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Verbal and visual learning and memory deficits as trait markers for psychosis in bipolar disorder

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VERBAL AND VISUAL LEARNING AND MEMORY DEFICITS AS TRAIT
MARKERS FOR PSYCHOSIS IN BIPOLAR DISORDER

by

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Bachelor of Arts
Wake Forest University
2006

A thesis submitted in partial fulfillment
of the requirements for the

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THE GRADUATE COLLEGE

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ABSTRACT

Verbal and Visual Learning and Memory Deficits as Trait Markers for Psychosis in Bipolar Disorder

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The presence of neurocognitive deficits in the affective and psychotic psychiatric disorders (i.e., bipolar disorder with psychotic features, bipolar disorder without psychotic features, and schizophrenia) has been well documented, with such these deficits having been found to overlap across these diagnostic categories to a degree. Along with other types of evidence reported, these findings suggest that bipolar disorder and schizophrenia may not be isolated disorders as suggested by the current diagnostic criteria outlined in the DSM-IV (APA, 1994), but rather may be related disorders on a spectrum marked by bipolar disorder without psychosis on one end and by schizophrenia on the other end, with bipolar disorder with psychosis and schizoaffective disorder occupying the middle of the spectrum, an idea known as the spectrum hypothesis.

The purpose of this study was primarily to examine the presence of and, if relevant, severity of verbal and visual learning and memory impairments in individuals with bipolar disorder with and without psychotic features. A secondary purpose of this study was to examine, if present, the severity of these same neurocognitive impairments in individuals with schizophrenia, who were included as a validity check for the expected spectrum of performance across the groups. It was anticipated that impairments would be

identified that would not only provide support for the spectrum hypothesis, but would also differentiate between psychiatric disorders with and without psychotic features.

TABLE OF CONTENTS

ABSTRACT.....	ii
LIST OF TABLES.....	vi
LIST OF FIGURES	vii
CHAPTER 1 INTRODUCTION.....	1
CHAPTER 2 LITERATURE REVIEW.....	3
The Spectrum Hypothesis.....	3
Bipolar Disorder.....	14
Psychotic/Affective Disorders: Bipolar Disorder with Psychosis.....	23
Psychotic/Affective Disorders: Schizoaffective Disorder.....	30
Schizophrenia.....	32
Significance of Research.....	41
Conclusion	43
Research Aims and Study Hypotheses	49
CHAPTER 3 METHOD.....	51
Participants.....	51
Measures	53
Procedure	62
Data Entry and Analyses.....	65
CHAPTER 4 RESULTS.....	71
Data Screening.....	71
Preliminary Analyses.....	72
Data Transformations.....	84
Analyses of the Main Hypotheses.....	87
CHAPTER 5 DISCUSSION.....	107
APPENDIX 1 DEMOGRAPHIC QUESTIONNAIRE.....	127
REFERENCES	131
VITA.....	156

LIST OF TABLES

Table 1	Summary of Research Findings to Date Regarding Executive Function and Verbal Learning and Memory Performance in Bipolar Disorder	46
Table 2	Summary of Reasons for Exclusion from Study for the BP+, BP-, and NC Participants.....	65
Table 3	Memory Factors and Corresponding Variables	69
Table 4	Demographic Characteristics of the Groups	73
Table 5	Clinical Characteristics of the Groups	75
Table 6	Pearson Correlation Coefficients between Symptomatology at Time of Testing and Non-Strategy-Based Learning and Memory Variables.....	80
Table 7	Pearson Correlation Coefficients between Symptomatology at Time of Testing and Strategy-Based Learning and Memory Variables	81
Table 8	Comparison of the Bipolar I and Bipolar II Disorder Groups on Age and Education	82
Table 9	Results of the MANOVAs Comparing the Bipolar I and Bipolar II Disorder Groups on Non-Strategy-Based and Strategy-Based Learning and Memory Variables	83
Table 10	Spearman Correlation Coefficients between Medication Status and Non-Strategy-Based Learning and Memory Variables.....	85
Table 11	Spearman Correlation Coefficients between Medication Status and Strategy-Based Learning and Memory Variables.....	86
Table 12	Unranked and Ranked Scores for the SZ Group.....	88
Table 13	Unranked and Ranked Scores for the BP+ Group	88
Table 14	Unranked and Ranked Scores for the BP- Group	89
Table 15	Unranked and Ranked Scores for the NC Group.....	90
Table 16	Comparison of the Raw Scores of the Groups for CVLT and Biber Primacy, Middle, and Recency Regions	91
Table 17	Results of the MANOVAs	95
Table 18	Neurocognitive Performance of the Groups on Non-Strategy-Based Learning and Memory Variables	96
Table 19	Neurocognitive Performance of the Groups on Strategy-Based Learning and Memory Variables.....	101
Table 20	Results of the MANOVAs Comparing the Neurocognitive Performance of the Previous Substance Use Diagnosis and No Previous Substance Use Diagnosis Groups on Non-Strategy-Based and Strategy-Based Learning and Memory Variables.....	111

LIST OF FIGURES

Figure 1	Phonological Loop, Visuospatial Sketchpad, Central Executive, and Composite Scores for the Groups 29
Figure 2	Brief Psychiatric Rating Scale (BPRS) Factor and Total Scores for 78 the Groups
Figure 3	Non-Strategy-Based Verbal Learning and Memory Performance of the Groups as Measured by the California Verbal Learning Test 98
Figure 4	Non-Strategy-Based Visual Learning and Memory Performance of the Groups as Measured by the Biber Figure Learning Test-Extended..... 99
Figure 5	Strategy-Based Verbal Learning and Memory Performance of the Groups as Measured by the California Verbal Learning Test 103
Figure 6	Strategy-Based Visual Learning and Memory Performance of the Groups as Measured by the Biber Figure Learning Test-Extended 104

CHAPTER 1

INTRODUCTION

Comparisons between bipolar disorder and psychotic disorders such as schizophrenia have long been explored. Similarities between the disorders have been repeatedly noted, including the neuropsychological profiles of the disorders (e.g., Hoff et al., 1990), although some differences have been noted as well (e.g., Mojtabai et al., 2000). Furthermore, comparisons between the two disorders have demonstrated that despite their similarities, schizophrenia often tends to be associated with more severe premorbid impairment, including social withdrawal (e.g., McClellan & McCurry, 1999), as well as more severe neurocognitive impairments (Gruzelier, Seymour, Wilson, Jolley, & Hirsch, 1988; Mojtabai et al., 2000; Dickerson et al., 2004).

Much debate currently exists regarding whether bipolar disorder, schizoaffective disorder, and schizophrenia represent distinct diagnostic categories or would be better conceptualized as falling along a spectrum which is bound by affective disorder on one end and schizophrenia at the other, with schizoaffective disorder assuming a position intermediate to the other two (Averill et al., 2004). If these two disorders do fall along a spectrum, then a number of predictions could subsequently be made. For example, it would be expected that they share symptoms, as a number of studies suggest have suggested (e.g., Toomey, Faraone, Simpson, & Tsuang, 1998; Strakowski, 2003). Furthermore, it would be expected that there would be some instances of a change in diagnostic category (e.g., Laursen et al., 2005), as well as evidence of shared genetic vulnerability (Gershon et al., 1982; Bertelsen & Gottesman, 1995; Berrettini, 2000; Laursen et al., 2005; Ghaemi et al., 2008). Finally, shared neurocognitive deficits should

be identified if such a spectrum were to exist (Beatty, Jovic, Monson, & Staton, 1993; Albus, Hubmann, Walheim, et al., 1996; Goldstein, Shemansky, & Allen, 2005).

The current study investigated the hypothesis of shared neurocognitive deficits by comparing two patient groups (i.e., bipolar disorder with and without psychotic features) to normal controls on measures of verbal and nonverbal (i.e., visual) memory, which have been identified as key neurocognitive domains in both affective and psychotic disorders. Additionally, a number of secondary comparisons were made with patients diagnosed with schizophrenia to further examine the role of psychotic features in memory functioning, and thus to explore in more depth the idea that schizophrenia and bipolar disorder with psychotic features are not isolated from one another, but are rather connected by some underlying factor perhaps associated with psychosis.

CHAPTER 2

LITERATURE REVIEW

The Spectrum Hypothesis

There are a number of various possible symptom combinations that warrant a diagnosis of bipolar disorder (BP), and thus a great deal of heterogeneity in the expression of the disorder. Specifically, there are more than 5 billion combinations of symptoms that can lead to a diagnosis of bipolar disorder when all of the specifiers listed in the DSM-IV are considered (Lieberman, Peele, & Razavi, 2008). As a result, many have posited the idea that the diagnostic criteria should be changed – that perhaps we are conceptualizing BP and its associated symptoms in an incorrect manner (e.g., Lieberman et al., 2008). In fact, the Diagnostic Guidelines Task Force has suggested that schizoaffective disorder be dropped from the DSM-V altogether (Ghaemi et al., 2008), while others have advocated a move away from the Kraepelinian dichotomy of affective and psychotic disorders (Craddock & Owen, 2005). One proposal which has resulted from research regarding the presence of psychosis and corresponding neurocognitive deficits in BP is the possibility of a spectrum of disorders, such that affective disorders and psychotic disorders are not separate diagnostic categories, but rather may represent a spectrum of disorders bounded on one side by schizophrenia, and on the other by BP, with schizoaffective disorder and bipolar disorder with psychotic features assuming intermediate positions on the spectrum (Laursen et al., 2005; Lake & Hurwitz, 2007; Cheniaux et al., 2008; Peralta & Cuesta, 2008; Ghaemi et al., 2008). And yet some others disagree (e.g., Evans et al., 1999). Nevertheless, a change in diagnostic criteria could allow for more flexibility in making diagnoses (i.e., by using such diagnostic terms

as “psychosis-spectrum illness” or “mood-reality disorder”), and thus address the conflict inherent in drawing distinctions between disorders that share many symptoms in common. It may also assist in avoiding damage done to the therapeutic relationship when clinicians and psychiatrists are uncertain which diagnosis to make and/or when there is a change in diagnoses over time (Craddock & Owen, 2005). Such a change could also help accurately determine which treatment approach(es) may be most appropriate for individuals, as different treatment approaches may vary in efficacy according to different diagnoses. If the hypothesis that a spectrum exists is correct, then several subsequent hypotheses can be posited, including: 1) temporal instability of diagnoses that are made based on the current DSM-IV nomenclature; 2) the presence of evidence supporting shared genetic vulnerability; 3) an overlap in symptoms, epidemiology, and clinical expression; and, 4) patterns of neurocognitive deficits that suggest similarities in brain dysfunction across diagnostic categories.

Temporal Instability of Diagnostic Categories

With regard to temporal instability of diagnoses, if the spectrum hypothesis is valid, then there should be reports of individuals who were originally diagnosed with schizophrenia, schizoaffective disorder, or an affective disorder (i.e., BP or major depressive disorder), but then later received one of the other diagnoses due to emerging or worsening (or, in some cases, resolving) symptomatology. These changes could reflect true psychiatric changes within the individual, factors related to disease course, individual differences in the diagnostic decision-making of clinicians, or some combination of these factors. However, these changes could also result from the use of faulty diagnostic criteria, with the error lying in the separation of the two disorders (i.e.,

BP and schizophrenia) rather than the consideration of the two disorders as lying on the same spectrum. Such findings have, in fact, been reported. Laursen and colleagues (2005), for example, found that more than half (specifically, 51% of females and 58% of males) of a large group of individuals who were diagnosed with schizoaffective disorder had been previously diagnosed with either BP or schizophrenia. Moreover, studies have repeatedly reported evidence of a subgroup of individuals with schizophrenia (as many as approximately 70% of cases examined) whose path towards a psychiatric diagnosis originally began with depression (Koreen et al., 1993; Høfner, Löffler, Maurer, Hambrecht, & an der Heiden, 1999). At least one other study, however, found diagnoses of schizophrenia, bipolar disorder, and schizoaffective disorder to be relatively stable over time (McClellan & McCurry, 1999). Research in this area has thus yielded mixed results.

Shared Genetic Vulnerability

A second subsequent hypothesis regards shared heritability, such that there should be some overlap in genetic vulnerability to schizoaffective disorder in groups of individuals with BP and schizophrenia. Berrettini (2000) reported evidence from a review of studies indicating that first-degree relatives of individuals with BP have been found to have an increased risk of bipolar I disorder, bipolar II disorder, schizoaffective disorder, and recurrent unipolar disorder, while other studies have found first-degree relatives of individuals with schizophrenia to have an increased risk for schizophrenia, schizoaffective disorder, and recurrent unipolar disorder. Taken together, this evidence does suggest a common increase in risk for schizoaffective disorder in the first-degree relatives of both individuals with BP and individuals with schizophrenia. Additionally,

genetic linkage studies have found several susceptibility loci which are common for both BP and schizophrenia, as well as several which are unique to these disorders (Berrettini, 2000; Baum et al., 2008). Overall, after reviewing the evidence Berrettini (2000) suggests that bipolar and schizophrenia share similarities, especially in individuals' genetic susceptibility to developing either of the disorders.

Furthermore, Laursen and colleagues (2005) examined the prevalence rates of BP, schizophrenia, and schizoaffective disorder in the citizens of Denmark who had been born after 1952. Participants' individual and family histories and diagnoses were examined, and cumulative incidence rates calculated. For BP, there was a 3.36% cumulative incidence of the disorder when there was a family history of hospitalization due to BP (as opposed to a 0.31% cumulative incidence when there was no such history), a 2.88% cumulative incidence of the disorder when there was a family history of schizoaffective disorder (as opposed to a 0.32% cumulative incidence when there was no such history), and a 1.20% cumulative incidence of the disorder when there as a family history of schizophrenia (as opposed to a 0.32% cumulative incidence when there was no such history). For schizoaffective disorder, there was a 1.84% cumulative incidence when there was a family history of schizoaffective disorder (as opposed to a 0.16% cumulative incidence when there was no such history), a 1.47% cumulative incidence when there was a family history of bipolar disorder (as opposed to a 0.16% cumulative incidence when there was no such history), and a 1.16% cumulative incidence when there was a family history of schizophrenia (as opposed to a 0.16% cumulative incidence when there was no such history). Finally, for schizophrenia, there was a 6.11% cumulative incidence when there was a family history of schizophrenia (as opposed to a 0.88%

cumulative incidence when there was no such history), a 3.64% cumulative incidence when there was a family history of schizoaffective disorder (as opposed to a 0.92% cumulative incidence when there was no such history), and a 3.22% cumulative incidence when there was a family history of bipolar disorder (as opposed to a 0.91% cumulative incidence when there was no such history). Overall, these results indicate that there is an increase in risk for developing each of these disorders (i.e., BP, schizoaffective disorder, and schizophrenia) when there is a family history of any of the disorders as compared to when there is no such family history, thus suggesting an overlap in genetic vulnerability among the disorders.

Similarly, Angst, Frey, Lohmeyer, and Zerbin-Rüdin (1980) followed a group of individuals with BP ($n = 95$) and their first-degree relatives ($n = 617$) for 16 years and found an risk of schizophrenia ($1.9 \pm 0.6\%$) and schizoaffective disorder ($1.5 \pm 0.5\%$) in the families of the BP group as compared to the normal population. These increased risks, however, were slight and not statistically significant.

Tsuang (1991) also collected diagnostic information from the first-degree relatives of a large group of individuals suffering from either schizophrenia ($n = 200$), BP ($n = 300$), unipolar depression ($n = 225$), or schizoaffective disorder ($n = 57$). The morbidity risks for the first-degree relatives of the patients were reported as follows: for the first-degree relatives of individuals in the schizoaffective disorder group, there was a 6.6% morbidity risk for schizophrenia and a 13.0% morbidity risk for affective disorder; for the first-degree relatives of individuals in the schizophrenia group, there was a 5.5% morbidity risk for schizophrenia and a 10.1% morbidity risk for an affective disorder; and, for the first-degree relatives of individuals in either of the affective disorder groups, there

was a 2.2% morbidity risk for schizophrenia and an 18.1% morbidity risk for an affective disorder. These are greater than the reported morbidity risk statistics for BP (1.8%; Weissman, Kidd, & Prusoff, 1982) and schizophrenia (0.3%; Baron, Gruen, Kane, & Asnis, 1985); no such data could be located for schizoaffective disorder. These similarities in increased morbidity risk across disorders are further indicative of the possible overlap in genetic heritability among individuals suffering from these disorders.

Gershon and colleagues (1982) similarly reported that the relatives of individuals with schizoaffective disorder were found to have significantly greater prevalence rates of affective disorders (including schizoaffective disorder) and schizophrenia than the relatives of individuals with other Axis I (e.g., generalized anxiety disorder, obsessive-compulsive disorder, etc.) or Axis II (e.g., antisocial personality disorder, etc.) disorders.

Similarities in Symptoms, Epidemiology, and Clinical Expression

Similar to shared heritability, individuals with these disorders should demonstrate some degree of shared epidemiology and symptomatology if the spectrum hypothesis is true. Regarding shared epidemiology, Berrettini (2000) and Maier, Zobel, & Wagner (2006) each identified commonalities between BP and schizophrenia in prevalence rate, age of onset (typically before age 25, but not prior to puberty), the presence of psychosis in a subset of individuals, the improbability of a full remission once a diagnosis has been made, increased risk of suicide, familial aggregation, and degree of heritability as measured and estimated from twin studies (approximately 65% for BP versus approximately 50% for schizophrenia). Marneros, Roettig, Roettig, Tschardtke, and Brieger (2008) similarly found that only approximately one-third of a group of individuals with BP ($n = 182$) had a history of only mood episodes; the remaining two-

thirds reported a history of at least one schizophreniform or schizoaffective episode, thus providing further evidence suggesting that BP lies on a spectrum with schizoaffective disorder and schizophrenia.

Furthermore, if these psychiatric disorders are related, then other clinical features, should also be similar at least for subgroups of patients in the different diagnostic categories. In this vein, Angst, Sellaro, Stassen, and Gamma (2005) reported that 50% of a group of individuals with BP studied both retrospectively and prospectively initially met criteria and/or received a diagnosis of unipolar depression. Similarly, Hünner and colleagues (2005) found that, when interviewed retrospectively, 83% of a group of individuals hospitalized for schizophrenia had had at least one major depressive episode in their lifetime. Moreover, the most common initial symptom of schizophrenia was a depressive mood, followed by the presence of negative symptoms and functional impairment. In fact, both the schizophrenia group and a comparison unipolar depression group reported prodromal symptoms of depression, including nervousness/restlessness (occurring in 88.3% of the schizophrenia group and 81.5% of the depression group), anxiety (occurring in 88.1% of the schizophrenia group and 81.5% of the depression group), difficulties in thinking/concentration (occurring in 93.8% of the schizophrenia group and 96.9% of the depression group), disturbed appetite and/or sleep (occurring in 93.8% of the schizophrenia group and 98.5% of the depression group), irritability (occurring in 65.4% of the schizophrenia group and 68.5% of the depression group), and dissocial behavior (occurring in 15.3% of the schizophrenia group and 14.6% of the depression group).

Similarly, Maj, Pirozzi, Formicola, Bartoli, and Bucci (2000) examined the reliability and validity of the diagnosis of schizoaffective disorder as compared to schizophrenia and schizophreniform disorder. All participants were diagnosed based on DSM-IV criteria (APA, 1994) and were diagnosed a second time 2 years later by a psychiatrist who was blind to the previous diagnosis. The diagnosis of schizoaffective disorder was found to be unreliable, as the symptoms upon which the schizoaffective disorder diagnoses were based could also have been considered to be indicative of the presence of either a mood episode or schizophrenia.

Patterns of Neurocognitive Deficits

Finally, if the spectrum hypothesis is accurate, research comparing BP, schizoaffective disorder, and schizophrenia would be expected to yield evidence of neurocognitive impairments which are more severe, if not unique, in individuals diagnosed with psychiatric illnesses with psychotic features as compared to those without psychotic features. However, results of such research have been mixed, as some have found no evidence of such differences (Miller, Swanson-Green, Moses, & Faustman, 1996).

Conversely, Goldstein, Shemansky, and Allen (2005) compared the neuropsychological performance of groups of males with schizophrenia ($n = 63$) and schizoaffective disorder ($n = 20$). The schizoaffective disorder group and the subgroup of individuals with paranoid schizophrenia exhibited significantly less overall neurocognitive impairment than did those with undifferentiated and residual schizophrenia. More importantly, the researchers suggested that the neuropsychological profile of a subgroup of individuals with schizoaffective disorder may resemble that of

individuals with non-psychotic major depressive disorder and/or BP. While these findings are by no means definitive, they are a step in the direction of support for the spectrum hypothesis, such that schizoaffective disorder seems to epitomize a disorder which falls between schizophrenia and BP on the spectrum.

Beatty, Jovic, Monson, and Staton (1993) similarly evaluated groups of individuals with schizophrenia ($n = 13$) and schizoaffective disorder ($n = 13$), with no significant difference in medication use between the two groups, as well as a group of normal controls ($n = 20$) and found both similarities and differences in the cognitive impairments of the schizophrenia and schizoaffective groups. Specifically, both groups were found to be significantly impaired as compared to the normal controls in the domains of attention, problem solving, and verbal and nonverbal fluency, with no significant differences in performance between the groups. Regarding verbal learning and memory, however, the two groups performed somewhat differently. While both groups demonstrated significant impairment in the area of verbal recall, but not in that of recognition, the schizophrenia group exhibited significantly more rapid forgetting than either of the other two groups. The results of the study therefore suggest that relative verbal learning and memory impairments may be a distinguishing factor between individuals with schizophrenia and those with schizoaffective disorder, with patterns of neurocognitive impairment being similar in other neurocognitive domains for the two groups.

McClellan, Prezbindowski, Breiger, and McCurry (2002) also compared the neuropsychological profiles of groups of adolescents who had been diagnosed with schizophrenia ($n = 27$), bipolar disorder ($n = 22$), or psychosis not otherwise specified (n

= 20). Participants were administered a neuropsychological battery which included measures of intelligence, executive function, verbal learning and memory, visual learning, and visual motor integration. All three psychiatric groups were found to be significantly impaired in the areas of attention and verbal learning and memory. No significant differences were found between any of the groups in any of the neurocognitive domains, suggesting that the neurocognitive impairments accompanying schizophrenia and bipolar disorder may be very similar in at least some neurocognitive domains.

Albus, Hubmann, Walheim, and colleagues (1996) also compared the neuropsychological performance of a group of individuals suffering from first-episode schizophrenia ($n = 27$), a group of individuals suffering from either first-episode unipolar depression ($n = 10$) or first-episode BP ($n = 17$), some with psychotic features ($n = 11$) and some without ($n = 16$), as well as a group of normal controls ($n = 27$). Results indicated that all three psychiatric groups performed significantly worse than the control group in the areas of verbal learning and memory. Interestingly, the affective disorders with psychosis subgroup performed no differently than the schizophrenia group in the neurocognitive domains of visual motor processing and attention, while the affective disorders without psychosis subgroup performed no differently than the normal control group.

Finally, Smith, Barch, and Csernansky (2009) compared the neuropsychological performance of groups of individuals with either schizophrenia ($n = 72$) or a psychotic mood disorder (i.e., schizoaffective disorder or bipolar disorder with psychotic features; $n = 25$) to a group of normal controls ($n = 72$). Participants were assessed in the neurocognitive domains of crystallized intelligence, working memory, episodic memory,

and executive functioning. Both psychiatric groups were found to be significantly impaired as compared to the normal controls in the areas of working memory, episodic memory, and executive functioning. Furthermore, there were no significant differences between the psychiatric groups in these domains, suggesting similar neuropsychological impairments in the schizophrenia, schizoaffective, and bipolar groups. With regard to intelligence, the schizophrenia group was found to be significantly impaired as compared to both the psychotic mood disorder and normal control groups, who in turn performed similarly to one another.

On the other hand, Reichenberg and colleagues (2008) did find differences in the neuropsychological profiles of individuals with schizophrenia versus other psychotic disorders. Specifically, the researchers administered a neuropsychological battery of eight neurocognitive domains (i.e., general verbal ability, verbal declarative memory, visual declarative memory, abstraction-executive function, attention and processing speed, simple motor skills, visual processing, and language ability) to groups of individuals diagnosed with schizophrenia ($n = 94$), schizoaffective disorder ($n = 15$), bipolar disorder ($n = 78$), and major depressive disorder ($n = 48$). Results indicated that all four psychiatric groups were significantly impaired in the neurocognitive domains of verbal and visual declarative memory, executive function, and attention and processing speed. The schizophrenia group, however, demonstrated significantly greater impairment across all of the domains, suggesting that schizophrenia may be accompanied by more severe cognitive deficits, at least in the neurocognitive domains examined in this study.

If the spectrum hypothesis is valid, there should also be observed differences in neurocognitive impairment between individuals suffering from disorders with and

without psychotic features, as well as similarities in neurocognitive impairment in disorders with psychotic features. Glahn, Bearden, and colleagues (2006), for example, evaluated working memory performance in groups of individuals with schizophrenia ($n = 15$), schizoaffective disorder ($n = 15$), BP with psychotic features ($n = 11$), and BP without psychotic features ($n = 15$), as well as a group of normal controls ($n = 32$). As compared to normal controls, all patient groups demonstrated significant impairment on Digit Span Backward. Furthermore, the psychosis groups (i.e., the BP with psychotic features, schizoaffective, and schizophrenia groups) were found to be significantly impaired on both Digit Span Forward and the spatial delayed response task (DRT). Group comparisons indicated no significant differences in neuropsychological performance between the BP with psychotic features and schizoaffective groups, or between the schizoaffective and schizophrenia groups, suggesting similar working memory deficits in the three psychosis groups.

The Spectrum Hypothesis: Conclusion

Overall, the results of diagnostic, genetic, epidemiological, clinical and neurocognitive studies support the hypothesis that affective disorders are better conceptualized as lying along a spectrum (as opposed to discrete diagnostic entities). For BP, the results also indicate that the presence of psychosis is an indicator of more severe neurocognitive impairment, at least in the area of working memory, as compared to the neurocognitive impairments observed in individuals with psychiatric diagnoses without concomitant psychotic features.

Bipolar Disorder

Characteristics of Bipolar Disorder

Bipolar disorder (BP) is a debilitating mood disorder with a community lifetime prevalence of 0.4-1.6% as reported by the DSM-IV (APA, 1994). Similarly, a recent epidemiological study reported a lifetime prevalence rate of 1.0% for bipolar I disorder and 1.1% for bipolar II disorder, and a 12-month prevalence rate of 0.6% and 0.8% for the disorders, respectively (Merikangas et al., 2007). Lifetime prevalence estimates from other countries have ranged from 0.5% to 5.1% in such areas as The Netherlands, Europe, Australia, and Hungary (Lewinsohn, Klein, & Seeley, 1995; Szádóczy, Papp, Vitrai, Ríhmer, & Füredi, 1998; Ten Have, Vollebergh, Bijl, & Nolen, 2002; Regeer et al., 2004; Goldney, Fisher, Dal Grande, Taylor, & Hawthorne, 2005; Pini et al., 2005), with Hungary reporting the highest lifetime prevalence at 5.1% (Szádóczy et al., 1998).

BP is a severe mental disorder which is often accompanied by significant psychosocial and occupational impairment, and for which hospitalization is often necessary (Mansell & Pedley, 2008). BP is characterized by the occurrence of manic, major depressive, and/or mixed mood episodes. While the presence of a single manic or mixed episode necessitates a diagnosis of BP, the typical BP patient experiences affective oscillations between depressive and manic episodes, often with interepisode periods of euthymia.

Manic episodes are primarily characterized by periods of euphoria and/or irritability accompanied by a combination of other symptoms, including feelings of grandiosity, a decreased need for sleep, an increase in speech (in both amount and speed), racing thoughts, distractibility, an increase in goal-directed activity, inappropriate

involvement in activities which may lead to dangerous and/or painful consequences, and in some cases, psychosis (APA, 1994). Symptoms must occur simultaneously for at least a week, unless hospitalization is necessary to regulate symptoms. As many as 70% of manic episodes may be severe (as defined by a Young Mania Scale rating of ≥ 25), with the majority of the remaining episodes being classified as mild (as defined by a Young Mania Scale rating of 9-14) to moderate (as defined by a Young Mania Scale rating of 6-10; Merikangas et al., 2007).

Conversely, major depressive episodes are characterized by periods of depressed mood and/or anhedonia accompanied by a variety of co-occurring symptoms, including significant weight loss or weight gain, hypersomnia or insomnia, psychomotor agitation or psychomotor retardation, fatigue, feelings of worthlessness, excessive or inappropriate guilt, diminished ability to think or concentrate, indecisiveness, recurrent thoughts of death, plans for suicide, and/or suicide attempts (APA, 1994). A review by Goodwin and Jamison (1990) reported a lifetime suicide rate of 19% in individuals suffering from “major mood disorders”, which included major depressive and bipolar disorders.

Mixed episodes may also occur during the course of bipolar I disorder and are marked by symptoms of depressed and manic episodes co-occurring within a one-week period (APA, 1994). Research on the neurocognitive deficits associated with mixed episodes is extremely limited.

A diagnosis of bipolar I disorder is made once a manic or mixed episode has occurred. Bipolar II disorder, on the other hand, is diagnosed when a depressive episode and a hypomanic episode have occurred. Thus, bipolar II disorder is characterized by oscillations between depressive episodes and hypomanic episodes, which are similar to

manic episodes but are characterized by attenuated symptoms that are shorter in duration, do not include symptoms of psychosis, do not cause significant social or occupational distress, and do not require hospitalization. Similar to bipolar I disorder, bipolar II disorder is also generally accompanied by interepisode periods of euthymia. One of the primary differences between the subtypes of bipolar disorder is that individuals with bipolar II disorder seem to demonstrate less severe neuropsychological impairments than do individuals with bipolar I disorder, although findings are inconclusive in this regard (Dittmann et al., 2008; Simonsen et al., 2008).

Neurocognitive Deficits Associated with Bipolar Disorder

In addition to the mood symptoms required to warrant a diagnosis of bipolar disorder, research has indicated that neurocognitive deficits often accompany the disorder irrespective of the subtype (e.g., Dickerson et al., 2004), with some deficits present as early as the first hospitalization (Gruber, Rosso, & Yurgelun-Todd, 2008). The presence of neurocognitive deficits in individuals with BP has led many researchers to hypothesize that structural brain deficits are present in such individuals which reflect the noted neurocognitive deficits.

The right hemisphere of the brain has historically been associated with BP, with the earliest such hypotheses being formulated by Flor-Henry (1976; 1983), who hypothesized the presence of right hemispheric dysfunction in such individuals after noticing a verbal-performance IQ split. It thus follows that deficits in the neurocognitive domains of visuospatial processing and memory have traditionally been considered to be characteristic of bipolar disorder (Flor-Henry, 1976, 1983). Subsequent studies have yielded mixed results, with some research being reported which has found support of

right hemispheric dysfunction in affective disorders (e.g., Wexler, 1980; Taylor, Redfield, & Abrams, 1981), and other research being reported which has not found evidence in support of this hypothesis (e.g., Calev, Korin, Shapira, Kugelmass, & Lerer, 1986; Newman & Silverstein, 1987). More recent research specifically investigating the right hemisphere hypothesis via the evaluation of performance of individuals with BP on visuospatial memory tasks has also yielded mixed results (Bearden, Hoffman, & Cannon, 2001).

Many studies of neurocognitive deficits in BP have grouped together individuals in depressive, manic and mixed episodes with patients who were euthymic, sometimes making little or no distinction between the episodes when evaluating neuropsychological functioning. These studies have identified neurocognitive deficits in the neurocognitive domains of executive functioning (Fleck, Shear, Madore, & Strakowski, 2008; Gruber et al., 2008; Simonsen et al., 2008), memory (Gruzelier, Seymour, Wilson, Jolley, & Hirsch, 1988), nonverbal learning and memory (Gruzelier et al., 1988), verbal learning and memory (Henry, Weingartner, & Murphy, 1973), and attention (Simonsen et al., 2008).

Manic episodes. Multiple studies have also investigated the neurocognitive deficits associated with specific mood episodes. Individuals in a current manic episode, for example, have been found to suffer from impairments in the area of verbal learning and memory, which has, in fact, also been found to be significantly more impaired during manic episodes than during periods of nonmania (Henry, Weingartner, & Murphy, 1971).

Furthermore, BP individuals in a current manic episode have been found to demonstrate more widespread and severe cognitive impairments as compared to those in either a current major depressive episode or euthymic state, especially in the areas of

executive functioning (Dixon, Kravariti, Frith, Murray, & McGuire, 2004), working memory, and problem solving skills (Sweeney, Kmiec, & Kupfer, 2000).

Major depressive episodes. The neurocognitive deficits that often accompany major depressive episodes have been examined in individuals suffering from unipolar depression and include verbal learning and memory impairments, possibly due to a deficit in the ability to encode information in an organized fashion – a deficit which resembles impairments commonly observed in individuals with Alzheimer’s disease (Weingartner, Cohen, Murphy, Martello, & Gerdt, 1981).

Periods of euthymia. Researchers have also investigated neurocognitive deficits during periods of euthymia, with the idea that these deficits may be trait markers of BP and not associated specifically with periods of affective dysregulation. Support for the hypothesis that there are such persisting neurocognitive deficits has been somewhat inconsistent (Fleck, Shear, Madore, & Strakowski, 2008). Nevertheless, the identification of stable deficits during periods of euthymia may in turn help identify vulnerability markers, thus potentially aiding in the development of screening tools for vulnerability to BP. Studies evaluating individuals with BP have found deficits during periods of euthymia, including in the neurocognitive domains of verbal learning and memory (Atre-Vaidya et al., 1998; van Gorp, Altshuler, Theberge, Wilkins, & Dixon, 1998; van Gorp, Altshuler, Theberge, & Mintz, 1999; Altshuler et al., 2004; Martínez-Arán, Vieta, Colom et al., 2004; Thompson et al., 2005; Robinson et al., 2006; Martínez-Arán et al., 2007; Martino et al., 2008), attention (Dickerson et al., 2004; Martínez-Arán, Vieta, Colom et al., 2004; Thompson et al., 2005; Arts, Jabben, Krabbendam, & van Os, 2008), nonverbal (i.e., visual) learning and memory (Glahn, Barrett et al., 2006; Arts et

al., 2008), verbal fluency (Atre-Vaidya et al., 1998; de Almeida Rocca et al., 2008) oral language (Dickerson et al., 2004), visual organization and reasoning (Atre-Vaidya et al., 1998), visuospatial processing (El-Badri, Ashton, Moore, Marsh, & Ferrier, 2001) and recognition memory for patterns and spatial locations (Rubinsztein et al., 2000; Thompson et al., 2005), immediate and delayed memory (Dickerson et al., 2004), psychomotor functioning (Thompson et al., 2005), spatial orientation (Atre-Vaidya et al., 1998), mental processing speed (Arts et al., 2008), and executive functioning (van Gorp, Altshuler, Theberge, Wilkins et al., 1998; Ferrier, Stanton, Kelly, & Scott, 1999; Altshuler et al., 2004; Martínez-Arán, Vieta, Colom et al., 2004; Thompson et al., 2005; Robinson et al., 2006; Martínez-Arán et al., 2007; Arts et al., 2008; Martino et al., 2008). At least one study, however, found deficits in executive functioning to improve during extended periods of euthymia, despite a continued impairment in visual memory during such periods (Rubinsztein, Michael, Paykel, & Sahakian, 2000). Similarly, evidence of neurocognitive deficits in the areas of visual and verbal memory have been found in a group of generally euthymic BP individuals (Frantom, Allen, & Cross, 2008; Savitz, van der Merwe, Stein, Solms, & Ramesar, 2008).

Neuroimaging studies have also identified structural and functional brain abnormalities that underlie these neurocognitive deficits, with the structural abnormalities observed in individuals with BP including lateral ventricular enlargement (Pearlson et al., 1984) and, in a group of males diagnosed with BP, larger caudate volumes (Aylward et al., 1994). For a review of such studies and for more in-depth information regarding structural abnormalities in individuals with BP, see Bearden, Hoffman, and Cannon (2001).

Verbal and Visual Learning and Memory in Bipolar Disorder

As previously mentioned, verbal learning and memory deficits have been studied extensively in individuals with bipolar disorder. At least one study, in fact, reported evidence of a specific genetic variation, specifically of the COMT gene on chromosome 22q11, that is both common in bipolar I disorder and associated with the verbal memory deficits observed in individuals with BP (Burdick et al., 2007). Furthermore, reduced frontal, posterior temporal, cingulate and occipital cerebral blood flow (CBF) has been noted in individuals with BP who also demonstrated impaired verbal learning and memory (Benabarre et al., 2005). Not only have such deficits been repeatedly reported, but some studies have found that verbal learning and memory is affected to a greater degree than other neurocognitive areas in individuals with BP. Martínez-Arán, Vieta, Reinares and colleagues (2004), for example, examined 108 individuals with BP, who were either currently in a major depressive episode ($n = 30$), in a manic or hypomanic episode ($n = 34$), or euthymic ($n = 44$), as well as normal control participants ($n = 30$). Results indicated that, overall, individuals with BP were significantly impaired as compared to the normal control participants, especially in the areas of executive functioning and verbal learning and memory, though they were also found to be impaired in the areas of attention, verbal fluency, and nonverbal learning and memory. There were also significant differences within the BP group in verbal learning and memory as measured by the California Verbal Learning Test. Specifically, while all BP individuals demonstrated significant impairments in relation to normal controls in short- and long-delay free recall and long delay cued recall. However, only those who were in a current

episode were found to be significantly impaired in the area of recognition as compared to normal controls; those who were euthymic performed similarly to normal controls.

A similar study, performed by Basso, Lowery, Neel, Purdie, and Bornstein (2002), compared a group of normal controls ($n = 31$) to individuals with BP who were either in a major depressive episode ($n = 25$), a manic episode ($n = 37$), or a mixed episode ($n = 24$) at time of testing. Results indicated that the bipolar group as a whole was significantly impaired compared to the normal control group in the domains of verbal learning and memory, executive functioning, speed of information processing, and fine motor skills. When the BP group was compared according to type of mood episode, however, no differences in degree of impairment were noted, thus suggesting that the neuropsychological profile demonstrated by individuals suffering from a mood episode is similar regardless of the type of episode (Basso et al., 2002).

Bearden and colleagues (2006) further explored the presence and nature of verbal learning and memory impairments in a group of individuals with BP ($n = 49$; 8% were currently euthymic, 29% were in a major depressive episode, and 33% were in a mixed, hypomanic or manic episode; the remaining 30% had mild to moderate symptomatology at time of testing) as compared to a group of matched normal controls ($n = 38$). The BP group was found to demonstrate significant verbal learning and memory impairment in relation to the normal controls with no significant differences in performance within the BP group according to type of current episode. Additionally, the nature of these impairments and the specific errors made suggested an encoding deficit in the group as evidenced by the fact that, while there was no significant difference between the two groups in number of words learned on trials 1 and 2 of the CVLT, the BP group was able

to recall significantly fewer words on trials 3 through 5 as compared to the normal controls, with the discrepancy growing more evident with each subsequent trial. Furthermore, the BP group's performance was significantly below that of the normal controls in number of words recalled on short- and long-delay free and cued recall. Nevertheless, the BP group forgot no more words than did the control group between the short- and long-delay tasks, thus again suggesting that the deficit was one of encoding. Another study reported very similar findings, but with a group of individuals with BP who were all currently euthymic at time of testing ($n = 30$; Deckersbach et al., 2004).

Evidence of visual learning and memory impairments have also been reported to be present in individuals suffering from BP, although findings have yielded mixed results. Martínez-Arán, Vieta, Reinares and colleagues (2004), for example, found evidence of visual memory impairment in a group of individuals with BP ($n = 108$; approximately 27.8% of whom were depressed, 31.5% manic or hypomanic, and 40.7% euthymic at time of testing) as compared to a group of normal controls ($n = 30$). The presence of such impairments, however, was found to be dependent on mood state and on severity. Specifically, only those who were acutely ill demonstrated impairments in visual delayed recall, and only those who were currently in a major depressive episode were impaired in demonstrated visual immediate recall. Furthermore, Altshuler and colleagues (2004) found a group of males diagnosed with BP ($n = 40$), all of whom were euthymic at time of testing, to perform worse than a group of normal controls ($n = 22$) in the neurocognitive domains of verbal memory and executive functioning. Furthermore, the BP group performed similarly to a group of males diagnosed with schizophrenia ($n = 20$) in the domain of verbal learning and memory, and significantly better than the

schizophrenia group in executive functioning. A subgroup of the BP participants, however, exhibited no impairments in executive function, suggesting that some individuals with BP may have spared executive function.

Furthermore, research has demonstrated a relationship between visual learning and memory deficits and the co-occurring presence of a genetic vulnerability to BP. Specifically, Frantom, Allen, and Cross (2008) found that healthy first-degree relatives of individuals with BP ($n = 19$) were significantly impaired in the domain of visual learning and memory as compared to a normal control group ($n = 19$). Such a finding suggests that, similar to impairments in verbal learning and memory, visual learning and memory deficits may be trait markers for the presence of BP.

Psychotic/Affective Disorders: Bipolar Disorder with Psychosis

Characteristics of Bipolar Disorder with Psychosis

In addition to mood symptoms, BP is sometimes accompanied by psychotic features in the form of delusions and/or hallucinations (APA, 1994), with one large-scale study reported a history of psychosis in 61% of a group of patients who had been hospitalized for either an affective disorder or schizoaffective disorder (Angst, Sellaro, Stassen, & Gamma, 2005). Psychosis within BP has been associated with a more severe course of illness (APA, 1994; Zubieta, Huguelet, O'Neil, & Giordani, 2001), especially in terms of more residual symptoms, an extensive course with little or no interepisode remission, and the presence of rapid cycling (Bora et al., 2007). BP with psychotic features has also been found to be associated with more impaired functional outcome when compared with individuals with BP without psychotic features (APA, 1994; Zubieta et al., 2001).

Once an individual has experienced a mood episode accompanied by psychotic features, he/she is more likely to have more such psychotic affective episodes. Additionally, the presence of psychosis within a manic episode is associated with a greater likelihood of future manic episodes with psychotic features, while the presence of mood-incongruent psychotic features is associated with a decreased likelihood of full interepisode recovery (APA, 1994), as well as greater social maladjustment and more severe symptoms over a 9-month post-hospitalization period (Miklowitz, 1992). In fact, while Tohen and colleagues (2000) found that 97.5% of a group of individuals suffering from a major affective disorder (i.e., either BP or major depressive disorder) with psychotic features demonstrated syndromal recovery within 2 years following first hospitalization, only 37.6% were found to demonstrate functional recovery (as measured via a return to at least baseline levels in both vocational status and living situation) during the same time period, with older age at onset and shorter hospitalization duration were both found to be associated with a greater likelihood of significant functional recovery.

Neurocognitive Deficits Associated with Bipolar Disorder with Psychosis

Recently, a number of investigations have found evidence of differences in neurocognitive performance to be associated with the presence or absence of psychotic symptoms in BP, with deficits having found to be significantly more severe when BP is accompanied by psychotic features (APA, 1994; Zubieta, Huguelet, O'Neil, & Giordani, 2001).

Zubieta, Huguelet, O'Neil, and Giordani (2001), for example, evaluated the neuropsychological performance of a group of individuals with BP with psychosis ($n = 15$), each of whom had been euthymic for at least 6 months, as compared to a group of

normal controls ($n = 15$). The BP with psychotic features group was found to be significantly impaired in verbal learning, executive functioning, and motor coordination. No BP without psychosis group was included for comparison. Additionally, a greater number of mood episodes (both depressive and manic) was associated with more severe impairment of executive functioning in the BP with psychosis group, while greater impairments in both executive functioning and verbal learning and memory were found to be associated with greater impairments in social and occupational functioning. These results suggest that at least some of the neurocognitive deficits associated with BP with psychosis may indicate the presence of a more severe course and greater impairments in functional outcome.

Moreover, Bora and colleagues (2007) compared a group of euthymic BP patients ($n = 65$) to a group of normal controls ($n = 30$) in several neurocognitive domains. Of the BP group, approximately 62% had experienced at least one mood episode which was accompanied by psychotic features. The BP group as a whole performed significantly worse than the normal controls in the areas of attention and psychomotor speed, as well as on some measures of verbal fluency. The psychotic BP subgroup further exhibited significant impairment in the areas of executive functioning as compared to both the normal controls and the individuals with BP without psychotic features.

In a similar study, Glahn and colleagues (2007) compared the neuropsychological profiles of individuals with BP with ($n = 34$) and without ($n = 35$) psychotic features to one another, as well as to a group of normal controls ($n = 35$). The makeup of the BP group was a combination of individuals in major depressive and manic episodes, as well as individuals who were currently euthymic. Compared to the normal controls, the BP

group as a whole performed significantly worse in the areas of attention, psychomotor speed, episodic memory, and executive functioning. Moreover, the BP with psychotic features group was significantly more impaired than the BP without psychotic features group in the areas of executive functioning and spatial working memory, further lending support to the hypothesis that psychosis may indicate more severe impairment. Greater severity in neuropsychological impairment was also found by Evans and colleagues (1999) to be associated with psychiatric disorders with psychosis as compared to those without psychotic features, specifically in the neurocognitive domains of psychomotor speed, abstract thinking, attention, and verbal learning and memory.

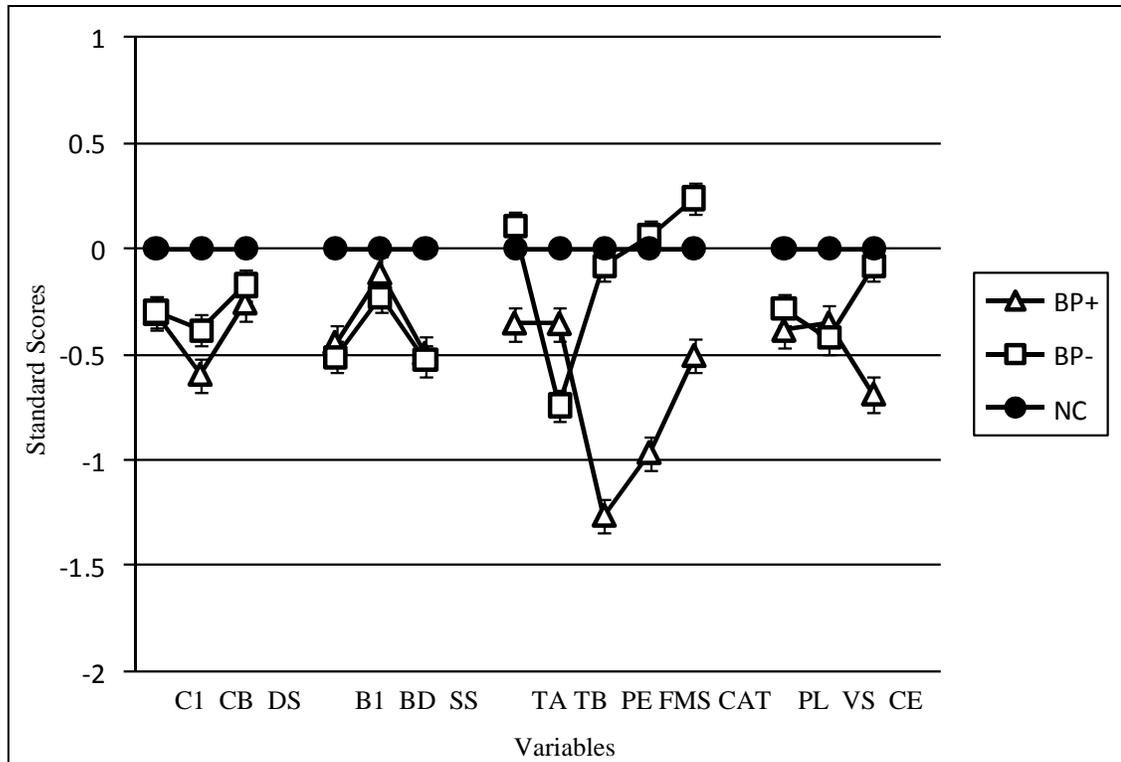
Another trend in BP research has been to investigate whether documented impairments are present very early on in the course of the disorder, which could lead to the identification of impairments that may be markers for the presence of the disorder, and perhaps for the presence of psychotic features within the disorder. Brickman and colleagues (2004), for example, examined the neuropsychological performance of a group of adolescents ($n = 29$) who were experiencing a psychotic episode for the first time and who thus had not been previously medicated for psychosis, and who were later diagnosed with schizophrenia. The psychotic group was found to be significantly impaired when compared to a group of age- and gender-matched control subjects ($n = 17$), especially in the areas of executive functioning, attention, and verbal learning and memory, and to a lesser degree in the areas of verbal fluency, perceptual motor processing, and motor speed.

Recently, Allen, Randall, Bello, Armstrong, Frantom, and Kinney (in press) evaluated working memory performance in individuals with BP with ($n = 24$) and

without ($n = 22$) and psychotic features, as well as a group of normal controls ($n = 31$). Working memory was conceptualized according to the model proposed by Baddeley and Hitch (Baddeley & Hitch, 1974), which includes three main components – the Phonological Loop, the Visuospatial Sketchpad, and the Central Executive. It was hypothesized that the BP group with psychotic features would perform significantly worse than the nonpsychotic BP and normal control groups on neurocognitive measures selected to assess these three working memory components. However, results indicated that only the Central Executive component significantly differentiated the psychotic and nonpsychotic BP groups (see Figure 1). These results support the idea that some aspects of working memory performance are trait markers for psychosis while others are not, and implicate the role of executive function deficits as key in predicting poorer working memory performance in patients with BP who also have experienced psychotic episodes.

Finally, Glahn et al. (2006) reported that performance on spatial working memory tasks differentiated between patients with histories of psychosis (BP with psychosis, schizoaffective disorder, and schizophrenia) from those without psychotic features (BP without psychosis), although differences were not present between these groups on auditory/verbal working memory tasks. It is interesting to note that the spatial working memory task used likely placed heavy demands on the Central Executive in addition to the Visuospatial Sketchpad. The results obtained thus may not be specific to the visual short-term store per se, but may have instead resulted from executive function deficits. In any case, there is a growing consensus that deficits in working memory, and potentially, executive function are markers for psychosis rather than for affective disorders.

Figure 1. Phonological Loop, Visuospatial Sketchpad, Central Executive, and Composite Scores for the Groups.¹



¹From “Are working memory deficits in bipolar disorder markers for psychosis?” by D. N. Allen, C. Randall, D. K. Bello, C. M. Armstrong, L. V. Frantom, and J. W. Kinney, 2010, *Neuropsychology*, in press. Adapted with permission of the author.

Note. NC = Normal control group. BP- = Bipolar disorder without psychotic features group. BP+ = Bipolar disorder with psychotic features group. C1 = California Verbal Learning Test List A, Trial 1. CB = California Verbal Learning Test List B. DS = Digit Span Total. B1 = Biber Figure Learning Test-Extended Trial 1. BD = Biber Figure Learning Test-Extended Distractor List. SS = Spatial Span Total. TA = Trail Making Test Part A. TB = Trail Making Test Part B. PE = Wisconsin Card Sorting Test Perseverative Errors. FMS= Wisconsin Card Sorting Test Failure to Maintain Set. CAT = Wisconsin

Card Sorting Test Categories Completed. PL = Phonological Loop Composite Score. VS = Visuospatial Sketchpad Composite Score. CE = Central Executive Composite Score.

Verbal and Visual Learning and Memory in Bipolar Disorder with Psychosis

Research regarding the presence of verbal and visual learning and memory deficits in individuals diagnosed with BP with psychotic features has been limited. Additionally, much of the research that has considered the co-occurrence of BP and psychotic features has not controlled well for the presence of absence of psychosis, which may be one of the reasons why mixed results have been reported in the BP research to date. As previously mentioned, Zubieta, Huguelet, O'Neil, and Giordani (2001) compared a group of individuals with BP with psychotic features ($n = 15$) to a group of normal controls ($n = 15$). Although a BP without psychosis group was not also used as a comparison, the BP with psychosis group did exhibit significant verbal learning and memory impairments, as well as impairments in executive functioning.

Brickman and colleagues (2004) also found evidence of significant deficits in the domains of executive functioning and verbal learning and memory in a group of previously unmedicated adolescents presenting with psychotic symptoms ($n = 29$) who went on to be diagnosed with schizophrenia as compared to a group of matched control subjects ($n = 17$).

McClellan, Prezbindowski, Breiger, and McCurry (2002) similarly compared a group of medication-naïve adolescents who had been diagnosed with BP with psychotic features ($n = 14$), schizophrenia ($n = 18$), schizoaffective disorder ($n = 7$), or psychosis not otherwise specified ($n = 11$) on various neurocognitive domains and found evidence

of impaired verbal learning and memory in all three groups. No significant difference, however, was noted between the three groups with regard to verbal learning and memory, suggesting that such a deficit may be a marker for psychosis.

Bora and colleagues (2007) also compared a group of individuals with BP with a history of psychotic features ($n = 40$) to a group of normal controls ($n = 30$) across several neurocognitive domains. Overall, the BP with psychosis group was found to be significantly impaired in the areas of attention, psychomotor speed, executive functioning, and some measures of verbal fluency. Furthermore, the executive function deficits which were noted in the BP with psychosis group were also significant as compared to a group of individuals with BP without a history of psychosis ($n = 25$), whose executive functioning overall was indistinguishable from that of normal controls. Executive functioning, and not verbal learning and memory thus differentiated between the presence and absence of psychosis in this sample.

Finally, neuropsychological findings from high-risk studies, retrospective studies, and birth cohort studies have demonstrated evidence of visuospatial memory deficits that existed prior to the onset of psychosis. Investigators in this review assert from these findings that visuospatial memory deficits may be viewed as trait markers for psychotic illness (Brewer et al., 2006).

However, despite evidence implicating visuospatial memory deficits, specific studies regarding whether visual learning and memory may be differentially impaired in individuals with BP with versus without psychotic features have yet to be conducted.

Psychotic/Affective Disorders: Schizoaffective Disorder

Characteristics of Schizoaffective Disorder

Schizoaffective disorder is a psychiatric disorder which is listed in the DSM-IV-TR in the “Schizophrenia and Other Psychotic Disorders” section, but which is expressed as a combination of the symptoms typically associated with schizophrenia and bipolar disorder (APA, 1994). Symptoms required to warrant a diagnosis of schizoaffective disorder include the presence of two or more of the characteristic symptoms of schizophrenia (i.e., delusions, hallucinations, disorganized speech, disorganized and/or catatonic behavior, and negative symptoms). The primary factor which distinguishes schizoaffective disorder from schizophrenia is the diagnostic criterion of at least one major depressive, manic, or mixed episode which occurs concurrently with the previously mentioned schizophrenia symptoms, while the primary factor which distinguishes schizoaffective disorder from BP is that the presence of delusions and/or hallucinations must be documented in the absence of prominent mood symptoms for at least a 2 week period. Research regarding the prevalence of schizoaffective disorder has been extremely limited (APA, 1994), with the only such study reporting a prevalence estimate of approximately 0.32% (Perala et al., 2007).

Neurocognitive Deficits Associated with Schizoaffective Disorder

Research regarding the neurocognitive deficits associated with schizoaffective disorder is limited, although there have been some reports of documented impairment in the neurocognitive domains of verbal memory, attention, and executive functioning (Torrent et al., 2007), as well as working memory (Gooding & Tallent, 2002).

Some studies have also compared the neuropsychological profiles of individuals with schizoaffective disorder as compared to individuals with schizophrenia. One such study, performed by Heinrichs, Ammari, Vaz, and Miles (2008), found the neurocognitive profiles of groups of individuals with schizophrenia ($n = 103$) and schizoaffective disorder ($n = 48$) to be statistically indistinguishable from one another, specifically in the neurocognitive domains of verbal learning and memory, processing speed, nonverbal reasoning, verbal fluency, and verbal skills. This similarity in performance was present despite the finding that the schizophrenia group was significantly more symptomatic than the schizoaffective group at time of testing.

Similarly, Szoke and colleagues (2008) compared groups of individuals with schizophrenia ($n = 48$), schizoaffective disorder ($n = 26$), bipolar disorder with psychosis ($n = 52$), and bipolar disorder without psychosis ($n = 40$), as well as a group of normal controls ($n = 48$) on two measures of executive functioning – the Wisconsin Card Sorting Test (WCST) and the Trail Making Test (TMT). Results indicated that all four psychiatric groups performed worse than normal controls on the TMT, although this difference was significant only for the schizophrenia and schizoaffective groups. Furthermore, degree of impairment of executive function as measured by the TMT was similar in the schizophrenia and schizoaffective disorder groups, and in turn for the two bipolar disorder groups. On the other hand, degree of impairment of executive function as measured by the WCST was most severe in the schizophrenia group, followed by the schizoaffective disorder, bipolar disorder with psychosis, and bipolar disorder without psychosis groups respectively. Only the WCST performance of the schizophrenia and

schizoaffective disorder groups, however, was significantly worse than that of the normal control group.

Verbal and Visual Learning and Memory in Schizoaffective Disorder

As with neurocognitive impairments in general, research regarding verbal and visual learning and memory in schizoaffective disorder is extremely limited. One study, however, performed by Torrent and colleagues (2007) compared a group of individuals with schizoaffective disorder ($n = 34$) to a group of individuals with bipolar disorder without psychosis ($n = 41$), as well as a group of normal controls ($n = 35$). All psychiatric participants were euthymic at time of testing. Results indicated that the schizoaffective group demonstrated more severe impairments in the neurocognitive domains of executive functioning, attention, and verbal memory as compared to both the bipolar disorder and normal control groups, with the bipolar disorder group performing similar to the normal control group.

Little research has been reported to date regarding the presence or absence of visual learning and memory deficits in individuals with schizoaffective disorder. The previously mentioned study conducted by Torrent and colleagues (2007), however, was unable to identify visual learning and memory deficits in a group of individuals with schizoaffective disorder as compared to a group of individuals with BP and a group of normal controls.

Schizophrenia

Characteristics of Schizophrenia

Schizophrenia is a typically debilitating psychiatric disorder which is characterized by a mixture of both positive and negative symptoms (APA, 1994).

Positive symptoms include delusions and hallucinations, disorganized speech, and disorganized or catatonic behavior, while negative symptoms include affective flattening, alogia, and avolition. Symptoms must have been present for at least a 1-month period of time (or shorter if treated), with at least some of the symptoms having been present for at least 6 months to warrant a diagnosis. Furthermore, symptoms must be causing or must have caused significant impairment in social and/or occupational functioning. Estimates of the prevalence of schizophrenia vary and typically range from approximately 0.5% to 1.5% (APA, 1994; Waldo, 1999; Chien et al., 2004; Xiang et al., 2008).

As with BP, much heterogeneity exists in the expression of schizophrenia. The DSM-IV delineates five subtypes of schizophrenia – paranoid, disorganized, catatonic, undifferentiated, and residual. Within and among these subtypes, neuropsychological performance may vary from significantly impaired to “neuropsychologically normal” (Palmer et al., 1997; Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000; Seaton, Goldstein, & Allen, 2001; Allen, Goldstein, & Warnick, 2003).

Also as with BP, attempts have been made to link the neurocognitive deficits commonly associated with schizophrenia to structural abnormalities of the brain. One such study found evidence, albeit from a relatively small sample of individuals with schizophrenia ($n = 12$), of impaired left hemisphere activation and apparent impaired phonological processing during verbal tasks as compared to a small group of normal controls ($n = 12$; Angrilli et al., 2009). Other studies have reported evidence for left temporal lobe dysfunction, where there may be a relationship between dysfunction and the presence of auditory hallucinations (e.g., Hugdahl et al., 2008). Furthermore, the presence of schizophrenia may be associated with decreased gray matter volume in areas

of the frontal and medial temporal lobes, especially those of the left hemisphere (Bonilha et al., 2008). For a review of early left hemisphere dysfunction research, see Maaser and Farley (1988).

Neurocognitive Deficits Associated with First-Break Findings

As with BP, attempts have been made to identify what, if any, neurocognitive impairments are present early in the course of schizophrenia. Lencz and colleagues (2006), for example, administered a battery of tests to a group of individuals who were determined to be susceptible to the onset of psychotic symptoms based on the presence of other positive symptoms. As compared to a group of normal controls, the vulnerable group demonstrated significant deficits in the areas of verbal learning and memory and executive functioning. Of the individuals in the vulnerable group, those who later went on to receive psychotic diagnoses (39%) had performed significantly worse in the area of verbal learning and memory than did those who did not go on to develop such disorders.

Furthermore, Albus, Hubmann, Ehrenberg and colleagues (1996) compared a group of individuals suffering from first-episode schizophrenia ($n = 40$) to a group of individuals with chronic schizophrenia ($n = 40$), as well as to a group of normal controls ($n = 40$). The schizophrenia groups demonstrated significant generalized cognitive impairment as compared to the normal controls, specifically in the areas of verbal intelligence, verbal learning and memory, spatial organization, visual memory, short-term memory, visual-motor processing selective attention, information processing, and abstraction, suggesting that the neurocognitive impairments commonly associated with schizophrenia may be present very early on in its course, and may thus potentially serve as prodromal markers for the onset of the disorder.

As previously mentioned, Albus, Hubmann, Walheim, and colleagues (1996) also compared the neuropsychological performance of several groups of psychiatric patients to one another and to a group of normal controls. One of these groups was a schizophrenia group, which was comprised of individuals who were experiencing their initial psychotic episode. Among other findings, the researchers found that the first episode schizophrenia group ($n = 27$) performed significantly worse than the normal control group ($n = 27$) in the area of verbal learning and memory.

Similarly, Saykin, and colleagues (1994) compared the neurocognitive performance of a group of individuals with first-episode, and thus never medicated, schizophrenia ($n = 37$), a group with schizophrenia who had been previously treated with medication ($n = 65$), and a group of normal controls ($n = 131$). The pattern of performance of the two patient groups was remarkably similar in the areas of sustained attention, verbal intelligence, spatial organization, visual memory (i.e., spatial recognition), speed of visual-motor processing, fine motor skills, and verbal learning and memory. While there were differences in performance between the two patient groups, both patient groups were significantly impaired compared to the normal controls in each of the domains. These results thus provide evidence that while these cognitive impairments may be more extreme following extensive course and/or medication use, they are, at least in some cases, present at the onset of the disorder and prior to treatment via medication.

Bilder and colleagues (2000) also compared the neuropsychological profiles of a group of individuals suffering from first-episode schizophrenia ($n = 94$), all of whom were tested only following stabilization of psychosis, to a group of normal control

participants ($n = 36$). Overall, the schizophrenia group demonstrated general cognitive impairments compared to the normal controls, with deficits lying specifically in the areas of learning and memory and executive functioning. Lower scores on measures of executive functioning were also found to be associated with more severe cognitive impairments in the psychiatric group. Furthermore, there was a significant relationship between more severe cognitive impairment and more severe impairments in premorbid adjustment, as well as between executive functioning deficits and both more severe outcome and greater global functioning impairment.

Another study, performed by Townsend, Malla, and Norman (2001), examined the neuropsychological functioning of a group of individuals, each suffering from first-episode psychosis with a diagnosis of a schizophrenia spectrum psychosis disorder (i.e., schizophrenia, schizoaffective disorder, or schizophreniform disorder); each participant was tested following stabilization of psychotic symptoms within the previous three months. No normal control group was used for comparison in this study. Instead, z-scores were calculated for each participant based on the normative values for the measures. Results indicated that each of the three groups performed in the impaired range in the domains of speed of information processing and executive functioning, although there was no significant difference in performance between the three diagnostic groups. These findings are thus concordant with other findings that neuropsychological deficits associated with psychosis may be evident early in the course of psychotic disorders.

Other deficits which have been noted as early as the first episode in individuals with schizophrenia have included visual sensory processing (Yeap, Kelly, Thakore, &

Foxe, 2008), attention (González-Blanch et al., 2007; Braw et al., 2008), spatial memory (Braw et al., 2008), sequence learning (Pedersen et al., 2008), executive functioning (Ilonen et al., 2000; Riley et al., 2000; Chan, Chen, & Law, 2006; González-Blanch et al., 2007), fine motor skills (González-Blanch et al., 2007), psychomotor speed (Riley et al., 2000), verbal fluency (Riley et al., 2000), nonverbal delayed memory (Riley et al., 2000), and working memory (Gooding & Tallent, 2002; Mathes et al., 2005). Furthermore, at least some of these findings were found to be significant regardless of whether the participants were being treated via medication for the presence of psychotic features (e.g., Riley et al., 2000). Studies evaluating verbal and learning and memory performance in first-episode schizophrenia patients, however, have yielded mixed results (Riley et al., 2000; Hill, Beers, Kmiec, Keshavan, & Sweeney, 2004; Nuyen, Sitskoorn, Cahn, & Kahn, 2005).

The structural abnormalities often associated with schizophrenia have also been noted as early as first-break in several groups of individuals. Such findings have included significantly less grey matter in the dorsolateral prefrontal and superior temporal gyrus in a group of individuals who were experiencing a psychotic episode and who were later diagnosed as having schizophrenia ($n = 37$) as compared to a group of normal controls ($n = 44$; Molina et al., 2006), as well as white matter abnormalities in a group of first-episode schizophrenia participants ($n = 25$) as compared to a group of normal controls ($n = 26$; Whitford et al., 2007). For an in-depth review of such findings, see Steen, Mull, McClure, Hamer, and Lieberman (2006).

Verbal and Visual Learning and Memory in Schizophrenia

As previously mentioned, findings have been mixed regarding the presence of verbal learning and memory deficits in first break schizophrenia. The presence of such deficits has, however, been repeatedly noted throughout the course of the disorder (Vaz & Heinrichs, 2002; Tuulio-Henriksson, Partonen, Suvisaari, Haukka, & Lönnqvist, 2004). In fact, verbal learning and memory impairments have been found to be associated with earlier age at onset in these populations (Tuulio-Henriksson et al., 2004), while verbal memory errors have been found to significantly predict general psychopathology as measured by the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) in individuals with schizophrenia (Heinrichs & Vaz, 2004). Interestingly, however, subgroups of schizophrenia have been delineated according to performance on verbal learning and memory tasks. Specifically, research has shown that there is a subpopulation of individuals with schizophrenia whose performance on verbal learning and memory tasks is comparable to that of normal controls, while other individuals demonstrate significant impairment (Paulsen et al., 1995; Turetsky et al., 2002; Vaz & Heinrichs, 2002, 2006). Relatively unimpaired performance on these tasks has been further found to be associated with the presence of fewer symptoms, both negative and positive (Turetsky et al., 2002; Vaz & Heinrichs, 2002, 2006), as well as better quality of life as quantified by amount of sleep and rest typically obtained as well as contact with family and friends. Some researchers, however, posit that such differences may have been in part due to differences in medication use (Vaz & Heinrichs, 2002, 2006).

Multiple studies have also documented the presence of visual learning and memory impairments in individuals with schizophrenia (e.g., Saykin et al., 1994). One

such study, for example, found visual learning and memory to be significantly impaired in a group of individuals with schizophrenia ($n = 41$) as compared to a group of normal controls ($n = 46$; Nestor et al., 2004), while another study found visual learning and memory as measured by the Biber Figure Learning Test-Extended (BFLT-E; Glosser, Deutsch, Cole, & Corwin, 1997) to become increasingly more impaired over time as age increased in a schizophrenia sample (Putnam & Harvey, 1999).

Finally, Tracy and colleagues (2001) specifically examined verbal and visual learning and memory in a group of individuals with schizophrenia ($N = 28$) using the CVLT to measure verbal learning and memory and the Biber Figure Learning Test-Extended (BFLT-E) to measure visual learning and memory. Interestingly, the results indicated that the group was significantly impaired on both the verbal and visual learning and memory measures, but that visual learning and memory was, overall, more impaired than verbal learning and memory.

Significance of Research

Neurocognitive Deficits and Outcome

One reason that the neurocognitive deficits associated with disorders such as BP have been a major focus of recent research is that neuropsychological performance may be more temporally stable than symptom presentation, and may also help to predict outcome and severity of course (e.g., Liu et al., 2002; Lewis, 2004). Individuals with BP, for example, tend to demonstrate impaired psychosocial and occupational functioning in addition to neurocognitive deficits. Martínez-Arán and colleagues (2007) compared a group of individuals with BP who had been euthymic for at least 6 months ($n = 77$) to a group of normal controls ($n = 35$) and found that, overall, the BP group demonstrated

more severe cognitive impairment compared to the normal controls, specifically in the areas of verbal memory and executive functioning. The BP group was further divided into two subgroups: a high-functioning group, described as having “a [Global Assessment of Functioning (GAF)] score higher or equal to 60, [representing] some mild difficulty in social, occupational or academic activities or satisfactory activity,...[but] in general, the patient works quite well and has significant interpersonal relationships”; and, a low-functioning group, described as having “[GAF] scores below 60, [indicating] moderate to severe impairment in functioning”. Upon examining differences between these two groups, the low-functioning BP group was found to be more severely impaired than the high-functioning BP group, especially in the areas of executive functioning and verbal memory. In fact, verbal memory was the best predictor of low psychosocial functioning.

Earlier studies performed by Martínez-Arán and colleagues also investigated the relationship between neuropsychological performance and psychosocial outcome. One study demonstrated a significant positive correlation between performance on verbal learning and memory tasks and psychosocial functioning as measured via the GAF (Martínez-Arán, Vieta, Reinares et al., 2004). Furthermore, significant negative correlations were found between performance on verbal learning and memory tasks and duration of illness, number of hospitalizations, number of manic episodes, and number of suicide attempts (Martínez-Arán, Vieta, Reinares et al., 2004). Another study performed by Martínez-Arán, Vieta, Colom and colleagues (2004) found evidence of the following: significant negative correlations between performance on verbal learning and memory tasks and number of manic episodes, number of hospitalizations, and chronicity; a

significant negative correlation between working memory and psychosocial functioning; a significant positive correlation between performance on verbal learning and memory tasks and psychosocial functioning; a significant negative correlation between performance on tasks of executive functioning and duration of illness; and, a significant positive correlation between performance on tasks of executive functioning and age of onset. Overall, these studies provide further evidence that neurocognitive deficits, especially in verbal learning and memory and executive functioning, are related to psychosocial functioning and outcome (Martínez-Arán, Vieta, Colom et al., 2004; Martínez-Arán, Vieta, Reinares et al., 2004).

Furthermore, given that episodes of mania are often associated with *both* psychosis and hospitalization (Mansell & Pedley, 2008), further research regarding the neuropsychological impairments, or lack thereof, which tend to accompany psychotic features may lead to a better and more thorough understanding of BP with psychosis and thus aid in treatment and intervention planning.

Genetic Markers for Psychosis

Finally, neuropsychological deficits may serve as trait markers for disorders, which may indicate a genetic vulnerability to psychotic features. Gourovitch and colleagues (1999), for example, compared the neuropsychological profiles of pairs of monozygotic (MZ) twins who were discordant for BP ($n = 7$) to those of pairs of normal control MZ twins ($n = 7$). Of the individuals in the discordant for BP group who had been diagnosed with BP, three were euthymic, two were in a major depressive episode, and two were in a manic episode at time of testing. Within the group of MZ twins discordant for BP, the affected twins performed significantly worse than did the

unaffected twins in the areas of attention (as measured via Digit Span Backward), facial recognition, and verbal learning and memory (as measured via the CVLT). When the two groups of twins were compared, the MZ twins discordant for BP were found to be significantly impaired as compared to the normal control twins on the Brown-Petersen test and in the domain of verbal learning and memory (as measured via the Wechsler Memory Scale and the CVLT). The researchers concluded that mild deficits in overall memory and/or retrieval may indicate a genetic vulnerability to BP. This study, however, was implemented with a very small sample size, thus necessitating further research in this area.

Conclusion

As has been demonstrated in the literature, multiple neurocognitive deficits are associated with the presence of psychiatric disorders such as BP (both with and without psychotic features), schizoaffective disorder, and schizophrenia. Recent research has demonstrated the importance of considering the presence or absence of psychosis as an important variable that is associated with unique patterns of cognitive deficits regardless of diagnosis or diagnostic category. In this regard, working memory has received much attention as a possible biobehavioral marker for psychosis, with preliminary results indicating that visuospatial working memory and executive function deficits are sensitive to psychosis in bipolar disorder and psychotic disorders. However, associations between psychotic symptoms and other aspects of memory function, such as encoding, storage and retrieval processes, have received much less attention. The research that has been conducted has produced findings suggestive of verbal learning and memory deficits in all

of these disorders, although findings have been mixed with regard to BP, with the role of psychotic symptoms in memory deficits in these patients remaining unclear.

Research regarding the presence or absence of visual learning and memory impairments in these disorders has been even less conclusive. There is however, some suggestion that visual memory deficits are present in patients with BP, although the role of psychotic symptoms in the expression of these memory deficits is not known. The presence of neurocognitive deficits sensitive to psychosis rather than to a particular diagnosis is consistent with recent research that has explored the idea that a spectrum of disorders exists, and that BP, schizoaffective disorder and schizophrenia are not separate disorders but are related on this spectrum. Given what appears to be the central role of memory encoding, storage and retrieval processes to each of these disorders, it is thus possible that a systematic careful examination of these processes may further understanding regarding brain dysfunction in these disorders, assist in the identification of endophenotypic markers that might distinguish between them, and clarify what up to now are mixed results vis a vis the learning and memory literature in bipolar disorder. See Table 1 for a visual representation of the findings to date regarding verbal and nonverbal learning and memory, as well as executive function, in individuals with bipolar disorder.

Table 1. Summary of Research Findings to Date Regarding Executive Function and Verbal Learning and Memory Performance in Bipolar Disorder.

State	Executive Function	Verbal and Nonverbal Memory
Mood states not differentiated	<ul style="list-style-type: none"> • Studies lumping individuals from varying mood states at time of testing have found deficits in executive function (e.g., Fleck, Shear, Madore, & Strakowski, 2008; Gruber et al., 2008; Simonsen et al., 2008). 	<ul style="list-style-type: none"> • Studies lumping individuals from varying mood states at time of testing have found deficits in verbal memory (e.g., Henry, Weingartner, & Murphy, 1973). • Deficits in nonverbal memory have also been reported in such samples (e.g., Gruzelier et al., 1988).
Manic episode	<ul style="list-style-type: none"> • Studies evaluating individuals in manic episodes at time of testing have demonstrated not only that impairments in executive function are present during such states, but that such deficits are more severe than those noted in individuals who were depressed or euthymic at time of testing (e.g., Dixon, Kravariti, Frith, Murray, & McGuire, 2004). 	<ul style="list-style-type: none"> • Studies evaluating individuals in manic episodes at time of testing have demonstrated verbal learning and memory impairments which have been significantly more severe than those observed during either depressed or euthymic states (e.g., Henry, Weingartner, & Murphy, 1971; Dixon, Kravariti, Frith, Murray, & McGuire, 2004).
Major depressive episode	<ul style="list-style-type: none"> • Individuals in depressed episodes at time of testing have also demonstrated deficits in executive function, although such deficits were noted to be modest in size (e.g., Malhi et al., 2007). 	<ul style="list-style-type: none"> • Verbal learning and memory impairments have been noted in such samples, with deficits primarily lying in the domain of encoding (e.g., Weingartner, Cohen, Murphy, Martello, & Gerdt, 1981).

Euthymia

- Individuals who were euthymic at time of testing have also demonstrated deficits in executive function (e.g., van Gorp, Altshuler, Theberge, Wilkins et al., 1998; Ferrier, Stanton, Kelly, & Scott, 1999; Altshuler et al., 2004; Martínez-Arán, Vieta, Colom et al., 2004; Thompson et al., 2005; Robinson et al., 2006; Martínez-Arán et al., 2007; Arts et al., 2008; Martino et al., 2008), although at least one study found such deficits to improve during euthymia (Rubinsztein, Michael, Paykel, & Sahakian, 2000).
- Research comparing individuals with BPI and BPII have found
 - Additionally, deficits in verbal recall have been found to be most severe in depressed individuals than in individuals in other mood states (e.g., Malhi et al., 2007).
 - Deficits in verbal learning and memory have been reported in a number of studies of individuals with bipolar disorder who were euthymic at time of testing (e.g., Atre-Vaidya et al., 1998; van Gorp, Altshuler, Theberge, Wilkins, & Dixon, 1998; van Gorp, Altshuler, Theberge, & Mintz, 1999; Altshuler et al., 2004; Martínez-Arán, Vieta, Colom et al., 2004; Thompson et al., 2005; Robinson et al., 2006; Martínez-Arán et al., 2007; Frantom, Allen, & Cross, 2008; Martino et al., 2008; Savitz, van der Merwe, Stein, Solms, & Ramesar, 2008).
 - Deficits in nonverbal learning and memory have also been reported in such samples (e.g., Glahn, Barrett et al., 2006; Arts et al., 2008; Frantom, Allen, & Cross, 2008; Savitz, van der Merwe, Stein, Solms, & Ramesar, 2008).
 - Some research regarding verbal learning and memory has identified

BPI versus BPII

evidence of impairment in executive function in both groups as compared to a normal control group, but with no significant differences between the BPI and BPII groups themselves (e.g., Dittmann et al., 2008). Other research, however, has reported significant differences between these groups, with the BPI group performing significantly worse than the BPII group, and with both groups performing significantly worse than a normal control group, in the domain of executive function (e.g., Torrent et al., 2006; Hsiao et al., 2009).

such impairments in individuals with BPI and BPII as compared to a normal control group, with no significant differences in the BPI and BPII groups themselves, (e.g., Dittmann et al., 2008), while other findings have included significant differences between these two groups, with the BPI group performing significantly worse than the BPII group, and with both groups performing significantly worse than a normal control group (e.g., Torrent et al., 2006; Hsiao et al., 2009).

BP+ versus BP-

- Deficits in executive function have been noted in BP+ individuals as compared to normal controls (e.g., Zubieta, Huguelet, O'Neil, & Giordani, 2001), and as compared to both normal controls and BP- individuals (e.g., Bora et al., 2007; Glahn et al., 2007).
- Research to date has found no evidence of differences between BPI and BPII regarding nonverbal learning and memory (e.g., Torrent et al., 2006; Hsiao et al., 2009).
- Verbal learning and memory impairments have been reported in BP+ individuals as compared to normal controls (e.g., Zubieta, Huguelet, O'Neil, & Giordani, 2001).

Note. BPI = Bipolar I disorder. BPII = Bipolar II disorder. BP+ = Bipolar disorder with psychotic features. BP- = Bipolar disorder without psychotic features.

Research Aims and Study Hypotheses

Based on these considerations, the goal of this study was to systematically examine learning and memory for verbal and nonverbal (i.e., visual) information in individuals with BP with and without psychosis in order to determine whether differential impairments exist that are associated with psychosis. A secondary purpose of this study was to compare the two BP groups to a group of individuals diagnosed with schizophrenia on the same measures of verbal and visual learning and memory, again to investigate whether these impairments differentiate among the groups either with regard to severity or pattern of deficit.

To accomplish these aims, two parallel measures were selected in addition to a standard battery of tests that allow for the examination of encoding, storage, and retrieval processes for verbal and nonverbal memory. These measures were selected because they have been previously used to assess memory functioning in affective and psychotic disorders, and have demonstrated reliability and validity in these populations. The California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) was used to assess verbal/auditory learning and memory, while memory for nonverbal/visual information was assessed using the Biber Figure Learning Test-Extended (BFLT-E; Glosser, Deutsch, Cole, & Corwin, 1997). These measures were administered to four groups, specifically 1) normal controls (NC), 2) BP without psychosis (BP-), 3) BP with psychosis (BP+), and 4) schizophrenia (SZ). Comparisons among the groups were made on CVLT and BFLT-E scores sensitive to encoding, storage and retrieval processes.

Given what appears to be the primary role of working memory deficits and executive function deficits in psychotic BP (and in psychosis more generally) our

overarching hypothesis was that participants with psychiatric disorders with psychotic features would perform more poorly on measures of verbal and nonverbal learning and memory than those without psychosis. These deficits are primarily due to 1) limitations in short-term memory capacity for verbal and nonverbal information (Phonological Loop and Visuospatial Sketchpad) and 2) deficits in executive functions. Deficits in short-term memory limits the amount of information that can be rehearsed and thus encoded into long term memory, while deficits in executive function disrupt strategies used to efficiently encode and later retrieve information. Because patients without psychosis demonstrate limited short-term memory capacity but do not demonstrate executive function deficits, it is anticipated that while learning may proceed at a slower rate than what is expected in normals, organizational and retrieval strategies would remain relatively intact in the BP without psychosis group. It also appears that there is a dose-dependent relationship between psychosis and neurocognitive impairment in psychotic disorders, such that patients with schizophrenia exhibit more severe deficits than those with schizoaffective disorder, who in turn exhibit more severe deficits than those with affective disorders. Thus, it was also expected that learning and memory would be better preserved in the BP with psychotic features group than in the schizophrenia group.

Based on these considerations and the literature reviewed, the following hypotheses were made according to predictions based on deficits in short-term memory and executive functions:

Hypothesis 1: Across all memory scores, degradation in learning and memory were expected to be present across all groups based on severity of psychosis, so that the NC

group was expected to exhibit normal performance, with the BP- group exhibiting the least severe deficits, followed by the BP+, and finally the SZ group, which was expected to perform the worst. These differences between groups were expected to be statistically significant ($p < .05$).

Hypothesis 2: In addition to a degradation in memory performance across the clinical groups, the BP- group was expected to exhibit relative sparing of ability on memory test scores that reflect strategy-based deficiencies in learning (e.g., semantic clustering) and retrieval (e.g., normal recall vs. recognition discrepancies), and was not expected to differ from the NC group on these measures. However, the psychosis groups were expected to perform significantly worse ($p < .05$) than the BP- and NC groups on these measures.

Hypothesis 3: No specific hypotheses were made regarding the interaction between lateralization effects in BP with or without psychosis given the current lack of information in this area. However, given that visual working memory deficits have been suggested as an endophenotype for psychosis and that the findings regarding differential hemispheric involvement in BP have been mixed, it was hypothesized that visual memory performance would be relatively preserved in the BP- group and impaired in the BP+ group.

CHAPTER 3:

METHOD

Participants

Twenty-five individuals with BP with psychotic features (BP+), 25 with BP without psychotic features (BP-), 25 individuals with schizophrenia (SZ), and 25 normal controls (NC) were included in this study. The participants were members of either the University of Nevada, Las Vegas community or the Las Vegas community in general, who were recruited as part of ongoing research studies investigating the neurocognitive functioning of individuals with affective and psychotic disorders. All participants were required to be between the ages of 18 and 65, and demonstrated no evidence of significant vision impairment as assessed in-session. In addition to these inclusionary criteria, the following exclusionary criteria were applied to all participants:

- a) English as a secondary language, as determined via self-report.
- b) A previous traumatic brain injury, as determined via self-report and medical record review.
- c) A neurological or seizure disorder, as determined via self-report and medical record review.
- d) Previous brain surgery, as determined via self-report and medical record review.
- e) A diagnosis of a chronic medical condition which has the potential to adversely affect central nervous system functioning (e.g., liver disease, HIV), as determined via self-report and medical record review.

- f) A current or recent (i.e., within the previous 6 months) diagnosis of a substance use disorder, as determined via the administration of the Structured Clinical Interview for the DSM-IV-TR (First, Spitzer, Gibbon, & Williams, 2002).
- g) Current (i.e., within the previous week) use of a prescribed or over the counter medication which has CNS effects, with the exception of medications that have been prescribed specifically for the purpose of treating and/or regulating BP or SZ and their associated symptoms, as determined via self-report and medical record review.
- h) A hearing impairment which would interfere with ability to understand verbal communication.
- i) Corrected vision worse than 20/50 as determined via the administration of a Visual Acuity test.
- j) A diagnosis of a mood episode in the past month.

Furthermore, the following exclusionary criteria were applied to the NC participants:

- a) A diagnosis of an Axis I disorder, as determined via the administration of the Structured Clinical Interview for the DSM-IV-TR (First, Spitzer, Gibbon, & Williams, 2002).
- b) A diagnosis of BP, major depressive disorder, or SZ in a first-degree relative, as determined via self-report using a standardized interview.

Measures

A battery of measures was selected to assess for diagnosis(es), as well as for symptoms, intellectual ability, and verbal and nonverbal memory. As previously

mentioned, these assessments were administered as part of a more extended neuropsychological battery.

Diagnostic and Clinical Symptom Measures

Structured Clinical Interview for the DSM-IV-TR. The Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID; First, Spitzer, Gibbon, & Williams, 2002) is a semi-structured interview that was developed for the purpose of diagnosing DSM-IV Axis I disorders and which is appropriate for use with both psychiatric and general medical patients, as well as individuals from the community, for whom no psychiatric diagnosis is expected. The interview is most commonly used with individuals age 18 or older with an eighth grade education or higher. The SCID was administered by qualified researchers trained in the DSM-IV-TR diagnostic system (APA, 1994) and will be used to establish the presence (or absence) of DSM-IV Axis I psychiatric disorders.

The inpatient version of the SCID (SCID-I) was used in this study. This version contains 10 modules, which are designed to assess for the presence of mood episodes, psychotic symptoms, psychotic disorders, mood disorders, substance use disorders, anxiety disorders, somatoform disorders, eating disorders, adjustment disorders, and optional disorders. All 10 modules were administered to each participant, as well as the screening module at the beginning of the SCID-I. The screening module consists of 12 questions which elicit basic information regarding possible diagnoses. This information was then used to guide the administration of more probing questions later in the interview. Each symptom in the SCID were rated on a scale of 1 to 3 (1 = symptom is absent; 2 = symptom is sub-threshold; 3 = symptom is present). Specific DSM-IV Axis I diagnoses were made following the scoring of each module. Regarding the psychometric properties

of the SCID-I, inter-rater reliability have been found to be excellent, with Kappa values ranging from .71 to .97, with an average Kappa value of .85 (Ventura, Liberman, Green, Shaner, & Mintz, 1998). Furthermore, the SCID-I has demonstrated high validity for the diagnosis of schizophrenia and bipolar disorder (Steiner, Tebes, Sledge, & Walker, 1995), with good sensitivity (.89), specificity (.96), and agreement (.86) when compared to best estimate diagnoses made by psychiatrists on first-admission psychotic patients (Fennig, Craig, Lavelle, Kovasznay, & Bromet, 1994).

While some participants demonstrated sub-threshold symptoms, any participant (with the exception of normal controls) who had experienced a depressive, manic, or mixed episode within the month prior to testing was excluded from the study, but was offered the opportunity to participate following a month of euthymia.

The Young Mania Rating Scale. The Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978) is an eleven-item clinician administered rating scale which is used to determine the presence and severity of symptoms of mania. The YMRS is not designed to be a diagnostic tool, but is meant to be used as a symptom rating scale in individuals previously diagnosed with BP. The scale was administered by a trained clinician, who conducted an interview and subsequently assigned a symptom severity rating for each item based on the behavioral observations made by the clinician, as well as the participant's self-report of symptom severity over the previous 2 weeks. Each item was rated on a scale of 0 (absent) to 4 (overtly present), with the exception of four items which were weighted doubly on a scale of 0 to 8. A score of four or less on the YMRS is generally considered to indicate an asymptomatic state (with regards to symptoms of mania).

The Hamilton Depression Rating Scale. The Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960, 1967) is a frequently used clinician-administered rating scale which assesses symptoms of depression as delineated by the DSM-IV. While the scale does help the clinician determine the severity any symptoms present, the HAM-D is not intended to be used as a diagnostic instrument. The current study used an abbreviated 21-item version of the HAM-D (HAM-D₂₁). Symptoms for which ratings were made included depressed mood, as well as vegetative symptoms of depression, cognitive symptoms of depression, and comorbid anxiety symptoms; this version did not assess for the presence of disturbances in the areas of sleeping habits, eating habits, or attention/concentration as related to the presence of depression. Each item was rated on a Likert scale ranging 0 to 2, 3, or 4 for a total of 63 possible points. A score of 8 or less was considered to be indicative of a relatively asymptomatic (i.e., euthymic) state, while a score which fell above this cutoff was indicative of the presence of significant symptoms of depression, with greater severity being associated with greater scores. The scale was administered by a trained clinician, who conducted an interview and subsequently assigned a symptom severity rating for each item based on the behavioral observations made by the clinician, as well as the participant's self-report of severity of symptoms over the prior 2 weeks.

Regarding the psychometric properties of the HAM-D₂₁, studies have found evidence in support of high internal consistency, as well as construct validity as demonstrated via the pattern of correlations between the HAM-D₂₁ and other measures of depression, anxiety, and depression-relevant cognition. Furthermore, factor analyses of the full (23-item) version of the HAM-D (HAM-D₂₁), as well as a 17-item abbreviated

version (HAM-D₁₇), have yielded four factors, which have accounted for 49% and 53% of the variance, respectively, in the responses of participants (Dozois, 2003). Thus the HAM-D₂₁ has been demonstrated to be a valid and reliable assessment tool when used to rate the severity of depression-related symptomatology.

The Brief Psychiatric Rating Scale. The Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) is an 18-item scale which is used to rate the presence and severity of a number of psychiatric symptoms, as well as to track temporal changes in symptomatology. Symptoms are rated following a 15-20 minute semi-structured symptom ratings interview. Rated symptoms include somatic concern, anxiety, emotional withdrawal, conceptual disorganization, guilt feelings, tension, mannerisms and posturing, grandiosity, depressive mood, hostility, suspiciousness, hallucinatory behavior, motor retardation, uncooperativeness, unusual thought content, blunted affect, excitement, and disorientation. Each symptom is rated on a 7-point Likert scale, with the following ratings representing the following corresponding levels of severity: 1 = not present; 2 = very mild; 3 = mild; 4 = moderate; 5 = moderately severe; 6 = severe; and, 7 = extremely severe. Some items are rated according to the individual's self-report, while others are rated based on the clinician's observations.

For each individual, four factor scores were calculated in addition to the total score. Mueser, Curran, and McHugo (1997) conducted an exploratory factor analysis of the BPRS in a sample of 474 individuals with schizophrenia, followed by a confirmatory factor analysis in a separate sample of 327 individuals with schizophrenia. A four-factor solution was found in the exploratory analysis and was confirmed via the confirmatory factor analysis. The first factor, named Thought Disturbance, is comprised of items 8

(Grandiosity), 11 (Suspiciousness), 12 (Hallucinatory Behavior), and 15 (Unusual Thought Content). The Thought Disturbance factor is thus considered to be a reflection of the positive symptoms (including hallucinations and delusions) commonly associated with schizophrenia. The second factor, named Anergia, includes items 3 (Emotional Withdrawal), 13 (Motor Retardation), 14 (Uncooperativeness), and 16 (Blunted Affect). The Anergia factor is therefore thought to be an indication of the negative symptoms generally related to schizophrenia. The third factor, named Affect, consists of items 1 (Somatic Concern), 2 (Anxiety), 5 (Guilt Feelings), 9 (Depressive Mood), and 10 (Hostility). The Affect factor is thus considered to be a reflection of emotional disturbances. Finally, the fourth factor, named Disorganization, is comprised of items 4 (Conceptual Disorganization), 6 (Tension), and 7 (Mannerisms and Posturing). The Disorganization factor is therefore thought to reflect the symptoms of disorganized behavior often associated with schizophrenia. Items 17 (Excitement) and 18 (Disorientation) were not included in the final reported four-factor structure due to the inconsistent loadings of these items on the exploratory factor analysis.

Regarding its psychometric properties, the BPRS has been found to have high rates of agreement for the rating of positive symptoms of schizophrenia, as well as for the symptoms of depression and mania (Andersen, Korner, Larsen, & Schultz, 1993). Additionally, overall inter-rater reliability coefficients have been found to range from 0.85 to 0.92, with at least one sample which was largely comprised (i.e., 94% of the sample) of individuals diagnosed with schizophrenia, bipolar disorder, or major depression (Engelsmann & Formankova, 1967; Bell, Milstein, Beam-Goulet, Lysaker, & Cicchetti, 1992; Ligon & Thyer, 2000). Other studies have found the inter-rater

reliability of the BPRS to be satisfactory when used to rate the psychiatric symptoms of individuals with schizophrenia (e.g., Andersen, Larsen, Schultz, & Nielsen, 1989).

Intellectual Functioning

Current intellectual functioning was assessed using a dyadic short form of the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997) in which the Vocabulary and Block Design subtests are used to estimate one’s current Full Scale Intelligence Quotient (IQ) based on a series of regression equations (Ringe, Saine, Lacritz, Hynan, & Cullum, 2002). The equation which was used has been found to estimate Full Scale IQ within 10 points in 81-93% of a mixed neurological/psychiatric sample (Ringe et al., 2002).

Additionally, premorbid intellectual functioning was assessed by taking an average of the scaled scores obtained on the Vocabulary and Information subtests from the WAIS-III (Wechsler, 1997). These subtests have been shown to have the highest reliability coefficients (.89 and .96, respectively) among the subtests of the WAIS-III Verbal Comprehension Index (Vanderploeg, Schinka, & Axelrod, 1996). Furthermore, they are considered to be “hold” tests which change little over time, including following brain dysfunction (Bilder et al., 1992; Vanderploeg, Schinka, & Axelrod, 1996).

WAIS-III Vocabulary Subtest. The Vocabulary subtest of the WAIS-III is comprised of 33 items of increasing difficulty which the participant is asked to define. Each response is given a score of 0, 1, or 2 points for a total possible score 66. Higher scores reflect more accurate definitions. Administration of the subtest is discontinued following four consecutive scores of 0. The Vocabulary subtest has demonstrated good reliability, reported to be approximately .96 (Vanderploeg, Schinka, & Axelrod, 1996).

WAIS-III Block Design Subtest. The Block Design subtest of the WAIS-III is comprised of 14 designs of increasing difficulty and complexity which the participant is asked to recreate using a set of either four (on earlier items) or nine (on more advanced items) blocks. The blocks are identical and each have two red sides, two white sides, and two sides that are half red and half white as divided diagonally. Items are scored according to accuracy with bonuses awarded for rapid completion times. The number of possible points awarded for each item varies according to the complexity of the item and the presence or absence of time bonuses. Overall, one can earn up to 68 points on the subtest. Administration of the subtest is discontinued following three consecutive scores of 0. A score of 0 is awarded if the design is completed incorrectly, or if the design is not completed correctly within the time limit. The time limit for each item varies according to the complexity of the item, with the time limit of the most complex items being 2 minutes.

WAIS-III Information Subtest. The Information subtest of the WAIS-III is comprised of a series of 28 increasingly difficult questions which are thought to test one's general fund of information. The items require broad knowledge of current and historical facts (e.g., "Who painted the Sistine Chapel?"). Items are given a score of either 0 or 1 depending on the correctness of the individual's response, allowing for a total possible score of 28. No points are given for incorrect guesses or partial answers. The subtest is discontinued following 6 consecutive scores of zero.

Verbal Learning and Memory

California Verbal Learning Test. The California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) is used to measure declarative verbal learning and

memory via the repeated administration of word lists across trials, as well as the participant's attempted recall of the lists. The measure is comprised of two lists of sixteen common shopping list items, List A (i.e., "Monday's Shopping List") and List B (i.e., "Tuesday's Shopping List"). List A is composed of shopping items in the categories of spices and herbs, household tools, fruits, and articles of clothing; List B is comprised of shopping items in the categories of spices and herbs, fruits, fish, and cooking utensils. List A is administered five consecutive times (Trials 1–5), with the participant being asked to recall as many words as possible following each trial, thus providing a measure of immediate free recall. List B, a distractor list, is then administered once, after which the participant is asked to recall as many words as possible from that list. The participant is then immediately asked to recall as many words as possible from List A as a measure of short-delay free recall and retroactive interference. Next, the participant is asked to recall as many words as possible from each category from List A, with the administrator providing cues for each category (e.g., "Tell me all of the shopping items from the Monday list which are fruits."), providing a measure of short-delay cued recall. Following approximately a twenty-minute delay, the participant is again asked to remember as many words as possible from List A, providing a measure of long-delay free recall, as well as to recall as many words as possible from List A with the administrator providing cues, providing a measure of long-delay cued recall. Finally, the participant is read a list of forty words – some of which were on List A, some of which on List B, and some of which were on neither – and asked to determine whether or not each word was on List A, providing a measure of long-delay recognition. Overall, the CVLT serves as a measure of learning across trials, whether the participant employs the use of various

learning strategies (i.e., serial versus semantic learning), retrieval/encoding difficulties, recognition, interference effects (both proactive and retroactive), hit rate, response bias, and discriminability.

Visual Learning and Memory

Biber Figure Learning Test-Extended. The Biber Figure Learning Test-Extended (BFLT-E; Glosser, Deutsch, Cole, & Corwin, 1997) is a measure of nonverbal (i.e., visual) or learning and memory. The BFLT-E is a modified version of the original Biber Figure Learning Test and has previously been described as a visual analog of the California Verbal Learning Test (Kurzman, 1996; Tracy et al., 2001; Glosser, Cole, Khatri, DellaPietra, & Kaplan, 2002). Similar to the CVLT, the BFLT-E is constituted of a series of five learning trials of a sequence of fifteen geometric designs constructed of simple shapes (i.e., circles, squares and triangles) which are used to construct novel stimuli. Each figure is shown for approximately 3 seconds during each round of item administration, and the participant is asked to draw as many shapes as possible from memory, in no particular order, following each trial, thus providing a measure of immediate free recall. A distractor set is then administered, with the individual being shown fifteen different figures and asked to reproduce as many as possible. Next, the participant is asked to reproduce as many of the figures as possible from the first series set of designs, providing a measure of long-delay free recall, after which a recognition task mirroring that of the CVLT is administered. Finally, the participant is shown the figures from the first series for approximately three seconds each and is immediately asked to subsequently draw each figure; if there are any figures which the participant does not draw correctly immediately following the three second viewing time, he/she is

asked to copy the figure while viewing it directly. Each design is scored on a range of 0 to 3 according to the accuracy of the reproduction.

The inter-tester reliability for the BLFT-E has been found to be .98 (Glosser, Cole, Khatri, DellaPietra, & Kaplan, 2002). Similarly, test-retest reliability and criterion validity have both been found to be good (Glosser et al., 2002). As previously mentioned, the BFLT-E has been described as a visual analog to the CVLT (Tracy, et al., 2001; Glosser, Cole, Khatri, DellaPietra, & Kaplan, 2002). While the CVLT and BFLT-E are not identically matched regarding difficulty level and item content, they can serve as comparative measures for the domains of verbal and non-verbal (i.e., visual) learning and memory, respectively (Tracy et al., 2001).

Procedure

The schizophrenia group was comprised of individuals who had participated in a research study conducted in 2006. These participants were recruited from Mojave Adult, Child, and Family Services in Las Vegas, NV, which is an outpatient facility which provides community services to the mentally ill.

Participants for each of the bipolar groups, as well as for the normal control group, were recruited through referrals from local physicians and mental health agencies, fliers posted on local campuses and around the community, advertisements posted in press releases and on listserves, and verbal advertisements at local support group meetings. Participants initially contacted the research team by telephone or e-mail. An initial phone screen was conducted during which time verbal informed consent was obtained for the procedures used in the phone screen (see Appendix I). The screen requested information relevant to study inclusion and exclusion criteria. If it was determined that the individual

may have met criteria to participate in the study, an initial evaluation session was scheduled in order to conduct a more extensive interview to establish the diagnosis and determine eligibility to participate based on the other aforementioned inclusion and exclusion criteria.

In addition to the participants included in the study, a total of 270 consecutive individuals contacted our research team but did not go on to participate. Of those 270 individuals, we lost contact with 100 (e.g., they failed to return our phone calls), 18 were scheduled to be included as participants but did not come to the scheduled appointment(s), and 13 were no longer interested in the research at the time of the phone screen. The remaining 139 individuals were excluded from participation in the study. See Table 2 for a visual representation of the reasons for exclusion.

The interviews, questionnaires and neuropsychological tests used in this study were administered as part of a larger battery of tests being conducted in the Neuropsychology Research Lab at UNLV. Administration was scheduled across two 3-hour sessions, with the entire battery lasting for a total of approximately 6 hours. The initial session consisted of the administration of diagnostic and clinical symptom measures, while the second session consisted of the administration of the neurocognitive measures. When possible, both sessions were scheduled on the same day, with a 1-hour lunch break in between sessions. Furthermore, several mandatory breaks were scheduled into each evaluation session in order to circumvent fatigue and maintain motivation. All participants were compensated for their time. If the participant was a psychology student seeking research credit for a psychology class, he/she was compensated one research credit per hour completed. If the participant was from the

Table 2. Summary of Reasons for Exclusion from Study for the BP+, BP-, and NC

Participants.

Reason for Exclusion	Number excluded	% of those excluded
Comorbid Axis I disorder	35	25.1
Sub-threshold psychiatric symptomatology	33	23.7
English as a second language	14	10.1
Neurological disorder	14	10.1
Traumatic Brain Injury (TBI)	9	6.5
Medical disorder interfering with the Central Nervous System	6	4.3
Instable mood episodes	6	4.3
Older than 65	5	3.6
Refused to participate in phone screen	4	2.9
Was calling for a relative	4	2.9
First-degree relative of an individual with bipolar disorder	3	2.2
Other	6	4.2
Total	139	100.0

Note. BP+ = Bipolar disorder with psychotic features. BP- = Bipolar disorder without psychotic features. NC = Normal control group.

community or was a university student who was not seeking research credit, he/she was be compensated \$5.00 for each hour completed, and also given a \$30.00 bonus for completion of all testing procedures, for a total of approximately \$60.00.

During the first session, each participant was given an Informed Consent (see Appendix B for the full consent forms for individuals recruited from the community and for individuals recruited from UNLV). The consent form was read aloud in its entirety to each participant, and an opportunity was provided for all questions/concerns to be addressed and clarified. Both the participant and the researcher signed two Informed Consents – one for the researcher to keep for the participant’s file and one for the participant to keep for his/her own records and information. Following informed consent,

a Demographics Questionnaire was administered in order to gain in-depth information regarding the participant's personal and family history (see Appendix I for the full Demographics Questionnaire). The participant was then administered the battery of interviews, questionnaires, and neurocognitive tests in the following order: 1) Structured Clinical Interview for DSM-IV-TR; 2) Hamilton Depression Rating Scale; 3) Young Mania Rating Scale; and, 4) Brief Psychotic Rating Scale. If the participant did not meet diagnostic criteria based on the Structured Clinical Interview for DSM-IV, the study was discontinued. If diagnostic criteria were met, the Biber Figure Learning Test – Extended and the California Verbal Learning Test were administered as part of a more extensive test battery. All assessment procedures were administered by doctoral level graduate students who had been extensively trained to do so in a reliable and valid manner.

Data Entry and Analyses

Data Entry and Screening

All tests were scored according to standardized procedures by two trained individuals. In the event that a disagreement occurred regarding the scoring of a measure (as occurred at times with the BFLT-E), a third opinion (Daniel N. Allen, Ph.D.) was used to resolve the discrepancy. Data was entered twice into a Microsoft Access database, and SPSS version 16.0 was used to analyze the data.

Before the primary hypotheses were evaluated, raw data from the neuropsychological measures was examined to confirm that assumptions for multivariate analysis of variance (MANOVA) were met (i.e., independence of samples, homogeneity of variance, and normality of the distribution). Skewness and kurtosis were examined in order to ensure that the variables are normally distributed. In the event that fewer than

10% of the variables were found to be non-normally distributed, appropriate transformations would be used in order to increase the normality of the distribution (Tabachnick & Fidell, 2001). In cases where more than 10% of the variables are non-normally distributed, nonparametric analyses would be conducted by rank ordering the data and subsequently running standard parametric analyses. Furthermore, box plots were utilized in the event of outliers, such that an outlier was defined as a score which fell 3.0 standard deviations either above or below the mean. When outliers were identified, the individual data for those participants were examined in order to determine whether they were representative of valid cases. If the case was in fact determined to be valid, the data was to be kept but would be converted in order to decrease its influence on the data, prior to multivariate analysis.

Data Analyses

Preliminary analyses. Several preliminary analyses were run before performing the primary analyses. Specifically, descriptive statistics were calculated for the groups for the demographic variables of age, education, estimated IQ, ethnicity, and gender. The demographic characteristics of the groups were compared using either analysis of variance (ANOVA) or chi-square in order to test for the presence of significant differences on these demographic variables. Significant demographic differences between the groups were not anticipated, however, since efforts were made to match the groups on these variables.

In addition, clinical variables were reported via the use of descriptive statistics, specifically regarding length of illness, current symptomatology and severity of symptoms (as measured via the Young Mania Rating Scale and the Hamilton Depression

Rating Scale), total number of mood episodes, number of hospitalizations, and current medication status.

Main analyses. The general approach to analyzing the data involved comparisons among multiple groups on multiple dependent measures, making multivariate analysis of variance (MANOVA) the most appropriate approach. More specifically, in order to determine if predicted differences in memory functioning were present, the four groups (i.e., NC, BP-, BP+, and SZ) served as the between subjects factor and were compared on the verbal and visual measures of learning and memory, which served as dependent variables in the analyses.

In order to select dependent variables to be included in the MANOVAs, studies regarding the factor structure of the CVLT were consulted. These studies generally suggested that between four and six factors account for the majority of variance among the CVLT scores (Donders, 2008; Delis et al., 2000). Factors that were particularly relevant to the current study and that could be calculated for both the CVLT and BFLT-E included the General Memory, Short-term Memory (also referred to as the Attention factor), Primacy/Recency Memory, and Response Discrimination Memory factors. The scores used to measure each of these factors and which were used as the dependent variables in the MANOVAs are presented in Table 3.

Additionally, a derived score was developed by subtracting total correct on List A Trial 5 from the total number correct on the Recognition Trial. Large values for this score were thought to indicate deficient retrieval processes.

Because the hypotheses were delineated by differences in memory functioning that result from impaired short-term memory versus impaired executive function, two

Table 3. Memory Factors and Corresponding Variables.

Memory Factor	CVLT	BFLT-E
General	Short Delay Correct	Short Delay Correct
	Long Delay Correct	Long Delay Correct
Short-term	List A Trial 1 Correct	Trial 1 Correct
	List B Correct	Distractor Correct
Primacy/Recency	% Recall Primacy Region	% Recall Primacy Region
	% Recall Middle Region	% Recall Middle Region
	% Recall Recency Region	% Recall Recency Region
Response Discrimination	Free Recall Intrusions	Free Recall Intrusions
	Response Bias	Response Bias
	Recognition False Positives	Recognition False Positives

Note. CVLT = California Verbal Learning Test. BFLT-E = Biber Figure Learning Test-Extended.

MANOVAs were run. The first included memory factors thought to be minimally influenced by executive function deficits, including the General Memory and Short-term Memory factors. The second MANOVA included those scores that are thought to be particularly susceptible to strategy-based memory failures, including the Primacy/Recency and Response Discrimination Memory factors, as well as the derived Recall/Recognition derived score.

Because memory scores were derived for both the CVLT and the BFLT-E, a within subjects factor was also included in the MANOVAs that represented the type of information contained in each task (i.e., verbal versus visual). Thus, Hypotheses 1, 2, and 3 were evaluated using two MANOVAs, each including one between subjects factor for group membership (NC, BP-, BP+, SZ), one within subjects factor for type of memory tested (verbal versus visual), and the memory test scores as dependent variables.

If the overall F for any MANOVA was significant, univariate F tests and post hoc comparisons were subsequently used to examine differences among groups on individual test scores.

Hypothesis 1 will have been supported if significant between group differences were present for the MANOVA examining memory tests scores that are not sensitive to executive function deficits (i.e., the General and Short-term Memory factors), such that the BP- and BP+ groups did not differ from each other, but performed significantly worse than the NC and significantly better than the SZ group.

Hypothesis 2 will have been supported if the MANOVA indicated significant between-subjects effects in which the BP- group 1) did not differ from controls on the memory tasks thought to be dependent on intact executive functions, and 2) performed significantly better than the BP+ and SZ groups. It was also anticipated that the BP+ group would perform better than the SZ group.

Finally, Hypothesis 3 will have been supported if there were significant effects for both of the MANOVAs indicating that the BP- group did not differ from the NC group on the visual memory tasks, but instead significantly differed from the BP+ and SZ groups.

CHAPTER 4

RESULTS

Data Screening

Preliminary analyses were conducted and raw data were examined in order to verify that the assumptions for MANOVA were met prior to the main analyses. Specifically, descriptive statistics and box plots were used to identify potential outliers, with outliers being defined as scores falling 3 standard deviations above or below the mean. All outliers identified were found to be the result of data entry errors and were subsequently corrected. Similarly, skewness and kurtosis were examined for continuous variables in order to verify that these variables were normally distributed, with the criteria for normal distribution being skewness and kurtosis of less than ± 1.0 . Although all variables for the first MANOVA were found to be normally distributed, the majority of the variables (12 of 14; 85.71%) for the second MANOVA were found to have skewness and/or kurtosis of greater than or equal to ± 1.0 , including: California Verbal Learning Test (CVLT) % Primacy Region, CVLT % Middle Region, CVLT % Recency Region, CVLT Free Recall Intrusions, CVLT Recognition False Positives, CVLT Recall/Recognition Score, Biber % Primacy Region, Biber % Middle Region, Biber % Recency Region, Biber Free Recall Intrusions, Biber Recognition False Positives, and Biber Recall/Recognition Score. All 14 variables for the second MANOVA were therefore converted to ranked scores to allow for a non-parametric MANOVA to be computed.

Preliminary Analyses

Subsequent to initial data screening, preliminary analyses were conducted to evaluate for the presence of differences among the groups (i.e., SZ, BP+, BP-, and NC) on a number of demographic variables, including gender, handedness, ethnicity, and marital status. Groups were also compared on several demographic variables which have been demonstrated to affect performance on neurocognitive measures, including age, education, and current and premorbid IQ. Additionally, groups were compared on a number of clinical characteristics commonly associated with neurocognitive performance, including number of hospitalizations, length of illness duration, global assessment of functioning, current symptomatology (as evaluated via the Hamilton Depression Rating Scale for symptoms of depression, the Young Mania Rating Scale for symptoms of mania, and the Brief Psychiatric Rating Scale for psychiatric symptoms), and current medication status, as well as proportion of individuals with bipolar II disorder (as opposed to bipolar I disorder) in the BP+ and BP- groups. Continuous variables were evaluated via analysis of variance (ANOVA), while categorical variables were compared via chi-square. When significant differences were found, post-hoc tests were used to identify specific between-group differences.

The demographic characteristics of the sample, as well as the results of the statistical analyses comparing the groups on these variables, are presented in Table 4. No significant differences were found among the groups for gender, chi-square (3) = 5.77, $p = .123$ or handedness, chi-square (3) = 7.56, $p = .056$. Conversely, significant group differences were found for age, $F(3, 96) = 5.59$, $p = .001$, with post-hoc analyses indicating that the schizophrenia group was significantly older than the BP- and NC

Table 4. Demographic Characteristics of the Groups.

Variables	Group								F	p	Scheffé
	SZ (n=25)		BP+ (n=25)		BP- (n=25)		NC (n=25)				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
Age	43.00	12.58	35.60	13.61	32.84	12.98	28.96	10.84	5.59	.001	SZ > BP-, NC
Education	12.26	2.10	14.40	2.52	14.44	2.29	14.12	1.45	5.97	.001	SZ < NC, BP+, BP-
Current IQ	77.33	11.63	106.24	10.20	106.89	13.20	103.62	15.24	31.21	<.001	SZ < NC, BP+, BP-
Premorbid IQ	6.70	2.71	12.56	2.01	12.22	1.57	11.80	2.45	38.47	<.001	SZ < NC, BP-, BP+
		%		%		%		%	χ^2	p	
Gender (% females)		32		64		56		56	5.77	.123	
Handedness (% right)		84		100		80		96	7.56	.056	
Ethnicity									42.66	.011	
Caucasian		40		60		76		44			
African American		44		4		0		24			
Hispanic/Latino		8		8		0		8			
Asian American		4		8		8		8			
Native American		0		4		0		0			
Biracial		4		12		0		12			
Other		0		4		8		4			
Marital Status									16.99	.009	
Single		96		60		72		56			
LTR		0		40		28		44			
Not reported		4		0		0		0			

Note. SZ = Schizophrenia group. BP+ = Bipolar disorder with psychotic features group. BP- = Bipolar disorder without psychotic features group. NC = Normal control group. SD = Standard deviation. IQ = Intelligence Quotient. LTR = Long-term relationship.

groups. Significant group differences were also found for education, $F(3, 96) = 5.97, p = .001$, current IQ, $F(3, 96) = 31.21, p < .001$, and premorbid IQ, $F(3, 96) = 38.47, p < .001$. Post-hoc analyses indicated that the SZ group had significantly fewer years of education, significantly lower current IQ, and significantly lower premorbid IQ than the BP+, BP-, and NC groups. Finally, significant group differences were found for ethnicity, chi-square (24) = 42.66, $p = .011$, and marital status, chi-square (6) = 16.99, $p = .009$.

The clinical characteristics of the sample, as well as the results of the statistical analyses comparing the groups on these variables, are presented in Table 5. No significant differences were found among the groups for length of illness, $F(2, 66) = 0.88, p = .421$. Significant differences were found, however, for number of hospitalizations, $F(2, 72) = 7.82, p = .001$, with post-hoc analyses indicating that the SZ group had significantly more previous hospitalizations than the BP- group. Additionally, there were significant group differences in global assessment of functioning (GAF) scores, $F(3, 82) = 88.93, p < .001$, with post-hoc analyses indicating that the SZ group had significantly lower GAF scores than the BP+, BP-, and NC groups, and that the BP+ and BP- groups also had significantly lower GAF scores than did the NC group.

Several measures of current symptomatology were used to evaluate for the presence of depression and mania in the BP+, BP-, and NC groups, and for the presence of psychiatric symptoms in all groups. Significant between-group differences were found for all symptom rating measures. Specifically, significant differences were identified for the presence of symptoms of depression, as measured via the Hamilton Depression Rating Scale, $F(2, 68) = 14.12, p < .001$, as well as symptoms of mania, as measured by the Young Mania Scale, $F(2, 68) = 11.68, p < .001$. Post-hoc analyses indicated that,

Table 5. Clinical Characteristics of the Groups.

Variables	Group								F	p	Scheffé
	SZ (n=25)		BP+ (n=25)		BP- (n=25)		NC (n=25)				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
Number of hospitalizations	5.36	5.41	2.88	3.47	1.12	1.51			7.82	.001	SZ > BP-
Illness duration	23.21 ^a	11.95	18.28	13.91	19.24	12.05			0.88	.421	
GAF	32.81 ^b	10.91	56.95 ^c	13.18	62.64	11.64	88.13 ^d	4.77	88.93	<.001	SZ < BP+, BP- < NC
HAM-D ₂₁			7.80	4.30	7.80	5.92	1.62 ^e	1.94	14.12	<.001	BP-, BP+ > NC
YMRS			3.36	2.77	3.20	2.55	0.43 ^e	0.75	11.68	<.001	BP-, BP+ > NC
BPRS											
TD	10.48	4.42	5.52 ^e	1.99	4.60	0.91	3.44	1.58	35.14	<.001	SZ > NC, BP-, BP+
Anergia	9.76	5.32	4.62 ^e	1.07	4.36	0.81	3.36	1.50	24.52	<.001	SZ > BP+, BP-, NC
Affect	10.44	4.36	9.05 ^e	2.38	9.96	3.21	5.20	2.60	13.29	<.001	SZ, BP-, BP+ > NC
Disorganization	5.96	2.56	3.38 ^e	0.74	3.28	0.46	2.68	1.25	23.07	<.001	SZ > BP+, BP-, NC
Total Score	39.56	8.57	25.00 ^e	3.48	24.48	4.11	16.44	7.51	56.59	<.001	SZ > BP+, BP- > NC
		%	%	%	%				χ^2	p	
Bipolar II			8		40				7.02	.008	
Medication status ^f											
Antipsychotic	96		56		32		0		22.04	<.001	
Mood stabilizer	60		80		36		0		10.01	.007	
Antidepressant	0		36		52		0		17.11	<.001	
Anti-anxiety	16		32		8		0		4.92	.086	
Not medicated	4		12		20		100		3.03	.220	

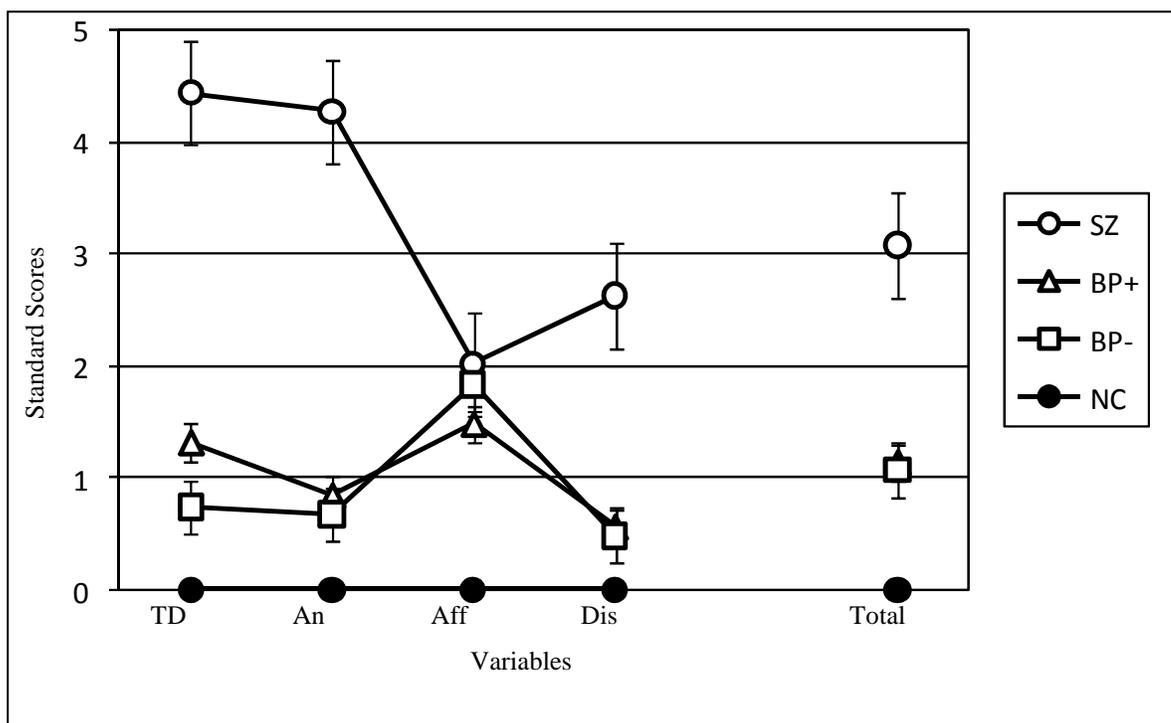
Note. SZ = Schizophrenia group. BP+ = Bipolar disorder with psychotic features group. BP- = Bipolar disorder without psychotic features group. NC = Normal control group. SD = Standard deviation. GAF = Global Assessment of Functioning. HAM-D₂₁ = Hamilton Depression Rating Scale. YMRS = Young Mania Rating Scale. BPRS = Brief Psychiatric Rating Scale. TD = Brief Psychiatric Rating Scale Thought Disturbance factor.

^an=19. ^bn=16. ^cn=22. ^dn=23. ^en=21. ^fGiven that none of the NC participants were taking any psychiatric medications, only the three psychiatric groups (i.e., SZ, BP+, and BP-) were included in the chi-square analyses for medication status.

although all groups were euthymic on average at time of testing, the BP+ and BP- groups reported and demonstrated significantly more sub-threshold symptoms of both depression and mania than did the NC group, although there were no significant differences between the BP+ and BP- groups themselves.

Groups were also compared on total Brief Psychiatric Rating Scale (BPRS) scores, as well as on four factor scores as identified by Mueser, Curran, and McHugo (1997). Significant between group differences were found for the BPRS total score, $F(3, 92) = 56.59, p < .001$, with post-hoc tests indicating that the SZ group demonstrated significantly more psychiatric symptoms at time of assessment than the BP+ and BP- groups (see Table 5, as well as Figure 2). Additionally, all psychiatric groups demonstrated significantly more psychiatric symptoms than did the NC group, as would be expected. Furthermore, there were significant differences among groups on the following: the BPRS Thought Disturbance factor, a measure of the positive symptoms commonly associated with schizophrenia, $F(3, 92) = 35.14, p < .001$; the Anergia factor, a measure of the negative symptoms generally related to schizophrenia, $F(3, 92) = 24.52, p < .001$; the Affect factor, a reflection of emotional disturbances, $F(3, 92) = 13.29, p < .001$; and, the Disorganization factor, a measure of the symptoms of disorganized behavior often exhibited in individuals with schizophrenia, $F(3, 92) = 23.07, p < .001$. Post-hoc analyses indicated that the SZ group demonstrated significantly more symptoms of thought disturbance and anergia than did the BP+, BP-, and NC groups, that the SZ, BP+, and BP- groups demonstrated significantly more symptoms of affect than the NC group, and that the SZ group demonstrated significantly more symptoms of

Figure 2. Brief Psychiatric Rating Scale (BPRS) Factor and Total Scores for the Groups.



Note. SZ = Schizophrenia group. BP+ = Bipolar disorder with psychotic features group.

BP- = Bipolar disorder without psychotic features group. NC = Normal control group.

TD = BPRS Thought Disturbance factor. An = BPRS Anergia factor. Aff = BPRS Affect

factor. Dis = BPRS Disorganization factor. Total = BPRS Total Score.

disorganization than the BP+, BP-, and NC groups, with the BP+ and BP- groups also having demonstrated significantly more symptoms of disorganization than the NC group.

Given the significant differences in symptomatology in the groups, Pearson correlations were used to evaluate the relationships between psychiatric symptomatology at time of testing and neurocognitive performance in the psychiatric groups (see Tables 6 and 7). Bonferroni corrections were used to account for inflated Type I error rates due to multiple correlations. No significant relationships were found between the ratings of the Young Mania Rating Scale or the Hamilton Depression Rating Scale and neurocognitive performance. Additionally, only two significant relationships were found between the Affect factor of the Brief Psychiatric Rating Scale, namely with CVLT % Recall Primacy and Recency Region. Conversely, multiple significant relationships were found between the remaining factor scores of the Brief Psychiatric Rating Scale, as well as the Total Score of the Brief Psychiatric Rating Scale. In fact, significant relationships were found for all variables with at least one of the remaining factor scores (i.e., Thought Disturbance, Anergia, and Disorganization) and/or the Total Score, with the exception of CVLT % Recall Primacy Region, Biber % Recall Primacy Region, Biber % Recall Middle Region, Biber % Recall Recency Region, Biber Free Recall Intrusions, and Biber Response Bias.

In other words, greater symptomatology at time of testing was generally associated with more impaired neurocognitive functioning, although mood symptoms at time of testing were not found to be significantly related to neurocognitive performance. Notably, however, the presence of negative symptoms, in addition to positive symptoms, did exhibit significant relationships with performance on neurocognitive variables,

Table 6. Pearson Correlation Coefficients between Symptomatology at Time of Testing and Non-Strategy-Based Learning and Memory Variables.

	CVLT Variables				Biber Variables			
	SD	LD	T1	Dis	SD	LD	T1	Dis
YMRS	-.10	-.04	-.06	-.20	-.21	-.16	-.37	.01
HAM-D ₂₁	-.08	-.22	.04	.19	-.30	-.42*	-.26	-.17
BPRS								
TD	-.57**	-.62**	-.50**	-.56**	-.49**	-.57**	-.39**	-.44**
An	-.54**	-.58**	-.55**	-.41**	-.56**	-.53**	-.48**	-.47**
Aff	-.04	-.11	-.01	.04	-.01	-.11	-.01	-.11
Dis	-.55**	-.62**	-.43**	-.42**	-.53**	-.53**	-.33*	-.47**
Total	-.65**	-.74**	-.59**	-.54**	-.61**	-.67**	-.47**	-.57**

Note. CVLT = California Verbal Learning Test. Biber = Biber Figure Learning Test-

Extended. SD = Short Delay. LD = Long Delay. T1 = Trial 1. Dis = Distractor. YMRS =

Young Mania Rating Scale. HAM-D₂₁ = Hamilton Depression Rating Scale. BPRS =

Brief Psychiatric Rating Scale. TD = Brief Psychiatric Rating Scale Thought Disturbance

factor. An = Brief Psychiatric Rating Scale Anergia factor. Aff = Brief Psychiatric Rating

Scale Affect factor. Dis = Brief Psychiatric Rating Scale Disorganization factor. Total =

Brief Psychiatric Rating Scale Total Score.

* $p < .05$ (with Bonferroni correction, when $p < .00625$).

** $p < .01$ (with Bonferroni correction, when $p < .00125$).

Table 7. Pearson Correlation Coefficients between Symptomatology at Time of Testing and Strategy-Based Learning and Memory Variables.

	CVLT Variables							Biber Variables						
	Pri	Mid	Rec	Int	RB	RFP	R/R	Pri	Mid	Rec	Int	RB	RFP	R/R
YMRS	-.04	-.01	.02	.05	.03	-.16	-.17	-.13	.08	.05	-.05	.00	-.23	.06
HAM-D ₂₁	-.09	-.14	.26	.07	-.22	-.05	.06	.03	.01	.00	.00	.19	-.27	-.15
BPRS														
TD	-.04	-.29	.21	-.33	-.43**	-.37*	-.28	.09	-.17	-.20	-.26	.06	-.48**	-.35*
An	.24	-.39*	.17	-.30	-.56**	-.20	-.18	-.03	-.02	-.16	-.14	.04	-.46**	-.27
Aff	-.42**	-.09	.36*	-.04	-.11	-.08	-.08	.05	-.11	.08	-.02	.21	-.18	-.14
Dis	-.03	-.44**	.40**	-.21	-.35*	-.42**	-.34	.10	.06	-.31	-.16	.05	-.41*	-.45**
Total	-.09	-.44**	.40**	-.35*	-.56**	-.40**	-.32	.06	-.10	-.22	-.25	.16	-.60**	-.46**

Note. CVLT = California Verbal Learning Test. Biber = Biber Figure Learning Teset-Extended. YMRS = Young Mania Rating Scale.

HAM-D₂₁ = Hamilton Depression Rating Scale. Pri = % Recall Primacy Region. Mid = % Recall Middle Region. Rec = % Recall Recency Region. Int = Free Recall Intrusions. RB = Response Bias. RFP = Recognition False Positives. R/R = Recall/Recognition Score. BPRS = Brief Psychiatric Rating Scale. TD = Brief Psychiatric Rating Scale Thought Disturbance factor. An = Brief Psychiatric Rating Scale Anergia factor. Aff = Brief Psychiatric Rating Scale Affect factor. Dis = Brief Psychiatric Rating Scale Disorganization factor. Total = Brief Psychiatric Rating Scale Total Score.

* $p < .05$ (with Bonferroni correction, when $p < .00357$).

** $p < .01$ (with Bonferroni correction, when $p < .000714$).

suggesting that it may be beneficial to focus future research on the influence of both positive and negative symptoms on impairment.

Significant group differences were also found for the proportion of individuals with bipolar II disorder (as opposed to bipolar I disorder) in the BP+ and BP- groups, chi-square (1) = 7.02, $p = .008$. Specifically, 40% of the BP- group had been diagnosed with bipolar II disorder, compared with only 8% of the BP+ group. As a result, the BP+ and BP- groups were re-evaluated according to type of diagnosis (i.e., bipolar I versus bipolar II disorder). Specifically, the groups were compared on age and education (see Table 8), as well as the non-strategy and strategy-based learning and memory variables via MANOVAs (see Table 9). Notably, the groups did not differ significantly on age or education.

Table 8. Comparison of the Bipolar I and Bipolar II Disorder Groups on Age and Education.

Variables	Group				<i>F</i>	<i>p</i>
	BPI (n=38)		BPII (n=12)			
	Mean	SD	Mean	SD		
Age	35.21	14.20	31.08	9.38	0.88	.352
Education	14.26	2.43	14.92	2.23	0.68	.413

Note. BPI = Bipolar I disorder group. BPII = Bipolar II disorder group. SD = Standard deviation.

Table 9. Results of the MANOVAs Comparing the Bipolar I and Bipolar II Disorder Groups on Non-Strategy-Based and Strategy-Based Learning and Memory Variables.

	<i>F</i>	<i>p</i>
Non-strategy-based learning and memory variables	1.10	.385
Strategy-based learning and memory variables	0.78	.683

Additionally, neither of the MANOVAs comparing the groups on the neurocognitive variables yielded significant differences (for non-strategy-based learning and memory variables, $F(8,41) = 1.10, p = .385$; for strategy-based learning and memory variables, $F(14, 35) = 0.78, p = .683$). This overall similarity in performance between the bipolar I and bipolar II disorder groups suggests that any differences in performance found between the BP+ and BP- groups were likely not due to differences in the make-up of the groups in terms of percentage of individuals diagnosed with bipolar I versus bipolar II disorder.

There were also significant differences in medication status among the groups, even with NCs excluded from the analyses. Differences in medication status were as follows: regarding antipsychotics, chi-square (2) = 22.04, $p < .001$, as 96% of the SZ group, 56% of the BP+ group, and 32% of the BP- group were taking antipsychotics at time of testing; regarding mood stabilizers, chi-square (2) = 10.01, $p = .007$, as 60% of the SZ group, 80% of the BP+ group, and 36% of the BP- group were taking mood stabilizers at time of testing; regarding antidepressants, chi-square (2) = 17.11, $p < .001$, as 0% of the SZ group, 36% of the BP+ group, and 52% of the BP- group were taking antidepressants at time of testing; and, regarding anti-anxiety medications, chi-square (2) = 9.16, $p = .010$, as 4% of the SZ group, 32% of the BP+ group, and 8% of the BP- group

were taking anti-anxiety medications at time of testing. There were also significant differences for the proportion of individuals who were un-medicated at the time of assessment, chi-square (2) = 3.03, $p = .220$, as 4% of the SZ group, 12% of the BP+ group, and 20% of the BP- group were not medicated at time of testing.

Given the significant differences in medication status in the groups, Spearman correlations were used to evaluate the relationships between medication status and neurocognitive performance (see Tables 10 and 11). The neurocognitive performance of the NC group was not included in these analyses, as none of the NC participants were taking psychiatric medications at time of testing. Additionally, Bonferroni corrections were used to account for inflated Type I error rates due to multiple correlations. Significant relationships were present between use of antipsychotics and of antidepressants at time of testing with both non-strategy-based and strategy-based learning and memory variables. In such cases, medication use was at times found to be associated with better performance on the neurocognitive variables, and at other times to be associated with worse performance on the neurocognitive variables.

Data Transformations

As previously stated, a number of the variables (specifically, CVLT Primacy, CVLT Middle, CVLT Recency, CVLT Intrusions, CVLT Recognition False Positives, CVLT Recall/Recognition, Biber Primacy, Biber Middle, Biber Recency, Biber Intrusions, Biber Recognition False Positives, and Biber Recall/Recognition) were not normally distributed, and were thus transformed into ranked data to accommodate for this non-normality. Additionally, given that these variables made up the vast majority (i.e., 12 of 14, or 85.71%) of those included in the second MANOVA, the remaining two

Table 10. Spearman Correlation Coefficients between Medication Status and Non-Strategy-Based Learning and Memory Variables.

Type of Medication	CVLT Variables				Biber Variables			
	SD	LD	T1	Dis	SD	LD	T1	Dis
Antipsychotic ^a	.43**	.47**	.28	.47**	.41**	.39**	.31	.49**
Mood Stabilizer ^a	.10	.17	.18	.09	.14	.22	.17	.15
Antidepressant ^a	-.39**	-.36*	-.37*	-.25	-.29	-.34*	-.22	-.41*
Anti-Anxiety ^a	.02	.10	.13	.04	.15	.16	.13	.15
Not Medicated ^a	-.18	-.17	-.11	-.18	-.18	-.18	-.13	-.19

Note. CVLT SD = California Verbal Learning Test. Biber = Biber Figure Learning Test-

Extended. SD = Short Delay. LD = Long Delay. T1 = Trial 1. Dis = Distractor.

^aNormal control participants were not included in these analyses.

* $p < .05$ (with Bonferroni correction, when $p < .00625$).

** $p < .01$ (with Bonferroni correction, when $p < .00125$).

Table 11. Spearman Correlation Coefficients between Medication Status and Strategy-Based Learning and Memory Variables.

Type of Medication	CVLT Variables							Biber Variables						
	Pri	Mid	Rec	Int	RB	RFP	R/R	Pri	Mid	Rec	Int	RB	RFP	R/R
Anti-psychotic ^a	.01	.19	-.16	.34*	.24	.33	.22	-.13	.06	.15	.19	.07	.22	.23
Mood Stabilizer ^a	.02	.10	-.14	.20	.08	-.07	-.03	.23	-.15	-.13	.20	-.08	.23	.14
Anti-depressant ^a	.10	-.25	.13	-.17	-.39**	-.24	-.24	.17	-.08	-.25	-.07	.05	-.21	-.22
Anti-Anxiety ^a	.15	.00	-.20	.11	.00	-.18	.02	-.03	.06	-.04	.10	-.23	.21	.23
Not Medicated ^a	-.16	.02	.07	-.21	-.02	-.11	-.11	-.04	.19	-.08	-.15	-.05	-.17	-.19

Note. CVLT = California Verbal Learning Test. Biber = Biber Figure Learning Test-Extended. Pri = % Recall Primacy Region. Mid = % Recall Middle Region. Rec = % Recall Recency Region. Int = Free Recall Intrusions. RB = Response Bias. RFP = Recognition False Positives. R/R = Recall/Recognition Score.

^aNormal control participants were not included in these analyses.

* $p < .05$ (with Bonferroni correction, when $p < .00357$).

** $p < .01$ (with Bonferroni correction, when $p < .000714$).

variables – that is, CVLT and Biber Response Bias – were transformed into ranked variables as well. However, several transformations were performed on these two variables before they were ranked. Specifically, standard scores were derived using the mean and standard deviation of the NC group for the two variables. Large z-scores, whether positive or negative, were indicative of greater positive and negative response biases, respectively. For this reason, the absolute value of the z-scores for each of the participants was taken, so that deviations from the mean, whether positive or negative, were equally weighted. These variables were then reverse scored so that higher scores reflected better performance. The variables were then ranked and included in the MANOVA.

Several other variables were also reverse scored so that higher scores reflected better performance, including CVLT Intrusions, CVLT Recognition False Positives, CVLT Recall/Recognition, Biber Intrusions, Biber Recognition False Positives, and Biber Recall/Recognition. It was at this point that the variables for the second MANOVA were converted to ranked scores. See Tables 12-15 for a comparison of unranked and ranked scores for each of the groups, as well as Table 16 for a comparison of the raw scores of the groups for CVLT and Biber Primacy, Middle and Recency.

Analyses of the Main Hypotheses

Following the completion of the preliminary analyses, multivariate analyses of variance (MANOVAs) were used to test each of the three main hypotheses and to evaluate for the presence of differences among the groups on the neurocognitive variables. The first MANOVA was performed using the general (i.e., CVLT and Biber Short Delay Correct and Long Delay Correct) and short-term (i.e., CVLT and Biber Trial 1 Correct

Table 12. Unranked and Ranked Scores for the Schizophrenia Group.

Variables	Unranked		Ranked	
	Mean	SD	Mean	SD
CVLT % Recall Primacy Region	28.63	13.27	50.62	39.30
CVLT % Recall Middle Region	37.04	10.53	32.74	28.43
CVLT % Recall Recency Region	34.33	17.88	63.88	37.78
CVLT Intrusions	5.44	6.25	29.14	22.43
CVLT Response Bias	-0.02	0.59	25.66	21.29
CVLT Recognition False Positives	4.84	5.74	28.44	26.36
CVLT Recall/Recognition	4.68	3.15	29.28	23.29
Biber % Recall Primacy Region	35.90	19.33	57.56	38.78
Biber % Recall Middle Region	42.06	16.69	42.34	36.07
Biber % Recall Recency Region	22.04	10.93	38.30	35.39
Biber Intrusions	4.08	6.61	37.02	28.51
Biber Response Bias	0.17	0.54	48.94	38.86
Biber Recognition False Positives	8.20	7.70	22.16	18.99
Biber Recall/Recognition	4.24	4.68	27.86	26.97

Note. CVLT = California Verbal Learning Test. Biber = Biber Figure Learning Test-Extended.

Table 13. Unranked and Ranked Scores for the Bipolar Disorder with Psychosis Group.

Variables	Unranked		Ranked	
	Mean	SD	Mean	SD
CVLT % Recall Primacy Region	29.46	5.42	55.10	27.45
CVLT % Recall Middle Region	43.42	7.58	52.42	30.38
CVLT % Recall Recency Region	27.12	4.74	48.06	25.76
CVLT Intrusions	1.12	1.54	60.76	25.95
CVLT Response Bias	-0.04	0.34	55.16	26.63
CVLT Recognition False Positives	0.76	1.27	56.98	24.72
CVLT Recall/Recognition	1.72	2.59	56.84	31.02
Biber % Recall Primacy Region	29.77	4.37	45.90	24.28
Biber % Recall Middle Region	43.18	10.09	55.74	29.29
Biber % Recall Recency Region	27.05	10.23	53.84	31.12
Biber Intrusions	0.96	1.46	51.84	25.31
Biber Response Bias	0.68	0.46	53.26	23.64
Biber Recognition False Positives	1.76	3.06	56.34	26.45
Biber Recall/Recognition	1.56	2.22	54.34	27.01

Note. CVLT = California Verbal Learning Test. Biber = Biber Figure Learning Test-Extended.

Table 14. Unranked and Ranked Scores for the Bipolar Disorder without Psychosis

Group.

Variables	Unranked		Ranked	
	Mean	SD	Mean	SD
CVLT % Recall Primacy Region	27.26	4.12	43.94	22.79
CVLT % Recall Middle Region	46.33	4.74	62.10	24.33
CVLT % Recall Recency Region	26.41	4.87	43.74	24.18
CVLT Intrusions	1.92	3.10	53.00	27.99
CVLT Response Bias	0.01	0.30	59.12	25.16
CVLT Recognition False Positives	0.84	1.28	54.08	24.53
CVLT Recall/Recognition	2.28	1.88	50.08	22.94
Biber % Recall Primacy Region	29.88	6.83	48.60	29.95
Biber % Recall Middle Region	44.06	5.48	53.40	27.26
Biber % Recall Recency Region	26.06	3.82	54.54	24.01
Biber Intrusions	0.76	1.51	56.46	23.31
Biber Response Bias	0.66	0.46	51.08	23.93
Biber Recognition False Positives	1.32	2.27	57.38	23.78
Biber Recall/Recognition	1.28	1.86	56.96	25.88

Note. CVLT = California Verbal Learning Test. Biber = Biber Figure Learning Test-

Extended.

Table 15. Unranked and Ranked Scores for the Normal Control Group.

Variables	Unranked		Ranked	
	Mean	SD	Mean	SD
CVLT % Recall Primacy Region	27.94	4.41	52.34	24.15
CVLT % Recall Middle Region	44.69	6.75	54.74	25.62
CVLT % Recall Recency Region	27.37	5.19	46.32	23.18
CVLT Intrusions	1.76	4.01	59.10	25.38
CVLT Response Bias	-0.11	0.18	62.06	16.47
CVLT Recognition False Positives	0.32	0.48	62.50	17.85
CVLT Recall/Recognition	1.12	1.76	65.80	24.69
Biber % Recall Primacy Region	29.91	2.47	49.94	20.06
Biber % Recall Middle Region	43.75	4.79	50.52	21.51
Biber % Recall Recency Region	26.34	3.50	55.32	21.59
Biber Intrusions	0.68	1.35	56.68	22.67
Biber Response Bias	0.65	0.50	48.72	21.00
Biber Recognition False Positives	0.48	0.82	66.12	18.19
Biber Recall/Recognition	0.84	1.43	62.84	21.73

Note. CVLT = California Verbal Learning Test. Biber = Biber Figure Learning Test-

Extended.

Table 16. Comparison of the Raw Scores of the Groups for CVLT and Biber Primacy, Middle, and Recency Regions.

Variables	Group							
	SZ (n=25)		BP+ (n=25)		BP- (n=25)		SZ (n=25)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
CVLT Primacy Region								
Number recalled from	8.88	5.11	15.88	2.74	15.32	2.87	16.92	3.24
Total number recalled	28.63	13.27	29.46	5.42	27.26	4.12	27.94	4.41
% Recalled from region	29.80	11.48	54.96	10.96	56.28	7.75	60.60	8.91
CVLT Middle Region								
Number recalled from	11.28	5.93	24.44	7.85	26.08	4.39	27.36	6.40
Total number recalled	37.04	10.53	43.42	7.58	46.33	4.74	44.69	6.75
% Recalled from region	29.80	11.48	54.96	10.96	56.28	7.75	60.60	8.91
CVLT Recency Region								
Number recalled from	9.64	4.88	14.64	2.80	14.88	3.24	16.32	2.25
Total number recalled	34.33	17.88	27.12	4.74	26.41	4.87	27.37	5.19
% Recalled from region	29.80	11.48	54.96	10.96	56.28	7.75	60.60	8.91
Biber Primacy Region								
Number recalled from	9.12	5.37	15.92	3.29	15.88	3.77	17.48	2.31
Total number recalled	35.90	19.33	29.77	4.37	29.88	6.83	29.91	2.47
% Recalled from region	25.36	12.56	54.16	11.50	53.44	10.77	58.72	8.15
Biber Middle Region								
Number recalled from	10.68	6.08	25.08	5.91	23.72	6.11	25.88	5.15
Total number recalled	42.06	16.69	43.18	10.09	44.06	5.48	43.75	4.79
% Recalled from region	25.36	12.56	54.16	11.50	53.44	10.77	58.72	8.15
Biber Recency Region								
Number recalled from	5.56	3.70	13.16	4.03	13.84	3.02	15.36	2.23
Total number recalled	22.04	10.93	27.05	10.23	26.06	3.82	26.34	3.50
% Recalled from region	25.36	12.56	54.16	11.50	53.44	10.77	58.72	8.15

Note. SZ = Schizophrenia group. BP+ = Bipolar disorder with psychotic features group.

BP- = Bipolar disorder without psychotic features group. NC = Normal control group. SD

= Standard deviation. CVLT = California Verbal Learning Test.

and Distractor Correct) memory factors. The second MANOVA was performed using

the primacy/recency (i.e., CVLT and Biber % Recall from the Primacy, Middle, and

Recency regions) and response discrimination (i.e., CVLT and Biber Free Recall

Intrusions, Response Bias, and Recognition False Positives) factors, as well as a derived Recall/Recognition score, also for both the CVLT and Biber. For each of the two MANOVAs, the neurocognitive variables served as the dependent factors, and the diagnostic category (i.e., SZ, BP+, BP-, and NC) served as the between-subjects factor. One-way analyses of variance (ANOVAs) were also run for all variables when the overall MANOVA was significant, with post-hoc tests used to identify significant between-group differences when ANOVAs yielded significant results.

For each of the two MANOVAs, analyses were initially conducted using age and education as covariates both individually and in combination with one another, given that significant group differences were found for these variables.

For the first MANOVA (i.e., evaluating the groups on the variables associated with the general and short-term memory factors), neither age ($F(8, 88) = 1.29, p = .258$) nor education ($F(8, 88) = 0.51, p < .846$) were found to be significant predictors when used as covariates individually, nor were they found to be significant predictors when used as covariates together (age $F(8, 87) = 1.47, p = .180$, education $F(8, 87) = 0.69, p = .704$). Additionally, there were no significant interaction effects between diagnosis and age ($F(32, 348) = 1.10, p = .333$) or diagnosis and education ($F(32, 348) = 0.84, p = .726$). As a result, neither of these variables was used as a covariate in the final evaluation of Hypothesis 1.

Similarly, for the second MANOVA (i.e., evaluating the groups on the variables associated with the primacy/recency and response discrimination factors, as well as the CVLT and Biber Recall/Recognition scores), neither age ($F(14, 82) = 1.37, p = .187$) nor education ($F(14, 82) = 0.63, p = .835$) were found to be significant predictors when used

individually as covariates, nor were they found to be significant predictors when used as covariates together (age $F(14, 81) = 1.53, p = .118$, education $F(14, 81) = 0.78, p = .686$). Additionally, there were no significant interaction effects between diagnosis and age ($F(56, 324) = 1.26, p = .111$) or diagnosis and education ($F(56, 324) = 1.11, p = .286$). As a result, neither of these variables was used as a covariate in the final evaluation of Hypothesis 2.

Although there were also significant differences between groups for premorbid ($F(3, 96) = 38.47, p < .001$) and current ($F(3, 96) = 21.21, p < .001$) IQ estimates, some researchers have argued that such differences, specifically that individuals with severe mental illness have significantly lower premorbid and current IQ estimates than do unaffected individuals, are characteristics of the disorders themselves, and thus should not be covaried out of statistical analyses when comparing these groups to one another and to unaffected individuals (Dennis et al., 2009). For this reason, neither premorbid nor current IQ was included in the analyses as a covariate.

Given the significant relationships identified between symptomatology at time of testing and neurocognitive performance across a number of the non-strategy-based and strategy-based learning and memory variables, symptomatology ratings were also considered as covariates for the two MANOVAs. Specifically, the significant relationships noted between the neurocognitive variables and the Thought Disturbance, Anergia, and Disorganization factors of the Brief Psychiatric Rating Scale suggested a potential influence of these factors on neurocognitive performance. A variable was therefore computed as the sum of these factor scores for each participant (including NCs) and was included as a covariate in each of the MANOVAs. This variable was not a

significant predictor when used as a covariate for either of the MANOVAs (first MANOVA $F(8, 84) = 1.32, p = .245$, second MANOVA $F(14, 78) = 1.19, p = .301$). This variable was therefore not included as a covariate in the final analyses of either of the hypotheses.

Box's Test of Equality of Covariance Matrices was computed to examine whether the assumption of normality of variance-covariance had been met for each of the two MANOVAs. Box's M was not significant for the first MANOVA, Box's $M = 124.05, F = 0.98, p = .555$. Conversely, Box's M was significant for the second MANOVA, Box's $M = 700.04, F = 1.63, p < .001$. Pillai's trace was thus used to calculate F (Tabachnick & Fidell, 2001) for both MANOVAs.

Hypothesis 1: Across all memory scores, degradation in learning and memory will be present across all groups based on severity of psychosis, so that the NC group will exhibit normal performance, with the BP- group exhibiting the least severe deficits, followed by the BP+, and finally the SZ group, which will have the worst performance. These differences between groups will be statistically significant ($p < .05$).

To evaluate Hypothesis 1, a MANOVA was computed using the general (i.e., Short Delay Correct and Long Delay Correct) and short-term (i.e., Trial 1 Correct and Distractor Correct) factor variables for both the CVLT and the Biber. Results indicated a significant difference among the groups, $F(3, 96) = 4.05, p < .001$ (see Table 17).

Given the statistical significance of the overall MANOVA, individual ANOVAs and subsequent post-hoc tests were used to identify group differences for each of the neurocognitive variables (see Table 18, as well as Figures 3 and 4). These analyses indicated that the SZ group performed significantly worse than the BP+, BP-, and NC

Table 17. Results of the MANOVAs.

	<i>F</i>	<i>p</i>
General Memory and Short-term Memory Factors	4.05	<.001
Primacy/Recency and Response Discrimination Factors, and Recall/Recognition Scores	2.25	<.001

Table 18. Neurocognitive Performance of the Groups on Non-Strategy-Based Learning and Memory Variables.

Variables	Group								Effect Size ^c					
	SZ (n=25)		BP+ (n=25)		BP- (n=25)		NC (n=25)		BP+ vs. BP-	BP+ vs. NC	BP- vs. NC	Scheffé		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	<i>F</i>	<i>p</i>	<i>d</i>		<i>d</i>	<i>d</i>
CVLT SD ^a	5.36	3.50	12.04	2.87	12.08	1.91	12.60	2.69	37.94	<.001				SZ < BP+, BP-, NC
CVLT LD ^a	5.16	3.44	12.04	2.91	12.24	1.92	13.00	2.53	44.03	<.001		0.2	0.2	SZ < BP+, BP-, NC
CVLT T1 ^b	4.20	1.71	7.20	2.29	6.96	1.46	8.40	1.80	23.28	<.001		0.3	0.4	SZ < BP-, BP+, NC
CVLT Dis ^b	3.84	1.82	6.80	2.02	7.28	2.07	8.24	2.33	21.02	<.001		0.3	0.2	SZ < BP+, BP-, NC
Biber SD ^a	14.60	11.24	33.56	8.47	33.16	6.76	36.32	7.34	33.43	<.001		0.2	0.2	SZ < BP-, BP+, NC
Biber LD ^a	14.44	10.78	34.76	8.66	35.48	7.45	38.32	7.27	40.30	<.001		0.2	0.2	SZ < BP+, BP-, NC
Biber T1 ^b	9.04	6.71	17.40	6.49	16.52	5.89	20.28	6.54	13.94	<.001		0.2	0.3	SZ < BP-, BP+, NC
Biber Dis ^b	4.72	4.29	15.96	6.84	15.84	7.99	17.96	6.15	21.68	<.001		0.2		SZ < BP-, BP+, NC

Note. SZ = Schizophrenia group. BP+ = Bipolar disorder with psychotic features group. BP- = Bipolar disorder without psychotic

features group. NC = Normal control group. SD = Standard deviation. CVLT SD = California Verbal Learning Test Short Delay.

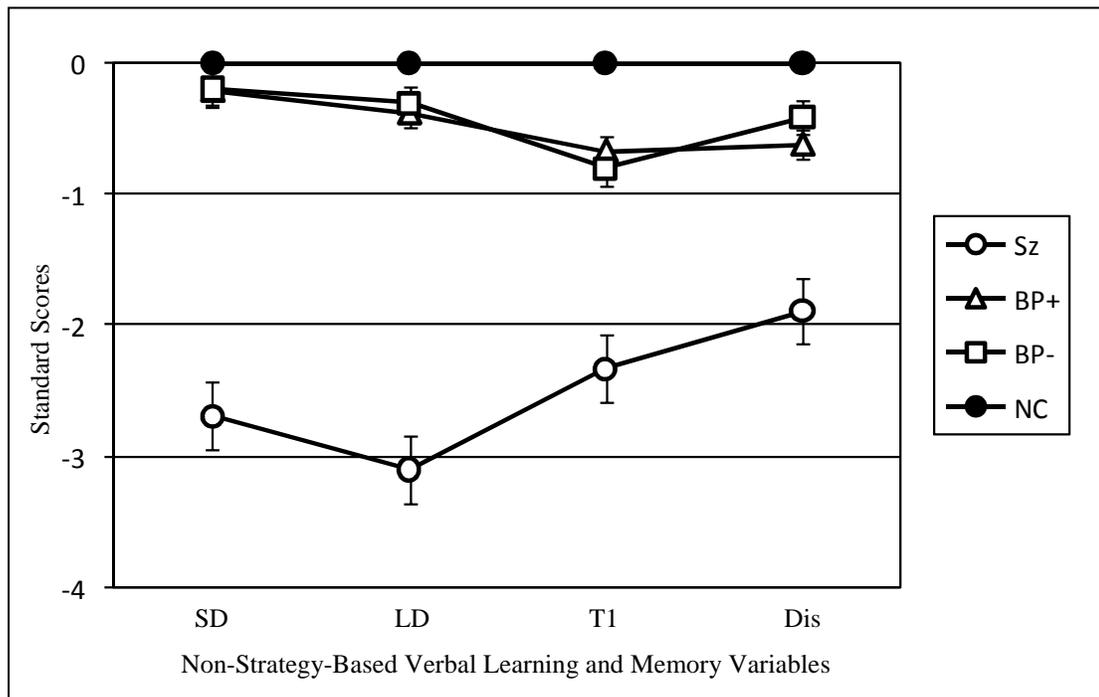
CVLT LD = California Verbal Learning Test Long Delay. CVLT T1 = California Verbal Learning Test Trial 1. CVLT Dis =

California Verbal Learning Test Distractor. Biber SD = Biber Figure Learning Test-Extended Short Delay. Biber LD = Biber Figure

Learning Test-Extended Long Delay. Biber T1 = Biber Figure Learning Test-Extended Trial 1. Biber Dis = Biber Figure Learning Test-Extended Distractor.

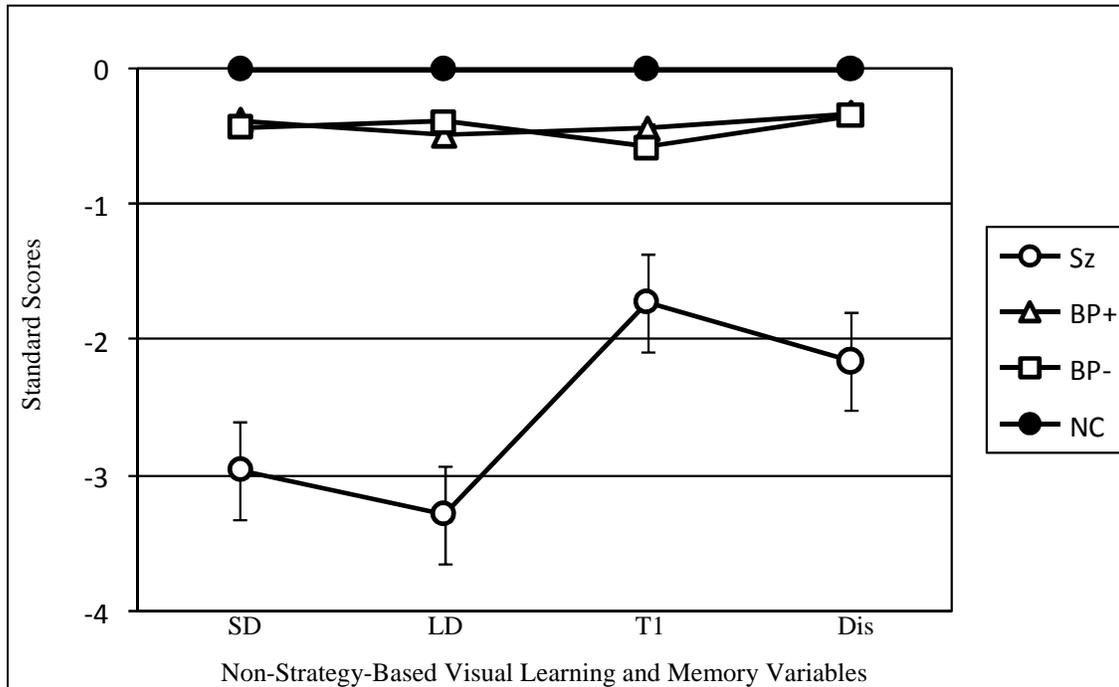
^aGeneral Memory Factor. ^bShort-term Memory Factor. ^cOnly effect sizes which were 0.2 or greater are reported.

Figure 3. Non-Strategy-Based Verbal Learning and Memory Performance of the Groups as Measured by the California Verbal Learning Test.



Note. Sz = Schizophrenia group. BP+ = Bipolar disorder with psychotic features group. BP- = Bipolar disorder without psychotic features group. NC = Normal control group. SD = California Verbal Learning Test Short Delay. LD = California Verbal Learning Test Long Delay. T1 = California Verbal Learning Test Trial 1. Dis = California Verbal Learning Test Distractor.

Figure 4. Non-Strategy-Based Visual Learning and Memory Performance of the Groups as Measured by the Biber Figure Learning Test-Extended.



Note. Sz = Schizophrenia group. BP+ = Bipolar disorder with psychotic features group. BP- = Bipolar disorder without psychotic features group. NC = Normal control group. SD = Biber Figure Learning Test-Extended Short Delay. LD = Biber Figure Learning Test-Extended Long Delay. T1 = Biber Figure Learning Test-Extended Trial 1. Dis = Biber Figure Learning Test-Extended Distractor.

groups on all measures of general and short-term memory. No significant differences were present, however, between the BP+, BP-, or NC groups on any of these variables. This is consistent with the expectation that the SZ group would perform worse than all other groups on these variables, but inconsistent with the hypothesis that the BP+ and BP- groups would perform significantly better than the SZ group, but significantly worse than the NC group. However, there were notable effect sizes, albeit small, for a number of the variables (see Table 18).

Hypothesis 2: In addition to a degradation in memory performance across the clinical groups, the BP- group will exhibit relative sparing of ability on memory test scores that reflect strategy-based deficiencies in learning (e.g., semantic clustering) and retrieval (e.g., normal recall vs. recognition discrepancies), and will not differ from the NC group on these measures. However, the psychosis groups will perform significantly worse ($p < .05$) than the BP- and NC groups on these measures.

To evaluate Hypothesis 2, a MANOVA was computed using the primacy/recency (i.e., % Recall from the Primacy, Middle, and Recency regions) and response discrimination (i.e., Intrusions, Response Bias, and Recognition False Positives) factors for both the CVLT and the Biber, as well as derived Recall/Recognition scores for both measures. Results indicated a significant difference among the groups, $F(3, 96) = 2.25$, $p < .001$ (see Table 17). Given the statistical significance of the overall MANOVA, individual ANOVAs and, when relevant, subsequent post-hoc tests were used to identify group differences for each of the neurocognitive variables (see Table 19, as well as Figures 5 and 6).

Table 19. Neurocognitive Performance of the Groups on Strategy-Based Learning and Memory Variables.

Variables	Group								Effect Size ^g			Scheffé		
	SZ (n=25)		BP+ (n=25)		BP- (n=25)		NC (n=25)		BP+ vs. BP-	BP+ vs. NC	BP- vs. NC			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	<i>F</i>	<i>p</i>	<i>d</i>	<i>D</i>	<i>d</i>	
CVLT Pri ^{a, b}	50.62	39.30	55.10	27.45	43.94	22.79	52.34	24.15	0.66	.577	0.2		0.2	
CVLT Mid ^{a, b}	32.74	28.43	52.42	30.38	62.10	24.33	54.74	25.62	5.23	.002	0.2			SZ < NC, BP-
CVLT Rec ^{a, b}	63.88	37.78	48.06	25.76	43.74	24.18	46.32	23.18	2.57	.058				
CVLT Int ^{b, c, e}	29.14	22.43	60.76	25.95	53.00	27.99	59.10	25.38	8.21	<.001				SZ < BP-, NC, BP+
CVLT RB ^{b, c, d, e}	25.66	21.29	55.16	26.63	59.12	25.16	62.06	16.47	13.66	<.001		0.2		SZ < BP+, BP-, NC
CVLT RFP ^{b, c, e}	28.44	26.36	56.98	24.72	54.08	24.53	62.50	17.85	10.26	<.001			0.2	SZ < BP-, BP+, NC
CVLT R/R ^{b, c}	29.28	23.29	56.84	31.02	50.08	22.94	65.80	24.69	9.15	<.001		0.2	0.3	SZ < BP-, BP+, NC
Biber Pri ^{a, b}	57.56	38.78	45.90	24.28	48.60	29.95	49.94	20.06	0.74	.533				
Biber Mid ^{a, b}	42.34	36.07	55.74	29.29	53.40	27.26	50.52	21.51	1.02	.390				
Biber Rec ^{a, b}	38.30	35.39	53.84	31.12	54.54	24.01	55.32	21.59	2.04	.114				
Biber Int ^{b, c, e}	37.02	28.51	51.84	25.31	56.46	23.31	56.68	22.67	3.41	.021				
Biber RB ^{b, c, d, e}	48.94	38.86	53.26	23.64	51.08	23.93	48.72	21.00	0.15	.932				
Biber RFP ^{b, c, e}	22.16	18.99	56.34	26.45	57.38	23.78	66.12	18.19	19.22	<.001		0.2	0.2	SZ < BP+, BP-, NC
Biber R/R ^{b, c}	27.86	26.97	54.34	27.01	56.96	25.88	62.84	21.73	9.25	<.001		0.2		SZ < BP+, BP-, NC

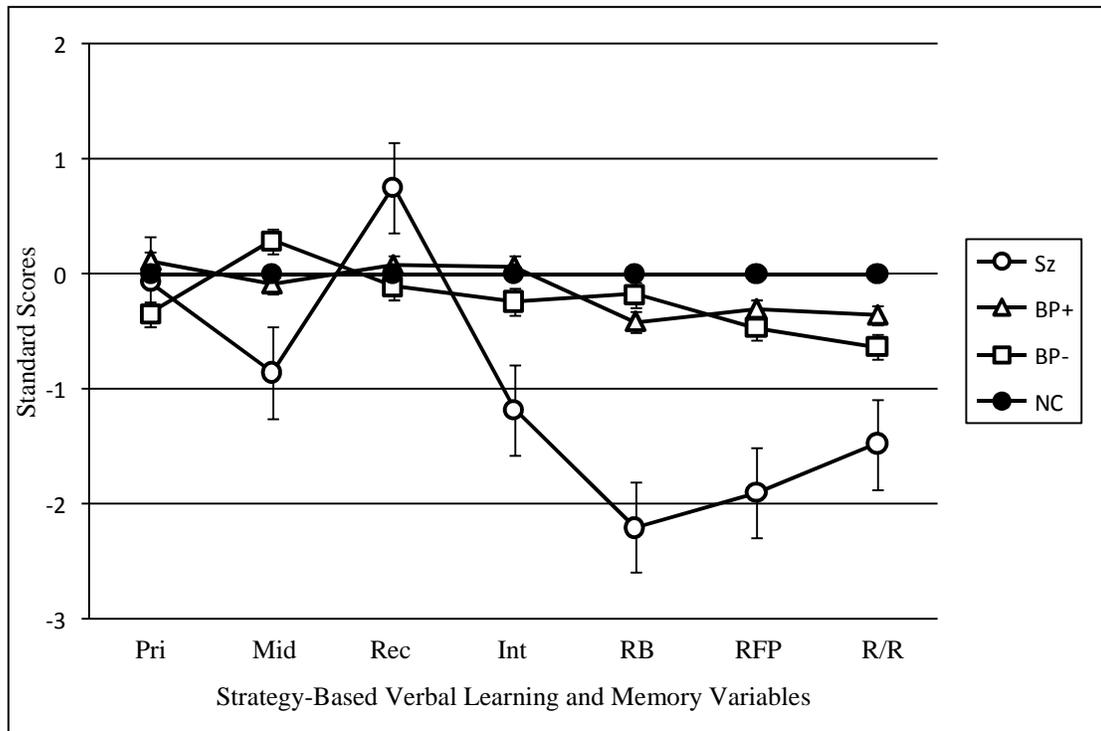
Note. SZ = Schizophrenia group. BP+ = Bipolar disorder with psychotic features group. BP- = Bipolar disorder without psychosis group. NC = Normal control group. SD = Standard deviation. CVLT Pri = California Verbal Learning Test % Recall Primacy Region. CVLT Mid = California Verbal Learning Test % Recall Middle Region. CVLT Rec = California Verbal Learning Test % Recall Recency Region. CVLT Int = California Verbal Learning Test Free Recall Intrusions. CVLT RB = California Verbal Learning Test Response Bias. CVLT RFP = California Verbal Learning Test Recognition False Positives. CVLT R/R = California Verbal Learning

Test Recall/Recognition Score. Biber Pri = Biber Figure Learning Test-Extended % Recall Primacy Region. Biber Mid = Biber Figure Learning Test-Extended % Recall Middle Region. Biber Rec = Biber Figure Learning Test-Extended % Recall Recency Region. Biber Int = Biber Figure Learning Test-Extended Free Recall Intrusions. Biber RB = Biber Figure Learning Test-Extended Response Bias. Biber RFP = Biber Figure Learning Test-Extended Recognition False Positives. Biber R/R = Biber Figure Learning Test-Extended Recall/Recognition Score.

^aPrimacy/Recency Factor. ^bRanked data used. ^cReverse scored. ^dDerived standard score used. ^eResponse Discrimination Factor. ^fn=24.

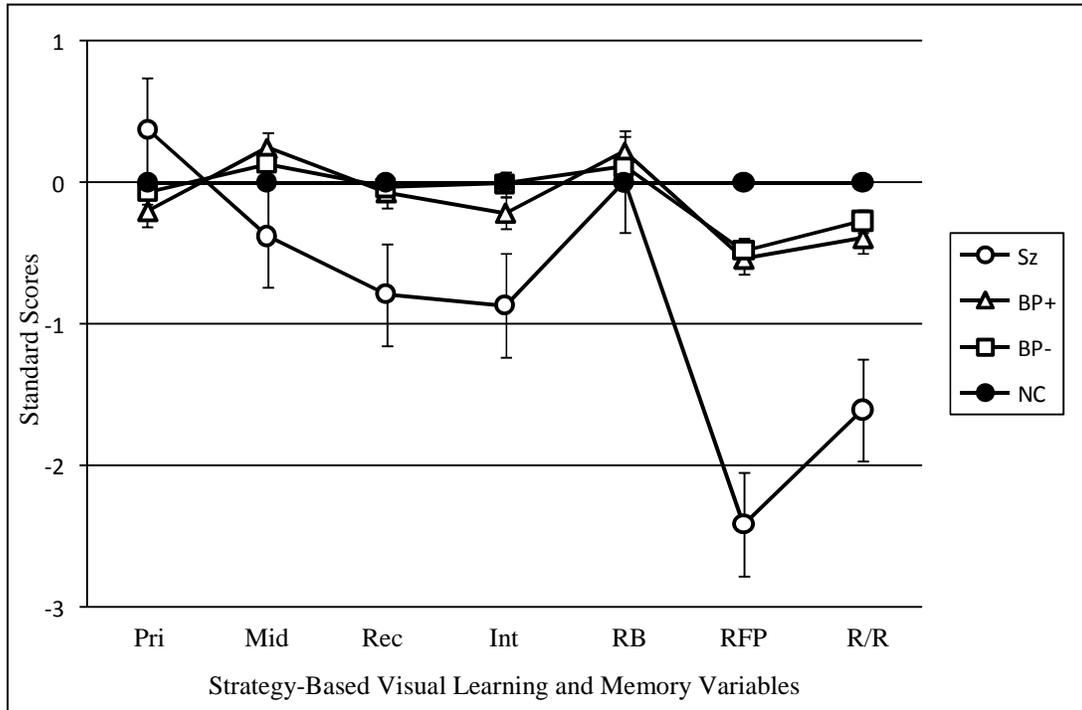
^gOnly effect sizes which were 0.2 or greater are reported.

Figure 5. Strategy-Based Verbal Learning and Memory Performance of the Groups as Measured by the California Verbal Learning Test.



Note. Sz = Schizophrenia group. BP+ = Bipolar disorder with psychotic features group. BP- = Bipolar disorder without psychotic features group. NC = Normal control group. Pri = California Verbal Learning Test % Recall Primacy Region. Mid = California Verbal Learning Test % Recall Middle Region. Rec = California Verbal Learning Test % Recall Recency Region. Int = California Verbal Learning Test Free Recall Intrusions. RB = California Verbal Learning Test Response Bias. RFP = California Verbal Learning Test Recognition False Positives. R/R = California Verbal Learning Test Recall/Recognition Score.

Figure 6. Strategy-Based Visual Learning and Memory Performance of the Groups as Measured by the Biber Figure Learning Test-Extended.



Note. Sz = Schizophrenia group. BP+ = Bipolar disorder with psychotic features group. BP- = Bipolar disorder without psychotic features group. NC = Normal control group. Pri = Biber Figure Learning Test-Extended % Recall Primacy Region. Mid = Biber Figure Learning Test-Extended % Recall Middle Region. Rec = Biber Figure Learning Test-Extended % Recall Recency Region. Int = Biber Figure Learning Test-Extended Free Recall Intrusions. RB = Biber Figure Learning Test-Extended Response Bias. RFP = Biber Figure Learning Test-Extended Recognition False Positives. R/R = Biber Figure Learning Test-Extended Recall/Recognition Score.

Post-hoc tests demonstrated that, within the primacy/recency factor, the SZ group remembered significantly fewer words from the middle portion of the CVLT word list than did the NC and BP- groups, and that the SZ group remembered fewer images from the primacy, middle, and recency portions of the series of figures from the Biber than did the BP+, BP-, and NC groups. Post-hoc tests computed for the response discrimination factor variables indicated that the SZ group had significantly more intrusions on the CVLT, greater CVLT Response Bias, and had significantly more false positives on the recognition portions of both the CVLT and the Biber as compared to the BP+, BP-, and NC groups. Finally, post-hoc analyses of the computed recall/recognition scores indicated that the difference between the number of words and images remembered when presented via the recognition tasks and when the participants were asked to remember the words and images independent of cues was significantly greater for the SZ group than the BP+, BP-, and NC groups for both the CVLT and the Biber, suggesting that the SZ group had greater retrieval difficulties than did any of the other groups. Overall, these findings generally support the hypothesis that the SZ group would perform worse than the BP+, BP-, and NC groups on strategy-based learning and memory variables. However, these findings do not support the hypothesis that the BP+ group would perform better than the SZ group, but worse than the BP- and NC groups, or the hypothesis that the BP- and NC groups would perform similar to one another. However, as with the first MANOVA, there were notable effect sizes, albeit small, for a number of the variables (see Table 19).

Hypothesis 3: No specific hypotheses will be made regarding the interaction between lateralization effects in BP with or without psychosis given the current lack of information in this area. However, given that visual working memory deficits have been suggested as an endophenotype for psychosis and that the findings regarding differential hemispheric involvement in BP have been mixed, it is hypothesized that visual memory performance will be relatively preserved in the BP- group and impaired in the BP+ group.

Finally, Hypothesis 3 was evaluated by comparing the performance of the BP+, BP-, and NC groups on the visual learning and memory variables from both MANOVAs. Contrary to what was expected, there were no significant differences among these groups on any of the visual learning and memory variables (see Tables 18 and 19, as well as Figures 4 and 6).

CHAPTER 5

DISCUSSION

The presence of neurocognitive deficits has been documented extensively in individuals with psychiatric disorders, including bipolar disorder and schizophrenia. Findings regarding such deficits, however, have been mixed across studies. One hypothesis regarding such mixed findings has been that a subset of neurocognitive deficits may successfully differentiate between psychiatric patients with and without concomitant psychotic features. Such deficits may thus be endophenotypic markers of psychosis, rather than an indicator of a particular diagnosis (e.g., SZ vs. BP), leading to the hypothesis that some neurocognitive deficits could potentially be used to identify individuals at-risk for psychosis. This study attempted to demonstrate that neurocognitive performance across a number of strategy-based learning and memory variables would differentiate between groups of individuals with and without psychotic features. In other words, this research explored the idea that schizophrenia and bipolar disorder are related disorders, rather than separate disorders as defined in the current nosological framework outlined by the DSM-IV (APA, 1994).

Based on these considerations, the purpose of this study was to examine the presence and, when applicable, severity of verbal and visual learning and memory deficits in individuals with bipolar disorder with (BP+) and without (BP-) psychosis. A secondary purpose of this study was to determine whether these neurocognitive domains were also impaired in a group of individuals with schizophrenia (SZ). A normal control group (NC) was included for purposes of comparison. Results were expected to indicate deficits in general and short-term verbal and visual learning and memory in all

psychiatric groups, with the most severe deficits anticipated to be found in the SZ group, followed by the BP+ and BP- groups, who were expected to perform similar to one another on these variables. Furthermore, a continuum of severity of deficits was expected to be exhibited across a number of verbal and visual learning and memory variables thought to be dependent on strategy-based learning, with the SZ group demonstrating the most severe deficits, followed by the BP+ group. The BP- group was expected to perform similar to the NC group on these variables. In this manner, learning and memory variables tapping into strategy-based learning were expected to differentiate between individuals with psychiatric disorders with (i.e., SZ and BP+) and without (i.e., BP-) co-occurring psychotic features.

Findings regarding the first hypothesis, namely that the NC group would perform better than the BP- and BP+ groups, who would in turn perform better than the SZ group, on measures of general and short-term memory were mixed. In partial support of this hypothesis, the SZ group did perform significantly worse than all other groups across all general and short-term memory variables. However, there were no significant differences in group performance among the BP+, BP-, and NC groups on any of these variables. Qualitatively speaking, the expected continuum of performance (i.e., SZ < BP+, BP- < NC) was evident, although not statistically significant, for all of the variables included in the general and short-term memory factors. Thus, the expected trend did occur, although the differences between the BP and NC groups were not great enough to allow for statistical significance. However, as previously mentioned there were notable effect sizes, albeit small, for a number of variables (see Table 18). It is possible,

therefore, that significant differences between these groups may have been evident with more power, for example if more participants had been included in the study.

The second hypothesis, in which the NC and BP- groups, and likewise the BP+ and SZ groups, were expected to perform similar to one another on variables of verbal and visual learning and memory thought to reflect strategy-based learning, also yielded mixed results. In partial support of our hypothesis, the SZ group did perform significantly worse than both the NC and BP- groups across many of these variables, while the BP- and NC groups performed similar to one another as expected. However, the BP+ did not demonstrate significant impairments similar to those of the SZ group as expected. Instead, the performance of the BP+ group was found to resemble that of the NC and BP- groups. As with the first hypothesis, performance across groups on the strategy-based learning and memory variables indicated a general trend in the expected direction (i.e., $SZ, BP+ < BP-, NC$) for three of these variables, although differences among the BP+, BP-, and NC groups were not statistically significant. However, for the other three variables in which there was a significant group difference overall, the SZ was found to be more impaired than the other three groups as expected, but the BP- demonstrated poorer performance on the tasks than the BP+ group, with the NC group having performed best (i.e., $SZ < BP- < BP+ < NC$). Yet as with Hypothesis 1, there were notable effect sizes, albeit small, for a number of variables (see Table 19). It is possible, therefore, that significant differences between these groups may have been evident with more power, for example if more participants had been included in the study.

Finally, our third hypothesis, namely that the BP+ group would perform significantly worse than the BP- group across all visual learning and memory variables,

was not substantiated. Qualitatively speaking, the BP+ group demonstrated poorer performance on several visual learning and memory variables, while the BP- group performed worse on others, although none of these differences was statistically significant.

Our findings are concordant with a handful of research which has also yielded unexpected findings regarding verbal learning and memory performance in individuals with BP. For example, van Gorp, Altshuler, Theberge, Wilkins and Dixon (1998) found that a BP with lifetime alcohol dependence group demonstrated significant impairment as compared to normal controls across a number of verbal learning and memory variables. However, a BP without lifetime alcohol dependence group demonstrated significantly lower performance on some (i.e., CVLT Trials 1-5 Correct, Short Delay Cued Recall, and Long Delay Cued Recall), but not all (i.e., CVLT Short Delay Free Recall and Long Delay Free Recall) verbal learning and memory variables. Impairment in short- and long-delay free recall of verbal information may thus be associated with factors other than bipolar disorder itself, such as previous substance dependence. If this is the case, then previous findings of verbal learning and memory impairment may have actually been reflections of comorbid substance dependence, rather than of impairments due to bipolar disorder itself. In consideration of this hypothesis, we compared the neurocognitive performance of psychiatric participants with and without a history of alcohol or substance abuse or dependence via two MANOVAs and found no significant differences between the groups in overall neurocognitive performance for either non-strategy-based ($F(8, 66) = 1.10, p = .374$) or strategy-based ($F(14, 60) = 0.84, p = .627$) learning and memory (see Table 20). It can therefore be assumed that the presence of a

significant substance use history likely had a minimal effect on neurocognitive impairment outside of the psychiatric diagnoses themselves. Additionally, a post-hoc chi-square analysis indicated no significant difference in the proportion of participants with a previous diagnosis of substance or alcohol abuse or dependence in the psychiatric groups (chi-square (2) = 1.71, $p = .424$), suggesting that any negative effect of a history of such diagnoses on neurocognitive function was spread equally among the groups.

Table 20. Results of the MANOVAs Comparing the Neurocognitive Performance of the Previous Substance Use Diagnosis and No Previous Substance Use Diagnosis Groups on Non-Strategy-Based and Strategy-Based Learning and Memory Variables.

	<i>F</i>	<i>p</i>
Non-strategy-based learning and memory variables	1.10	.374
Strategy-based learning and memory variables	0.84	.627

Other research has found evidence of verbal learning and memory impairment in individuals diagnosed with BP to be present only when variables such as age and education have not been used as covariates in the model. Ferrier, Stanton, Kelly, and Scott (1999), for example, compared a group of individuals with BP with no distinctions made between bipolar I disorder and bipolar II disorder, nor between bipolar disorder with and without psychotic features to a group of normal controls. Initial statistical analyses revealed evidence of impairments in both verbal and nonverbal (i.e., visual) learning and memory in the BP group. However, once the analyses were re-run using age, premorbid intelligence, and current depressive symptoms (as measured by the Hamilton

Depression Rating Scale) as covariates, these differences in learning and memory performance were no longer statistically significant for both verbal and visual learning and memory. Upon examination of the study procedures, it is understandable that HDRS scores were used as a covariate, given that there was a statistically significant difference in the degree of depressive symptomatology noted in the BP and normal control groups. However, the authors reported that there were no significant between-group differences with regards to either age or premorbid intelligence. It is therefore unclear why these two variables were included as covariates, other than perhaps due to the traditional use of these variables as covariates within this research area. Nevertheless, the inclusion of such variables as covariates may result in the perhaps erroneous covarying out of effects of the disorders themselves, an argument which has been previously mentioned (Dennis et al., 2009). Given that no variables such were included as covariates in our own research, our findings are concordant with those of Ferrier and colleagues.

Finally, our findings are also somewhat in agreement with research comparing individuals with bipolar disorder with and without psychotic features that have not identified significant group differences on measures of verbal learning and memory. For example, Glahn and colleagues' (2007) evaluation of individuals with bipolar I disorder with and without psychosis found some, but not all, measure of verbal learning and memory to differentiate between the groups, despite significant impairment of both groups on all measures of verbal learning and memory as compared to a normal control group. However, Glahn and colleagues included a sample whose characteristics were more convoluted than that of our own. Specifically, the participants in Glahn and colleagues' research included individuals who were euthymic, depressed, and manic at

time of testing, as well as a large number (specifically, 69% of the participants) of individuals who had a comorbid diagnosis for premorbid substance abuse (as compared to 47% of all psychiatric participants, and 52% of the BP participants, in our own sample). It may therefore be that the presence of such deficits in these populations is reflective of mood state and/or a comorbid substance use diagnosis, rather than to the nature of the psychotic features themselves.

Bora and colleagues (2007) also found no evidence of differential verbal learning and memory impairment according to the presence or absence of psychosis in individuals with BP. However, they did identify significant verbal learning and memory impairment in the BP+ group as compared to the NC group, a finding which is discordant with our own.

The inability of verbal learning and memory level of performance to differentiate between the BP+ and BP- groups in this study is thus in agreement with the findings of a number of other researchers.

In contrast, our failure to find evidence of significant verbal learning and memory deficits in the BP groups compared to the NC group is surprising given a number of previous research studies which have reported such findings (e.g., Atre-Vaidya et al., 1998; van Gorp, Altshuler, Theberge, Wilkins, & Dixon, 1998; van Gorp, Altshuler, Theberge, & Mintz, 1999; Altshuler et al., 2004; Martínez-Arán, Vieta, Colom et al., 2004; Thompson et al., 2005; Robinson et al., 2006; Martínez-Arán et al., 2007; Martino et al., 2008).

Zubieta, Huguelet, O'Neil, and Giordani (2001), for example, found evidence of neurocognitive impairment in a group of individuals diagnosed with BP with psychotic

features in the domains of executive functioning, verbal fluency, attention and concentration, and psychomotor speed. The BP group was also found to have exhibited significant verbal learning and memory deficits as compared to the normal control group in the domain of verbal learning and memory, albeit only on tasks requiring learning and memory of word lists, and not on tasks requiring learning and memory of verbally administered passages, thus suggesting a deficit in the organizational strategy component of memory.

Martínez-Arán and colleagues (2004) reported similar findings, in that individuals with bipolar disorder, whether depressed, manic, or euthymic at time of testing, were found to demonstrate significantly impaired performance in the domain of verbal learning and memory compared to the NC comparison group as measured by the CVLT, although no comparisons were made between the BP+ and BP- groups. Furthermore, the verbal learning and memory impairments were found to be significantly more severely impaired than were other noted neurocognitive impairments, especially in executive functioning, attention and concentration, and verbal fluency. Overall, these findings are obviously discordant with our own, in that we failed to find evidence of impaired verbal learning and memory in either of our BP groups as compared to our NC group. It is unclear, however, whether there was differential impairment according to the presence or absence of psychosis, as no comparisons were made between these groups. It is also unclear whether there were differences according to mood state, as individuals in current episodes were included in addition to euthymic individuals, with no comparisons made between these subgroups. Such studies reporting memory deficits in non-remitted patients, whether depressed or manic at time of testing, may simply reflect state

neurocognitive impairment due to symptomatology, rather than to characteristics of the disorder per se. This hypothesis is in agreement with our failure to find significant correlations between ratings of affect at time of testing and neurocognitive performance; given that all participants were euthymic, no relationship with neurocognitive performance was evident.

Regarding our failure to find evidence of significant group differences on measures of nonverbal (i.e., visual) learning and memory, our findings are in agreement with those of several other studies. For example, as previously mentioned, Ferrier, Stanton, Kelly, and Scott (1999) reported evidence of visual learning and memory deficits in a group of euthymic and non-euthymic individuals diagnosed with bipolar disorder, some with a history of psychosis and some without, as compared to a group of normal controls. However, these differences were no longer significant once age, premorbid intelligence, and current depressive symptomatology were included as covariates in the analysis. Given that the ratings of depressive symptomatology at time of testing were the only of these covariates to have been significantly different between the BP and NC groups, these results suggest that the differences in visual learning and memory performance may have been accounted for by the significantly greater symptoms of depression in the BP group as compared to the NC group. If this is the case, then we could again hypothesize that the initial findings of significantly impaired visual learning and memory in the BP group were present due to the presence of individuals in a current depressed episode at the time of testing, and would not have been evident had only individuals in a current state of euthymia been included, thus potentially providing support for our own findings.

Our findings of no significant impairment in the neurocognitive domain of visual learning and memory in the BP groups are also in agreement with research conducted by Zubieta, Huguelet, O'Neil, and Giordani (2001), as well as Martínez-Arán, Vieta, Reinares, and colleagues (2004), both of whom evaluated individuals diagnosed with bipolar disorder who were in a euthymic state at the time of testing. Martínez-Arán, Vieta, Reinares, and colleagues (2004) also included individuals who were in depressed and manic episodes at time of testing, and included individuals both with and without a history of psychosis, although they were not separated out for purposes of comparison or data analysis. Neither study found evidence of visual learning and memory deficits in the euthymic individuals with BP as compared to normal controls, although Martínez-Arán, Vieta, Reinares, and colleagues did identify deficits in immediate and delayed recall for visual information in the depressed BP group, and in delayed recall for visual information in the manic BP group. Altogether, these results are in agreement with our own in that visual learning and memory impairments were not noted in individuals with BP who were euthymic at the time of testing. It may be that previous research has failed to separate out participants in mood episodes prior to data analysis, and that visual learning and memory impairments are only present during mood episodes and do not persist during periods of euthymia, and thus may not serve as endophenotypic markers of psychosis outside of mood episodes. We may have found differences, therefore, had we evaluated participants who were in a mood episode, and thus actively psychotic in the BP+ group, at time of testing.

A handful of studies have also reported evidence of visual learning and memory deficits in individuals with BP (e.g., Glahn, Barrett et al., 2006; Frantom, Allen, & Cross,

2008), also in contrast to our own findings. Such findings have also been reported in a review conducted by Arts, Jabben, Krabbendam and van Os (2008), who reported evidence of visual learning and memory impairments in euthymic individuals diagnosed with BP.

In contrast to the unexpected nature of our results regarding the bipolar disorder groups, our findings of verbal learning and memory impairment in the schizophrenia group are in agreement with multiple accounts of such deficits in these individuals, independent of the subtype of the disorder (e.g., Brazo et al., 2002; Brickman et al., 2004). Riley and colleagues (2000), for example, found significant deficits in individuals with first-episode schizophrenia, schizophreniform disorder, or schizoaffective disorder as compared to the normal controls on some (i.e., CVLT Trials 1-5), but not all (i.e., CVLT Long Delay Free Recall) measures of verbal learning and memory, as well as on delayed, but not immediate, nonverbal (i.e., visual) learning and memory. Our SZ group, in contrast, was found to demonstrate impairments on both immediate and delayed measures of verbal and visual learning and memory, but was a group of only SZ participants and may thus have been a more pure sample than was that of Riley and colleagues.

Furthermore, Brewer and colleagues (2006) conducted a review of studies which had evaluated the neuropsychological performance of individuals who were deemed “at-risk” for psychosis and determined impairments in olfactory perception and spatial working memory to be vulnerability markers for psychosis. Verbal memory, on the other hand, was not identified as a consistent marker for later development of psychosis. Conversely, Lencz and colleagues (2006) assessed individuals who were demonstrating symptoms which were later determined to have been prodromal symptoms in the onset of

schizophrenia. Upon comparison of individuals who went on to develop psychotic symptoms within the disorder and those who did not, the psychosis participants were found to have demonstrated significantly greater impairment within the verbal learning and memory domain as compared to the non-psychosis participants during the prodromal phase, suggesting that verbal learning and memory impairments may be markers of psychotic features in individuals with schizophrenia. Thus, while our findings are in agreement with some research and in disagreement with other research regarding the identification of verbal learning and memory deficits, our findings fall in line with the “mixed results” nature of investigations into this research idea thus far.

In consideration of this idea, Depp and colleagues (2007) found evidence of a spectrum of verbal learning and memory impairment in a group of psychiatric and non-psychiatric patients, with schizophrenia participants demonstrating the most severe impairment, followed by individuals with bipolar disorder, compared to normal controls. Despite this continuum in performance, however, current positive symptoms were found to not correlate significantly with verbal memory scores. This suggests that, while greater impairment may be expected in individuals with schizophrenia, followed by individuals with bipolar disorder, this continuum of severity in verbal learning and memory impairment may not be due to psychotic symptoms per se, but may be due to some other characteristics of the disorders. In other words, verbal learning and memory performance may not be the discriminating factor for which we are searching, especially given the significant negative relationships found in our sample between increased prevalence and severity of negative symptoms and decreased neurocognitive performance.

Finally, our findings are in disagreement with those of Albus and colleagues (1996), who found evidence of a spectrum of disorders. When psychiatric patients were compared according to the presence or absence of psychotic features, the affective disorders with psychosis group performed similarly to the schizophrenia participants, while the affective disorders without psychosis group performed similarly to the normal controls in the neurocognitive domains of visual motor processing, attention, and verbal learning and memory. These findings are thus in support of the spectrum hypothesis, and thus in contrast to our own, in that we did not find evidence of such differences as evidence of a spectrum of disorders.

Overall, the fact that our research failed to identify verbal and learning memory impairments in a group of individuals diagnosed with bipolar disorder is surprising and somewhat puzzling, especially given our relatively large sample size and the purported sensitivity of the CVLT to verbal learning and memory impairments (Delis, Kramer, Kaplan, & Ober, 2000). Additionally, the lack of differences in verbal and visual learning and memory according to the presence or absence of psychotic features was unexpected.

One potential reason for these unexpected findings is the method of recruitment used throughout the study. As previously mentioned, recruitment efforts focused on referrals from local physicians and mental health agencies, fliers posted on local campuses and around the community, advertisements posted in press releases and listserv e-mails, as well as advertisements at local support group meetings. Furthermore, while there were a number of individuals with bipolar disorder who were recruited from the community (e.g., via Craig's List, announcements made at local bipolar disorder support

group meetings, etc.), the academic campuses of University of Nevada Las Vegas and College of Southern Nevada (formerly Community College of Southern Nevada) were heavily targeted and turned out to be especially fruitful areas to find research participants. Many normal controls were also recruited from these areas. In fact, 80% of the BP+ group, 72% of the BP- group, and 84% of the NC group had at least some education past high school, while only 36% of the SZ group had a greater than high school education.

It is thus possible that, by relying on these locations so heavily for recruitment, our sample became a reflection of a subset of the bipolar disorder population that was generally higher functioning than the typical individual with bipolar disorder, and particularly those who might be recruited from out-patient community mental health facilities, where BP may be more severe and associated with higher levels of disability. Specifically, one study reported that approximately 60% of individuals with bipolar disorder enter college (Glahn, Bearden, Bowden, & Soares, 2006), a figure which is lower than that of our own, in that 76% of the BP+ and BP- participants in the current study completed at least one year of college. In other words, those with bipolar disorder who are high functioning, intelligent and motivated enough to attend college and/or community college may be qualitatively different than those without such qualities, including in the neurocognitive domains of verbal and visual learning and memory. Additionally, the vast majority of the SZ participants were recruited from a community mental health facility (intensive case management) which is a resource for individuals with severe mental illness to receive counseling, access to appropriate psychiatric consultation and treatment, and community support. Individuals who participate in this treatment program are generally lower functioning and more severely impaired than are

those who are able to function on a day-to-day basis without needing to utilize such a resource. These differences in functional impairment may have been compounded by the fact that a greater proportion of the SZ participants (specifically, 84%) were unmedicated at time of testing as compared to the BP+ (12%) and BP- (20%) groups. The disparity in impairment – psychological, neurocognitive, social, occupational, intellectual, etc. – between the SZ and BP groups, not to mention the NC group, may have therefore been even greater than what is typical in the research setting.

The average Global Assessment of Functioning (GAF; APA, 1994) ratings for the groups, however, suggest differences in overall functioning. Specifically, the average GAF scores for the groups were as following: 32.81 for the SZ group, suggesting “some impairment in reality testing or communication *or* major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood”; 56.96 for the BP+ group, suggesting “moderate symptoms *or* any moderate difficulty in social, occupational, or school functioning; 62.64 for the BP- group, suggesting “some mild symptoms *or* some difficulty in social, occupational, or school functioning, but generally functioning pretty well, has some meaningful interpersonal relationships”; and, 88.13 for the NC group, suggesting “absent or minimal symptoms, good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns”. And yet these differences in functioning, while notable, may not have been reflective of true differences in the respective populations. In other words, the SZ group overall may have been lower functioning than the typical individual with schizophrenia, and the BP and NC groups

may have been higher functioning than the typical individual with bipolar disorder and the typical “normal” adult, respectively.

Additionally, previous research with individuals with bipolar disorder has demonstrated that greater neuropsychological impairments are associated with poorer functional outcome (Denicoff et al., 1999), a finding which lends support to the hypothesis that the relatively high-functioning nature of the BP group, both as compared to the SZ group and potentially as compared to a “typical” individual with bipolar disorder, may have at least partially accounted for our inability to find significant evidence of verbal learning and memory impairment in the BP group. Bilder and colleagues (2000) also found that verbal learning and memory impairment alone may not be associated with greater impairment in individuals with schizophrenia, and that instead such impairments in combination with deficits in executive functioning may be more indicative of greater neuropsychological impairment. Taken together, these findings lend support to the hypothesis that our inability to find deficits in verbal learning and memory in either of the BP groups is a reflection of the relatively high functioning nature of the participants in these groups.

Another potential reason for our findings lies in our inclusion of individuals diagnosed with bipolar I disorder and bipolar II disorder in the BP+ and BP- groups. The primary difference between the diagnostic criteria for the two subtypes of the disorders is that, while a diagnosis of bipolar I disorder requires a history of at least one manic or mixed episode, a diagnosis of bipolar II disorder necessitates a *lack* of manic episodes in the individual’s history, and is instead marked by depressive and hypomanic episodes, which are notably less severe in nature than are the traditional manic episodes. As a

result, psychotic symptoms associated with bipolar II disorder occur less frequently and, if present, always occur during episodes of major depression. In contrast, psychotic symptoms are more commonly experienced by individuals suffering from bipolar I disorder, especially during the manic phases of the illness, during which psychotic features are present in approximately 50-68% of cases of mania within bipolar disorder over the lifetime (Keck et al., 2003; Canuso, Bossie, Zhu, Youssef, & Dunner, 2008). Therefore, the significantly greater percentage of individuals diagnosed with bipolar II disorder in the BP- group (40%) as compared to the BP+ group (8%) may at least partially account for our failure to find significant between group differences as expected. In other words, our findings may reflect a lack of significant difference in verbal and visual learning and memory performance in individuals with bipolar I versus bipolar II disorder rather than in individuals with bipolar disorder with and without psychotic features. This hypothesis is supported by the fact that a comparison of the bipolar I and bipolar II participants on the neurocognitive variables in this study yielded significant differences on only two variables, specifically CVLT Distractor and CVLT % Recall Primacy Region.

Additionally, previous research has yielded mixed results concerning the nature of symptomatology associated with deficits in verbal learning and memory. Heinrichs and Vaz (2004), for example, found number of free recall intrusions on the CVLT to be associated with the presence of negative symptoms in a group of 55 individuals diagnosed with schizophrenia, with more intrusions being related to more severe negative symptoms. Conversely, there was no relationship found between verbal learning and memory performance as measured by the CVLT and positive symptoms (i.e., delusions

and hallucinations). This suggests that the strategy-based learning and memory variables used in our own analyses may not be predictive of positive symptoms (i.e., psychosis), but in fact may be related to negative symptoms. In support of this hypothesis, significant correlations were found between the Thought Disorder, Anergia, and Disorganization Factor Scores, as well as the Total Score, of the Brief Psychiatric Rating Scale and all of the non-strategy-based and a majority of the strategy-based learning and memory variables. This suggests that the presence of positive symptoms may not be the only factors we need to be considering.

In contrast, Vaz and Heinrichs (2002) found in the same sample that fewer words recalled on CVLT Trials 1-5 were associated with greater positive, or psychotic, symptoms. Overall, these findings suggest that while some variables may successfully predict positive symptoms, others may not be associated with positive symptoms and may be more strongly predictive of negative symptoms. Unfortunately, our study used a combination of these variables in an attempt to differentiate between individuals experiencing positive (i.e., psychotic) symptoms, and those that were not experiencing such symptoms. Therefore, these findings provide encouragement for our own research, in that the search for variables that consistently differentiate between psychiatric patients suffering from psychosis and those not suffering from psychosis obviously still has strides to make before consistently predictive variables are identified.

A final potential reason for our unexpected results is that neurocognitive factors other than verbal and/or visual learning and memory may be the differentiating factor(s) between psychiatric patients with and without co-occurring psychotic features. Previous research, for example, has yielded evidence of impairments in domains such as working

memory (e.g., Glahn et al., 2006) and executive functioning (e.g., Allen, Randall, Bello, Armstrong, Frantom, & Kinney, in press) as successfully differentiating between such individuals. Whether or not deficits in these domains could also directly or indirectly affect verbal and/or visual learning and memory performance is yet to be determined.

Taking these hypotheses and previous and current research findings into consideration, ideas for future research include replicating this study with a few alterations in protocol. For example, future studies should include only individuals with bipolar I disorder. In this manner, the identification of between-group differences can be more confidently attributed to differences in the presence of psychosis (i.e., BP+ vs. BP-), rather than differences in the presence of manic, hypomanic and/or depressed episodes (i.e., BPI vs. BPII). Future research could also focus on obtaining a more representative sample of BP, including some individuals who exhibit lower functioning.

It may also be beneficial to include a greater variety of verbal and visual tasks in future assessment batteries in addition to those included in this study, especially given the consistency of identification of verbal learning and memory impairments in individuals with bipolar disorder, and the well-founded hypothesis that bipolar disorder is associated with right hemispheric deficits, with the right hemisphere thought to be associated with visual and spatial information processing. The inclusion of tasks which tap into the working memory aspect of verbal and visual learning and memory may additionally allow for the identification of differences in neurocognitive performance in individuals with and without psychosis.

Although research to date has included only limited evidence in support of a spectrum of severity of neurocognitive deficits such as that posited in our own study (i.e.,

SZ < BP+ < BP- < NC), our findings demonstrate a lack of support for this hypothesis remain surprising. A review of prior research led us to hypothesize that differential verbal and visual learning and memory impairments may be the neurocognitive link between these groups of individuals. The presence of psychosis in most individuals with schizophrenia, as well as in a subset of individuals with bipolar disorder, certainly suggests that the two disorders are related. If this is a valid hypothesis, then similarities in neurocognitive deficits may not only present, but should be identifiable. It is our hope that future research may be more successful in pinpointing these deficits, and thus in help to delineate how to best diagnose and treat these often devastating psychiatric illnesses.

APPENDIX 1
DEMOGRAPHIC QUESTIONNAIRE

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

HEALTH-RELATED QUESTIONS

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

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

FAMILY HISTORY QUESTIONS

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

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

- a. What is the disorder?
- | | | | |
|------|---------------------------------|-----|----|
| i. | Schizophrenia | Yes | No |
| ii. | Affective disorder | Yes | No |
| iii. | Alcoholism | Yes | No |
| iv. | Parkinsonism | Yes | No |
| v. | Movement disorder | Yes | No |
| vi. | Schizophrenia spectrum disorder | Yes | No |
| vii. | Other _____ | | |

32. Please list any medications you are currently taking

Current Medications	Dosage	Date Started
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

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Publications:

Allen DN, Donohue B, **Sutton GP**, Haderlie M, LaPota H (accepted 6/23/09).
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