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ABSTRACT

A critical review of neuropsychological results for subjects with bipolar disorder was compared to magnetic resonance imagining (MRI) findings. Studies containing both neuropsychological and MRI outcomes were limited. Therefore, the neuropsychological literature was independently critiqued, then compared to the MRI results from a prior review by Norris, Krishnan, and Ahearn (1997) on structural changes in the brains of patients with bipolar disorder. The reviewed literature appeared to have numerous strengths in research design, but the major limitation was a failure to control statistically for subjects' demographic variables and mediation. The neuropsychological results of persons with bipolar disorder did not reveal generalized deficit but specific functional deficits in memory, learning, and problem solving. These cognitive deficits were well associated with the MRI findings of impaired connections between temporal lobe structures and the prefrontal cortex. Additional analyses of neuropsychological measures and neuroimaging within the same study are strongly suggested. (Contains 32 references.) (Author/CR)

FUNCTIONAL IMPAIRMENT OF BIPOLAR DISORDER: A REVIEW OF THE LITERATURE

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Doctor of Psychology

by

Laura J. Hanisch

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by

Laura J. Hanisch

APPROVED:

Sherwood O. Cole Ph.D
Sherwood Cole, PhD Date 8/29/00

Paul G. Longobardi, PhD
Paul G. Longobardi, PhD Date 8/29/00

APPROVED:

Patricia L. Pike, PhD, Dean

8/29/00
Date

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A critical review of neuropsychological results of subjects with bipolar disorder was compared to magnetic resonance imaging (MRI) findings. Studies containing both neuropsychological and MRI outcomes were limited. Therefore, the neuropsychological literature was independently critiqued then compared to the MRI results reviewed in Norris, Krishnan, and Ahearn (1997). The reviewed literature appeared to have numerous strengths in research design, but the major limitation was a failure to statistically control for subjects' demographic variables and medication. The neuropsychological results of persons with bipolar disorder did not reveal generalized deficit but specific functional deficits in memory, learning, and problem solving. These cognitive deficits were well associated with the MRI findings of impaired connections between temporal lobe structures and the prefrontal cortex. Additional analyses of neuropsychological measures and neuroimaging within the same study are strongly suggested.

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FUNCTIONAL IMPAIRMENT OF BIPOLAR DISORDER: A REVIEW OF THE LITERATURE

Introduction

Diagnosis of bipolar disorder can be a complicated task. The Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV; American Psychiatric Association, 1994) distinguishes four primary bipolar disorders, which are Bipolar I Disorder, Bipolar II Disorder, Cyclothymia, and Bipolar Disorder Not Otherwise Specified (NOS). However, a numerous 32 diagnostic codes, derived from multiple specifiers and criteria sets, identify bipolar subtypes according to the most recent affective episode.

Previous editions of the DSM (American Psychiatric Association, 1980, 1987) have similar bipolar diagnoses but are not as extensive in their diagnostic coding. For example, they do not diagnostically delineate the cycles of major depression or mania followed by hypomanic episodes. Rather, they subsume these possible relationships under the category of Bipolar Disorder NOS or the equivalent Atypical Bipolar Disorder. An additional difference is that the previous manuals do not include as many specifiers, including atypical features and rapid cycling. The comparison of bipolar disorder diagnoses in the DSM editions demonstrates the

evolutionary recognition of the illness' complexity as evidenced by the multiple bipolar disorder codes in the DSM-IV (American Psychiatric Association, 1994).

Not only is diagnosis complicated, but also the etiology of bipolar disorder is unclear. Hilty, Brady, and Hales (1999) reviewed the etiological literature and concluded that there is no explanative theory connecting the genetic, biochemical, and anatomical research. Family, twin, and genetic linkage studies have provided statistical probability of a genetic basis; however, the less than 100% concordance rates in identical twins indicates that factors other than genetics contribute to the causation of the illness (Alda, 1997). The fact that psychopharmacological agents reduce the symptomatology of bipolar illness indicates that neurotransmitters play a role in its existence, and the research has implicated norepinephrine, dopamine, and serotonin.

Evidence of a biological etiology also stems from the results of neuroanatomical and neuroimaging studies. According to Hilty et al. (1999), lesions in the frontal and temporal cortical areas have produced symptoms of bipolar disorder, with left-sided lesions associated with depression and right-sided lesions associated with mania. However, most functional brain imaging techniques have not produced consistent abnormal findings.

The present study is a continuation of researching the possible etiological factors of bipolar disorder by comparing neuropsychological

assessment outcomes to magnetic resonance imaging (MRI) results. Studies containing both neuropsychological assessment and neuroimaging measures were limited. Therefore, the comparison of neuropsychological and MRI results is accomplished in three steps. First, a critical review of studies containing neuropsychological assessment of patients with bipolar disorder is performed. Second, Norris, Krishnan, and Ahearn's (1997) literature review on structural changes in the brain of patients with bipolar disorder by magnetic resonance imaging is summarized. The results from neuropsychological assessments are then compared to those presented in Norris et al. (1997) to determine consistencies and differences and to suggest directions for future research.

Journal articles published during the 1990s and meeting the following criteria were sought in psychology's Psych Lit database. First, studies containing subjects with current or remitted manic symptoms, which satisfied criteria for a mood disorder, were accepted for review. Most subjects had experienced both depressive and manic episodes. Second, studies using more than one neuropsychological measure to assess cognitive abilities were included. Neuropsychological measures from either fixed or flexible batteries were accepted. Third, the bipolar subjects' neuropsychological performances needed to be empirically compared with performances of healthy controls or other psychiatric subjects. Psych Lit results excluded from review included articles containing a combined unipolar and bipolar subject

group and a diagnosis of bipolar disorder resulting from substance abuse, medical illnesses, or brain injury.

The reference sections of the remaining articles were read to ensure that pertinent articles from the 1990s and 1980s were not omitted. Referenced articles were evaluated according to the aforementioned criteria for inclusion. Eighteen studies met criteria and are subsequently reviewed.

Evaluation of Neuropsychological Results

In this section, neuropsychological results of people with bipolar disorder are evaluated according to their common affective episode and to a comparison group. First, people with bipolar disorder are compared to healthy controls. Second, bipolar subjects are compared to what a majority would describe as the most severe mental disorder, schizophrenia. Third, we will compare the two primary affective disorders, bipolar and unipolar depression. Finally, the section will conclude by reviewing the differences within bipolar subjects.

Comparison of Bipolar and Healthy Controls

The first comparison of bipolar and healthy subjects reviews studies using bipolar subjects in the euthymic state. The relevancy of this subject group is to determine if cognitive deficits persist even when bipolar subjects are stabilized on medication. The kind of affective episode was not reported in these studies, so the impact of the most recent mood episode cannot be

known. Following the comparison of euthymic subjects, bipolars with manic, depressive, unspecified, and combined episodes will be compared to healthy controls.

Sapin, Berrettini, Nurnberger, and Rothblat's (1987) research focused on the information processing strategies that contribute to cognitive deficits within bipolar disorder. They analyzed the neuropsychological performance of 20 bipolar subjects, recruited from an outpatient affective disorder clinic, and 20 volunteers, who did not have a history of psychiatric illness or first-degree relatives with psychiatric illness. Subjects' mean intellectual ability, as measured by the Altus Brief Intelligence Test (BIT), was above average, and most subjects had more than a high school education. Bipolar subjects were assessed to be euthymic for one month, stabilized on lithium, but had medication withheld two weeks before testing. No exclusionary criteria were mentioned.

Tests administered included the First Face Recognition Task, Second Face Recognition Task, Benton Visual Retention Test (BVRT), a modified version of Street Gestalt Completion Test (SG), and the Wechsler Adult Intelligence Scale-Revised Edition, selected subtests (WAIS-R: Block Design and Digit Span). The authors noted Block Design and the BVRT to be sensitive to right hemisphere functioning, Digit Span and the BIT to be sensitive to left hemisphere pathology, and face recognition sensitive to hemispheric functioning depending on the visual field tested. Lezak's (1995)

description of the SG indicated that poor performance is associated with right-sided dysfunction.

Results nearing statistical significance included bipolar subjects performing better on the number of correct inverted faces, and controls performing better on the number of correct masked faces. The only significant difference after Bonferoni correction was for control subjects committing fewer errors than bipolar subjects on the SG test. The authors concluded from these results that bipolar subjects have difficulty integrating the various components of visual items and instead rely on details for differentiation. Despite using euthymic, unmedicated, and bright subjects, results indicate that right hemisphere dysfunction cannot be ruled out in bipolar disorder.

Paradiso, Lamberty, Garvey, and Robinson (1997) investigated whether chronic, and subsequently older, unipolar and bipolar subjects would continue to demonstrate cognitive impairment during the euthymic stage as compared to healthy controls. A small psychiatric sample, consisting of 20 unipolar and 11 bipolar subjects, was recruited based on the criteria of hospitalization or two or more acute episodes in a 2-year time period. Patients were stabilized for an average of 38 weeks on an assortment of medications, some of which have adverse effects on neuropsychological performance. Nineteen controls, with statistically comparable ages and education, participated. All subjects were male, right-handed, and were

excluded if they had a neurological disorder or active substance abuse diagnosis.

Tests administered included the Trail Making Test (TMT-A & TMT-B), Consortium to Establish a Registry for Alzheimer's Disease, selected item (CERAD: word list memory-trial 1), Stroop Color and Word Test (SCWT), and the WAIS-R Digit Symbol. Although bipolar subjects performed less well on all tests, none of these differences reached statistical significance. The most notable differences included mild deficits on the TMT-A and Digit Symbol, which exclude language abilities of the left hemisphere. These findings were unexpected due to the recent severity of bipolar illness and subjects' medicated status. Replication with bipolar groups consisting of a larger population, all female subjects, and younger subjects is indicated.

van Gorp, Altshuler, Theberge, Wilkins, and Dixon's (1998) study expanded the neuropsychological domains investigated in previous studies. Twenty-five subjects with a diagnosis of chronic bipolar disorder were euthymic for a minimum of 3 months before testing and had no past or current Axis I comorbidity, except for 12 bipolar subjects meeting criteria for alcohol dependence. Consecutively-admitted bipolar subjects and 22 healthy controls were recruited from an outpatient clinic and veterans affairs medical personnel, respectively. All subjects were male, medically determined to be cortisol- and drug-free before testing, statistically matched for age, premorbid intelligence, and education, and met rigorous

exclusionary criteria. Lithium was the only medication specified, but the authors reported that bipolar subjects had equivalent proportions in types of medications taken. No significant correlations between lithium amounts and test performances were found.

Tests included the California Verbal Learning Test (CVLT), Rey-Osterrieth Complex Figure Test (RCFT), Controlled Oral Word Test (FAS), Wisconsin Card Sorting Test (WCST), SCWT, TMT-A, TMT-B, and the WAIS-R Block Design and Vocabulary. Authors noted that TMT-B performance requires frontal lobe functioning and WCST performance utilizes the hipppocampal function of memory and learning. Both groups of bipolar subjects recalled significantly fewer words than controls within and across the five CVLT trials and after semantic cues. Compared to healthy controls, only the bipolar subjects with alcohol dependence remembered significantly fewer words on short- and long-delay free recall and achieved fewer categories on the WCST.

Analysis of the results indicates that people with bipolar disorder have deficits in memory and learning, but the addition of alcoholism adversely affects problem solving ability and encoding processes necessary for longer-term memory. However, the authors hypothesized that those bipolar subjects, who abused alcohol, had a more severe form of bipolar disorder as evidenced by the greater mean number of episodes and months manic.

Therefore, their cognitive deficits could be a result of both severe bipolar disorder and alcoholism.

Ferrier, Stanton, Kelly, and Scott (1999) investigated whether cognitive deficits persist in bipolar patients during the euthymic phase and if the course of outcome has an effect on cognitive functioning. Patients with a minimum five-year history of Bipolar I Disorder were randomly selected from a list of referred patients and were found to have an average recovery duration of 21 months. Twenty-one bipolars were included in the good-outcome group, as determined by ≤ 2.0 affective episodes in the last 5 years and a maximum 12-week recovery after treatment. Twenty patients were included in the poor-outcome group, as determined by ≥ 3.0 affective episodes or 1 year of unremitting illness within the past 2 years. Outcome criteria were concluded to be face-valid. Twenty healthy controls, who did not have a history of psychiatric illness or first-degree relatives with bipolar disorder, participated. All subjects passed extensive exclusionary criteria and were well matched for age, gender, and premorbid intelligence.

Tests included the Rey Auditory Verbal Learning Test (RAVLT), Visual Memory Span (VMS), Digit Symbol, Digit Span, Letter Cancellation, TMT-A, TMT-B, RCFT, FAS, and the Tower of London. The selected tests were identified as assessing broad cognitive categories. Significant differences were found between good-outcome patients and controls on the RAVLT-Learning, RCFT-Recall, Tower of London, VMS-Backward and

between poor-outcome patients and controls on the VMS-Backward and Letter Cancellation. The authors further compared neuropsychological performances by controlling the effects of age, premorbid intelligence, and depressive symptoms, the last of which was significantly different for bipolar groups compared to controls. Results differed after controlling the effects of subject variables. Significant differences were found between poor-outcome patients and controls on the TMT-A and TMT-B and between good-outcome patients and controls on the TMT-B, FAS, and Digit Span-Backward. The number and kinds of errors were not reported for any tests.

Considering contradictory findings of good-outcome patients' inferior performance on most tests as compared to poor-outcome patients, the two bipolar groups will be considered together. The possible cause of this discrepancy might be due to the authors' definitions of poor- and good-outcome. They chose to compare the severity of illness within a 5-year time period, but perhaps the aggregate effect of life-time illness is a better indicator of outcome. Another possibility is that after 5 years of the illness, cognitive differences between the groups become indistinguishable. Notwithstanding, their results demonstrate that a subset of people with bipolar disorder performs in the impaired range on a variety of tests. However, results are confounded by the unaddressed issue of subjects' medications, which included lithium and unspecified antidepressants, anticonvulsants, and neuroleptics.

The previous four studies of subjects with bipolar disorder demonstrate that cognitive deficits are present even when subjects have been psychiatrically stabilized. These deficits appear to be primarily in auditory memory processes and are not found across a wide spectrum of cognitive abilities. Thus, generalized cognitive deficit is not a consistent trait of bipolar disorder. Rather, Paradiso et al.'s (1997) findings of lower cognitive levels and Ferrier et al.'s (1999) significant findings of diffuse impairment suggest that people with bipolar disorder are vulnerable to acquiring broader and more severe cognitive impairment.

According to Taylor and Abrams (1986), electrophysical studies have found nondominant hemisphere impairment in bipolar subjects; and therefore, the authors sought establishment of cortical function through neuropsychological measures. Thirty inpatients from a short-term psychiatric hospital met criteria for a manic episode, and 42 healthy participants were found free of psychiatric, neurological, and substance disorders. Most bipolar subjects were taking primarily lithium or lithium plus a neuroleptic.

Tests included the Evaluation of soft neurological signs, Aphasia Screening Test, Folstein MiniMental State Examination (MMSE), Halstead-Reitan Test Battery, selected items (HRB: finger tapping and tactile form recognition), Luria-Nebraska Battery, selected items (LNB: motor function tasks, visual perception and spatial orientation items, phonemic hearing,

expressive speech items, naming, reading comprehension, arithmetical operations, verbal and visual memory, logical relationships, discursive intellect items, rhythm reproduction cutaneous and kinesthetic functions, and spatial orientations), and Tachistopsic Stimulation. The dominant hemisphere was determined by handedness; left-handed subjects having a right dominant hemisphere and mixed-handed and right-handed subjects as having a left-dominant hemisphere.

Cognitive performances were not analyzed per test. Instead, the test scores were combined and analyzed according to the cerebral location measured by the neuropsychological tests. Therefore, cognitive impairment ratings of dominant and nondominant hemispheres, dominant and nondominant cortical regions, and global functioning were presented. Hierarchical multiple regression analysis was used to test for the variances explained by age, gender, and handedness. Analyses indicated manic subjects, as compared to healthy controls, showed significantly more global, bifrontal, and nondominant parieto-occipital impairment. When impaired frontal lobe symptoms of reaction time and concentration were added to the regression, only dominant hemisphere functioning proved not to be significantly impaired.

The authors concluded that their findings were consistent with electrophysiological studies of bipolar patients. They stated their findings were not surprising due to the frontal lobe's premotor areas being considered

as an associational cortex of the limbic system and the nondominant hemisphere's relationship to emotion. Critiques of the study include failure to discuss medication effects, subjects' intellectual ability, and current psychiatric symptoms, as well as a list of tests' corresponding cerebral location. Furthermore, determination of subjects' dominant hemisphere by means other than handedness is desirable in light of Lezak's (1995) statistics for language localization in right- and left-handed people.

Pre-frontal functioning of 60 schizophrenic and 20 manic subjects was assessed by Morice (1990) because of its importance in treatment and cognitive rehabilitation. Psychiatric subjects were recruited from outpatient and short- and long-term inpatient facilities and compared to 34 healthy controls. Subject groups differed for age, gender, and marital status, but not education level. Most psychiatric subjects were specified to be in a remitted state of chronic psychotic illness.

Test scores included the WCST-categories achieved, WCST-perseverative errors, and all WAIS-R subtests and IQs. Significant differences included poorer performance for bipolars than controls on both WCST factors and all WAIS-R performance subtests, except for Object Assembly. No significant differences were found on Verbal, Performance, and Full Scale IQs. The authors speculated that the bipolars' WCST performance could be associated with right pre-frontal dysfunction. The totality of the results implicates deficits in cognition associated with right

hemisphere functioning. Critiques of the study include failure to take into account the groups' differences on age, gender, and medication status.

Wolfe, Granholm, Butters, Saunders, and Janowsky (1987) investigated the memory ability of subjects with unipolar depression, bipolar depression, Huntington's disease, and no psychiatric illness, given the hypothesized link in neurological studies between affective disorders and dysfunction of subcortical areas. Twenty unipolar and 12 bipolar subjects were recruited from inpatient psychiatric facilities. All bipolar subjects had at least one prior manic episode, but all patients were currently hospitalized for a depressive episode and were medication-free for 1 week before testing. Healthy controls were recruited through newspaper advertisements and were statistically matched for age and education.

Tests administered included the Mattis Dementia Rating Scale (DRS), FAS, and the RAVLT. Control subjects recalled significantly more words than the depressed bipolars across the five trials of the RAVLT test and had a higher learning curve. There were no significant differences between controls and bipolars on the short- and long-delay recall, but the controls recognized significantly more words on the test's recognition section. False positive and false negative errors during recognition performance were no different between the bipolar and healthy groups. On the FAS test, controls produced significantly more words than the bipolar subjects, but perseverative, intrusive and variation errors were consistent across groups.

These results indicate that nondemented patients with bipolar disorder have difficulties with working memory, learning, and verbal fluency. Of interest, the bipolar's performance qualitatively resembled the neurologic patients' performance.

Only 3 of the 12 studies comparing healthy controls and bipolar subjects controlled for mood by using subjects in only a depressed or manic state. These three studies differed in their assessment of the test results and number of tests administered. Therefore, it is difficult to identify any generalized or specific deficits during a depressed or manic episode. However, there was a trend for right hemisphere dysfunction.

Robertson and Taylor (1985) investigated affective disorders in a male prison population. Forty-one control subjects were recruited based upon a lack of psychiatric history and violent crime and were compared to 16 inmates with manic-depression. The manic-depressive group consisted of all affective episodes and ranged from euthymic to manic.

Exclusion criteria included a history of organic illness and substance addiction, although the manic-depressives had the highest amount of illegal drug use. They also had significantly higher IQs as determined by the Wechsler Adult Intelligence Scale (WAIS) Vocabulary test, but comparable levels of education. No mention of patients' medication regimen was noted.

Tests administered were selected subtests of the WAIS (Vocabulary, Similarities, Digit Span, Picture Completion, Block Design, and Picture

Arrangement), FAS, Visual Retention Test, and the Visual Recognition Test. The Visual Retention Test was described as assessing right hemisphere functioning. Comparison of the manic-depressive and control subjects revealed that the bipolar subjects did significantly better on the Similarities subtest and prorated Verbal IQ. They did significantly less well on nonverbal tests, such as the Visual Retention Test and Visual Recognition Test. Bipolars' superior verbal reasoning highlights the specific deficits in visual memory processes. These results did not account for subject differences in IQ and illegal drug use.

Coffman, Bornstein, Olson, Schwarzkopf, and Nasrallah (1990) investigated young patients with psychotic bipolar disorder on a series of neuropsychological measures and MRI findings. The Structured Clinical Interview for Diagnosis confirmed diagnostic criteria for the 30 bipolar outpatients and lack of psychiatric illness in 52 controls. The bipolar subjects were noted to have had frequent hospitalizations.

Tests administered included the Verbal Concept Formation Test (VCFT), Wechsler Memory Scale or Wechsler Memory Scale-Revised Edition (WMS/WMS-R), WAIS-R, WCST, and an expanded HRB. Left hemisphere function was inferred from Verbal IQ, percentage retention of verbal material from the WMS/WMS-R, VCFT, and right-hand scores on finger agnosia, dysgraphesthesia, Finger Tapping, and Grooved Pegboard Test. Right hemisphere functioning was inferred from Performance IQ, percentage

retention of nonverbal material from the WMS/WMS-R, and left-handed performance of finger agnosia, dysgraphesthesia, Finger Tapping, and the Grooved Pegboard Test. Tests sensitive to general integrity are the Category Test, Tactile Performance Test-memory and -location scores (TPT), TMT-A, TMT-B, Speech Sounds Perceptions Test, Seashore Rhythm Test, WCST-perseverative errors, and the Knox Cube Test.

Differences between the subject groups' neuropsychological performances were analyzed per test. Most tests demonstrated impaired bipolar ability even when covariance was applied for symptomatic severity, age, education, and neuroleptic dose. Only verbal memory, WAIS-R Verbal and Performance IQs, and selected HRB subtests (Seashore Rhythm Test, Speech Sounds Perception, Finger Taping-right hand, Sensory Agnosia-left hand) showed no significant differences. The cognitive impairment of bipolar subjects was diffuse; however, there was some trend toward greater right hemisphere impairment.

The authors compared neuropsychological results to MRI measures of cranial, cerebral, frontal, corpus callosum, and cerebellar areas. Correlations between neuropsychological summary scores of general, left, and right functioning and brain areas indicated associations between smaller cerebral and frontal areas and each neuropsychological domain. Small differences between the general, left, and right domains reflected a lack of lateralization. The authors concluded that their study identified diffuse cognitive

impairment in psychotic bipolar patients with bipolars' smaller cerebral and frontal size significantly contributing to poorer neuropsychological performance.

Dupont et al. (1990) examined bipolar patients and controls using MRI and cognitive measures. Nineteen Bipolar Affective Disorder, Type I patients were recruited from mental health facilities and compared to 10 controls with no history of psychiatric illness or first-degree relatives with psychiatric or substance abuse histories. Bipolar subjects taking benzodiazepines (BDZs) or antihypertensives were excluded, but most subjects were taking lithium or lithium plus a tricyclic (TCA), antiepileptic (AED), or neuroleptic.

Subjects were administered the Vocabulary Test, Confrontation Naming Test, Controlled Oral Word Association Test (COWA), Judgment of Line Orientation Task, Embedded Figures Test, Digit Symbol Substitution, CVLT, and the TMT-B. Authors described these tests as being sensitive to basal ganglia dysfunction and Digit Symbol as highly sensitive to cerebral dysfunction in general.

Psychiatric and control groups were equivalent in age, gender, handedness, and education. There was minimal evidence of general cognitive impairment in the bipolar subjects. Instead, bipolar subjects performed significantly less well than controls on the Digit Symbol test, compared to normals performing more poorly than bipolar patients on the

Confrontation Naming Test. Limitations of this study included a failure to independently compare the bipolar subjects with and without lesions to controls, as well as not controlling for the significant depression levels and medication status of bipolar subjects.

Souza et al. (1995) investigated auditory P300 event-related potential and neuropsychological outcomes in bipolar, schizophrenic, and control subjects. Twenty-six schizophrenic and 19 bipolar subjects were recruited from either outpatient or inpatient populations, and 27 healthy controls were recruited from hospital staff or volunteers in the community. All subjects were right-handed.

Assessment measures included the National Adult Reading Test (NART), selected WAIS subtests, (Similarities, Digit Span, Digit Symbol, and Object Assembly), FAS (Letters and Categories), Benton Copying of Designs, Hebb's Recurring Digits, Corsi Block Tapping, and Verbal Recall (VR). Tests assessing frontal lobe functioning included the FAS, which measures left frontal. The Copying of Designs is sensitive to right frontal functioning but associated with right hemisphere functioning. Hebb's Recurring Digits Test was reported to be sensitive to left hippocampal functioning, and the Corsi's Block Tapping test sensitive to right hippocampal functioning.

NART scores and age showed a significant correlation with neuropsychological test scores. Thus, they were entered as covariates in the Analysis of covariance (ANCOVA) procedure. Results revealed no

significant differences between normals and bipolar subjects on any of the neuropsychological tests, despite bipolar subjects' medicinal regime of lithium, TCAs, BDZs, monoamine oxidase inhibitors (MAOIs), carbamazepine, or neuroleptics. The authors hypothesized that bipolar subjects' significant P300 latency results without amplitude reduction suggest a different and less extensive underlying pathology than evidenced in schizophrenia. Thus, the less severe illness of bipolar disorder has an undifferentiating impact on cognitive functioning as compared to healthy controls. Replication of the study using a larger sample of bipolar subjects and a specific affective episode is suggested.

Hawkins et al. (1997) investigated the effects of negative and positive symptoms of schizophrenic and bipolar subjects on cognitive functioning. Forty-six schizophrenic and 22 bipolar subjects from outpatient treatment programs participated with compensation. Twenty-six employees with fewer than 4 years of college and no history of psychiatric illness were also included.

Tests administered included the Boston Naming Test (BNT), Cookie Theft Test, Gates-MacGinite Reading Vocabulary Test, Level 7/9, Form K (G-MRVT), selected WAIS-R subtests (Digit Span, Digit Symbol, Arithmetic, Similarities), TMT-A, TMT-B, and the FAS. Authors noted that the Digit Symbol, TMT-A, and TMT-B tests are highly sensitive to generalized brain dysfunction.

Bipolar subjects had significantly more depressive symptoms than controls, but no significant correlations between depression and cognitive tests were found. This finding is most likely due to the mild depressive symptoms present in the psychiatric groups. No significant cognitive differences existed between controls and bipolars, despite bipolar subjects taking lithium, carbamazepine, or neuroleptics. However, bipolar subjects scored approximately one standard deviation below controls on Digit Symbol and the TMT-B. These results demonstrate intact intellectual ability and a lack of global cognitive deficiency in bipolar disorder. The multiple cognitive functions utilized in Digit Symbol and the TMT-B inhibits specification of localizing significance in the brain.

Gourovitch et al. (1999) compared the neuropsychological performances of young monozygotic twins. A small sample of 15 healthy twins and 7 unaffected twins, whose twin siblings had bipolar disorder, were included in the study. The bipolar group was composed of various affective episodes and was in different stages of remission. Medications included lithium, neuroleptics, TCAs, and anxiolytics. In 5 of the 7 unaffected twins, symptoms of dysthymic disorder in remission and avoidant personality traits were assessed. All twins were statistically matched for age and education. Only control twins were screened for neurological disorders.

Tests administered included the Wide Range Achievement Test, selected subtest (WRAT: Reading), Continuous Performance Task (CPT),

Test of Facial Recognition (TFR), Brown-Petersen Test (BPT), Judgment of Line Orientation, Digits Forward and Backward, BNT, WAIS-R, FAS, TMT-A, TMT-B, RCFT, WCST, WMS, and the CVLT. Authors used conservative analyses due to their small sample sizes, such as values of $p < .01$ for significance and noting effect sizes greater than 0.8 as large.

Comparison of discordant twins revealed that bipolar twins' IQs had not deteriorated. However, they performed significantly less well than their siblings on the TFR and CVLT-total recall, -short-delayed cued recall, and -recognition hits. Comparison of the unaffected twins and healthy control twins revealed significantly poorer performances of unaffected twins on the WMS Mental Control, WMS Memory Quotient, CVLT immediate total recall, CVLT long-delay free and cued recall, CVLT discriminability, and BPT total recall and intrusive responses. Bipolar twins performed significantly less well than healthy control twins on the WMS Mental Control, WMS Memory Quotient, CVLT total immediate recall, CVLT short- and long-delay cued recall, CVLT long-delay free recall, CVLT recognition, CVLT discriminability, BPT total recall, and BPT intrusions. Mood symptomatology did not account for these differences.

The authors summarized the bipolar twins' performances as revealing deficits on select visual processing measures and in short- and long-term verbal learning and memory. The authors also hypothesized that the unaffected twins' poor performance is a result of retrieval difficulties and not

memory consolidation, which could be possible markers for the risk of bipolar disorder.

The previous six studies analyzed the performance of bipolar subjects in various mood states. Most studies did not reveal generalized cognitive deficit but demonstrated specific impairment. Only one study demonstrated diffuse impairment in subjects, who were psychotic during manic episodes and hospitalized multiple times. Thus, it appears that cognitive impairment in bipolar disorder generalizes as the illness' severity increases.

Comparison of Bipolar and Schizophrenic Subjects

This section compares subjects with bipolar disorder and schizophrenia. Six studies are reviewed. Three have been addressed previously; therefore, only a synopsis of the test results will be presented. Studies comparing these psychiatric groups only used bipolar subjects with manic, unspecified, or combined episodes.

Taylor, Redfield, and Abrams (1981) investigated neuropsychological profiles of various psychiatric illnesses. Seventeen schizophrenic, 43 manic, and 9 depressed subjects from an acute psychiatric unit were included. No exclusion criteria were used, but most subjects' medication was withheld until testing was completed.

Tests reported to assess dominant hemisphere included the WAIS Verbal IQ, Peabody Picture Vocabulary Test (PPVT), Benton Sentence Repetition, Grooved Pegboard-right-hand speed, Simultaneous Stimulation-

right-sided errors. Tests more sensitive to right hemisphere functioning included the WAIS Performance IQ, Simultaneous Discrimination-left-hand errors, Grooved Pegboard-left-hand speed, BVRT, Raven's Progressive Matrices (RPM), and the Hooper Visual Organization Test (HVOT).

Multiple regression equations were used to control for effects of sex, age, handedness, educational level, and drugs so as to examine differences in test performance among diagnostic groups. Yet, the study did not assess subjects' severity of illness or current psychiatric symptoms. Test scores were collectively analyzed according to either dominant or nondominant functioning. Comparison of manic and schizophrenic subjects revealed a significant difference for dominant hemisphere functioning with schizophrenic subjects performing more poorly. There were no significant differences on the nondominant domain.

Hoff et al. (1990) investigated cognitive differences of 35 bipolar and 30 schizophrenic inpatients. All bipolar subjects were diagnosed as having mania, but the schizophrenic group varied as 14 were paranoid, 8 disorganized, 6 undifferentiated, and 2 schizoaffective. Twenty-one patients were not receiving medication, but the others were taking alone or in combination lithium, neuroleptics, and Tegretol.

Administered tests included the Ravens Colored Progressive Matrices (RPM-C), Symbol Digit Modalities Test (SDMT), WAIS-R, selected WMS subtests (Logical Memory, Associate Learning, & Visual Reproduction),

CVLT, BVRT, HVOT, TMT-A, TMT-B, and the Purdue Pegboard Test. Factor analysis of these tests revealed three dimensions of cognitive performance - a Verbal factor, Spatial factor, and Speed factor. The Verbal factor was identified by the authors as assessing left hemisphere function and the Spatial factor as assessing right hemisphere function. Using these factors as dependent variables, multiple regression analyses found diagnosis unrelated to factor performances after controlling for education, sex, age, number of hospitalizations, duration of illness, and medication status. Therefore, the authors concluded there are no significant cognitive differences between patients with schizophrenia and bipolar disorder, despite a lack of group comparison of mood, negative, and positive symptoms.

Compared to his manic subjects, Morice's (1990) schizophrenic group was younger with correspondingly fewer admissions and a shorter duration of illness. However, the schizophrenic group had more psychiatric symptoms and greater doses of neuroleptics. Performance comparisons demonstrated no significant differences on the WCST-categories achieved and -perseverative errors, but the schizophrenic subjects performed significantly less well on all WAIS-R IQs and on two subtests, Information and Vocabulary. Considering similar WCST performances and manic subjects having significantly higher IQs and receiving less neuroleptic medication, the author concluded that pre-frontal functioning is similar for people with psychotic mania and schizophrenia.

Goldberg et al. (1993) investigated the neuropsychological differences between consecutively-admitted inpatients with schizophrenia, unipolar depression, and bipolar disorder. Fifty-seven schizophrenics met criteria for either paranoid or undifferentiated type. Of the 16 bipolar subjects, 10 were in a manic or mixed episode and 6 were depressed. Six bipolar subjects also exhibited psychotic features. Twenty-nine unipolar subjects participated.

Tests administered included the WAIS-R short form, Wide Range Achievement Test - Revised, selected subtest (WRAT-R: Reading), TMT- B, Wechsler Memory Scale, Form II, selected subtests (WMS-II: Memory Quotient, Paired Associate Learning, Logical Memory, and Visual Reproduction), Category Test short form, WCST short form, Line Orientation, and Facial Recognition. The WCST was noted to be sensitive to prefrontal dysfunction, Line Orientation to parietal lesions, and the TMT-B and Category Test to generalized cerebral dysfunction.

Inpatients with schizophrenia had poorer performances than bipolar subjects on all tests, but significant differences were found on the WAIS-R Full Scale IQ, all WMS-II subtests, WCST categories, WCST perseverative errors, and Line Orientation. Despite the authors' findings of significant correlations between cognitive tests and symptoms and duration of illness, they did not statistically control for these factors during their evaluation of diagnostic test differences. In addition, they did not account for face-valid differences of age, chronicity, or medication regime.

Despite Souza et al.'s (1995) schizophrenic and bipolar groups having no significant differences in age of onset, duration of illness, number of prior admissions, and current depressive or manic symptoms, schizophrenic subjects performed significantly lower than bipolars in verbal fluency. The psychiatric groups did not differ in P300 amplitude and latency leads, but only schizophrenic's verbal fluency was significantly associated with P300 latency increase. Thus, the authors specified frontal lobe impairment in schizophrenia and not bipolar disorder. Possible confounding medication effects were addressed by finding insignificant correlations between medications and tests.

Results of Hawkins et al.'s (1997) study revealed that schizophrenic subjects scored lower than bipolars on all cognitive variables, but only four were found to be significantly lower. These were Reading Vocabulary, Digit Symbol, TMT-A, and Naming. Of interest, the performance profile of the two psychiatric groups revealed similar profiles but at different levels of severity. When bipolar subjects were compared to schizophrenic subjects, who did not have negative symptoms, no significant differences were found. Therefore, negative symptoms of psychosis appear to contribute to the cognitive impairment of schizophrenia. Within the bipolar group, positive and negative symptoms were limited, so additional analyses between groups did not occur. The significant difference in reading vocabulary was interpreted by the authors as indicating that schizophrenia interferes with

learning processes at an earlier age than bipolar disorder. Weaknesses of this study include no statistical consideration of medications and psychiatric symptoms between the psychiatric groups.

Studies comparing people with schizophrenia and bipolar disorder revealed cognitive differences. Schizophrenic subjects were shown to have poorer test scores on some tests, including measurements of current and premorbid intellectual ability. Tests sensitive to frontal lobe functioning did not have consistent results when comparing schizophrenic and bipolar subjects. This may be a result of the tests' varying psychometric properties.

Comparison of Bipolar and Unipolar Subjects

Five studies compared subjects with bipolar disorder and unipolar depression. All studies but one have been reviewed previously. Unipolar subjects are compared to bipolar subjects in euthymic, manic, depressed, and unspecified or combined mood states.

Tham et al. (1997) investigated the relationship between neuropsychological profiles of euthymic patients with recurring affective episodes. A small sample of randomly-selected patients participated, including 9 bipolar subjects with manic episodes only, 7 bipolars with both manic and depressive episodes, and 10 patients with unipolar depression. Medication consisted of neuroleptics, antidepressants, lithium, and carbamazepine.

Tests administered were the Synonym, Reasoning, and Block-Test Battery (SRB), selected HRB subtests (TMT-A, TMT-B, Finger Tapping, Rhythm Test), the Claeson-Dahl Verbal Learning and Retention Test, and the Memory for Designs Test. Significantly more bipolar patients, who were hospitalized with manic and depressive episodes, performed lower on the TMT-B compared to the unipolar patients. Significantly more bipolar patients in both mood episode groups performed lower than unipolar subjects on the Synonym subtest. These results indicate poorer ability on tests of set-shifting and language comprehension for bipolar subjects. The subjects were analyzed together and were determined to show lowered cognitive function correlated to the number of hospitalizations and not to the polarity of recurring mood disorder.

Paradiso et al.'s (1997) unipolar and bipolar subjects were statistically matched on several psychiatric variables, including disease duration, remission time, mental status, and depression, except for bipolar subjects having more manic symptoms than unipolars. The authors also assessed medication status between the two groups. They found no significant differences between groups on individual comparisons of each drug category, but more unipolar subjects were taking BDZs, TCAs, or trazodone in combination or alone.

Comparison of subjects revealed unipolar patients were significantly slower on the TMT-B as compared to bipolar subjects. Number and kinds of

errors were not reported. All tests required use of visual abilities, and more than one test required executive ability, so the cognitive factor(s) that distinguished the TMT-B performances are unclear. Along with impaired cognitive abilities, medication effects could have contributed to unipolars' TMT-B performance. The second largest difference, although nonsignificant, was that unipolar subjects remembered fewer words from the CERAD word list. The authors hypothesized that the differences in test scores may be a result of dissimilar depressive effects on bipolar and unipolar subjects.

Wolfe et al.'s (1987) study revealed that unipolar patients recalled significantly more words across the RAVLT five trials and recognized more words on recognition than equally-depressed bipolar subjects. No differences were found on learning ability and short- and long-delay recall. Types of recognition errors were not significantly different between the two groups. Unipolar patients generated significantly more words than the bipolars on the FAS test, but committed similar error types. Of interest, a negative correlation was found between the Beck Depression Inventory (BDI) and RAVLT-delayed recall and between the BDI and RAVLT-recognition for only the unipolar subjects, despite no significant difference on the BDI between the unipolar and bipolar groups. The significantly different performances could be a result of either a qualitative difference between bipolar and unipolar depression or are possibly caused by a more severe illness in the bipolar sample as evidenced by their twice as many hospitalizations.

Of the two remaining studies, one found a significant cognitive difference between bipolar and unipolar depression. Goldberg et al.'s (1993) study revealed no significant differences between affective groups on measures of psychomotor speed, attention, memory, and problem solving, except for poorer performance of bipolar subjects on Judgment of Line Orientation. Taylor et al.'s (1981) comparison of manic and unipolar subjects revealed no differences between dominant and nondominant cognitive indices.

Comparisons of cognitive ability between subjects with unipolar and bipolar depression varied. The inconsistencies are likely a result of different assessment measures utilized and subjects' moods. To note, two studies hypothesized that depression could have had a differentiating impact on unipolar and bipolar subjects, despite equivalent depressive levels.

Within Bipolar Subjects

In this last section, performances between bipolar groups are compared. Seven studies are summarized with only one original study reviewed. Most studies included bipolar subjects in an euthymic state.

Dewan, Haldipur, Boucher, Ramachandran, and Major (1988) compared bipolar patients with computerized tomography (CT) abnormalities and those without on tests of neuropsychological functioning. Abnormalities included enlarged third ventricles, as well as increased density of anterior cortical white matter bilaterally, of caudate nuclei

bilaterally, of thalamic nuclei bilaterally, and of the right temporal lobe. Patients were euthymic on lithium primarily, but some also were taking carbamazepine and antipsychotics. Bipolar subjects were statistically matched on numerous variables, including age, number of hospitalizations, substance abuse histories, and positive and negative symptoms.

Tests were administered by a neuropsychologist and included the WAIS and the HRB. Average Impairment Rating (AIR), Halstead Impairment Index (HII), and Percent Impaired Ratio (PIR) were reported. Statistical comparison of test performances revealed that bipolar subjects with abnormal MRI demonstrated significantly more cognitive impairment only on the HII score. The HII was significantly associated with lateral ventriculomegaly, but the lateral ventricle was not significantly enlarged. Therefore, the authors concluded that their study failed to differentiate between bipolar subjects with abnormal and normal CT findings. Of interest, this study replicated previous studies demonstrating no relationship between lateral ventriculomegaly with duration of illness, age, or sex, and no relationship between ventricular enlargement and severity of illness, euthymic functioning, mania, delusions, and hallucinations.

van Gorp et al. (1998) found no differences between their bipolar subjects with and without alcohol dependence on current psychiatric symptoms and severity of illness. These comparable bipolar groups demonstrated no significant difference in neuropsychological performances.

However, bivariate correlations revealed that bipolar patients, who had been hospitalized for either depression or mania in the last 5 years, demonstrated the most variability across the five trials of the CVLT.

Three studies reported previously did not find significant differences between their bipolar groups. Ferrier et al. (1999) did not find significant differences between their good- and poor-outcome bipolar groups on a wide range of neuropsychological measures. Tham et al.'s (1997) bipolar groups consisted of those who had had only manic episodes versus those who had had both manic and depressed episodes. They found no differences on abilities of language comprehension, visuoconstruction, verbal memory, nonverbal memory, visuoperception, set-shifting, motor speed, as well as auditory-perception, -attention, and -concentration. Last, WCST performance was not significantly different for those recovering from an acute episode and those who had been in remission (Morice, 1990).

MRI images in Dupont et al.'s (1990) research discovered subcortical signal hyperintensities involving white matter in 9 of the 19 bipolar subjects. Bipolar subjects with lesions had more psychiatric hospitalizations than those without, but the bipolar groups had equivalent age of onset, duration of illness, and current age. In addition, history of psychosis was not associated with the lesions. Neuropsychological test results revealed bipolar subjects with abnormal MRI findings performed significantly less well on the COWA and Digit Symbol tests than those with normal findings. Results

nearing significance included bipolar subjects with hyperintensities scoring lower on CVLT recall and Line Orientation. The neuropsychological results were interpreted by the authors to suggest deficits in the initiation of systematic retrieval strategies and confirm the MRI findings of subcortical impairment.

Methodological Considerations

The 18 articles were critiqued on a variety of research design factors. The following presents the strengths and weaknesses of the methodology, which includes selection of the subjects, demographic variables, confounding factors, and assessment measures used. The section begins with a critique of the subject factors controlled by the researchers, such as sample sizes and diagnostic classification.

Subject Selection

Most studies had 20 or more bipolar subjects, but some whose numbers were low noted their study to be of an exploratory nature. Mean subject size across studies was 22.5 and ranged from 7 to 43 bipolar subjects. Most did not note the method of selecting subjects, but the implication is that the subjects were patients at inpatient or outpatient settings and consented to participate.

Diagnoses were primarily established by use of the three most recent DSM (American Psychiatric Association, 1980, 1987, 1994) manuals. At times,

valid adjunctive measures, such as the Structured Clinical Interview for Diagnostic Symptoms and the Diagnostic Interview Schedule, were used to substantiate diagnoses. Despite using valid criteria, most studies did not provide a comprehensive diagnosis of bipolar disorder. For example, the subjects were diagnosed as having bipolar disorder, but there was no mention of either the most recent affective episode or the specifiers, such as mild versus severe with psychotic features.

The concern with not providing a comprehensive diagnosis is that the performances of various bipolar subtypes were analyzed collectively thus possibly limiting effect sizes by averaging out the differences between bipolar subtypes. Independent analysis of recognized bipolar subtypes (e.g., Akiskal, 1996; Akiskal & Pinto, 1999; American Psychiatric Association, 1994; Pergui, Toni, & Akiskal, 1999) could have revealed corresponding neuropsychological profiles. Of interest, Goldberg et al. (1993) did not find any significant neuropsychological differences between bipolar subjects in a depressed versus manic state and between psychotic versus nonpsychotic bipolar subjects. However, the bipolar subgroups' sample sizes were small.

Despite the lack of bipolar subtype specification, it is suspected by this researcher that across the 18 studies inclusion of bipolar subtypes was limited. The majority of the subjects do not appear to have a severe case of bipolar disorder. They appear to be a relatively healthy subgroup of people with bipolar disorder due to various factors. Most subjects in the 18 studies

were receiving treatment on an outpatient basis. Forty-three percent of the research subjects in the 18 studies were stated to be euthymic, whereas more than 56% are estimated by this reviewer to be euthymic based on their outpatient treatment. It is assumed that subjects with more severe cases of bipolar disorder would be not be in outpatient settings or be euthymic. Rather, they would be noncompliant with medication, abuse substances, or meet criteria of without full interepisode recovery or rapid cycling. However, it is reasonable to hypothesize that bipolar subjects would be euthymic during testing due to the hardship or impossibility of testing while in a manic or severely depressed state.

The number of hospitalizations and number of affective episodes would aid in determining severity, but most studies did not provide these statistics. Reported medication status varied in specificity of drug name and regimen (e.g., dosage, number of medications), which also makes severity of illness unclear. Evidence against outpatients having a less severe illness was provided only by Morice (1990), who did not find a significant difference between his inpatient and outpatient bipolar groups' scores on the WAIS-R and the WCST.

Demographic Variables

There are multiple subject variables that could contaminate results if they differ within or between subject groups. To prevent such contamination, researchers can statistically match subject groups or

statistically control the proportion of variance of these variables on neuropsychological performance (e.g., ANCOVA). The following addresses the variables of sex, handedness, age, education, and psychiatric symptoms.

Sex is an important demographic variable to consider in neuropsychological assessment for two reasons. The first reason is that men and women differ in abilities. Some quantified differences are that females tend to be more fluent in the use of language and are better at perceptual speed and visual memory. In contrast, males tend to be better at visuospatial analysis and mathematical ability and are more physically aggressive (Kolb & Whishaw, 1996). The second reason to consider sex effects is due to the possible sex-related differences in cerebral organization of abilities. Studies of lateralization, blood flow, and brain lesions suggest that there are lateralization and intra-hemispheric differences between the sexes (Kolb & Whishaw, 1996). However, Lezak (1995) cautioned against interpretation of test performance as a result of gender differences because it is rare for differences of one-half standard deviation to occur. This implies that there is more similarity than difference between the sexes. In this review, nine studies controlled for gender effects by using only male subjects, matching sex ratios between subject groups, or by accounting for the variance due to gender differences in statistical procedures.

Lezak (1995) reported that as many as 90% to 95% of adults are right-handed, and that 95.5% to 99.67% of right-handed persons and two thirds of

left-handers are estimated to have left-hemisphere language dominance. When injured, the remaining left-handed subjects have aphasic disorders associated with right-sided lesions, but half of these also demonstrated bilateral speech ability. Research has suggested that left-handers' speech comprehension is located in the left hemisphere and expressive ability in the right hemisphere (Lezak, 1995). Twelve studies did not describe handedness in their research. However, due to Lezak's statistics, the likelihood of misinterpreting focal structural impairment as a result of significant effects of handedness on neuropsychological results appears minimal.

According to Lezak (1995), within the 50 to 65 age range, physiological changes take place with increasing rapidity and include such changes as brain volume diminution, cortical atrophy, ventricular enlargement, and reduction in subcortical areas. There are also documented cognitive changes, such as memory changes, which can start as early as in the third decade of life (Lezak, 1995). In the current studies, the mean age and standard deviation across studies was 41.78 ± 9.51 and ranged from an average of 21.6 years to 57.0 years. Nine studies found no significant age differences between subject groups, whereas five studies had significantly older bipolar subjects. Among these five studies and the remaining four studies, six accounted for age effects in their statistical procedures. Therefore, age effects are well examined in the reviewed studies.

Most of the studies intentionally matched subjects on reported years of education because education is significantly correlated with various neuropsychological performances. Differences in educational levels between subject groups were found to be nonsignificant in nine studies, whereas an additional two studies stated the educational differences between their subject groups were nonsignificant despite a lack of testing. Despite similar educational levels, subjects' ability can vary greatly. Therefore, use of reading vocabulary measures or IQs can better demonstrate ability. Of the studies not comparing educational levels, one study had nonsignificant reading levels between subject groups, whereas an additional two studies had nonsignificant IQ differences.

Psychiatric variables are additional research factors that should be commensurate across psychiatric subject groups or be accounted for in statistical procedures to prevent contaminated results. First, the severity of illness is important due to the known cognitive differences in mild versus severe psychiatric illness (Denicoff et al., 1999; van Gorp et al., 1998). Second, current and past psychiatric symptoms need to be similar across groups to have comparable cognitive performances. Therefore, depressive, manic, negative, and positive symptoms, as well as chronicity, age of onset, and number of episodes and hospitalizations will be assessed. To note, four studies are not considered because their bipolar subjects were compared only to normal controls.

Severity of illness can be determined by length of illness, number of acute episodes, and severity of the symptoms. Length of illness was quantified by reports of chronicity and age of onset. For these two variables, six studies had comparable lengths of illness between psychiatric subject groups. One study's bipolar group was more chronically ill than the schizophrenic group as measured by statistical comparison, and of the seven remaining studies, four did not compare their psychiatric subjects or statistically control the proportion of variance due to length of illness.

Acute episodes can be quantified by the number of affective episodes or number of hospitalizations. The number of depressive, manic, and psychotic episodes across psychiatric subject groups was not addressed in 13 out of 14 articles. This overlooked issue is likely correlated with the numerous bipolar groups experiencing unspecified or combined affective episodes. However, eight studies took into consideration the effects of number of hospitalizations on neuropsychological results.

Most studies did not account for current psychiatric symptoms by either matching subject groups or examining these factors during statistical procedures. No studies mentioned the severity of symptoms in past episodes. Current depressive symptoms were not accounted for in eight studies, and four out of the five studies comparing bipolar subjects did not account for manic symptoms. Negative and positive symptoms of mental illness also have significant, negative effects on cognitive functioning, and

six studies accounted for these symptoms (Atre-Vaidya et al., 1998). The mood and psychopathology assessment instruments, such as the Beck Depression Scale and the Brief Psychiatric Rating Scale, are considered in the research literature to meet adequate validity and reliability standards.

Confounding Variables

Structural impairment as determined from poor neuropsychological performance may not be accurate or may not be solely caused by psychiatric illness. Motivation, fatigue, tardive dyskinesia, and other factors can have confounding effects. Therefore, subjects' medication and the researchers' exclusionary criteria will be considered.

Seventeen of the 18 studies addressed the effects of medication on neuropsychological performance. Most studies addressed medication effects by researching the literature and summarizing the findings. Other methods of addressing medication effects included discontinuing subjects' medication, excluding subjects with questionable medications, matching subject groups' drug regimen, or including medication as a variable during statistical procedures. Four of the 18 studies found no significant associations between medication and neuropsychological outcomes, compared to two studies with significant findings. Hoff et al. (1990) found increased lithium to be associated with poor performance on verbal subtests and tests of speed. Taylor et al. (1981) found neuroleptic exposure associated with greater

impairment and lithium with less impairment on tests assessing nondominant hemisphere functioning.

Stein and Strickland (1998) reviewed the literature concerning the impact of various medications on cognitive functioning. Cognitive impairment resulting from antidepressants was found to be dependent upon the class of drugs used. High sedating-TCAs and -heterocyclics are reported to have moderate to large adverse effects on attention, psychomotor speed, and memory, whereas low sedating-TCAs and -heterocyclics have mild to moderate effects. MAOIs and serotonergic reuptake inhibitors (SSRIs) were stated to be superior to TCAs and theorized to have mild effects on neurocognitive functioning. Further research was suggested.

The same variability was found for anxiolytic and antiepileptic medication. All BDZs were reported to affect psychomotor ability negatively until tolerance was attained, but memory impairment persisted. In contrast, buspirone was found to have no adverse effects. Within the classification of AEDs, carbamazepine demonstrated the smallest negative effect. However, it still showed mild to moderate adverse effects on psychomotor speed.

Honig, Arts, Ponds, and Riedel (1998) and Bilder, Turkel, Lipschutz-Broch, and Lieberman (1992) reviewed the literature concerning the effects of lithium and antipsychotic medication, respectively. Honig et al.'s (1998) qualitative analysis identified 4 out of 17 studies meeting criteria for methodological quality, and their results revealed that lithium had

significantly adverse effects on memory and information processing. Bilder et al.'s (1992) review concluded that antipsychotics improve sustained and selective attention and complex problem solving but negatively affect response planning, motor control, learning, and memory ability. However, their study only reviewed research using schizophrenic subjects.

A total of 47 articles researching the effects of lithium, antidepressants, neuroleptics, anticholingerics, and carbamazepine on neuropsychological performance were reviewed by the 18 articles critiqued in this paper. Taking into consideration the articles they reviewed and their own empirical results, most of the 18 studies concluded that the subjects' medications did not significantly influence test results. However, Honig et al. (1998), Bilder et al. (1992), and Stein and Strickland's (1998) review of literature would challenge their conclusions.

Subjects should be excluded from studies if they have illnesses or other conditions that would contaminate the interpretation of cognitive impairment. Use of exclusionary criteria varied across studies. Some had extensive and rigorous criteria, whereas two studies used none. The two most common exclusionary criteria were neurological disorders and substance abuse. Substance abuse is an important confounding factor to rule out in bipolar disorder. Data from an epidemiological study indicated that bipolar disorder was associated with the highest risk of any Axis I disorder for drug or alcohol comorbidity, and alcohol abuse or dependence was found to

be the most common substance abuse disorder in people with bipolar disorder (Hilty et al., 1999).

Assessment Measures

Most tests administered can be found in Lezak (1995) and Spreen and Strauss (1998) and are recognized by neuropsychologists to have satisfactory reliability and validity. A shortcoming of the neuropsychological results in the 18 studies is the authors' failure to report the subjects' solution strategy or kind of errors. Tests are polyfactorial; therefore, exclusion of the aforementioned performance characteristics limits assessment of cognitive and associated structural impairment (Lezak, 1995; Bilder et al., 1992; Sapin et al., 1987). For example, perseverative errors on the BNT suggest posterior left hemisphere dysfunction, whereas responses reflecting perceptual fragmentation suggest right hemisphere dysfunction (Lezak, 1995).

Summary of MRI Review

Norris et al. (1997) reviewed the literature on structural changes in the brain of patients with bipolar disorder by magnetic resonance imaging. Eight studies reviewed detected more hyperintensities in bipolar subjects compared to controls, and only one study, whose psychiatric group contained several diagnoses, demonstrated no differences. The authors specified localization in the basal ganglia-thalamo-cortical circuits, and explained that

the local fibers connect the medial temporal gray matter and limbic structures, such as the amygdala and hippocampus, to the prefrontal cortex.

Two studies reviewed did not find any significant associations between hyperintensities and current age or age of onset. However, one study reported a significant positive correlation for number of psychiatric hospitalizations. In comparison, two studies found significantly more lesions in older adults. The authors concluded that bipolar patients appear to have a greater frequency of lesions than normals, especially in patients over the age of 46.

Likewise, Norris et al. (1997) reviewed MRI research of six brain structures but found inconsistent relationships between bipolar disorder and these structures. Explanations for these findings include a limited number of studies and small sample sizes. The results of original research and results confirmed by more than one study will be summarized next.

The results of three studies indicated larger right than left temporal volume within bipolar subjects, but one study noted similar results for the control and schizophrenic groups. Temporal lobe comparison of control and bipolar groups consistently differed. Two studies comparing subjects with schizophrenia and bipolar disorder indicated bilateral enlargement in bipolar subjects, whereas a third study supported only larger left than right temporal lobe in bipolar subjects.

Five original studies were reviewed. One study comparing the hippocampus of control and bipolar subjects reported smaller volume in bipolar subjects, and one study that compared normals and subjects with their first episode of mania found significantly larger third ventricles in bipolar subjects. Two studies researching basal ganglia structures found no significant differences between either subjects with varying diagnoses or young bipolar subjects compared to controls. One study found no significant differences in callosal widths, callosal area, callosal length, or callosal to cerebral area between diagnostic groups. However, the subjects with schizophrenia had a reduction in cerebral volume and increase in sulcal volume compared to bipolar subjects. Of interest, these abnormalities were not noted in bipolar subjects with psychotic features.

Discussion and Conclusion

Despite numerous research factors that varied across studies, several trends were established. First, bipolar subjects did not cognitively perform at a consistent level below that of healthy controls or unipolar depressives. In fact, bipolar subjects had comparable scores on a variety of tests and at times, achieved better scores than healthy controls. Bipolar subjects did not achieve significantly lower cognitive scores than schizophrenics, who demonstrated generalized cognitive deficit. This suggests that bipolar illness affects specific areas of the brain rather than causing diffuse impairment. However, the

addition of psychotic features and substance abuse was indicated to significantly deteriorate existing cognitive deficits and abilities that were within normal limits. Therefore, bipolar patients with comorbid disorders or severe forms of bipolar disorder may show generalized deficit. Generalized deficit is also hypothesized to occur when people are experiencing an acute mood episode.

Second, subjects with bipolar disorder were found to experience cognitive deficits in specific domains of functioning as compared to healthy controls. A majority of studies assessed intellectual functioning of subjects with bipolar disorder and demonstrated IQs in the average range or greater. This finding was constant for bipolar subjects with varying lengths of illness. Studies that administered tests of premorbid intelligence determined that the bipolar subjects' intelligence had not deteriorated from the onset of illness. Therefore, it appears that the illness does not significantly impair intellectual abilities longitudinally in a subgroup of people with bipolar disorder. Furthermore, the average intellectual ability of subjects with bipolar disorder magnifies the discrepant, impaired abilities demonstrated in these studies.

Most domains of functioning were not significantly impaired. The majority of the research did not reveal significant impairment of auditory or visual attention. Processing speed, as measured by the Digit Symbol test, revealed inconsistent results. The lack of a significant difference in attention is hypothesized to be a result of the majority of subjects being in a euthymic

state. It would be predicted that in acute episodes of mania or depression the ability to attend would be impaired. Language abilities also did not appear to be affected by the illness; in fact, bipolar subjects performed significantly better than healthy controls in some studies. Impairment of visuoperceptual abilities was not clear due to limited assessment and the different measures used. However, visuoconstructional ability was established to be within normal limits.

Impairment of memory processes was indicated. Tests assessing auditory and verbal memory included the CVLT and RAVLT. These tests along with additional measures demonstrated that subjects with bipolar disorder learned fewer words than healthy controls across and within learning trials. Their impaired ability to learn information is further reflected in poorer performance on recognition and cued recall subtests. Visual or non-verbal memory was harder to assess because of the different measures used and inconsistent results. The WMS results demonstrated impaired ability, but the RCFT-recall did not. Further testing is warranted.

Depending upon the function assessed and measures used, frontal lobe impairment was found. The WCST and Category tests indicated impairment, but the TMT-B and Stroop Color-Word subtest did not. Adequate performance on these four tests requires utilization of multiple abilities. Cognitive abilities common to the former and latter tests include attention, working memory, inhibition, and set-shifting, whereas unique

abilities required on the TMT-B or the Stroop subtest include visuomotor speed, reading speed, and recall of remotely-learned information. Therefore, the WCST and Category performances demonstrated impairment in the specific ability of abstract problem solving. Motor ability was only assessed in two studies, one of which combined various tests scores to assess cortical regions and demonstrated bifrontal impairment. The second study found no significant differences between dominant and nondominant hands in motor ability.

Studies comparing the psychiatric groups were limited. Therefore, the following conclusions are tentative. Schizophrenic subjects were shown to have poorer current and premorbid intellectual ability. Although schizophrenic subjects were significantly more impaired than bipolars on additional tests, further delineation of specific deficits cannot be determined. The studies comparing the affective disorder subjects suggested equivalent abilities across domains, but additional testing is needed for confirmation.

The totality of the neuropsychological results does not clearly demonstrate dysfunction in unilateral or bilateral hemispheres, although there was a trend toward greater impairment in the nondominant hemisphere of subjects with bipolar disorder. Rather, the specific abilities of memory, learning and abstract problem solving were indicated to be impaired and are notably associated with the structural MRI findings of Norris et al. (1997). The MRI findings demonstrated that subjects with

bipolar disorder have hyperintensities affecting connections between the medial temporal gray matter and limbic structures, such as the amygdala and hippocampus, to the prefrontal cortex. These cerebral structures and regions are well known to have a structure-function relationship with learning, emotion, and problem solving (Bear, Connors, & Paradiso, 1996).

Comparisons of cognitive performance on different measures and the associations between brain structures and functions further demarcate the impaired cognitive abilities in bipolar disorder. The first two cognitive abilities needed for memory and learning are attention and working memory. The lack of impairment noted on the TMT-A, Digit Span, and Stroop subtests indicate that these abilities, associated with the prefrontal lobe, do not substantially contribute to the learning difficulties in bipolar disorder (Bear et al., 1996).

Learning and memory are closely related. We could not learn without memory, and there would be little to remember if we did not learn. The ability to learn is strongly associated with lesions to the hippocampus, but the abilities of remote and working memory are not (Carlson, 1992; Walsh, 1994). However, the hippocampus is involved in the conversion of immediate memory into long-term memory (Carlson, 1992). The test results found that bipolar subjects have difficulty learning as many words as controls. It is reasonable to hypothesize that the MRI findings of impaired connections to the hippocampus (Norris et al., 1997) are responsible for the memory and

learning deficits in bipolar disorder. This is further confirmed by bipolars' intact remote memory and most other cognitive abilities as evidenced by the subjects' stable IQs. The bipolars' impaired recall and recognition appear to be due to the limited number of words originally learned.

It is also reasonable to hypothesize that the impaired problem solving skills and emotional-behavioral deficits seen in bipolar disorder are a result of impaired learning processes. Learning is defined as a process of forming associations between stimuli and other events (Gordon, 1989). On the WCST and Category tests, adequate performance is achieved by learning the associations between the examiner's positive reinforcement and conceptual principle of the cards. These tests also require the ability of abstraction, which is associated with frontal lobe functioning (Walsh, 1994). The risky behaviors engaged in by bipolar subjects could also be a result of not learning when to stop. The amygdala controls the autonomic and behavior components of conditioned emotional responses, and its stimulation causes increases in heart rate and blood pressure (Carlson, 1992). It also influences sexual behavior, aggression, and maternal behavior (Carlson, 1992). Therefore, the impaired connections to the amygdala proposed by Norris et al. (1997) might contribute to the emotional displays and behaviors seen in bipolar disorder.

Additional findings of Norris et al. (1997) further confirmed impairment of the connections to the hippocampus, amygdala, and pre-

frontal areas. Temporal lobe comparisons between controls and bipolars consistently differed. This suggests that the entire temporal lobe does not contribute to bipolar disorder but only the medial portion, which is involved in memory and learning ability. Also, there were no significant differences in basal ganglia structures, implying that only connections of the basal ganglia were involved in deficits for bipolar subjects. Last, one study in Norris et al.'s review demonstrated smaller hippocampal volume of bipolar subjects, which could be a causal factor for bipolar subjects' impaired learning and memory.

Other MRI findings by Norris et al. (1997), such as differences in lesion frequency, temporal lobe volume, and third ventricle size of bipolar patients, do not appear to be correlated with or add further insight into the neurological findings reviewed in the present paper. In addition, the trend toward greater cognitive impairment in the nondominant hemisphere of subjects with bipolar disorder was not substantiated by MRI findings due to the lack of research comparing left- versus right-hemisphere structural abnormalities.

Methodological review of the studies indicated numerous strengths and weaknesses that need to be addressed in future research. Issues of particular importance include the need to statistically control for demographic variables and medication, as well as the nature and severity of symptoms.

Additional directions for future research are limited. To strengthen the relationship between neuropsychological and medical procedures, comparison of cognitive measures to other neuroimaging, such as PET, SPECT, and CT can be pursued. Analysis of neuropsychological measures and neuroimaging within the same study is also strongly suggested. Since it is difficult to test subjects with bipolar disorder when they are in an acute state, using the least resistive measures, such as measuring blood levels or using cognitive assessments that require limited responses might be appropriate (e.g., PPVT).

In summary, the review of neuropsychological results of persons with bipolar disorder revealed specific functional deficits. These cognitive deficits were indicated to be primarily in learning but also in problem solving and memory. The cognitive deficits were well associated with the structural changes in the brain of patients with bipolar disorder as revealed by magnetic resonance imaging (Norris et al., 1997). Additional studies comparing the structural and functional impairment of people with bipolar disorder are warranted, specifically studies using more sophisticated statistical methods.

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VITA

NAME:

Laura J. Hanisch, M.A.

EDUCATION:

Rosemead School of Psychology Clinical Psychology	Psy.D.	(Cand.)
Rosemead School of Psychology Clinical Psychology	M.A.	1996
College of New Jersey Psychology Concentration	1993 -	1994
Wheaton College Political Science	B.A.	1993

INTERNSHIP:

John Umstead Hospital Butner, North Carolina	1999 -	present

PRACTICA:

Harbor UCLA Medical Center Inpatient Program	1998 -	1999
Augustus F. Hawkins Comprehensive Community Mental Health Center Outpatient Program	1997 -	1998
Biola Counseling Center Outpatient Program	1996 -	1998
Garden Grove United School District	1996 -	1996

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