CVLT1 = California Verbal Learning Test- List A, Trial 1; CVLTB = California Verbal Learning Test- List B; DIGTot = Digit Span Total

Hypothesis 2: Visuospatial Sketchpad.

Compared to participants with bipolar disorder and no history psychotic features, those who have a history of psychotic features will evidence more impairment of tasks that assess the visuospatial sketchpad.

For Hypothesis 2, MANOVA revealed no significant overall difference among the three groups, \( F = 1.21 \) (3, 72), \( p = .30 \), on tests assessing the visuospatial sketchpad (see Table 6, Appendix I).

In that data from the BFLT-E, Trial 1 was found to be abnormally distributed, nonparametric MANOVA were performed in which ranked data were analyzed. Results
obtained by way of ranked data MANOVA were similar to results of unranked data MANOVA (see Table 7, Appendix I).

In that in the post hoc preliminary analyses premorbid IQ was found to be significantly higher in the NC group than in the BP groups, MANCOVA was utilized. As can be seen from Table 7 (Appendix I), results from these analyses were similar to those wherein premorbid IQ was used as a covariate.

Subsequent contrasts of unranked data in which premorbid IQ was not used as a covariate revealed a trend in which the BP- performed worse than the NC group on Spatial Span Total (contrast, \( p = .07 \)), though this difference did not achieve significance. Another interesting finding was that the BP+ group performed at a non-significant but slightly better level than did the BP- group on all measures within this domain, performing at an intermediate level between the BP- and NC groups (see Table 6, Appendix I).

*Figure 3* presents a comparison of the standard scores for each of the tests used to assess the integrity of the visuospatial sketchpad for each group. As can be seen from *Figure 3*, the expected pattern of performance was not achieved in that the BP+ group did not demonstrate impairment relative to the BP- group, with the BP groups performing in a very similar manner on all measures of this domain.
Hypothesis 3: Central Executive.

Compared to participants with Bipolar disorder and no history psychotic features, those who have a history of psychotic features will evidence more impairment of tasks that assess central executive functioning.

In the central executive domain, MANOVA revealed an overall difference in performance among the three groups, $F = 2.82 (10, 142), p = .003$. In that data from various measures within this domain were found to be abnormally distributed, nonparametric MANOVA were performed in which ranked data were analyzed. However, ranked data MANOVA and parametric test results were found to be similar (see Table 7, Appendix I).

In that in the post hoc preliminary analyses premorbid IQ was found to be significantly higher in the NC group than in the BP groups, MANCOVA was utilized.
However, as can be seen from Table 7 (Appendix I), results from these analyses were similar to those achieved by way of MANOVA.

Univariate analyses revealed that significant differences between the BP+ group relative to the other groups were demonstrated, with the BP+ group performing worse than the other groups on WCST Perseverated Errors, $F = 6.75$ (2, 74) $p = .002$, WCST Categories Completed, $F = 3.70$ (2, 74) $p = .029$, and WCST Failure to Maintain Set, $F = 5.06$ (2, 74) $p = .009$.

Subsequent contrasts of unranked data in which premorbid IQ was not used as a covariate indicated that the BP+ group performed significantly worse than the BP- and NC groups on WCST Perseverated Errors ($p = .004$ and $p = .001$, respectively), WCST Categories Completed ($p = .010$ and $p = .05$, respectively), and WCST Failure to Maintain Set ($p = .008$ and $p < .006$, respectively). No significant differences were detected between group performance on TMT-A and TMT-B.

*Figure 4* presents a comparison of the standard scores for each of the tests used to assess the integrity of the central executive for each of the three groups. In this figure, higher scores indicate more impaired performance. As can be seen from *Figure 4*, the expected pattern of performance was achieved on all measures with the exception of TMT-B, on which the BP+ group performed better than the BP- group.
Figure 4. Central Executive Performance of BP+, BP-, and NC groups

![Graph showing central executive performance](image)

TrailsA = Trail Making Test A; TrailsB = Trail Making Test B; WCSTPE = Wisconsin Card Sorting Test- Perseverative Errors; FailMain = Wisconsin Card Sorting Test- Failure to Maintain Set; CatComp = Wisconsin Card Sorting Test- Categories Completed.

The working memory composite scores are represented in Figure 5. Consistent with the results of the MANOVA, the largest group differences were found among the groups on the central executive composite. It is also apparent that the BP groups tended to perform more poorly than the NC group on all of the composites, although the central executive was the only one to reach statistical significance.
Figure 5. Comparison of Composite Scores for BP+, BP-, and NC groups.

Phono = Phonological Loop Composite score; VisuoSk = Visuospatial Sketchpad Composite score; CentralEx = Central Executive Composite score.
CHAPTER 5

DISCUSSION

The literature has been divided as to the nosological status of the affective and psychotic disorders. This division stems largely from the overlap in these disorders with regard to phenomenology and impairment, with BP with psychotic features and schizoaffective disorder sharing many of the features and deficits associated with both affective and psychotic disorders. Although working memory impairment has been implicated as a potential endophenotype for psychosis, there is still a lack of sufficient neurocognitive data with which these implications can be more definitively validated and illuminated.

The aim of this study was to investigate the impact that psychosis has on working memory in individuals with BP with the intent of identifying whether these deficits might serve as an endophenotype for psychosis in general. With these goals in mind, individuals with bipolar disorder with and without psychotic features and healthy controls were compared on measures intended to assess the three components of working memory, namely the phonological loop, the visuospatial sketchpad, and the central executive. Results are discussed relative to the three proposed hypotheses outlined in the literature.
In support of the first hypothesis, no significant differences were found between the BP+ and BP- groups with regard to the phonological loop domain overall. The BP-group performed at an intermediate level among the three groups on all phonological loop measures. The BP+ group did perform significantly worse than did the BP- group on the distracter list of the CVLT, but examination of the composite score for this domain revealed no significant differences between the BP groups.

Although various studies have identified phonological loop and auditory memory deficits in schizophrenic populations, (Lencz et al., 2005; Conklin et al., 2000), our findings are consistent with previous reports in which phonological loop and auditory memory function was found to not differ in BP populations with psychosis and without psychosis (Bora et al., 2007). There is strong evidence in support of phonological loop impairment in BP populations in general, but reports indicate that these deficits cut across the disorders and do not differentiate those with psychosis from those without psychosis.

For example, Glahn et al. (2006) compared groups with schizophrenia, schizoaffective disorder, and BP with and without psychosis on various domains of working memory function. They found that all groups were impaired on measures that assessed phonological loop function, but only those with a history of psychosis demonstrated impairment on measures of visuospatial sketchpad function. These findings were consistent, regardless of diagnosis. In a subsequent study, Glahn et al. (2007) compared BP groups with and without a history of psychosis on measures of processing speed, attention/vigilance, and various domains of working memory. Results revealed that those with a history of psychosis performed worse than those without a
history of psychosis only on measures of central executive and visuospatial sketchpad function. Performance on the WAIS-III Digit Span subtest did not differentiate those with psychosis from those without.

These findings corroborate results found in this domain and support the assertion that phonological loop deficits in BP, with and without a history of psychosis, may generally be less severe and more restricted than those more frequently found in schizophrenia.

The second hypothesis predicted differences would be found between BP+ and BP- groups such that those with a history of psychosis would evidence more impairment on tasks assessing the visuospatial sketchpad. Results demonstrated that hypothesis 2 was not supported in that the BP+ and BP- groups not differ in this domain. Although there were no significant differences found among the groups in general or between the BP+ and BP- groups as expected, the BP groups did perform worse than the controls. These findings demonstrate a trend consistent with a visuospatial sketchpad impairment that cuts across the disorder in general.

Various studies have been consistent with these results in identifying visuospatial working memory deficits in BP populations as a whole, (Bearden et al., 2001; Basso et al., 2002), with some even demonstrating such impairment in unaffected, first degree relatives of individuals with BP. In a study in which individuals with BP were compared to their unaffected first degree family members and healthy controls, the BP group and their first degree family members performed significantly worse than controls on measures of visuospatial/constructional ability, executive function, and motor function, with the first degree relatives performing at an intermediate level between the other two groups (Frantom, Allen, & Cross, 2007).
These findings are not completely consistent throughout the literature, however. In one study in which BP individuals were compared to healthy controls on various cognitive tasks, the BP group did not show significant impairment on performance of a visual memory task designed to minimally tax central executive function, suggesting that executive function impairment may underpin the deficits frequently demonstrated on many visuospatial memory measures (Thompson et al., 2006).

The literature is conflicting with regard to visuospatial working memory impairment in psychotic populations as well. In a study in which euthymic BP individuals with and without a history of psychosis were compared on measures of verbal learning and memory, sustained attention, psychomotor speed, executive function, and visuospatial abilities, researchers found differences between the BP groups only on measures of executive function, specifically cognitive flexibility as measured by the WCST Categories Completed (Bora et al., 2007).

Similar findings were demonstrated in another study in which individuals at high-risk for the development of psychosis (met criteria for attenuated positive symptoms) were tested on measures of attention, memory (verbal and visuospatial), motor speed, visuospatial processing, executive function, and language abilities. In this study, results revealed that visuospatial functioning was relatively spared in these individuals. These findings were demonstrated even on measures assessing visuospatial memory (Lencz et al., 2005).

Other studies have countered these findings, with some reporting that visuospatial sketchpad deficits differentiate psychotic from non-psychotic populations and identifying this impairment as a potential endophenotype for psychosis (Warrick et al.,
2006). Such results were found in a study referred to in the previous section wherein groups with schizophrenia, schizoaffective disorder, BP with psychosis, and BP without psychosis were compared on various working memory measures. In this study, researchers found that only those groups with a lifetime history of psychosis, regardless of diagnosis, demonstrated visuospatial sketchpad deficits as measured by a spatial delayed response task (Glahn et al., 2006). Without a thorough description of this visuospatial working memory measure (for which no reference was provided), however, it is difficult to discern whether other cognitive impairments (ex. executive function) may better explain the results found in this study.

A similar finding was suggested in a review article in which individuals at high-risk for psychosis were assessed on various working memory measures. In this review, it was revealed that impairments specific to high-risk individuals who later went on to develop psychosis were found only with regard to performance on the Wechsler Memory Scale Visual Reproduction subtest (Brewer et al., 2005). It is important to note that this task is not a pure measure of working memory and requires visual learning and memory, and visuospatial and constructional abilities. Thus, it may be that at least some of the inconsistency found across studies is task dependent, with those visual working memory tasks that place greater demands on executive function demonstrating greater impairment in these populations than those tasks that are more specific to the visuospatial sketchpad.

Although our findings are not inconsistent with some of the outstanding literature and may reflect a true lack of differential impairment with regard to visuospatial sketchpad function, it is possible that performance on the BFLT-E was confounded by
visuo-constructional deficits of some individuals within our BP sample. If such impairment was present, it could conceivably have made the task demands of even simple geometric shape reproduction difficult for these individuals. If this was the case, this difficulty could have made measurement of visuospatial sketchpad function less specific and potentially inaccurate. This same argument cannot be made with regard to the Spatial Span subtest, however, in that there is not a constructional aspect to this subtest; yet the pattern of performance among the groups on all measures within the visuospatial sketchpad domain fell in a similar pattern.

Another potential reason that visuospatial sketchpad impairment in the BP+ group was not found may be due to the level of psychosis severity and/or other sample characteristics of our BP+ group. This sample was relatively high functioning, had slightly more years of education than both the BP- and the NC groups, and had a somewhat higher current IQ than did the BP- group. These findings may simply indicate that visuospatial sketchpad deficits are more sensitive to severe psychosis or are rather an indicator of psychosis disease severity or chronicity. Thus, visuospatial sketchpad impairment may differentiate only those populations that have more severe and/or a longer history of psychosis than was represented by our BP+ group.

The third hypothesis, which concerned central executive functioning, was supported. Specifically, the overall pattern of performance among the groups was in the predicted direction, with the BP+ group demonstrating significant impairment overall in this domain relative to the BP- and the NC groups.

Examination of the various subtests comprised by this domain revealed that although not significant, the performance pattern of the groups on the TMT-A was in the expected
direction, with the BP+ group demonstrating a greater degree of impairment than the BP- group. The pattern of performance among the groups on the TMT-B was not, however, as expected. On this measure, the BP- group demonstrated more impairment than did the BP+ group, which performed at an intermediate level between the other two groups.

Although task demands placed on working memory during performance of the WCST overlap and co-vary with task demands of the TMT, not all task demands for these tests have commonality. Performance of the WCST utilizes various cognitive processes that are not employed or are employed to a lesser degree by the TMT. These processes include prolonged and sustained attention, performance monitoring (in which monitoring and interpretation of task cues are required to guide behavior), feedback integration, rule induction (in which one must consider, evaluate, and select from various rule options), and suppression of previous sorting rules. Results in this domain suggest that the neurocognitive processes that are taxed by the WCST may be more sensitive to psychosis than those demanded during task execution of the TMT.

The performance among the groups on all WCST variables was clearly consistent with our hypothesis and in harmony with the majority of findings reviewed in the literature. Moreover, the overall findings in this domain corroborate the results of numerous other studies reviewed. Our findings are particularly consistent with results reported by Bora, et al. (2007) in which individuals with BP with a history of psychosis were significantly more impaired on WCST Categories Completed relative to the non-psychotic BP group indicating that cognitive flexibility (central executive) impairment may be a trait marker for psychosis.
Taken together, our results support the assertion that central executive impairment is particularly susceptible to the affects of psychosis. The WCST is most commonly characterized as a measure of executive function, but it can also be conceptualized as a working memory measure in that the task requires an examinee to simultaneously store and use information, while continually processing new incoming information (Cohen and O’Reilly, 1995). In a recent study, older adults were assessed using the WCST and an updating working-memory task, for which factor analysis indicated the employment of two independent processes: a storage process and an updating process. The WCST sub-measures were found to be significantly associated with the “updating process” factor in which information is continually updated by working memory processes. It was suggested that this updating process factor is consistent with the tasks of the central executive (Doiseau & Isingrini, 2005). Various clinical populations experience difficulty in this regard on the WCST, and studies have consistently demonstrated that individuals with schizophrenia and other psychotic disorders are significantly impaired on this task (Glahn, 2003; Gold et al., 1997).

These findings indicate that the central executive is most impaired with regard to working memory in individuals with BP with psychotic features, while the phonological loop and visuospatial sketchpad account for only a very small portion of the variance between BP+ and BP- groups. Moreover, the fact that our findings in the central executive domain are of such a magnitude and that they so clearly differentiate the BP+ group in our study from the groups without a history of psychosis strongly suggests that central executive dysfunction may be an endophenotype for psychosis.
From a clinical perspective, results of this study have a number of significant implications. Deficits in neurocognitive function, particularly verbal memory and executive function impairment, are strongly associated with functional outcome measures in psychotic illness. Specifically, poor executive function and verbal memory performance are solid predictors of poor functional outcomes (greater psychosocial impairment, less favorable response to psychopharmacological and behavioral treatments, etc.) in individuals with schizophrenia, even more so than are symptoms.

In that significant central executive impairment is strongly implicated as an endophenotype for psychosis, understanding and effectively addressing this vulnerability could translate into important improvements in functional outcomes for psychotic populations. Although many of these findings have been indicated in studies primarily involving individuals with schizophrenia and other psychotic disorders, and in that BP is generally considered to be a less severe illness than schizophrenia, an important next-step to our findings would be to investigate whether working memory impairments, and other neurocognitive deficits, are predictive of functional outcomes in BP populations. There is some evidence in the literature to support this assertion (Martinez-Aran, Vieta, Torrent et al., 2007). An accurate neurocognitive profile for BP individuals (with and without psychosis) could be extremely beneficial with regard to improving functional outcomes.

Furthermore, the findings of this study are consistent with a spectrum conceptualization of the affective and psychotic disorders. In that at the present time, current nosology conceptualizes these disorders as distinct constructs that are clinically unique, having different and exclusive etiologies, findings that refute this
conceptualization may serve to bring us closer to a nosological redefinition. It is hoped that such a redefinition of the affective and psychotic disorders would account for common genetic susceptibilities that are suggested in studies such as this. It is anticipated that as we come closer to a more accurate nosology of the affective and psychotic disorders, our ability to diagnose and treat these illnesses will likewise be refined. The development of more appropriate psychopharmacological and behavioral interventions that target associated neurophysiological and neurocognitive deficits more specifically may become a reality.

With regard to future research, in that these findings implicate central executive deficits as potential endophenotypes in BP+, it is suggested that inconsistencies in the literature with regard to working memory deficits in BP may be the result of a failure of some studies to control for psychosis. In evaluating BP populations as a whole without taking into account the unique and powerful effects that psychosis may have on individuals sampled can confound overall findings. It is recommended that special care be taken to account for psychosis in future studies.

The challenges encountered in this study with regard to choosing appropriate assessment instruments and achieving accurate and specific measurement of the working memory domains highlight the difficulty that is met in this type of investigation. There is much overlap in the various components of working memory. Further, there is a lack of consistency or consensus within the field with regard to the instruments that best measure these constructs. A careful selection of assessment instruments on the part of researchers to ensure that measures are specific to the domain under investigation is
highly recommended. Standardization of measures across studies and within the field could also serve to reduce the variability that currently exists in research findings.

There were several factors that may have limited the findings in this study that are of note. Group sizes were small, which may have limited the strength of results. Also, the BP groups in our study varied with regard to prescribed psychotropic medications. Though this is expected when comparing different psychiatric populations, this factor makes the effects of medication on working memory among the groups difficult to evaluate. We cannot completely rule out, therefore, the possibility that psychotropic medications had a variable impact on group performance.

In summary, as these findings and those of similar studies continue to add to the mounting evidence that suggests working memory deficits may be potent genetic markers for psychosis, it is hoped that more accurate detection of these and other vulnerabilities will facilitate earlier and more affective intervention strategies and more favorable outcomes for individuals with these disorders. Perhaps one day, even preventing these debilitating illnesses will become a reality.
Table 2. Demographic characteristics for the BP+, BP- and NC groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>BP+ (n=24)</th>
<th>BP- (n=22)</th>
<th>NC (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>35.75</td>
<td>3.25</td>
<td>32.59</td>
</tr>
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</tr>
<tr>
<td></td>
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<td>0.39</td>
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<tr>
<td>Sex (% females)</td>
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<td>68.18</td>
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<tr>
<td>Race (%)</td>
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<tr>
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</tr>
<tr>
<td></td>
<td>BP+ (n=24)</td>
<td>BP- (n=22)</td>
<td>NC (n=31)</td>
</tr>
<tr>
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<td>Mean</td>
<td>SD</td>
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Table 7. Comparison of data analyses.

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<th>Premorbid IQ Covariate $F$</th>
<th>Parametric Data $F$</th>
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<td>0.94</td>
<td>0.38</td>
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<tr>
<td></td>
<td>$p$</td>
<td>0.10</td>
<td>0.47</td>
<td>1.08</td>
</tr>
<tr>
<td>Visuospatial Sketchpad</td>
<td>$F$</td>
<td>1.39</td>
<td>0.22</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>$p$</td>
<td>1.00</td>
<td>0.43</td>
<td>1.21</td>
</tr>
<tr>
<td>Central Executive</td>
<td>$F$</td>
<td>2.94</td>
<td>.02</td>
<td>2.82</td>
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<tr>
<td></td>
<td>$p$</td>
<td>.002</td>
<td>0.02</td>
<td>.003</td>
</tr>
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</table>
APPENDIX II

UNIVERSITY OF NEVADA, LAS VEGAS
INFORMED CONSENT FORM

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

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

Benefits of Participation: By participating in this study, you will gain a research participation credit for every hour of research participation. Participation time in this study is expected to be approximately 6 credits.

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

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

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

Voluntary Participation: Your participation in this study is voluntary. You may refuse to participate in this study or in any part of this study. You may withdraw at any time without prejudice to your relations with the university. You are encouraged to ask questions about this study at the beginning or any time during the research study.
Confidentiality: All information gathered in this study will be kept completely confidential. No reference will be made in written or oral materials that could link you to this study. All records will be stored in a locked facility at UNLV for at least 3 years after completion of the study. After this three-year period, all test materials will be destroyed.

Participant Consent:

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

________________________________________  __________________________
Name                                                Date

________________________________________  __________________________
Signature                                           Date
Witness
COMMUNITY OF LAS VEGAS, NEVADA
INFORMED CONSENT FORM

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

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

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______________________________  ________________________
Name                                      Date

______________________________  ________________________
Signature                             Date
Witness

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Demographic Questionnaire

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

1. Birth Date ______ / ______ / ______
   Month    Day   Year

2. Gender  Male  Female

3. What ethnicity do you identify with:
   ______ Asian Amer.    ______ American Indian/Alaska Native
   ______ African Amer.  ______ Hawaiian/Pacific Islander
   ______ Hispanic/Latino ______ Biracial
   ______ Caucasian      ______ Other: _______________________

4. Highest Level of Education Completed _________(Years of formal educ.) _____GED?

5. Marital Status: ______ Married    ______ Widowed    ______ Divorced
   ______ Remarried    ______ Separated    ______ Never married
   ______ Committed relationship
   If married, how many times have you been married? ________

6. Current Occupation _________________________________

7. How long have you been employed in this position? ____________________________

8. What is the source of your income? (Check all that apply)
   __ Paid employment          ______ Unemployment compensation
   __ Social Security Dis. Income (SSDI) ______ Retirement, investment or savings
   __ Supplemental Security Income (SSI) ______ Alimony or child support
   __ Veterans disability or pension benefits ______ General assistance
   __ Money shared by your spouse/partner ______ Money from your family
   __ AFDC                        ______ Other source: __________

9. Usual living arrangements (past 3 yr.):
   ______ With partner and children    ______ With partner alone
   ______ With children alone          ______ With parents
   ______ With family                   ______ With friends
   ______ Alone                         ______ Controlled environment
   ______ No stable arrangements        ______ Other ______________________
10. Who would you like to live with? (Check all that apply)

_______With partner and children
_______With partner alone
_______With children alone
_______With parents
_______With family
_______Alone
_______With friends
_______Controlled environment
_______No stable arrangements
_______Other________________

11. During the past four weeks, you lived primarily: (Check one)

_______in an apartment/home
_______at school/college
_______in a boarding home
_______in an institution (i.e. hosp.)
_______in a group home or halfway house
_______in jail/prison
_______homeless
_______Other________________

12. Where would you like to live: (Check one)

_______in an apartment/home
_______at school/college
_______in a boarding home
_______in an institution (i.e. hosp.)
_______in a group home or halfway house
_______in jail/prison
_______homeless
_______Other________________

13. Do you have any children?  Yes  No  How many children do you have? ______

14. Have you ever been homeless?  Yes  No

15. Do you have a twin?  Yes  No

16. Are you left handed, right handed, or ambidextrous?  Left  Right  Ambidextrous

HEALTH-RELATED QUESTIONS

17. Are you color-blind?  Yes  No

18. Do you have diabetes?  Yes  No

19. Is your vision corrected (glasses/contacts)?  Yes  No
   Are you wearing them now?  Yes  No

20. Do you have severe visual impairments, such as cataracts or glaucoma?  Yes  No

21. Do you have any hearing loss (hearing aid)?  Yes  No

22. Have you ever or do you now have seizures?  Yes  No

23. Have you ever had a head injury (e.g., automobile accident, fall, sports injury)?  Yes  No

24. Have you ever been unconscious?  Yes  No  If so, for how long? _______________
25. Do you have any medical conditions? **Yes** **No** *(please describe)*

26. Do you have any neurological disorders? **Yes** **No** *(please describe)*

27. Do you have a learning disability? **Yes** **No**
Has this been formally diagnosed? **Yes** **No** Diagnosis: _________________

28. Have you ever had any kind of brain surgery? **Yes** **No** If yes, type: _________________

29. Have you ever received psychosurgery? **Yes** **No**

30. Have you ever been hospitalized for a psychiatric/mental condition? **Yes** **No**
Date Location

31. Have you ever been hospitalized for a physical condition? **Yes** **No**
Date Location

(Patient group only)
32. How many months since your last mood episode: _________________
33. What type of mood episode was it? Depressed Manic Mixed Hypomanic

34. Have you ever seen a counselor, psychotherapist or other mental health professional?
**Yes** **No**

If yes, please describe dates and reason:
35. Do you smoke? Yes No
   a. Cigarettes? Yes No
   b. Cigars / Pipes? Yes No
   c. Chewing tobacco? Yes No
   d. How much do you smoke/chew per day? _______________________

36. When you were born...
   a. Were you born full term? Yes No Don't Know
      i. If premature, how many months was the pregnancy? _________________
   b. Were there any prenatal complications? Yes No Don't Know

(please describe) __________________________________________

   c. Was your mother exposed to anything during her pregnancy (e.g., disease, toxins, alcohol, etc.)? Yes No Don't Know
   d. Was your birth normal (e.g., head first, natural birth)? Yes No Don't Know
   e. Did your mother smoke when she was pregnant? Yes No Don't Know

FAMILY HISTORY QUESTIONS

The following questions concern your family. Please DO NOT list any specific names or identify any specific person in your answers.

37. Has anyone in your family seen a counselor or mental health professional? Yes No
(please describe) __________________________________________

38. Does anyone in your family have a mental disorder? Yes No

39. Do you have any first degree relatives (e.g., mother, father, brother, child) with a mental disorder? Yes No
   a. What is the disorder?
40. Do you have any second degree relatives (e.g., aunt, uncle, grandmother, grandfather) with a mental disorder? **Yes**  **No**
   a. What is the disorder?
      i. Schizophrenia **Yes**  **No**
      ii. Affective disorder **Yes**  **No**
      iii. Alcoholism/Substance Abuse (circle) **Yes**  **No**
      iv. Parkinsonism **Yes**  **No**
      v. Movement disorder **Yes**  **No**
      vi. Schizophrenia spectrum disorder **Yes**  **No**
      vii. Other

41. Please list any medications you are currently taking

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<th>Current Medications</th>
<th>Dosage</th>
<th>Date Started</th>
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**SUICIDE HISTORY**

42. Have you had thoughts of suicide in the past? **Yes**  **No**

43. Have you had thoughts of suicide within the last week? **Yes**  **No**

44. Have you had any suicide attempts? **Yes**  **No**  If yes, how many? ______

Please use the following lines to note the date and method of past suicide attempts:
Date Method

Suicide History Rating scale
1 – No history of any suicidal ideations
2 – History of suicidal ideation only, no self-injury
3 – Minor self-injury / suicidal gesture(s) only
4 – One serious suicide attempt either alone or in presence of prior ideation/self-injury/gestures
5 – More than one serious suicide attempt
Overall Rating: __________

**SUICIDE RISK ASSESSMENT**

Check and describe if present:

___ Yes ___ No Plan:
___ Yes ___ No Lethality:
___ Yes ___ No Availability Means to carry out the plan:
___ Yes ___ No Significant Loss:
___ Yes ___ No Substance Abuse:
___ Yes ___ No Family History of Suicide:
No Suicide Contract

I, ________________________________, agree to not kill myself, or cause harm to myself during the period of time from ________________ to ________________.

I agree to get enough sleep and eat well.

I agree to get rid of things that I could use to kill myself (guns, pills, etc.).

I agree that if I have a bad time and feel that I might hurt myself, I will call my counselor, ________________________________, at ________________________________.

I will also call the Suicide Prevention Center at 731-2990.

Signed: ________________________________

Witnessed: ________________________________

Date: ________________________________
APPENDIX III

UNLV
BIPOLAR
DISORDER
RESEARCH
STUDY

- To be eligible, you must be between the ages of 18 and 65, primarily English speaking and have a diagnosis of Bipolar disorder.

- Participants will be asked to do various tests, which will take approx. 6 hours, and will be compensated $5 per hour with a $30 bonus for completion of all testing.

- Please contact Christina at 217-5365 or UNLV.BipolarResearch@unlv.edu if you are interested or would like additional information.
UNLV
BIPOLAR
DISORDER
RESEARCH STUDY

- To be eligible, you must be between the ages of 18 and 65, primarily English speaking and have a diagnosis of Bipolar disorder.

- Participants will be asked to do various tests, which will take approx. 6 hours, and will be compensated $5 per hour with a $30 bonus for completion of all testing.

- If interested, speak to your case manager or email UNLVBiDolarResearch@yahoo.com for additional information.
DO YOU EXPERIENCE DEPRESSION??

• Are you between the ages of 18 and 65 and English is your first language?

• Do you sometimes get very depressed for periods lasting at least two weeks? Have you also had a period of time when you felt unusually energetic, had a decreased need for sleep, or felt like you could conquer the world?

• If so, we invite you to participate in our study. Please email us at UNLVBipolarResearch@yahoo.com or call Christina Armstrong at XXX-XXXX for additional information.
REFERENCES


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*Bipolar Disorders, 9*, 103-113.


VITA

Graduate College
University of Nevada, Las Vegas

Carol Randall

Home Address:
9828 Meandering Creek Court
Las Vegas, Nevada 89117

Degrees:
Associate of Arts, Liberal Arts, 1992
Rancho Santiago College, California

Bachelor of Arts, Psychology, 2004
University of Nevada, Las Vegas

Special Honors and Awards:
1992 The National Dean’s Honor List
1992 Graduated with High Honors
2000 Stan Fulton Honors Program Scholarship
2001 Stan Fulton Honors Program Scholarship
2001 Dee Smith Endowment Scholarship
2004 Dean’s Commendation Award
2004 Outstanding Graduate Recognition
2004 Graduated Summa Cum Laude and Department Honors Scholar
2003 The National Dean’s Honor List
2004 The National Dean’s Honor List
2005 Honors Convocation Ceremony Undergraduate Research Award
2006 Graduate & Professional Student Association Grant
2006 Jean Nidetch Women’s Center Re-Entry Scholarship
2007 Graduate College Summer Session Scholarship
2007 Ruth Faddis Kennedy Scholarship
2007 SLEAP- Nevada Student Incentive Grant
2007 Graduate & Professional Student Association Grant
2007 Graduate & Professional Student Association Research Poster Award
2008 SLEAP- Nevada Student Incentive Grant

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Publications:

**Refereed Articles**


**Book Chapters/Encyclopedia Entries**


**Refereed Abstracts**


Thesis Title: Working Memory Deficits in Psychotic Bipolar Disorder: Trait Marker for Psychosis

Thesis Examination Committee:

Chairperson, Dr. Daniel N. Allen, Ph.D.
Committee Member, Dr. Christopher Heavey, Ph.D.
Committee Member, Dr. Bradley Donohue, Ph.D.
Graduate Faculty Representative, Dr. Chad L. Cross, Ph.D., NCC, MAC, SAP, CCH, LADC