NEUROCOGNITIVE FUNCTIONING IN SEVERE DEPRESSION

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Dedicated in loving memory to

Carolyn Ann Meza and Domony Wesley McClintock II

NEUROCOGNITIVE FUNCTIONING IN SEVERE DEPRESSION

By

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DISSERTATION

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ABSTRACT

Research has suggested that major depressive disorder can negatively impact neurocognitive functioning. Depression has been implicated in affecting many cognitive domains, including executive function, attention, memory, and psychomotor and processing speed. However, there has been limited examination of the relationship between neurocognitive functioning and depressive characteristics such as depression severity, depressive subtypes, number of depressive episodes, and episode duration. The primary goal of this study was to explore the relationship between neurocognitive functioning and depressive characteristics in severe unipolar major depressive disorder. Baseline socio-demographic, clinical, and neuropsychological information was examined in 145 inpatients enrolled in a large electroconvulsive therapy study (the Consortium for Research in ECT). Results revealed that depression severity was unrelated to global cognitive functioning and executive functioning. However, performance on certain neurocognitive variables accounted for 25% of the variability in the magnitude of

depression severity. Various clinical dimensions of depression, including depressive subtype, number of episodes, and episode duration did not show a systematic relationship to neurocognitive functioning. Patients with psychotic depression performed similarly to patients without psychosis, and the ability to predict the presence of psychosis by neuropsychological performance was low. Those with atypical depression performed similarly to patients with typical depression, although patients with atypical depression showed better performance on a measure of verbal memory. No significant differences were found between subjects with multiple versus single episodes of depression, and the number of depressive episodes was unrelated to neurocognitive performance. These data indicate that the depressive characteristics examined were not systematically related to neurocognitive functioning among severely depressed patients in this well characterized and carefully selected sample.

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CHAPTER 1

INTRODUCTION

Clinical research and experience have shown that major depressive disorder (MDD) can negatively affect neurocognitive function (Schatzberg, 2002; Shenal, Harrison, & Demaree, 2003; Zakzanis, Leach, & Kaplan, 1999). The majority of studies have focused on MDD collectively in relation to cognitive functioning and do not comment on additional depressive information including depressive subtypes, symptoms, and clinical characteristics. This emphasis on MDD collectively has left a gap in the research concerning the relationship between MDD subtypes (e.g., atypical, melancholic, psychotic), magnitude of severity, recurrent depression, and neurocognitive function (Zakzanis et al., 1999).

Subtypes and clinical characteristics of MDD are important to understand as they have been clinically implicated in treatment course, development of efficacy-based algorithms, and relapse prevention (Fava & Davidson, 1996; Vuorilehto, Melartin, & Isometsa, 2005). While there is a plethora of information regarding MDD subtypes and depressive characteristics, there has been limited exploration and understanding of the effects of MDD subtypes and clinical characteristics on neurocognitive functioning. While questions concerning the neurocognitive effects of recurrent and single episode MDD, atypical, melancholic, and psychotic depressive symptoms have been posed, few answers have been suggested (Fava, 2003). For instance, the different depressive subtypes have distinct symptom patterns which differentially affect the person and they may differentially affect cognitive domains. Also, recurrent depression has been found to

be more severe than single episode depression, thus it may be possible that neurocognitive functioning is also more severely impacted.

Major depression has been negatively associated with the neuropsychological domains of executive function (Harvey et al., 2004), attention and concentration (Kampf-Sherf et al., 2004), memory (Fossati, Amar, Raoux, Ergis, & Allilaire, 1999), processing speed (Nebes et al., 2000), and intelligence (Shenal et al., 2003). In a meta-analysis of twenty-two studies, Zakzanis and colleagues (1999) showed that episodic memory (i.e., explicit memory) and attention were the cognitive domains most affected by depression. Moreover, neurophysiological studies have implicated the role of the prefrontal cortex and the hippocampus in MDD (Elliott, Rubinsztein, Sahakian, & Dolan, 2002; Schatzberg, 2002).

Before presenting the purpose of this investigation, it is important to review the literature to understand what previous studies have shown regarding the constructs of MDD subtypes and clinical characteristics, neurocognitive domains, and understand why it is important to measure their interactions.

CHAPTER 2

LITERATURE REVIEW

Major Depressive Disorder

Major Depressive Disorder (MDD) is a serious, chronic, and debilitating disease (Minor, Champion, & Gotlib, 2005; Vuorilehto et al., 2005). The lifetime prevalence of MDD ranges between 5% and 20% (Hamet & Tremblay, 2005; Kessler et al., 2003). The annual incidence of MDD has been found to be three to five adults per 1000 (J. M. Murphy, Laird, Monson, Sobol, & Leighton, 2000) and it has been estimated that 5% to 25% of the population will experience depression at some point (Kessler et al., 2003). Women are consistently diagnosed with MDD more frequently than men at a ratio of 2:1 (Kessler, 2003; Marcus et al., 2005), and younger cohorts (50 years and younger) have higher rates of depression relative to older (51 years and older) cohorts (Husain et al., 2005). Persons diagnosed with MDD have also been found to be at greater risk for comorbid psychiatric illnesses, including anxiety, substance abuse, and impulse control disorders (Kessler et al., 2003). In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study of over 4,000 participants with MDD, 25.6% of participants had at least one diagnosed comorbid psychiatric disorder (e.g., anxiety, somatoform, substance abuse), 16.1% had two, and 20.2% were diagnosed with three or more (Rush et al., 2005).

Major depressive disorder can be classified as unipolar or bipolar depression. Unipolar depression involves only having depressive episodes whereas bipolar involves having both depressive and manic episodes. According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), a Major Depressive Episode

(MDE) is diagnosed when there has been a period of two weeks in which the symptoms of either depressed mood or anhedonia are present with a minimum of four additional symptoms including changes in sleep, appetite/weight, psychomotor activity, energy, decreased self-esteem, decreased concentration, and feelings of increased worthlessness, guilt, and suicidal ideation (APA, 1994). The MDE must also cause impairment in important areas of functioning, occupational, and social domains (APA, 1994). In contrast to a depressive episode, a manic episode consists of elevated, expansive, or irritable mood that lasts for a minimum of one week (APA, 1994). Additionally, during the time of the elevated mood, a minimum of three other symptoms must be present such as feelings of grandiosity, pressure to talk, and increased sexual indiscretion (APA, 1994). While there is unipolar and bipolar MDD, the primary focus of this paper concerns unipolar depression given that it is more common (Kessler et al., 2003).

Unipolar MDD has been found to be the fourth leading cause of disability worldwide (WHO, 1996) and those with depression have a higher mortality rate relative to those persons not depressed (Cuijpers & Smit, 2002). Reports estimate that the United States alone loses between $30 and $40 billion annually secondary to depression-related medical and productivity costs (Elinson, Houck, Marcus, & Pincus, 2004). MDD can impair both vocational and social functioning and may compromise physical health and functioning (Katon, 2003; Paradis, Reinherz, Giaconia, & Fitzmaurice, 2006). In the 10-year National Health and Nutrition Survey, results indicated that depressed men and women had a 71% and 73% greater chance, respectively, of developing heart disease (Ferketich, Schwartzbaum, Frid, & Moeschberger, 2000). Further substantiation of the

medical risks of depression is that over 20% of persons presenting for treatment of a medical illness have been found to have depressive symptoms (Tylee & Gandhi, 2005).

Probably one of the most significant risks and complications related to MDD is suicide. The lifetime risk of completed suicide secondary to MDD has been estimated to range between 3.4% and 6% for outpatients never hospitalized (Blair-West, Cantor, Mellsop, & Eyeson-Annan, 1999; Nierenberg et al., 2004), 2.2% to 8.6% for those with a minimum of one psychiatric hospitalization (Bostwick & Pankratz, 2000), and 15% to 20% for inpatients (Simon, Savarino, Operskalski, & Wang, 2006). Preventing suicide is thought to be difficult for many reasons including medication non-compliance and unsupervised outpatient treatment (Nierenberg et al., 2004). Research has shown electroconvulsive therapy (ECT) to be an effective and speedy remedy for those depressed persons in acute suicidal risk (Husain et al., 2004; Kellner et al., 2005; Petrides et al., 2001).

Two large scale studies that provided vital information regarding MDD were the Epidemiological Catchment Area (ECA) study which included approximately 20,000 participants (Eaton et al., 1997; Eaton et al., 1984; Regier et al., 1984) and the National Comorbidity Survey Replication (NCS-R) which included approximately 9,000 participants (Kessler et al., 2003). Risk factors and models for the development of unipolar MDD include genetic approaches (Hamet & Tremblay, 2005; Levinson, 2006; Sullivan, Neale, & Kendler, 2000), stress-diathesis (Kessler, 1997; O'Sullivan, 2004), and individual susceptibility (Nettle, 2004). The genetic model assumes that depression is related to genetic heritability as found in studies of monozygotic and dizygotic twins (Sullivan et al., 2000). For instance, it has been suggested in the Utah pedigree study that

a certain gene cluster found on chromosome 12 is a predisposition for the development of depression (Abkevich et al., 2003). The stress-diathesis model, which was first introduced in the mid 1990s (Harris & Brown, 1996) explains depression in terms of the relationship between innate vulnerability to stress and external stressors. According to the model (O'Sullivan, 2004), people have an internal regulatory system that when stressed to a high degree will become impaired and lead to depression. The individual susceptibility model posited by Nettle (2004) is an evolutionary model which suggest that depression occurs when persons are adapting to their environment and that depression can have both positive and negative consequences.

The symptoms listed in the DSM-IV can form over 100 unique combinations to produce a diagnosis of MDD, and while there exists significant depressive clinical heterogeneity among individuals (Hamet & Tremblay, 2005), within individuals there tends to be symptomatological stability (Blazer, Swartz, Woodbury, & Manton, 1988; Minor et al., 2005). For instance, 71 adults with MDD were found to have the same depressive symptoms at a 10-month follow up as they did at baseline. Although the severity of the symptoms fluctuated, the symptoms nonetheless remained the same (Minor et al., 2005). That is to say individuals may be diagnosed with MDD; however, each individual may present over time with a different, stable depressive symptom set.

State and Trait Depression

Depression has been hypothesized to exist as either a state, a trait, or both. State depression is defined as the present experience of depressed mood, whereas trait depression is the general experience of depressed mood (Endler, Macrodimitris, & Kocovski, 2003; Parker, Wilhelm, & Asghari, 1998). That is, state depression can be

seen as having current depressed mood that may not meet diagnostic criteria for MDD, and trait depression can be viewed as having depressive symptoms that may meet diagnostic criteria for an MDE (Hartlage, Arduino, & Alloy, 1998). Per some scholars, state depression is temporary and brief whereas trait depression is stable and long lasting (Brewin, Smith, Power, & Furnham, 1992; Ingram, Partridge, Scott, & Bernet, 1994). State depression can be assessed by asking a person how he/she is presently feeling and trait depression can be assessed by asking a person how he/she generally feels. Common measurement tools used for assessment of state and trait depression are the Self Analysis Questionnaire (Spielberger & Ritterband, 1996) and the State-Trait Depression Scales (Krohne, Schmukle, Spaderna, & Spielberger, 2002).

The distinction between state and trait depression has received limited study (Endler et al., 2003), but the two unidimensional constructs may be different. In a 15 year longitudinal study of 156 participants, there were significant differences between the groups with MDD, minor depression, and no depression in terms of the number of depressed mood states experienced with the MDD group having the highest amount (Parker et al., 1998). A study with the same cohort also found that there were no gender differences in the experience of state or trait depression with both sexes reporting similar scores on both clinician (state) and self report (trait) depression measures (Wilhelm, Parker, & Asghari, 1998). An important difference between state and trait depression is negative cognitive schema processing. Persons with trait depression have been found to have stable, automatic negative schemas, whereas those with state depression mainly have negative schemas only during the context of the depressed state (Derry & Kuiper, 1981; Svrakic, Przybeck, & Cloninger, 1992). During the depressed mood state, some

persons may be diagnosed with personality disorders due to the inflation of symptoms resulting from the negative affective state (Chien & Dunner, 1996; Joffee & Regan, 1988). Regarding trait depression, it has been hypothesized that the negative cognitive processes are a main factor in determining the depression severity (Teasdale, 1988). In a NIMH collaborative study on the psychobiology of depression, it was found that state depression enhanced trait depression characteristics such as emotional lability, hypersensitivity, and dependency (Hirschfeld et al., 1983; Reich, Noyes, Hirschfeld, Coryell, & O'Gorman, 1987).

Major Depressive Disorder DSM-IV Subtypes

With the advent of the DSM-IV, MDD was formulated into various subtypes based on the presence of specific depressive symptom patterns. The MDD subtypes listed in the DSM-IV include catatonic, melancholic, atypical, and postpartum (APA, 1994).

Melancholic Depression

Melancholic depression, also known as “typical” or “endogenous” depression, is the most studied depressive subtype and is associated with neurovegetative symptoms such as decreased appetite and weight, energy, psychomotor retardation or agitation, and initial morning insomnia, excessive guilt, and diurnal variation (Melartin et al., 2004; Rush & Weissenburger, 1994). Research suggests that 25%-30% of persons diagnosed with unipolar MDD meet diagnostic criteria for melancholic depression (Hill & Gorzalka, 2005). Depression with melancholic features has a distinct symptom pattern, usually responds favorably to biological antidepressant interventions such as electroconvulsive

therapy (Husain et al., 2004), and may negatively impact neurocognitive functioning (Sackeim et al., 1990).

To be diagnosed with melancholic depression, the symptoms of anhedonia and lack of mood reactivity must be present with a minimum of three of the above listed depressive symptoms (APA, 1994). Melancholic depressive symptoms have not been found to be stable across MDEs, indicating intraindividual symptom shifting, that is melancholic symptoms may change throughout the course of the depressive episode (Melartin et al., 2004). Further, psychomotor disturbances have been found to be indicative of and distinguish melancholic depression from the atypical subtype (Parker, 2000).

A symptom unique to the melancholic depression subtype is diurnal variation; a change in mood secondary to time of day (i.e., morning, afternoon, evening) that has been found to correlate with cortisol levels. For example, high cortisol levels in the morning or evening may be associated with worse mood at those times of day (Mofoot et al., 1994). Research has suggested that diurnal variation might affect memory function, too, with improvement of memory correlating with diurnal improvement. Mofoot and colleagues (1994) showed that 20 participants with diurnal variation performed significantly better on the Rey Auditory Verbal Learning Test (Rey, 1964), a common measure of verbal list learning, on list learning and delayed recall, during the time of day when their mood had improved.

Further evidence substantiates the deleterious neurocognitive effects of melancholic MDD. Some neuroimaging studies have suggested there is decreased metabolism in the inferior frontal lobes (Sackeim et al., 1990) and decreased regional

cerebral blood flow (rCBF) in the left anterior cingulate and left dorsolateral prefrontal cortex (Bench et al., 1992). Melancholic depression, relative to non-melancholic, has been hypothesized to have more pronounced negative cognitive effects on selective attention and set-shifting (Austin et al., 1999; Porter, Gallagher, Thompson, & Young, 2003). However, the authors note the differences between the melancholic and non-melancholic groups could have been due to depression severity rather than melancholia.

Atypical Depression

Atypical depression was first identified by West and Dally (1959) when they noticed a distinct sample of patients with MDD responded better to monoamine oxidase inhibitors (MAOIs). Later, atypical depression was operationalized by Liebowitz and colleagues at Columbia University (1988; 1984) as depression with mood reactivity. Prevalence rates for atypical depression vary between 1.4% and 2.8% (Angst, Gamma, Sellaro, Zhang, & Merikangas, 2002; Horwath, Johnson, Weissman, & Hornig, 1992), and a lifetime prevalence of 0.7% was found in the ECA study (Levitan, Lesage, Parikh, Goering, & Kennedy, 1997). According to Henkel and colleagues (2004), approximately 30% of persons diagnosed with unipolar MDD may meet criteria for atypical depression. Atypical depression is distinct from typical depression in that it has a different symptom profile and clinical course, and responds differently to antidepressant treatment.

In order to meet criteria for atypical depression, a patient must have mood reactivity (i.e., feeling better when experiencing a positive event) and at least two of the following four symptoms: hyperphagia (increased appetite) or weight gain, hypersomnia, leaden paralysis, and interpersonal (rejection) sensitivity. These criteria, developed by the Columbia group (Quitkin & Davies, 2004; Quitkin, Stewart, & McGrath, 1993), were

incorporated into the DSM-IV. Those persons diagnosed with atypical depression have been found to have an earlier age of onset, be younger, and have a longer course of illness (Posternak & Zimmerman, 2001; Zubieta, Pande, & Demitrack, 1999). Common comorbidities with atypical depression have included obsessive compulsive personality disorder, body dysmorphic disorder (Nierenberg, Fava, & Rosenbaum, 1996), and panic attacks (Quitkin & Davies, 2004).

Physiological support for the concept of atypical depression has been found in the differential response to antidepressant treatment and hypothalamic-pituitary-adrenal (HPA) axis function. The HPA axis regulates hormonal release (i.e., cortisol) and is affected by depression, and stress, as evidenced through associated increased or decreased hormonal secretions (Heit, Owens, Plotsky, & Nemeroff, 1997). Those with atypical depression respond less favorably to tricyclic antidepressants (TCA), electroconvulsive therapy (West and Dally, 1959), have diminished HPA axis activity (Stewart, Quitkin, McGrath, & Klein, 2005), and less robust adrenocorticotropic hormone (ACTH) which is believed to be the cause of the reversed neurovegetative (i.e., hypersomnia) symptoms (Nierenberg, Alpert, Pava, Rosenbaum, & Fava, 1998). ACTH is a hormone secreted by the pituitary gland that regulates the production and release of other hormones of the adrenal cortex (Rosenzweig, Breedlove, & Leiman, 2002). Moreover, level of arousal, autonomic sympathetic activity, body mass index, and immune functioning, have been found to be different between those with atypical and melancholic depression (Gold & Chrousos, 2002).

There is no consensus as to whether atypical is less or more severe than typical depression (Benazzi, 2002; Henkel et al., 2004; Parker, Parker, Mitchell, & Wilhelm,

2005) as studies have found conflicting information. For instance, Parker (2000) created a hierarchical continuum showing depression severity to vary by subtype, with atypical being first indicating less severity, and psychotic being at the top, indicating greater severity. However, the Columbia group has indicated that atypical can be as severe as melancholic depression (Quitkin & Davies, 2004). To date, there is no information regarding the effects of atypical depression on neurocognitive functioning.

Major Depressive Disorder Hypothesized Subtypes

Although not listed in the DSM-IV, other subtypes of MDD that have been codified include anxious depression (Fava et al., 2004; Joffee, Bagby, & Levitt, 1993), treatment-resistant depression (Fava & Davidson, 1996), and psychotic depression (Jeste et al., 1996).

Anxious Depression

Depression with comorbid anxiety has been linked to increased suicide risk (Fawcett & Kravitz, 1983; Lydiard & Brawman-Mintzer, 1998), poorer prognosis (Joffe, Bagby, & Levitt, 1993), greater chronic course and functional impairment (Lydiard & Brawman-Mintzer, 1998), and familial pattern of illness (Clayton et al., 1991). The National Comorbidity Survey (Kessler et al., 1996) found that between 60% to 65% of patients with MDD had comorbid anxiety and a prevalence rate of approximately 30% of anxious depression has been documented in several clinical trial depressive samples (Russell et al., 2001; Tollefson, Holman, Sayler, & Potvin, 1994). For instance, in a sample of 635 patients, 229 were diagnosed with anxious depression (Russell et al., 2001) and in a sample of 1261, 606 met criteria for anxious depression (Tollefson et al., 1994).

Also, approximately 20% to 30% of those with anxious depression have panic disorder (Lydiard, 1991).

Research investigations have varied by their operational definition of anxious depression and treatment outcome, as well as by initial severity, treatment duration, and pharmacotherapy regimen (Delini-Stula, Mikkelsen, & Angst, 1995; Fava et al., 1997; Singh & Mukandan, 2003). The above differences make it difficult to establish whether a distinct pattern of treatment response exists for those with anxious depression.

Three definitions of anxious depression have been found in the literature. The first defines anxious depression as comorbid MDD and anxiety, the second as MDD with subthreshold anxiety, and the last as minor depression with minor anxiety (Silverstone & VonStudnitz, 2003). Physiologically, anxious depression has been related to a deficit in the 1A subtype serotonin receptors (Alpert, Franznick, Hollander, & Fava, 2004; Stahl, 1994). While there is no one agreed upon definition, there is consensus that both depression and anxiety rating measures should be used when anxious depression is diagnosed (Silverstone & VonStudnitz, 2003).

Anxious depression is considered to be distinct in that the significant symptoms are somatic complaints (i.e., increased heart beat, shortness of breath, dry mouth, excessive sweating), feelings of detachment, and psychic anxiety (Parker et al., 1999). Compared to those with melancholic depression, anxious depressed persons were found to have higher suicide attempt rates, alcohol abuse, and Axis II pathology (Parker et al., 1999). As found in the STAR*D trial, sociodemographic variables also differed between those with and without anxious depression, with the former more likely to be older, unemployed, and less educated (Fava et al., 2004). Anxious depression may also be

associated with cognitive difficulties. As posited by Eysenck and Calvo (1992), persons with anxiety have limited attention capacity which may interfere with memory processes. According to Airaksinenen and colleagues (2004), patients with mixed anxiety and depression showed significant impairment on memory tests relative to those without anxiety who only showed impaired processing speed. Additional research (Bierman, Comijs, Jonker, & Beekman, 2005; Paterniti, Dufouil, Bisserbe, & Alperovitch, 1999) has further shown that anxiety comorbid with depression significantly decreased learning and memory relative to depression alone. For instance in one study (Kizilbash, Vanderploeg, & Curtiss, 2002), patients with comorbid depression and anxiety showed impaired performance , relative to those patients with only depression, on immediate recall and delayed recall of the California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987), a common measure of verbal memory and learning.

The treatment of anxious depression has received limited research. Those with anxious depression have shown clinical response to minor tranquilizers, selective norepinepherine reuptake inhibitors, and SSRIs (Lydiard & Brawman-Mintzer, 1998; Parker et al., 1999; Silverstone & VonStudnitz, 2003). While clinical response has been documented, those with anxious depression have been found to have a less favorable outcome and longer recovery time with antidepressant treatment than those with MDD without anxiety (Clayton, Grove, & Coryell, 1991; Joffee et al., 1993).

Psychotic Depression

Classifying psychotic depression (also known as delusional depression) as a distinct depressive subtype remains under debate (Jeste et al., 1996). For example, in the DSM-IV, it is listed as a marker of severity rather than a subtype (APA, 1994). Psychotic

symptoms, within the context of depression, usually consist of auditory and/or visual hallucinations and/or delusions that may center around content of punishment, guilt, nihilism, somatic, or financial poverty (APA, 1994).

Psychotic depression has been reported to be biologically and neurocognitively distinct from non-psychotic depression (Nelson, Khan, & Orr, 1984; Sands & Harrow, 1994). Various studies have suggested that those persons diagnosed with psychotic depression were older, had worse premorbid functioning and longer MDE length, and were more prone to future psychotic depressive episodes and poorer prognosis (Sands & Harrow, 1995; Schatzberg & Rothschild, 1992). Those with psychotic depression show differential antidepressant treatment response with better response to ECT (Husain et al., 2004; Petrides et al., 2001) and/or combination neuroleptics and antidepressants (Meyers, 1995). Psychotic depression may be associated with structural brain abnormalities such as increased ventricle-to-brain ratio and greater parietal region atrophy (Rothschild et al., 1989), or excessive HPA axis activity (Anton, 1987; Schatzberg et al., 1983).

Some patients with psychotic depression have been found to perform worse in many neuropsychological domains such as executive function, verbal and visual memory, and psychomotor skills, compared to those without psychotic features (S. K. Hill, Keshavan, Thase, & Sweeney, 2004; Jeste et al., 1996; Rund et al., 2004). Furthermore, patients with psychosis have been reported to show more perseverations on the Wisconsin Card Sorting Test (Heaton et al., 1993), a commonly used measure of executive functions. High commission errors have also been reported by one study (Belanoff, Kalehzan, Sund, Ficek, & Schatzberg, 2001) using the Wallach Memory Recognition Test, a test of verbal memory in which the participant learns a list of 16

words (Wallach et al., 1980). Studies have suggested that the cognitive profile of psychotic depression resembles that of schizophrenia, given the poor performance specifically in the domains of executive function and processing speed (Albus et al., 1996; Mojtabai et al., 2000; Nelson, Sax, & Strakowski, 1998). However, discrepancies in the neurocognitive profile of psychotic MDD have been noted, with studies finding limited cognitive differences between those with and without psychosis (Kim et al., 1999; Simpson, Baldwin, Jackson, & Burns, 1999). The main cognitive domain that was found to be impaired across many of the studies was psychomotor speed (Fleming, Blasey, & Schatzberg, 2004) as measured on part A of the Trail Making Test (part of the Army Individual Test Battery, 1944, as cited in Lezak et al., 2004). While some of the above studies suggest there is a neurocognitive distinction between those with and without psychotic MDD, they were limited by small sample sizes, not controlling for depression severity and age, and they varied per research diagnostic criteria. Additional research may be needed in order to see if there are differences between those depressed persons with and without psychosis.

Treatment Resistant Depression

Treatment Resistant Depression (TRD) has been defined as depression that does not resolve after a minimum of six weeks of adequate antidepressant treatment (Fava & Davidson, 1996). TRD subtype is considered different from chronic depression and those persons with major depression who show partial response. Chronic depression indicates a prolonged condition that is time dependent, and partial response is defined as a 25% decrease in depression severity. TRD is not dependent on length of time, nor do those persons who carry the diagnosis partially respond (Links & Akiskal, 1987). In a meta-

analysis of 36 clinical studies, Fava and Davidson (1996) estimated that between 29% and 46% of persons with MDD fail to fully respond (i.e., 50% decrease in depression severity) to treatment, with 12% to 15% showing partial response, and 19% to 34% showing no response. Thus, there are a high percentage of persons diagnosed with MDD who may be treatment resistant.

Treatment-resistant depression may be related to increased cognitive impairment; however, to date, there is limited information. In a study comparing antidepressant responders to non-responders (Baldwin et al., 2004), it was found that the two groups differed on tests of visual-spatial functioning and executive functioning, with greater impairment found in the non-responder group. Specifically, non–responders showed worse performance on the Rey Complex Figure Test (a common measure of visual-spatial memory, Rey & Osterrieth, 1993) immediate and delayed recall, Stroop (Stroop, 1935), and verbal fluency, compared to responders. The authors hypothesized that the difference between the groups was due to the increased white matter lesions and atrophy (measured by magnetic resonance imaging) found in the non-responders (Baldwin et al., 2004) relative to the responders. Although it is unclear why those with TRD may show worse performance than those without TRD on neurocognitive measures, Kampf-Sherf and colleagues (2004) suggest that it may be due to a low production of serotonin. While not substantiated, decreased levels of serotonin have been hypothesized to increase impulsivity and decrease concentration for complex tasks (Hegerl & Juckel, 1993). Nevertheless, depressed persons, regardless if they are treatment resistant or not, may have variable levels of serotonin or other neurotransmitters (McAllister-Williams, Ferrier, & Young, 1998).

Recurrent and Single Episode Depression

For those persons diagnosed with MDD, between 50% and 75% experience more than one depressive episode (Gold & Chrousos, 2002; Harkness, Monroe, Simons, & Thase, 1999; Kennedy & Paykel, 2004). Typically, the subsequent depressive episode occurs within six months after recovering from the first episode, with recurrence increasing proportionally to the number of subsequent episodes (Angst, 1999). Illustrating the high recurrence rate, a longitudinal study following 69 participants with MDD over a 20 year time period showed that over 92% recovered on average by 12 months (median recovery time was 7 months) and 67% of those who recovered later had a recurrence of depression (Kennedy, Abbott, & Paykel, 2003). The predictors that MDD will be recurrent include female gender, low-severity residual depressive symptoms, comorbid generalized anxiety disorder, and high severity index episode (Judd et al., 2000; Keller et al., 1992; Kornstein et al., 2000; Wilhelm, Parker, Dewhurst-Savellis, & Asghari, 1999).

Recurrent depression has been suggested to be more severe and disabling than single episode depression. Those with chronic, recurrent depression have been shown to have more Axis I (i.e., anxiety, substance abuse), Axis II (i.e., cluster B), and Axis III (i.e., somatic complaints, somatic diseases) comorbidities (Vuorilehto et al., 2005). Moreover, recurrent depression has been associated with increased negative perceptions of social stimuli (i.e., vocal expressions, facial expressions) and negative self perceptions (Bos et al., 2005) as well as poor marital and interpersonal relationships and poor employment functioning (Kennedy & Paykel, 2004; Wilhelm et al., 1999) which suggests recurrent depression, relative to single episode, may be more deleterious. However, in

the Netherlands Mental Health Survey and Incidence Study (Kruijshaar, Hoeymans, Bijl, Spijker, & Essink-Bot, 2003), the severity of the depressive episode was found to be more related to increasing levels of disability as opposed to the number of depressive episodes. Thus, there is conflicting evidence as to whether depression severity or the number of depressive episodes may be accountable for the level of physiological and functional impairment.

Physiological correlates of recurrent MDD have been found to include increased cortisol (Bos et al., 2005), glucocorticoids (Lampe et al., 2003), and decreased hippocampal volume (Neumeister et al., 2005). The reduction in the hippocampus was found to be most prominent in the posterior region which has specific implications in spatial learning and memory (Porter et al., 2003). A relationship has been shown to exist between recurrent MDD and increased cortisol and decreased hippocampal volume, as well as reduced cerebral gray matter volume (i.e., decrease in neuron and glial cell density and size) (Cotter, Mackay, Landau, Kerwin, & Everall, 2001; Rajkowska, 2000).

There is conflicting information regarding the cognitive impact of recurrent depression. An MDE can be conceptualized as a traumatic event that potentially could harm the brain and negatively impact cognitive functioning, with more MDEs causing more harm than one (Altshuler, 1993; Fossati, Coyette, Ergis, & Allilaire, 2002; Rapp et al., 2005). Various researchers (T. Burt, Prudic, Peyser, Clark, & Sackeim, 2000; Grant, Thase, & Sweeney, 2001) have speculated that there is a cumulative, neurotoxic effect of MDEs on brain physiology which causes associated neuropsychological deficits. For example, the number of depressive episodes has been associated with a decrease in cognitive performance (Kessing, 1998) on the Cambridge Cognitive Examination total

score (CAMCOG, Huppert, Brayne, Gill, Paykel, & Beardsall, 1995), a computerized neuropsychological screening tool. Also, those with recurrent depression were found to be more impaired on the Wisconsin Card Sorting Test (Heaton et al., 1993), Paced Auditory Serial Addition Test, a common test of verbal attention and working memory (Gronwall, 1977), and the Stroop test, a common test of executive function (Stroop, 1935), compared to control participants (Stordal et al., 2004). While correlations can be made between the number of depressive episodes and cognitive dysfunction, the study by Stordal and colleagues (2004) lacked a single-episode comparison group which may limit the comparison to the cognitive effects of a single episode. However, the study suggests that recurrent depression may have negative effects on executive functioning.

Contrary to the above studies, research by Grant and colleagues (2001) showed no relationship between the number of MDEs and performance on the Cambridge Neuropsychological Test Automated Battery (CANTAB, Fray, Robbins, & Sahakian, 1996), a computerized screening battery that assess memory, attention, and executive function. While the number of MDEs may have a cumulative effect on cognitive function, studies have shown that after the depressive episodes remit, cognitive functioning returns to the level of functioning before the MDEs. During the euthymic state, it is believed that the brain heals itself, in turn improving and returning cognitive functioning back to normal (Hammar, Lund, & Hugdahl, 2003; Neu et al., 2005). The length of the depressive episode, rather than the number of episodes, has been implicated in affecting cognitive abilities in one investigation (Lampe, Sitskoorn, & Heeren, 2004).

MDD and Global Cognitive Impairment: Neurophysiology

In general, MDD has been associated with neurophysiological changes (Liotti & Mayberg, 2001). Neuroimaging techniques such as single-photon emission computed tomography (SPECT), and positron emission computed tomography (PET) allow for multiple measurements including regional cerebral blood flow (rCBF) and glucose metabolism by using radioactive isotopes. Also, like SPECT and PET, functional magnetic resonance imaging (fMRI) is a structural imaging technique that can be utilized to show the relationship between behavior, rCBF, and metabolism (Salloway & Blitz, 2002). Studies using PET have shown decreased rCBF in the medial prefrontal cortex, anterior cingulate, and orbital frontal cortex, areas that have been implicated in affective disorders (Dolan, Bench, Brown, Scott, & Frackowiak, 1994; Elderkin-Thompson, Boone, Hwang, & Kumar, 2004). Moreover, in a study of ten depressed patients assessing mood-congruent processing biases using fMRI, it was found that abnormal responses were associated with the medial and orbital prefrontal cortices (Elliott et al., 2002).

Neurophysiological differences, identified with neuroimaging techniques, have also been found in some depressed samples. For example, neuroimaging studies have shown abnormal functioning with frontal and limbic connections (Krishnan, Hays, & Blazer, 1997) using fMRI, and increased glucose metabolism in the caudate nucleus (Drevets, 2000), and the limbic regions (Alexopoulos et al., 2005) using PET. In the study by Krishan et al. (1997), late life depression was hypothesized to be related to vascular lesions (classified by a clinical rating system) in the frontal and limbic connections which may dysregulate norepinephrine and serotonin circuitry (Krishnan,

1993). That is to say, Krishan et al. (1997) suggested the depression in the patients resulted from cerebral infarction and related it to the way vascular changes may lead to dementia. The clinical classification system provides an estimate of subcortical gray matter, deep white matter, and periventricular changes as seen via MRIs (Fazekas, Chawluk, & Alavi, 1987).

Neurobiologically, serotonergic and HPA Axis dysfunction have been suggested to impact neurocognitive functioning in those persons with depression (McAllister-Williams et al., 1998). As identified in PET studies, the serotonergic system is abnormal in depressed patients as there are fewer serotonin receptors (i.e., 5-HT_{1A}) and the serotonin transportation mechanism (5-HTT) is inefficient (Drevets, Frank, & Price, 1999). The number of serotonin receptors was determined by assessing 5-HT_{1A} binding potential using the 5-HT_{1A} receptor radiogland [carbonyl-^{11}C] WAY-100635 (Drevets et al., 1999). The above information helps to support the possible negative impact of MDD on neuroanatomical regions which in turn may affect neuropsychological processes.

There is further evidence to suggest differential depressive effects on the cerebral hemispheres. A study assessing electroencephalogram (EEG) activity found greater left than right frontal alpha power as well as right posterior hypoactivity (Rabe, Debener, Brocke, & Beauducel, 2005). The hypothesis of decreased right hemispheric functioning has been evidenced on poor performance of neuropsychological measures such as dot localization and line orientation tasks (Henriques & Davidson, 1997). The dot localization task has been found to be dependent on the right hemisphere (Miller, Fujioka, Chapman, & Chapman, 1995).

MDD and Global Cognitive Impairment: Clinical Information

Cognitive deficits related to depression have been reported in different models (Murphy, Michael, Robbins, & Sahakian, 2003; Shenal et al., 2003) with varying degrees of severity (Landro, Stiles, & Sletvold, 2001). In a study comparing 22 patients with nonpsychotic MDD to 30 healthy control patients, Landro and colleagues (2001) found that those with depression performed significantly worse in the domains of attention, working memory, verbal long-term memory, and verbal fluency. This is commensurate with other study findings indicating impairment in verbal fluency and cognitive flexibility (Beblo, Baumann, Bogerts, Wallesch, & Herrman, 1999; Leuchter et al., 2004). For example, Beblo et al. (1999) found that 41 depressed patients, compared to a control group, performed more poorly on verbal fluency (COWAT, Benton & Hamsher, 1983) and design fluency (Regard, Strauss, & Knapp, 1982).

Research comparing bipolar MDD, unipolar MDD, and controls found the unipolar group performed poorly in the domain of episodic memory (Sweeney, Kmiec, & Kupfer, 2000) which was assessed with the Match to Sample Task (part of CANTAB computerized battery), a visual memory test. Those patients with unipolar depression were found to have a mean of 94.5 ($\pm$5.5) % correct compared to 97.2 ($\pm$2.6) % by the control group (Sweeny et al., 2000). While many of these studies provide neuropsychological and neurophysiological information, they have been limited by small sample sizes (i.e., depression sample size of 27 in the Beblo study) which may limit the effect size and external validity. Also, by including those with unipolar and bipolar depression, it may be difficult to specify which type of depression is associated with the respective cognitive deficits. For instance, manic episodes may affect cognitive functioning in different ways than depressive episodes.

Clinically, the relationship of MDD and global cognitive function may be modulated by depression severity, as it has been suggested to be associated with the amount of cognitive impairment. For example, those patients who required hospitalization due to their depression have been found to have greater cognitive deficits (Rohling, Green, Allen III, & Iverson, 2002). Even during euthymic and remission phases, the effects of depression severity may linger, influencing cognitive effectiveness. Due to the negative effects of the MDE, the brain, during the euthymic phase, is in a period of healing and may not function at its normal level (Kessing, 1998; Paradiso, Lamberty, Garvey, & Robinson, 1997). This is contradictory to the research by Hammar et al. (2003) who found that cognitive functioning returns to normal. Thus, there appears to be disagreement as to whether or not cognitive functioning returns to normal after the depressive episode remits. It may be possible that immediately after remission the brain is healing itself as suggested by Kessing et al. (1998), and that cognitive levels return to normal after a period of time after remission as noted by Hammar et al. (2003).

Depression severity may particularly impact aspects of memory. In research comparing 26 patients with MDD and 28 with minor depression, those with MDD were found to be significantly more impaired on a test of working memory and those with minor depression were found to be mildly impaired on a measure of executive functioning (Elderkin-Thompson et al., 2003). Minor depression, as defined in the DSM-IV (APA, 1994), is similar to MDD, except it consists of having only two to five depressive symptoms (one symptom must be either sad mood or anhedonia) for a minimum of two weeks. Working memory was assessed with the Digit Span subtest of the revised Wechsler Memory Scale (Wechsler, 1987) and executive functioning was

measured with a modified version of the Wisconsin Card Sort Test (Nelson, 1976). In the modified version of the WCST, ambiguous cards are removed and the participant is warned when the sorting rule changes. Supporting the above, additional research has suggested that those with minor depression perform as well as controls on cognitive measures (Airaksinen et al., 2004). In addition, subjective cognitive complaints may be related to depression severity. Although not correlated with objective neuropsychological measures, the Beck Depression Inventory (BDI, Beck, 1978) has been found to be positively correlated with the degree of subjective memory complaints (Neu, Kiesslinger, Schlattman, & Reischies, 2001; Rohling et al., 2002).

Although the above information suggests that MDD negatively affects cognitive functioning, some research disagrees, noting no significant relationship between MDD and cognitive functioning (Austin, Mitchell, & Goodwin, 2001). Moreover, in a study of 30 patients with unipolar MDD, executive function was found to improve after remission was achieved (Biringer et al., 2005).

MDD and Attention and Memory

Attention and memory may be impacted by MDD. Both automatic and effortful attention can be negatively affected, as exemplified by the need for greater reaction time while completing neuropsychological tests or performing daily activities. One study has shown in a sample of 102 males with unipolar MDD, when compared to 59 males without, that those with MDD performed significantly worse in the domain of attention (Farrin, Hull, Unwin, Wykes, & David, 2003). Attention in this study was measured by the Sustained Attention to Response Task (SART, Robertson, Manly, & Andrade, 1997), a computer-administered test of visual attention, and the Cognitive Failures

Questionnaire (CFQ, Broadbent, Cooper, & Fitzgerald, 1982), a self report measure of difficulties in attention and other cognitive domains. Also, impairment in divided attention, defined as difficulty in attending to both visual and auditory stimuli, was found to be predictive of the outcome of the depressive course in one study (Majer et al., 2004).

Depression may negatively impact many types of memory, including explicit, implicit, short term, long term, and working memory (Nitschke, Heller, Etienne, & Miller, 2004). The differences in memory may result from poor frontal-temporal lobe functioning, preoccupation with negative thoughts, and decreased processing speed (Nebes et al., 2000). In a study examining the relationship of the BDI to different versions of the California Verbal Learning Test (e.g., adult, child), once adjusted for age, gender, and intelligence, depression accounted for 2% of the variance in the CVLT score (O'Jile, Schrimsher, & O'Bryant, 2005). This finding suggests that the effect size of MDD impacting verbal memory may be small and that other domains of cognitive functioning (i.e., processing speed) need to be examined if memory differences are found. While this study has important implications, it was limited as primary diagnoses were not defined by research diagnostic criteria which may limit internal validity due to not using a standardized method of defining diagnoses. Contrary to the above, depressed persons have been found to score between one-half standard deviation and one standard deviation (corrected for age and education) below the normative population on the CVLT List A total trials 1-5 (Otto et al., 1994). Thus, there is an indication that those with MDD may not perform as well as those without MDD on measures of attention and/or memory.

Depression, when very severe, may cause such significant memory impairments that persons may be diagnosed with pseudodementia. Pseudodementia is defined as

impairment of memory secondary to depression without significant decline of other cognitive domains (Salzman & Guitfreund, 1986). Although it may be difficult to differentiate dementia from pseudodementia, in true dementia, cognitive decline progresses over time whereas in pseudodementia the cognitive loss follows after the onset of MDD (McBride & Abeles, 2000). Moreover, MDD may decrease instrumental activities of daily living (i.e., ability to use the telephone, managing money), which when decreased, could impair cognitive test taking performance (Kiosses & Alexopoulos, 2005).

MDD and Executive Function

Executive functioning (EF) is a concept that has been receiving a great deal of attention in persons with depression (Carpenter, Just, & Reichle, 2000; Harvey et al., 2004; Karatekin, Lazareff, & Asarnow, 2000). Executive functioning is defined as "the ability to maintain an appropriate problem-solving set for attainment of a future goal" (Welsch & Pennington, 1988, p. 201). Expanding this definition, Welsh, Pennington, and Groisser (1991) added that EF includes the abilities of planning, performing organized searches, and controlling impulses.

Executive functioning can be negatively affected by depression. MDD has been shown to decrease problem solving and initiation (Harvey et al., 2004; Kiosses, Klimstra, Murphy, & Alexopoulos, 2001), affect planning (Rogers et al., 2004), impair verbal fluency (Henry & Crawford, 2005), and impede cognitive flexibility in some patients with depression (Baudic, Tzortzis, Barba, & Traykov, 2004; Butters et al., 2004). While there is no consensus on the mechanisms of action, it is believed that depression causes frontal cortical impairment which in turn leads to executive dysfunction, since EF is

mainly governed by the frontal cortices (Alvarez & Emory, 2006; Carpenter et al., 2000; Dolan et al., 1994; Kaiser et al., 2003).

Research has also indicated that depression severity may play a role in the degree of executive impairment (W. D. Taylor, Wagner, & Steffens, 2002). In a small sample (N=13), depression severity, as measured by the Hamilton Rating Scale for Depression (HRSD, Hamilton, 1960), was found to be an independent predictor of total errors, perseverative responses, and failure to maintain set on the WCST (Martin, Oren, & Boon, 1991). Contrary to this finding, Harvey and colleagues (2004) found no relationship between depression severity and the WCST; however, they found it was related to poor performance on the n-back test, a measure of working memory (Bravers et al., 1997). It is unclear as to why no relationship was found between the WCST and the HRSD in Harvey and colleagues (2004) study; particularly since other studies have substantiated the findings of Martin and colleagues (1991). Also, in one study, those with unipolar depression were found to perform similarly to those with schizophrenia on the Delis Sorting Test (Delis, Squire, Bihrle, & Massman, 1992). Both groups were found to be impaired in generating spontaneous sorts and they were unable to identify some of the sorting principles in the structured sort.

Rationale for Current Proposal

Studies examining cognitive deficits associated with MDD tend to not provide extensive qualitative information such as depressive subtypes, depressive severity, or number of depressive episodes (Zakzanis et al., 1999) which has limited the understanding of the relationship between depression and neurocognitive function (Naismith et al., 2003). This tendency to not provide extensive qualitative information in

research may be attributed to many factors such as the newness of depressive subtypes as well as new understandings of depressive symptoms (Gullion & Rush, 1998). Although there is limited information regarding the cognitive effects of depressive subtypes and clinical characteristics, this does not necessitate that this area is not deserving of attention. On the contrary, this paucity in research demonstrates the importance of conducting further research in the relationship between cognitive functioning and intradomain specific MDD effects (Ebmeier, Donaghey, & Steele, 2006).

While depression, on a global level, can negatively impact cognitive functioning (Shenal et al., 2003), it is important to understand what specifically about MDD is affecting cognitive abilities. Furthermore, the factors associated with cognitive dysfunction in depression are not well understood. There is considerable variability and not all persons with MDD show cognitive dysfunction, although estimates of dysfunction have been found to range from mild to severe in this population (Elliott, 1998; Veiel, 1997). For example, is the variability in cognitive performance related to the number of depressive episodes, the severity of the MDE, or the MDD subtype. Prior research has helped increase the understanding of the cognitive impacts of depression; however, this understanding has been limited by small sample sizes, limited neurocognitive battery, and using either self-report or clinician rated depressive instruments as opposed to both. By only using a self-report measure of depression severity, it is possible to have over reporting of depressive symptoms. That is, the patient may exaggerate his/her depression severity level (Rohling et al., 2002). Utilizing both self-report and clinician rated depressive instruments may help clarify the relationship between objective and subjective ratings on cognitive abilities. Given these limitations, it seems further research is needed

to help clarify the relationship between depression and cognitive functioning. By doing so, it could help clinicians and researchers alike to understand the cognitive ramifications related to specific depressive clinical characteristics and subtypes for the purpose of developing efficacious treatment.

Purpose of the Current Study

The purposes of the current study are to examine whether or not (a) depression severity is associated with neurocognitive impairment, (b) MDD with psychotic features is associated with greater cognitive impairment than MDD without psychotic features, (c) recurrent MDD is associated with greater cognitive impairment relative to single episode MDD, (d) melancholic MDD and atypical MDD are similar and/or different, and (e) depressive episode length is associated with neurocognitive impairment.

CHAPTER 3

METHOD

Participants

As of 2005, 183 participants between the ages of 18 and 85 were recruited for the National Institutes of Health (NIH) funded, multi-center study "Comparing Three Electrode Placements to Optimize ECT." The participating centers were the University of Texas Southwestern Medical Center (UTSW), Medical University of South Carolina (MUSC), Mayo Foundation, Hillside Hospital/Northshore Long Island Jewish Health System, and the University of Medicine and Dentistry of New Jersey (UMDNJ). MUSC was the center responsible for data management.

Male and female participants were included who received a DSM-IV diagnosis of unipolar or bipolar MDD, had a pretreatment Hamilton Rating Scale for Depression ($HRSD_{24}$, Hamilton 1960, 1967) score of 21 or greater, electroconvulsive therapy (ECT) was clinically indicated, were able to provide informed consent, and were able to cooperate in neuropsychological testing. Exclusion criteria included a life-time history of schizophrenia, schizoaffective disorder, mental retardation, and current primary diagnosis of anxiety, obsessive-compulsive disorder, or eating disorder. Participants were also excluded if they had a current diagnosis of delirium, dementia, amnestic disorder or any other active general medical condition (i.e., heart disease) or central nervous system disease as well as active substance abuse or dependence. The above exclusion criteria were determined by a review of available medical records, physician assessment, and structured clinical interview. Those participants with a baseline Mini Mental State

Examination (MMSE, Folstein, Folstein, & McHugh, 1975) score less than 21, or who received ECT within the past six months, were excluded.

For the purposes of this dissertation, participants with a diagnosis of bipolar MDD were excluded. Also, those with a MMSE score of 23 or less were excluded in order to decrease the possibility of pseudodementia. A MMSE score less than 24 has been found to be suggestive of borderline dementia (Brown, Scott, Bench, & Dolan, 1994; Lamberty & Bieliauskas, 1993; Lockwood, Alexopoulos, Kakuma, & Gorp, 2000). All participants signed informed consent for this Institutional Review Board approved study (IRB File# 0402-216).

Clinical Materials

Hamilton Rating Scale for Depression (HRSD, Hamilton, 1960, 1967). The 24-item HRSD ($HRSD_{24}$) is considered the "gold standard" clinician rated instrument used to rate depressive symptoms and severity. The original HRSD consisted of seventeen items measuring affective and somatic symptoms such as mood, guilt, weight loss, suicidal ideation, and somatic anxiety. Over time, additional items were added to allow for comprehensive symptom assessment which has resulted in versions containing 21 items, 24 items, 28 items, and 30 items (Bagby, Ryder, Schuller, & Marshall, 2004; Cleary & Guy, 1977; Overall & Rhoades, 1982). The $HRSD_{24}$ consists of the original seventeen items plus an additional seven measuring paranoia, depersonalization, hypochondriasis, obsession-compulsion, hopelessness, helplessness, and worthlessness. The items are rated on different scales with some items rated on a range of 0-2 and others rated 0-4 (Hamilton, 1969, 1980). The grading guidelines for the 0-4 range are as follows: 0 indicates symptom absence, 1-mild, 2-mild to moderate, 3-moderate to severe,

and 4-severe. For the range of 0-2, 0 indicates symptom absence, 1-mild, and 2-moderate to severe. Bagby et al. (2004), in a meta analysis, provided comprehensive psychometric information for the HRSD showing internal reliability to range between .46 and .97, Pearson's *r* for interrater reliabilities ranged from .82 to .98, and the intraclass *r* ranged from .46 to .99. To ensure reliability of the $HRSD_{24}$ ratings for this study, each baseline assessment was videotaped and the videotapes were randomly selected and assessed by an independent masked rater.

Inventory of Depressive Symptomatology (IDS-SR, Rush et al., 1986; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996). The 30-item IDS self report is a depression severity measure used to evaluate and measure the DSM-IV MDD symptoms including both melancholic and atypical symptoms (Gullion & Rush, 1998; Rush et al., 1996). The $IDS\text{-}SR_{30}$ was developed, in combination with the clinician rated version ($IDS\text{-}C_{30}$), in order to develop a unique, psychometrically sound, and comprehensive depressive symptom measure. Each item is equally weighted, measures a single symptom domain, and is sensitive to change over time (Biggs et al., 2000; Rush, Carmody, & Reimitz, 2001). All items are rated on a four point scale ranging from 0 to 3 with 0 indicating no depression severity, 1-mild, 2-moderate, and 3-severe. The total score consists of summing 28 items, which ranges from 0 to 84, and is indicative of five severity levels: $\leq$ 15, normal; 16-24, mild; 25-32, moderate; 33-40, moderate to severe; and $\geq$ 41, severe. The two items that are excluded from the total score are item 11 (decreased appetite) or item 12 (increased appetite) and item 13 (decreased weight) or item 14 (increased weight). The $IDS\text{-}SR_{30}$ has shown excellent psychometric properties with a Cronbach's alpha level of .93, and correlations of .91 and .88 with $IDS\text{-}C_{30}$ and $HRSD_{17}$, respectively

(Rush et al., 2001). In an inpatient setting, the IDS-SR_{30} had a Chronbach alpha coefficient of .80 and a Pearson correlation coefficient of .84 with the SCL-90R depression subscore (Corruble, Legrand, Duret, Charles, & Guelfi, 1999).

Structured Clinical Interview for the DSM-IV (SCID-I, First, Gibbon, Spitzer, & Williams, 1996). The SCID-I is a semistructured diagnostic interview, administered by a trained certified clinician, used to diagnose DSM-IV Axis-I pathology. It is appropriate for persons ages eighteen and older and with a minimum of an eighth grade education. The SCID-I consists of ten modules including: Module A (Mood Episodes), Module B (Psychotic Symptoms), Module C (Psychotic Disorders), Module D (Mood Disorders), Module E (Substance Use Disorders), Module F (Anxiety Disorders), Module G (Somatoform Disorders), Module H (Eating Disorders), Module I (Adjustment Disorders), and Module J (Optional Module) (First et al., 1996).

The SCID-I allows for a systematic and cohesive collection of clinical and research information within a time frame of sixty to ninety minutes. Reliability of the SCID-I varies depending on its use and setting with kappa coefficients ranging between .70 to 1.00. Reliability and validity of the SCID-I are increased if the interview is videotaped and rated by an independent, masked rater (First et al., 1996). For the purposes of this study, SCID-I interviews were videotaped and randomly selected and independently rated to ensure interrater reliability of psychiatric diagnosis.

Neuropsychological Materials

Autobiographical Memory Index (AMI, Sackeim et al., 1993; Weiner, Rogers, Davidson, & Squire, 1986). The AMI is a semi-structured interview designed to measure retrograde amnesia for autobiographical information following electroconvulsive therapy.

The goal of the AMI is to quantify the extent of retrograde amnesia post ECT treatment. The AMI consist of six separate sections: 1) Family Member, 2) Travel, 3) New Year's Eve, 4) Birthday, 5) Employment, and 6) Physical Illness. At baseline only, scores are assigned as either 0 or 2 meaning not-remembering and remembering, respectively. On subsequent testing, scores are assigned as 0, 1, or 2 depending on the quality of the response. Each section is totaled and then the six sections are added together producing a grand total (McElhiney, Moody, & Sackeim, 2001).

Category Fluency. The Category Fluency test is an individually administered test of verbal fluency. The test consists of the examinee saying as many words as he/she can within one minute on three separate categories: animals, fruits, or vegetables. A total score is computed based on the total number of words produced (excluding repeated words and words that do not fit in the category). The raw score can be converted into a T-score. In a study by Hart and colleagues (1988), those with depression showed more word production than those with dementia but less than control participants.

Controlled Oral Word Association Test (COWAT, Benton & Hamsher, 1983). The COWAT is an individually administered test of verbal fluency. The test consists of three, one minute word-naming trials with the letters "F-A-S", "P-R-W", or "C-F-L". The examinee is instructed to say as many words he/she can that begin with the specific letter, without using proper names, numbers, and not using the same word with a different ending. To score the test, the number of words is tallied. The raw score can be converted into a T-score. Also, the number of perseverations and loss of set can be collected. Spreen and Strauss (1998) noted there were no differences on test performance between men and women. The COWAT has been found to have modest test-retest

reliability (r_{icc}=.80) (Ross et al., 2005), and to be sensitive to brain dysfunction and frontal lesions (Lezak, Howieson, Loring, Hannay, & Fischer, 2004, pp. 519-520).

Delis Kaplan Executive Function System Sorting Tests (CCST, Delis et al., 1992; Squire, Wetzel, & Slater, 1979). The Delis Kaplan Executive Function System Sorting Test (Delis, Kaplan, & Kramer, 2001) is an individually administered test designed to measure components of executive functioning including initiation, concept formation, problem solving, cognitive flexibility, perseveration, and behavior regulation (Lezak et al., 2004, pp. 637-638). The CCST consists of two sorts, a free sort and a structured sort. In the free sort, the examinee sorts the cards based on self-determined rules that are scored for total number of sorts, correct sorts, erroneous sorts, and the examinee's explanation. In the structured sort, the cards are sorted based on different principles including card size, shape, and color. The sorting rules are governed by verbal and perceptual properties as the cards contain both words and pictures. For the structured sorting condition, the examiner arranges the cards according to a principle and the examinee's goal is to identify the sorting principles. The CCST contains four card sets. Each card set was administered individually, as opposed to all four being administered as stated in the manual, in order to allow for retesting with alternate versions. The CCST has been examined in various neuropsychological populations and has been found to discriminate between patients with and without frontal damage (Delis et al., 1992). Relative to other executive function measures, it has been found to be advantageous due to assessing both nonverbal and verbal abilities (Greve, Farrell, Besson, & Crouch, 1995). Also, the median internal consistency score has been found to be .78 and a modest correlation of .84 was found with the WCST (Lezak et al., 2004, p. 637).

Mini Mental State Examination (MMSE, Folstein et al., 1975). The MMSE is a 30-item test of global cognitive functioning that is a popular screening instrument (Crum, Anthony, Bassett, & Folstein, 1993). The test produces one score derived from a total of the thirty items which can be converted into a standard score. Using data from the ECA study, the following cutoff scores for the MMSE were recommended: $\geq$24 = no cognitive impairment, 18-23 = mild cognitive impairment, and $\leq$17 = severe cognitive impairment (Tombaugh & McIntyre, 1992). In a community sample of 4, 917 people, the overall Chronbach's alpha was found to be .77 (Holzer, Tischler, Leaf, & Myers, 1984). Also, the internal consistency has been found to range from r=.764 to r=.803, depending on the cut off score used (Lopez, Charter, Mostafavi, Nibut, & Smith, 2005).

Rey Auditory Verbal Learning Test (RAVLT, Rey, 1964). The RAVLT is a verbal learning and memory test consisting of a 15 word list, five learning trials, a 15 word interference list read once, an immediate recall and 20-minute recall of the first list, and a recognition trial. The words, which are not related to each other, are read at the rate of one per second. For the recognition trial, the examinee was handed a sheet with 50 words and was instructed to circle the 15 correct words from the five learning trials. Four versions of the RAVLT were used, AB, CD, Cr-AB, and Ge-AB (Schmidt, 1996). In addition to memory and learning, perseveration and intrusion can also be recorded. The RAVLT has moderate to high test-retest reliability (i.e., .61 to .86 for the five learning trials and .51 to .72 for delayed recall and recognition) and alternate form reliability for versions AB and CD (i.e., .36 for trial I, .49 for trial V, .60 for delayed recall) (Uchiyama et al., 1995). Also, it correlates well with other verbal learning measures (Lezak et al., 2004, pp. 422-429). When compared to the California Verbal

Learning Test, correlations for trial 1 were .32, trial 5 were .33, total words recalled were .47, and short delayed recall were .37 (Crossen & Wiens, 1994). The RAVLT has been found to be associated with the Wechsler Memory Scale-Revised (Wechsler, 1987) subtests Logical Memory and Associative Learning (Schmidt, 1996).

Rey-Osterrieth Complex Figure Test (CFT, Rey & Osterrieth, 1993). The CFT is an individually administered test designed to evaluate visuospatial construction ability, visual memory, and a variety of cognitive processes including planning, organizational skills, and problem solving. The test involves three parts: 1) copy of the design, 2) immediate recall of the design after the figure is removed, and 3) 30 minute delayed recall of the design. In one common administration procedure, the examinee copies the figure with three different colored pencils which are interchanged by the examiner based on the amount of design drawn. In this study, the figure was copied using a #2 lead pencil. The amount of time to copy the design is recorded. The CFT can be scored using the Osterrieth and Taylor method (Loring, Martin, Meador, & Lee, 1990; Spreen & Strauss, 1998) in which 18 elements are scored on a four point rating scale of 0 to 2, with a maximum score of 36. Scores are assigned based on correct design and correct placement of the element. Reliability of the CFT varies per scoring system used with most scoring systems interrcorrelated in range from r=.34 to .84. Interrater and intrarater reliability was found to be greater than 0.8, reliability for scoring individual elements ranged from .14 to .96, and test-retest reliability ranged from .60 to .76 (Fastenau, Denburg, & Hufford, 1999; Knight & Kaplan, 2003).

Squire Self-Rating Scale of Memory Function Questionnaire (SSMQ, Squire et al., 1979). The SSMQ is an instrument designed to measure subjective memory

symptoms relative to ECT treatment. Eighteen items are self rated on a 10-point scale ranging from -4 to +4, with -4 indicating worse change, 0 no change, and +4 better change. The SSMQ was shown to differentiate between memory complaints related to depressive illness before and after ECT (Squire et al., 1979). Items 1-9 were found to be related to amnesia experiences whereas items 10-18 were found to be more associated with memory complaints related to depression (Squire et al., 1979). All items are summed, producing a grand total. The SSMQ, in one study, was found to be sensitive to depression (Coleman et al., 1996), and correlated with inconsistent personal memories ($r(37) = -.40$), more definitive complaints ($r(37) = .32$), and depression severity as measured by the HRSD ($r(59) = -.48$) (Coleman et al., 1996).

Stroop Color Word Test (Stroop, 1935). The Stroop is a three trial individually administered test designed to assess executive functioning (i.e., inhibition). The three trials differ in the level of difficulty, with the first two trials being of mild complexity (read words printed in black ink, name the colored ink) and the last trial being of moderate complexity (read the word printed in different colored ink). Five versions of the Stroop were used, the original version and four alternate versions. The four alternate versions were created by successively rotating the columns beginning with column one. The examinee is handed a card consisting of 100 items divided into 5 vertical columns with each column containing 20 items. The three colors used are red, green, and blue (Golden & Freshwater, 2002). The test produces two scores, a raw score of the total number correct and a second raw score containing the first raw score plus the number of self-corrections made. The second raw score can be converted into a T score. The Stroop has shown moderate ($r=.46$, G. P. Strauss, Allen, Jorgensen, & Cramer, 2005) to

good (r=.84, Dikmen, Heaton, Grant, & Temkin, 1999) test-retest reliability. Also, the Stroop has been found to correlate with stopping probability (r=.33) and time (r=.56) of the stop-signal task (deFrias, Dixon, & Strauss, 2006), and it has shown sensitivity to traumatic brain injury and frontal lobe lesions (Lezak et al., 2004, pp. 365-367). In a study comparing 227 depressed inpatients with 112 control persons, matched for age, gender, and education, the depressed group performed more poorly as noted on total reading errors, time to complete line one in relation to total time of the Color-Word card, and the difference in score times for the Color-Word and Color cards (Raskin, Friedman, & DiMascio, 1982).

Taylor Complex Figure Test (CFT, E. Strauss & Spreen, 1990; L. B. Taylor, 1969)

The Taylor CFT was created to provide an alternate form for the Rey Osterrieth CFT (Gagnon, Awad, Mertens, & Messier, 2003). Like the Rey Osterrieth CFT, it is an individually administered test designed to evaluate visuospatial construction ability and visual memory; however, it has been suggested that the Taylor CFT is less complex and easier to remember (Tombaugh & Hubley, 1991). The test involves three parts: 1) copy of the design, 2) immediate recall of the design after the figure is removed, and 3) 30 minute delayed recall of the design. The examinee copies the figure with a #2 lead pencil. The amount of time to copy the design is recorded. The CFT can be scored in the same manner as the Rey Osterrieth CFT in which 18 elements are scored on a four point rating scale of 0 to 2, with a maximum score of 36 (Awad et al., 2004). Scores are assigned based on correct design and correct placement of the element. Interrater reliability has been found to be greater than 0.87 (Awad et al., 2004), and internal

consistency has been found to be high with Chronbach alphas ranging from .92 to .94 (Tombaugh, Schmidt, & Faulkner, 1992). In a study with 40 healthy participants, the Rey-Osterrieth and Taylor CFTs were found to be equal in difficulty in terms of copy, but the recall of the Rey-Osterrieth was found to be more difficult than recall of the Taylor CFT (E. Strauss & Spreen, 1990).

Trail Making Test (TMT, War Department, 1944). The TMT consists of two parts, TMT A and TMT B, and assesses visuomotor speed, attention, and cognitive flexibility. TMT A involves a series of numbers (1-25) in which the subject must draw a line with a pencil connecting the circles (with numbers inside each circle) beginning with the first number and ending with the last. In part B, the stimuli contains both letters and numbers in which the subject must draw a line connecting the letters and numbers, alternating between the two in ascending manner. Four versions of TMT B were used, the original version and three alternate versions (see Appendix A). The subject is timed and the time can be converted into a T-score. Also, the number of errors can be recorded. The TMT is a widely utilized neuropsychological measure that was originally included in the Army Individual Test Battery (Lezak et al., 2004, pp. 371-374). Spreen and Strauss (1998) reported the reliability to vary between .60 to .90 with an average around .80. Research by King and colleagues (1993) showed TMT B to be sensitive to those with emotional problems, particularly depression, as reflected in longer length of time needed to complete the task.

Wide Range Achievement Test 3 (WRAT-3 Reading subtest, Wilkinson, 1993). The WRAT3 reading subtest consists of two parts, letter reading and word reading. The test is designed to assess word reading and pronunciation, and does not assess reading

comprehension. There are a total of 15 letters and 42 words which combined produce a total of 57 points (one point for each correct item). The words are administered first, and if a minimum of five words are scored correct, credit is automatically given for the letters. The examinee is handed a card with the printed letters and words to which he/she is asked to read. The test is discontinued after 10 consecutive incorrect responses. The WRAT-3 reading subtest has two alternate forms (Tan and Blue) with a correlation coefficient of .984 (Wilkinson, 1993). The WRAT-3 was normed on a nation wide sample of 5,000 people between the ages of 5 and 75. The reading subtest of the WRAT-3 has been suggested to be an estimate of premorbid intelligence (E. Strauss, Sherman, & Spreen, 2006, p. 387). It was found to correlate with the Wechsler Adult Intelligence Test, Revised (WAIS-R, Wechsler, 1981) Verbal Scale IQ (r=.63), Performance Scale IQ (r=.31), and Full Scale IQ (r=.53) (Wilkinson, 1993).

Procedure

A total of 145 participants' files were included in the analyses (see Figure 1). Analyses were also conducted with the 82 participants who met criteria for unipolar depression with a score of 24 or greater on the MMSE. All clinician rated and neuropsychological measures were administered by trained, certified clinical raters and psychometrists at baseline. All baseline assessments (clinical and neuropsychological) took place 24 hours to 48 hours before the participants received their first ECT treatment. Most neuropsychological assessments took place in the morning (i.e., between the hours of 7am and 9am) in a private, distraction-free room with one examiner and one examinee. The order of the neuropsychological tests was standardized and counterbalanced into five test schedules. The neuropsychological battery (see Figure 2 for neurocognitive domains

assessed) took approximately 60 minutes to 90 minutes to administer and the clinical battery took approximately 120 minutes to administer. The participants were assigned to one of two groups for respective analyses based on the SCID-I diagnosis including psychotic or non-psychotic MDD, single episode or recurrent MDD, and atypical or non-atypical MDD. All neuropsychological raw scores were transformed into standard z-scores. Transforming neurocognitive raw scores into z-scores has previously been conducted in neurocognitive research with patients with depression (Naismith et al., 2003; Sackeim et al., 1993).

Hypotheses

The following hypotheses were tested to examine the relationship of neurocognitive functioning to MDD clinical and depressive characteristics:

Hypothesis 1: Depression severity will be negatively correlated with global cognitive functioning. Method: A global cognitive function score was created using the neuropsychological measures (NP) in the database (excluding the Squire and AMI). Raw scores from individual tests were transformed into z-scores and a grand mean z-score was derived and served as the global cognition index (GCI; see Figure 3). Depression severity was measured using the $HRSD_{24}$ total score, and a secondary depression measure that was examined in exploratory fashion was the IDS-SR_{30} total score. It is predicted that the GCI will be negatively correlated with the $HRSD_{24}$ and the IDS-SR_{30}.

Hypothesis 2: Executive function will show strong negative association with depression severity relative to other cognitive functions. Method: Neuropsychological measures including RAVLT, CCST, COWAT, FAS, CFT, Stroop, and TMT A and B, were correlated with the $HRSD_{24}$ and the IDS-SR_{30}.

Hypothesis 3: Psychotic depression will be associated with greater cognitive deficits than non-psychotic depression. Method: The GCI was compared between the psychotic and nonpsychotic depressed groups as defined by the SCID-I. Those with psychosis were compared to those without psychosis using ANCOVA as indicated (potential covariates include age, education, and depression severity as measured by the $HRSD_{24}$).

Hypothesis 3a: Psychotic depression will show a strong negative association to executive function relative to other cognitive functions. Method: A correlation matrix was conducted to examine the relationship between those with and without psychosis on the following neuropsychological measures: RAVLT, CCST, COWAT, FAS, CFT, Stroop, and TMT A and B.

Hypothesis 4: Persons with recurrent depression will show lower scores on cognitive measures than those with single episode depression. Method: Recurrent depression was defined as greater than one depressive episode as noted on the SCID-I. NP measures included the RAVLT, CCST, COWAT, FAS, CFT, Stroop, and TMT A and B. Those with recurrent depression were compared to those with single episode depression using MANOVA. Covariates included age, education, and depression severity, as indicated.

Exploratory Hypothesis: Participants with typical depression will show greater cognitive deficits than those with atypical depression. Method: Non-atypical and atypical depression were defined using the SCID-I. NP measures included RAVLT, CCST, COWAT, FAS, CFT, Stroop, and TMT A and B. Those with non-atypical

depression were compared to those with atypical depression using MANOVA. Covariates included age, education, and depression severity, as needed.

Exploratory Hypothesis: The length of the current depressive episode will be negatively correlated with neurocognitive functioning. Method: Length of depression as noted on the SCID-I was correlated with the GCI, MMSE, RAVLT, CCST, COWAT, FAS, CFT, Stroop, and TMT A and B. It is predicted that the neurocognitive measures will be negatively correlated to greater lengths of the current depressive episode.

Due to the large number of comparisons, a more stringent alpha level of .01 was used to determine significance for primary analyses. Also, Cohen's (1977) guidelines for interpreting effect were used, thus a correlation of 0.1 suggested a small effect, 0.3 was a medium effect, and 0.5 was regarded as a large effect.

CHAPTER 4

RESULTS

Overview of Data Collection and Statistical Analyses

All data were collected on triplicate case report forms. One copy was retained at each respective site and two copies were sent to the data management center at MUSC. The data were independently entered into the database by two separate data entry technicians. A computerized query system was developed to track and record all queries and responses. Data were transferred, imported, and managed by SAS version 8.2 (SAS Institute, Inc., Cary, North Carolina) at MUSC. The data were sent to UTSW and then were imported and managed by SPSS® version 14.0 (SPSS, Inc., Chicago, Illinois). Power analyses were performed using Power and Precision™ version 2.1. For the correlation analyses and analysis of variance, power was estimated to be .36 and .29, respectively, based on a sample size of 82. To achieve a power of .80 for the analysis of variance a sample size of 200 would be required with 100 patients per group.

Descriptive Statistics

The database contained information on a total of 183 participants. Due to missing data, 145 data files were analyzed for the full data set. After excluding patients with bipolar disorder or for having a MMSE score less than 24, 82 patients comprised the unipolar depressed group. Demographic information for the total sample of 145 patients and for the 82 unipolar patients is provided in Table 1.

Insert Table 1 here

The sample as a whole had a mean age of 52.3 (SD = 15.5) and was mainly comprised of women (% female = 67.8). Eighty-seven percent of the sample was Caucasian, 7.4% African American, and 4.7% other (i.e., Hispanic, Native American). The mean years of education was 13.9 (SD = 2.7) and the majority of patients (90.6%) were right handed. The demographic information for the unipolar group was comparable to the total sample.

Clinical information for the total and unipolar sample is provided in Table 2. The majority (78.2%) of the total sample had unipolar depression, with the remainder diagnosed with bipolar disorder (i.e., bipolar I, bipolar II). Twenty-two percent of the total sample had psychotic features, 79.5% had melancholic features, and 7.9% had atypical features. Most participants (93%) had recurrent depression with a mean of 4.0 (SD = 4.4) major depressive episodes. Overall depression severity was severe with a mean $HRSD_{24}$ score of 34.7 (SD = 7.2) and a mean IDS-SR_{30} score of 45.6 (SD = 12.1). The clinical features of the total sample were comparable to the unipolar sample.

Insert Table 2 here

Neurocognitive raw scores for the total sample, the unipolar group, and for a normative sample, are presented in Table 3. Demographic adjusted neuropsychological scores for the unipolar sample are presented in Table 4. The total sample and unipolar group were relatively similar on most neurocognitive measures. The overall sample had a mean MMSE score of 26.7 (SD = 2.8) and a mean WRAT-3 Reading score of 98.7 (SD = 13.8), and the unipolar sample had an overall mean MMSE score of 27.4 (SD = 1.9) and a mean WRAT-3 Reading score of 98.9 (SD = 15.2). Relative to the normative

sample data (see Table 3 for cited normative data references), the unipolar sample had lower raw scores on all neurocognitive measures except the COWAT, Trail Making Test (parts A and B), and the DKEFS Sorting Test correct sort.

Insert Tables 3 and 4 here

Hypothesis One

Hypothesis 1 stated that depression severity would be negatively associated with global cognitive functioning. This hypothesis was tested using both the total sample (see Table 5) and the unipolar sample (see Table 6) with the $HRSD_{24}$ and the $IDS\text{-}SR_{30}$ as the primary and secondary depression severity measures, respectively. For the total sample (N = 145), no statistically significant correlations were found between the $HRSD_{24}$ and the GCI, WRAT-3 Reading subtest, or the MMSE. However, the $IDS\text{-}SR_{30}$ was significantly correlated with the GCI ($r = .245$, $p=.017$), but not in the expected direction. A partial correlation was computed between the GCI and the $IDS\text{-}SR_{30}$ holding age constant. The partial correlation was not significant ($r = .027$, $p = .803$).

Insert Table 5 here

For the unipolar group, this hypothesis was not supported. No statistically significant correlations were found between the $HRSD_{24}$ and the GCI, WRAT-3 Reading subtest, or the MMSE, although a significant negative correlation was found between the $IDS\text{-}SR_{30}$ and the WRAT-3 Reading subtest ($r = -.277$, $p= .027$).

Insert Table 6 here

Hypothesis Two

Hypothesis 2 stated that executive function would show a strong negative association with depression severity relative to other cognitive functions. This hypothesis was not supported. To test this hypothesis, a correlation matrix of the depression severity measures (i.e., $HRSD_{24}$ and IDS-SR_{30}) and the neurocognitive variables was examined. No significant correlations were found between the $HRSD_{24}$ and the neurocognitive variables. Significant correlations were found between the IDS-SR_{30} and the reading subtest of the WRAT-3 ($r = -.277$, $p = .03$), RAVLT total list A ($r = .293$, $p = .02$), RAVLT immediate recall ($r = .256$, $p = .04$), RAVLT recognition ($r = .319$, $p = .01$), and part A of the Trail Making Test ($r = -.331$, $p = .01$). The correlations between the IDS-SR_{30} and the RAVLT variables, and part A of the Trail Making Test, were not in the expected direction. Partial correlation coefficients were computed for the IDS-SR_{30} and the respective neurocognitive variables holding age as a constant variable. No significant associations were found between the IDS-SR_{30} and RAVLT total list A ($r = .115$, $p = .381$), RAVLT immediate recall ($r = .146$, $p = .264$), or part A of the Trail Making Test ($r = -.138$, $p = .292$). However, a significant association, in the unexpected direction, was found between the IDS-SR_{30} and RAVLT recognition ($r = .293$, $p = .023$). A multiple regression analysis was conducted with two models and depression severity measured with the IDS-SR_{30}. The first model included all five significant neurocognitive variables. The second model, which was based on the results of model 1, consisted of the top three

variables with the highest beta coefficients. The results of the two models are shown in Table 7.

Insert Table 7

Model 1 was statistically significant and showed that part A of the Trail Making Test and the reading subtest of the WRAT-3 were predictors of depression severity, R^2 = .23, F (5, 59) = 4.61, p =.001. Model 1 was also conducted with depression severity measured with the $HRSD_{24}$; however, it was not found to be significant, R^2 = -.052, F (5, 68) = .324, p = .897. Model 2 excluded total list A and immediate recall scores of the RAVLT and also showed to be a significant predictor of depression severity, R^2 = .25, F (3, 59) = 7.68, p < .0001.

Hypothesis Three

Hypothesis 3 stated that the patients with psychotic depression would perform worse on cognitive measures compared to patients without psychosis. This hypothesis was not supported.

Demographic information for the psychotic (N = 14) and non-psychotic (N = 67) group is provided in Table 8. No significant difference between the groups was found for education (F (1, 78) = .16, p = .690); however, the small age difference between the groups approached significance (F (1, 81) = 3.88, p = .052) as did differences in gender ($X^2_{[1]}$ = 3.40, p = .064).

Insert Table 8 here

As shown in Table 9, there were no significant differences between the psychotic and non-psychotic groups in terms of clinical characteristics. The current major depressive episode age of onset approached significance between the two groups ($F(1, 81) = 3.72$, $p = .057$). The psychotic and non-psychotic groups showed similar levels of depression severity as reflected in the $HRSD_{24}$ (35.0 vs. 33.9, respectively) and the $IDS\text{-}SR_{30}$ (46.9 vs. 45.9, respectively).

Insert Table 9 here

Regarding neurocognitive performance (see Table 10), the non-psychotic group was able to significantly generate more words on immediate recall of the RAVLT relative to the psychotic group ($F(1, 76) = 4.86$, $p = .031$). No other statistically significant differences were found between the two groups.

Insert Table 10 here

Hypothesis Three-Part A

Hypothesis 3-A posited that psychotic depression would show a strong negative association to executive function relative to other cognitive functions. This hypothesis was not supported. A correlation matrix of the psychosis variable and the executive function variables was examined. No significant correlations were found between psychosis and the executive function variables. To further test this hypothesis, a

discriminant analysis was conducted to determine whether five predictor variables could predict psychosis. The five predictor variables were the RAVLT total list A, RAVLT immediate recall, RAVLT recognition, part A of the Trail Making Test, and the reading subtest of the WRAT-3. The five predictor variables were chosen based on the correlation matrix conducted for Hypothesis 2 and a correlation matrix of psychosis and the neurocognitive variables. The overall Wilk's lambda was significant ($\Lambda = .83$, X^2 (5, $N = 69) = 11.80$, $p < .04$), indicating overall that the predictors differentiated the classification of psychosis. The Eigenvalue was .20 and the corresponding canonical correlation was .41. With the five predictor variables, 94.9% of those patients without psychotic features were correctly classified and only 10.0% of those with psychotic features were correctly classified. Table 11 shows the within-group correlations between the predictors and the discriminant function as well as the standardized weights. Also, a logistic regression was conducted which showed similar results to the discriminant analysis.

Insert Table 11

Hypothesis Four

Hypothesis 4 stated that patients with recurrent depression would perform worse than patients without recurrent depression on neurocognitive measures. This hypothesis was not supported.

Demographic information for the recurrent (N = 75) and single episode (N = 7) group is provided in Table 12. Those patients with single episode depression were found

to be older than those with recurrent depression ($F (1, 81) = 5.72$, $p = .019$). No other significant differences were found between the two groups regarding sociodemographic variables

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Insert Table 12

Regarding clinical characteristics (see Table 13), the recurrent group had a mean of 4.4 (SD = 4.3) major depressive episodes. Those with recurrent depression were found to have significantly more psychiatric hospitalizations ($F (1, 79) = 5.42$, $p = .023$), an earlier age of onset of first psychiatric illness ($F (1, 72) = 33.91$, $p < .0001$), and an earlier age of onset of current MDE ($F (1, 81) = 5.87$, $p = .018$). The recurrent and single episode groups showed similar levels of depression severity as shown on the $HRSD_{24}$ (34.1 vs. 33.5, respectively) and the IDS-SR_{30} (46.4 vs. 42.2, respectively).

Insert Table 13

As seen in Table 14, the single episode group took significantly more time to complete Trail Making Test Part A ($F (1, 73) = 6.00$, $p = .017$); however, when age was used as the covariate, no difference was found ($F (2, 73) = 9.48$, $p = .119$). No other significant neurocognitive performance differences were found between the two groups before and after using age as a covariate. Moreover, no significant correlations were found between the number of depressive episodes and the neurocognitive or clinical variables.

Insert Table 14

Exploratory Hypothesis One-Atypical Depression

This hypothesis stated that patients with atypical depression would show better performance on neuropsychological measures than those without atypical depression. This hypothesis was partially supported.

Demographic and clinical information for those depressed patients with atypical features (N=7) and without atypical features (N=74) are provided in Tables 15 and 16, respectively. There were no significant differences between groups in terms of age ($F(1, 80) = 1.97$, $p = .164$), education ($F(1, 77) = .109$, $p = .742$) or other sociodemographic variables including gender, race, dominant hand, employment, and marital status. No significant differences were found between groups in terms of clinical variables.

Insert Tables 15 and 16

The atypical and non-atypical groups significantly differed only in the neurocognitive domain of verbal memory and learning. On the RAVLT (see Table 17), the atypical group generated more words over five trials ($F(1, 75) = 9.50$, $p = .003$), recalled more words on both immediate ($F(1, 75) = 4.28$, $p = .042$) and delayed recall trials ($F(1, 72) = 6.49$, $p = .013$), and showed better recognition discrimination ability ($F(1, 72) = 4.48$, $p = .038$).

Insert Table 17

Exploratory Hypothesis Two-Major Depressive Episode Length

This hypothesis posited that the length of the depressive episode would be negatively correlated with cognitive functioning. This hypothesis was not supported. Significant negative correlations (see Table 18) were found between length of the current depressive episode and RAVLT immediate recall ($r = -.491$, $p = .039$) and the reading subtest of the WRAT-3 ($r = -.575$, $p = .013$). As shown in Table 19, the length of the current depressive episode was found to be significantly positively correlated with the IDS-SR_{30} ($r = .539$, $p = .025$). However, three patients had significantly lengthy depressive episodes which skewed the data. After those three patients were removed from the analyses, duration of the depressive episode did not correlate with the RAVLT immediate recall trial ($r = .034$, $p = .903$), the reading subset of the WRAT-3 ($r = .278$, $p = .316$), or the IDS-SR_{30} ($r = -.134$, $p = .647$).

Insert Tables 18 and 19

CHAPTER 5

DISCUSSION

The primary goal of the current study was to examine the neurocognitive functioning of patients with severe major depressive disorder. Three primary aims and two exploratory aims were established to help attain the above goal. The three primary aims were to (a) examine the impact of depression severity on global neurocognitive function, (b) determine if MDD with psychotic features is associated with greater cognitive impairment, and (c) determine if recurrent MDD is associated with greater cognitive impairment. The two exploratory aims were to (a) examine the similarities and differences between atypical and typical MDD, and (b) determine if depressive episode length is associated with neurocognitive impairment.

Impact of Depression Severity on Neurocognitive Function

Global cognitive functioning was not found consistently to be related to depression severity overall. The $HRSD_{24}$, a popular clinician-rating scale for depression, was not significantly correlated with cognitive measures in the full sample or the unipolar sample. In the unipolar sample, the IDS-SR_{30}, a self-report measure of depression severity, was negatively correlated with only one cognitive measure, the reading subtest of the WRAT-3, which is a measure of sight-word reading ability that correlates highly with IQ (Strauss et al., 2006, p. 387). In the full sample, the IDS-SR_{30} positively correlated with the GCI, although after holding age constant, the correlation was not significant.

Finding no association between depression severity and global cognitive function may be understood from a psychometric, methodological, clinical, and statistical

viewpoint. For example, the $HRSD_{24}$ does not assess cognitive complaints (Hamilton, 1960); however, the IDS-SR_{30} does. Item 15 (concentration/decision making) of the IDS-SR_{30} assesses concentration, attention, and decision making (Rush et al., 1996). The IDS-SR_{30} also measures other depressive symptoms not assessed by the $HRSD_{24}$ (i.e., atypical depressive symptoms, pain complaints). Because of the comprehensive assessment of depressive symptoms, the IDS-SR_{30} assesses symptoms that may affect neurocognitive function that are not assessed by the $HRSD_{24}$. In a study of the psychometric properties of the IDS-SR_{30} in a cohort of depressed outpatients, Rush et al. (1996) found it was significantly correlated ($r = .88$, $p < .0001$) with the $HRSD_{17}$. For this current study, the IDS-SR_{30} and $HRSD_{24}$ were significantly correlated ($r = .584$, $p < .0001$), albeit at a lower level. One of the differences between this study and that of Rush et al. (1996) was the current investigation examined hospitalized depressed patients, whereas the former study measured depressed outpatients. It may be possible that hospitalization status affects the reporting of depressive symptoms. Also, this study employed the $HRSD_{24}$ and the former study used the $HRSD_{17}$. Thus, the differences in the patient samples and versions of the HRSD utilized may account for the lower correlation between the IDS-SR_{30} and the HRSD found in this study relative to that of Rush et al. (1996).

The MMSE is a widely accepted measure of global cognitive function that has been utilized in many studies. In the original article on the MMSE by Folstein et al. (1975), the total score on the MMSE was found to separate three diagnostic groups (dementia, depression, depression with cognitive impairment) and a control group. The authors found that the MMSE was lower in patients with depression when compared to

controls (Folstein et al., 1975). However, a later study suggested that the MMSE was not sensitive to the cognitive effects of depression (Forsell, Jorm, & Winblad, 1994), a finding similar to this study. Alpert et al. (1995) examined the performance of 148 depressed patients (age range = 18-65) on the MMSE and found no significant correlation between the MMSE and the $HRSD_{17}$ ($r = -0.11$, $p = .20$). The authors also noted that after the patients' depression remitted, the MMSE score at end of treatment did not correlate with the end $HRSD_{17}$ score ($r = -0.11$, $p = .35$) (Alpert et al., 1995). The sample in the study by Alpert et al. (1995) differed from the sample in the current study as the patients in the Alpert et al. (1995) study were non-hospitalized and had lower levels of depression severity. It may be possible that the MMSE is not sensitive to clinician rated or patient rated depression severity in hospitalized patients, and thus may not be a useful indicator of cognitive difficulties in that population.

Methodologically, the reason a lack of association between depression severity and the MMSE was found may have been due to the restricted ranges of the MMSE and the $HRSD_{24}$. Entry criteria into the study required a score of 21 or greater on the MMSE, and for additional analyses, the MMSE score was restricted to 24 or greater, a score that is typically considered to be in the normal range (Folstein et al., 2001). By requiring the score to be 24 or greater the range of scores was restricted on the MMSE, which could have limited the association with the depression severity scores. Also, the inclusion criteria required a $HRSD_{24}$ score of 21 or greater thus all patients had severe depression, which limited the range of depression scores. Thus, by having a limited range on both the MMSE and the depression severity measures, the ability to assess the relation

between a continuum of depression severity scores (i.e., mild, moderate, severe) and cognitive functioning was not possible.

Clinically, depression severity has been inconsistently associated with neurocognitive functioning (Gualtieri, Johnson, & Benedict, 2006). Examining differences between 38 patients with MDD and 69 control patients, Gualtieri et al. (2006) noted that patients with depression performed worse in the domains of cognitive flexibility, complex attention, vigilance, and global function. The combination of seven test scores was used to assess global function. The authors posited that poor performance in global functioning resulted from decreased cognitive flexibility and attention. Similarly, in a study of 23 patients with severe depression (Trichard et al., 1995), no correlation was found between depression severity and neuropsychological performance. Rather, the researchers noted that significant negative correlations were found between measures of verbal fluency and the depressive symptom "Lassitude" on the Montgomery Asberg Depression Rating Scale (Montgomery & Asberg, 1979) which assesses difficulty initiating and performing daily activities (Trichard et al., 1995). No other significant correlations were found between other neurocognitive domains and the Lassitude item of the Montgomery Asberg Depression Rating Scale. Moreover, depression severity, as measured with the Beck Depression Inventory in 115 depressed outpatients (Beck & Steer, 1993), was found to be unrelated to objective or subjective neuropsychological measures (Rohling et al., 2002). Thus, the total depression severity score may not be related to neuropsychological performance, but individual depressive symptom scores may. This may imply that individual depression symptom items should be examined with regard to neurocognitive function versus using the total depression severity score.

This would help clarify what depressive symptoms may be related to cognitive functioning.

Differences in cognitive function may be systematically related to various psychiatric syndromes (Albus et al., 1996). The reason for finding a correlation between the IDS-SR_{30} and CGI in the full sample, but not the unipolar sample, could be due to the psychiatric diagnostic composition of the group. Approximately 22% of the patients in the whole sample were diagnosed with bipolar depression, and this may have influenced the relationship between the GCI and level of depression severity. For example, Sackeim et al. (1992) suggested that patients with bipolar depression show similar neuropsychological test performance as controls (i.e., patients with no psychiatric diagnosis), but that patients with unipolar depression show worse performance. However, in a comprehensive review of the literature, it was concluded that no significant differences exist in the neuropsychological profile between unipolar and bipolar depression (Quraishi & Frangou, 2002). Furthermore, subjects in the full and unipolar samples of the current investigation showed similar performance on the neurocognitive tests that made up the GCI, thereby suggesting that bipolar depression did not mediate the relationship between depression severity and cognitive function.

To further explore the relationship between depression severity and neurocognitive function, specifically executive function, a correlation matrix was created to examine relationships between the IDS-SR_{30} and all 24 neurocognitive variables. No significant relationships between depression severity and executive function measures (e.g., Trail Making Test Part B, DKEFS-Sorting Test, Stroop color-word) were found. Rather, depression severity (as measured by the IDS-SR_{30}) was found to correlate only

with two scores, including measures of verbal memory (i.e., RAVLT) and simple attention/psychomotor speed (i.e., Part A of the Trail Making Test). A meta analysis of 122 studies of severely depressed patients with an age range of 19 to 84 found that depression was related to memory impairment (D. B. Burt, Zembar, & Niederehe, 1995). However, Rohling et al. (2002) compared 115 patients with low depression (defined as a BDI score of 10 or less) to a group of 112 with high depression (BDI score $\geq$ 25) and found no difference on the California Verbal Learning Test (CVLT, Delis et al., 1987), a common test of verbal memory. The difference between the studies of Burt et al. (1995) and Rohling et al. (2002) may be due to methodological differences. Burt et al. (1995) included a diverse group of patients with affective disorders in their meta analytic studies with different verbal memory measures; however, they did not define depression severity, whereas Rohling et al. (2002) had a controlled study that directly compared two defined groups on the CVLT. The findings of the current research are similar to those of Rohling et al. (2002) given the research diagnostic criteria used as well as the measurement of depression severity.

The observed association between depression severity and verbal memory in the current study was strongly mediated by age. Older patients were found to have lower depression severity and younger patients had higher depression severity scores. When partial correlations were computed holding age as a constant, depression severity was not associated with memory performance. In the meta analysis by Burt et al. (1995), depression was associated with memory impairment, particularly verbal immediate recall. However, they too, found that age moderated the level of memory impairment in patients with depression, with older subjects (> 60 years) showing more immediate verbal recall

difficulties than younger subjects (< 60 years). This finding is consistent with the current thought that verbal memory test scores decline beginning at age 60 (Lezak et al., 2004, p. 427). Austin et al. (1999) also found no association between depression and immediate recall on the RAVLT. Thus, based on the findings of Austin et al. (1999) and the results of the current investigation, depression severity does not appear to be systematically related to immediate verbal recall.

There have been mixed results regarding the effects of depression on psychomotor speed. Schatzberg et al. (2000) showed no differences between depressed patients and a control group on Trail Making Test Part A. Also, in an investigation comparing 77 depressed patients to a control group, no differences were found between the groups in terms of time needed to complete Part A of the Trail Making Test (Austin et al., 1999). However, a study that matched depressed and control patients on age found that the groups differed only in the domain of psychomotor speed, as assessed on a computerized task of reaction time and attention, with the depressed group requiring more time to complete the task (Pardo, Pardo, Humes, & Posner, 2006). Also, when performance on the Trail Making Test was compared between patients with schizophrenia, depression, and a control group, it was found that the depressed group took more time on Part A than the control group (Mahurin et al., 2006).

In their comprehensive review, Zakzanis et al. (1999) posited that Part A of the Trail Making Test was one of the neuropsychological variables that was least sensitive to the effects of depression (effect size = .18). In the current study; however, depression severity (as measured on the IDS-SR_{30}) was negatively related to Trail Making Test Part A. This suggests that patients with the highest depression severity scores among this

severely depressed sample took *less* time to complete the task. Thus, contrary to expectation, higher depression severity was related to *faster* psychomotor speed. However, the correlation between depression severity and psychomotor speed may be attributed to other factors (i.e., age) that may affect psychomotor speed. As found in this study, the patients who took the longest length of time to complete Trail Making Test Part A were 71 years of age or older, and they also had corresponding IDS-SR_{30} total scores less than 40. For example, one patient who took 96 seconds to complete Part A was 87-years-old and had an IDS-SR_{30} total score of 18.

Given that age is positively related to increased time to complete the Part A of the Trail Making Test (Lezak et al., p. 373), it is possible that age affected the correlation between depression severity and psychomotor speed. Five patients were found to have a depression severity score less than 30, but took over 80 seconds to complete Part A of the Trail Making. When a partial correlation was computed keeping age as a constant variable, the IDS-SR_{30} was not associated with Part A of the Trail Making Test. Thus, although there are some mixed findings (Sackeim et al., 1992) regarding the relationship between depression and psychomotor speed, the current investigation as well as the reports by others (Rohling et al., 1992; Trichard et al., 1995; Zakzanis et al., 1999) posit that the severity of the depressive episode is not related to psychomotor speed.

Three multiple linear regressions were conducted to further explore the relationship between depression severity and neurocognitive function. All three analyses were conducted to predict depression severity as measured with the IDS-SR_{30}. In the first regression, all 24 neurocognitive variables were entered as predictor variables, but the results were non-significant. The second (Model 1 in Table 6) and third (Model 2 in

Table 6) regression models were significant, however. In Model 1, five neurocognitive variables (RAVLT total list A, immediate recall, recognition, Trail Making Test Part A, WRAT-3 reading subtest) were used as predictors based on the significant correlations with the IDS-SR_{30}. Of these five predictor variables, the WRAT-3 reading test was most strongly related to depression severity, followed by Trail Making Part A, and RAVLT recognition. Based on the significant relation to depression severity, these three neurocognitive measures were used as predictors in Model 2. In Model 2, the three variables were found to be significantly related to depression severity in the same order as they appeared in Model 1.

Models 1 and 2 differed in terms of the significance attributed to each predictor variable. For example, in Model 1, the p-value of the RAVLT was .24, whereas in Model 2 the p-value was .02. The differences in the p-values may be related to collinearity among the neurocognitive variables. For example, the three RAVLT variables (total list A, immediate recall, recognition) were highly correlated with each other, as expected. Part A of the Trail Making Test significantly correlated with RAVLT total list A ($r = -.459$, $< .0001$) and immediate recall ($r = -.358$, $p = .002$). Furthermore, the WRAT-3 reading test significantly correlated with RAVLT immediate recall ($r = .285$, $p = .013$). Collinearity between the three neurocognitive variables suggests that there is some overlap between the variables which can influence the interpretation of the results.

The number of statistical analyses conducted in this study may account for the few findings that reached statistical significance. For example, the correlations between the IDS-SR_{30}, the GCI, and the reading test of the WRAT-3 could have been significant by chance. A total of 480 correlations were conducted which inflated the possibility of

making a Type I error (i.e., failing to accept a true null hypothesis). Using a conservative approach by applying a Bonferroni correction, the p-value required for significance would range from p = .0001 to p = .00002.

Overall, depression severity was not related to global cognitive function or executive function. Moreover, although depression may affect neurocognitive function (Airaksinen et al., 2004; Sackeim et al., 1992), the severity of the depressive episode may not account for neuropsychological difficulties. As shown in Table 3, comparing the neurocognitive raw scores of the unipolar group to the scores of normal controls, the depressed group showed lower scores on measures of verbal and visual memory, verbal fluency, attention and inhibition, and problem solving. When the raw scores of the unipolar group were converted to demographic adjusted standard scores (see Table 4), the unipolar group, on average, showed relatively reduced performance only on verbal recognition memory and delayed visual recall scores. For example, the RAVLT recognition and Complex Figure Test delayed recall scores were in the low average range. Porter et al. (2003) reported that patients with depression often demonstrate intact neurocognitive performance, which may be dependent on factors such as age and motivation. Further, variables such as psychomotor retardation and education have been found to moderate neuropsychological test performance in some depressed samples (Den-Hartog, Derix, VanBemmel, Kremer, & Jolles, 2003). Thus, various factors (i.e., age, education) may mediate the neurocognitive performance of patients with depression, and whereas some individuals with depression may show reduced cognitive performance, depression per se does not appear to negatively influence cognition universally.

Impact of Psychotic Features on Neurocognitive Function

The psychotic and nonpsychotic depressed groups were found to be similar in terms of socio-demographic and clinical characteristics. Both groups were comparable in terms of number of psychiatric hospitalizations, age of onset of first psychiatric illness, and age of onset of the current depressive episode. Additionally, both groups had similar levels of depression as measured on the $HRSD_{24}$ and the $IDS\text{-}SR_{30}$. These findings are consistent with previous reports suggesting similarities between psychotic and non-psychotic depressed samples (Hill et al., 2004; Jeste et al., 1996). The sociodemographic and clinical similarities between the groups suggests that differences in these samples was the presence or absence of psychotic features.

Prior research has indicated that severely depressed patients with psychosis perform worse on neurocognitive measures than depressed patients without psychosis (Hill et al., 2004; Schatzberg et al., 2000; Jeste et al., 1996). In a study of 10 psychotically depressed patients compared to 31 non-psychotic depressed patients and a control group, Schatzberg et al. (2000) noted that those persons with psychotic depression showed significant difficulties in the domains of attention, executive function, and verbal memory. This study and that of Schatzberg et al. (2000) used similar tests such as the Trail Making Test and the Stroop Color-Word test. Contrary to the findings of Schatzberg et al. (2000); however, the current study only showed that the psychotic and non-psychotic depressed groups differed only on the immediate recall component of the RAVLT. The nonpsychotic group recalled an average of 8.4 (SD = 3.7) words relative to the average of 5.8 (SD = 4.4) words recalled by the psychotic group.

The differences between the findings of the study by Schatzberg et al. (2000) and this study may be due to the chronicity of the patient sample. The patients with psychotic depression in the research by Schatzberg et al. (2000) had a mean depressive episode duration of 67 months (SD = 45), indicating that some of those patients may have met criteria for dysthymia or "double depression", i.e., two separate psychiatric diagnostic categories, due to the duration of the depressive episode. Also, those patients had an average of five depressive episodes (SD = 6), versus 1.8 (SD = 1.5) in the current sample, though there were limited data regarding characteristics of the depressive episode duration. Based on the longer depressive episode lengths and the greater number of depressive episodes, the sample in the research by Schatzberg et al. (2000) may be more chronically depressed compared to the sample in the current study. Also, the investigation by Schatzberg et al. (2000) did not perform post-hoc analyses to determine the significance of the difference between the control, nonpsychotic depressed, and the psychotic depressed groups. Thus, although significant differences were found between groups on neuropsychological measures, it is unclear if those differences between specific groups (i.e., psychotic and nonpsychotic depressed) were of statistical or clinical significance.

The difference between the groups' performance on the immediate recall task of the RAVLT may be viewed from a cognitive, clinical, and psychometric standpoint. Both groups showed equivalent performance on RAVLT total list A and total list B. The groups may have differed on the immediate recall trial of the RAVLT due to the interference list (i.e., list B) which could have resulted in retroactive inhibition. Retroactive inhibition is the inability to recall previously learned material because of

learning new material (Loring, 1999). Depressed patients with psychosis may have difficulty with cognitive flexibility (Hill et al., 2004; Schatzberg et al., 2000) and as such, may have had difficulty immediately recalling the words from list A due to the interference of recalling the words from list B. However, in this sample, cognitive inflexibility cannot explain the difference in immediate recall, as the depressed patients with psychosis showed no differences on measures of cognitive flexibility.

Examining the performance on individual neuropsychological measures, instead of neurocognitive domain performance, may have been the reason no significant differences were found between the psychotic and nonpsychotic groups. For example, in the study by Hill et al. (2004), neuropsychological measures were grouped into domains made up of an average of several test scores. The creation of composite scores allows for more comprehensive assessment of performance (Hill et al., 2004), and thus may have been more representative of the cognitive domain assessed. For example, Hill et al. (2004) combined five scores from the CVLT (Delis et al., 1987) to form the verbal memory domain in their investigation. However, the creation of composite scores does not necessarily increase sensitivity. For example, the combination of neuropsychological test variables to create domains was exemplified in this study by the GCI. Although not statistically significant, the mean GCI of the psychotic group ($M = -1.2$, $SD = 3.2$) was one standard deviation lower than the nonpsychotic group ($M = 0.1$, $SD = 2.6$), suggesting that the psychotic group showed poorer overall cognitive performance. Per the classification of ability level by z-scores according to Lezak et al. (2004, p. 146), the psychotic group showed low average ability and the nonpsychotic group showed average ability on the GCI. However, the standard deviations were greater than the means of both

groups, indicating significant variability within each group which limits the interpretation of the z-score. Overall, significant differences may not be found in composite scores if significant differences are not found between the individual test scores.

Clinically, psychotic depression is deemed to be more severe than nonpsychotic depression. According to the DSM-IV depression severity continuum (APA, 1994), the highest level of severity involves psychosis. Based on the DSM-IV severity continuum and prior researching indicating neurcognitive differences between depressed patients with and without psychosis (i.e., Hill et al., 2004), it was hypothesized that the presence of psychosis would be related to neuropsychological performance. However, the presence of psychosis itself may not uniformly be indicative of neuropsychological differences between depressed patients. For example, Fleming et al. (2004) observed there exists no consistent overall neuropsychological profile for psychotic depression.

Prior research has resulted in mixed findings regarding the interaction of psychosis and cognitive function. In a meta analysis of five studies, psychotic depression was found to be similarly related to the domains of executive function, attention, memory, and psychomotor speed (Fleming et al., 2004). However, Schatzberg et al. (2000) found that psychosis was related to executive dysfunction as measured by Part B of the Trail Making Test and the Stroop Color-Word test. The relationship between executive function and psychosis was addressed in Hypotheses 3 and 3a in the current investigation. Neither hypothesis supported a relationship between psychosis and executive function. The three instruments that assessed executive function in this study were the Trail Making Test Part B, Stroop Color-Word test, and the DKEFS Sorting Test. Both the psychotic and nonpsychotic depressed groups performed similarly on the three

measures. For example, on the DKEFS Sorting test, the performance on the free sort, correct sort, verbal sort, and the perceptual sort for both groups was nearly identical.

To further explore the relationship between executive function and psychosis, correlations between psychosis and executive function were examined, and none reached significance. Logistic regression and discriminant function analyses were also conducted to predict psychosis with all 24 neurocognitive variables as predictors. Neither the logistic regression nor the discriminant analyses were significant. Since the inclusion of neurocognitive variables that may be unrelated to psychosis or depression may have limited the potential for selected measures to distinguish groups, a second discriminant analysis (see Table 10) was conducted with five neurocognitive variables (i.e., RAVLT: Total List A, Immediate Recall, Recognition, Trail Making Test Part A, WRAT-3 Reading) as predictors. Although statistically significant, the ability to classify psychosis based on five neuropsychological variables was low, as only two patients in the psychotic group were correctly classified. Thus, the use of the performance on these five neuropsychological variables to classify the presence or absence of psychosis is not a reliable method of classification, furthermore suggesting that there is no relationship between psychosis and these neurocognitive variables.

The finding of a difference between psychotic and nonpsychotic groups on the immediate recall trial of the RAVLT may have been due to chance. The psychotic group recalled an average of 5.8 words with a standard deviation of 4.4, reflecting significant variance within the group. Also, due to multiple neurocognitive comparisons between the groups, it is possible that a Type I error occurred (i.e., failure to accept a true null hypothesis). Conducting numerous comparisons inflated the possibility of finding a

significant difference by chance. Lastly, the sample size of the psychotic group was extremely limited and much smaller than the non-psychotic group. The difference between group size increased the possibility of making a Type II error, thus indicating that true differences may exist between groups, but due to small sample size of the psychotic group they were unable to be detected. Overall, there were no differences found between groups in terms of global cognitive functioning, nor were any relationships found between psychosis and specific neurocognitive abilities.

Impact of Recurrent Depression on Neurocognitive Function

There has been limited research examining the relationship between the number of major depressive episodes and neurocognitive function, and the results have been mixed. Kessing (1998) reported that the more MDEs a person has, the worse their neurocognitive performance as measured on the CAMCOG, a computerized neuropsychological screening tool. In contrast, Grant et al. (2001) found no relation between the number of MDEs and neurocognitive performance on another computerized test battery (CANTAB) that assesses memory, attention, and executive function. However, the two investigations differed in terms of the patient sample as well as the cognitive tests utilized. In the research by Kessing (1998), the sample included patients with unipolar or bipolar depression with a mean age of 70 (SD = 12.7) for the unipolar group and 59 (SD = 54.2) for the bipolar group. In the investigation by Grant et al. (2001), the sample included only patients with unipolar depression and the mean age was 39.0 (SD = 10.4). These different findings between these studies could have been related to sample differences such as age and psychiatric diagnosis, suggesting that additional

research is needed to examine the association between the number of depressive episodes and neuropsychological variables.

The relationship between recurrent depression and neurocognitive performance was explored in Hypothesis 4. The recurrent depressed group was defined as those persons with two or more major depressive episodes, a definition used in the STAR*D Trial (Hollon et al., 2006). The recurrent group had an average of 4.4 MDEs, and as expected, had more psychiatric hospitalizations than the single episode group. The recurrent group was also found to have an earlier age of onset of the current depressive episode and was relatively younger than the single episode group (M = 50.8 vs. M = 64.9). This is consistent with the findings of the STAR*D group regarding the clinical similarities and differences of patients with recurrent or single episode depression (Hollon et al., 2006). The two groups in this study showed similar depression severity levels, again consistent with the findings from STAR*D (Hollon et al., 2006). The clinical similarities between this study and those of the STAR*D trial suggest that depressed outpatients and inpatients with recurrent severe depression have similar clinical features. Although it has been suggested that those with recurrent depression have more psychosocial stressors such as unemployment or divorce (Wilhelm et al., 1999), no differences between groups were seen in terms of socio-demographic characteristics in the present sample.

Regarding neurocognitive performance, the recurrent depressed group took less time than the single episode group to complete Part A of the Trail Making Test. However, the single episode group was found to be significantly older than the recurrent group. After adjusting for age, there was no significant difference between the groups.

No other significant differences were found between the two groups on the neurocognitive measures before or after covarying for age. This indicated that both groups performed similarly on neuropsychological tests and that recurrent depression as defined herein did not relate to cognitive performance.

There is limited research examining the neurocognitive performance of patients with recurrent depression. In a study of 40 non-psychotic depressed patients with recurrent depression, it was found that subjective memory complaints were related to the prior number of depressive episodes. Patients with five or more MDEs had more cognitive complaints relative to patients with one prior episode (MacQueen, Galway, Hay, Young, & Joffe, 2002). This suggested that patients with multiple depressive episodes tended to view themselves as having more memory problems than patients with only one depressive episode. Also, patients with recurrent depression have been reported to show reduced performance in the domains of working memory and executive function (Stordal et al., 2004). The study by Stordal et al. (2004) included 45 patients with recurrent depression compared to a control group. The recurrent depressed patients produced fewer correct responses on the Paced Auditory Serial Addition Test (PASAT, Gronwall, 1977), a measure of sustained concentration and working memory, generated fewer words on the COWAT, and showed more set failure errors on the WCST.

The differences between the study by Stordal et al. (2004) and this investigation may be explained in terms of neurocognitive measures utilized as well as comparative groups. Regarding neuropsychological measures, this study employed the DKEFS Sorting Test, whereas the study by Stordal et al. (2004) employed the WCST. Although both tests assess executive function, they have different administration procedures. For

example, during the administration of the WCST, feedback is provided to the examinee regarding whether or not a sort is correct or incorrect, but in the DKEFS Sorting Test, feedback is not provided. Feedback on the WCST may be frustrating for some patients (Lezak et al., 2004, pp. 591-592), and this may potentially affect performance on the WCST, perhaps particularly among depressed patients with negative mindsets. Also, the study by Stordal et al. (2004) utilized a measure of concentration and working memory, whereas this study employed no such measures. Regarding comparison groups, Stordal et al. (2004) compared patients with recurrent depression to a control group, whereas subjects with recurrent depression were compared to those with single episode depression in the present investigation. As Grant et al. (2001) also reported, patients with one MDE showed similar neurocognitive performance as patients with two or MDEs. Thus, patients with depression may differ from normal controls on executive function measures as found in the study by Stordal et al. (2004); however, depressed patients with recurrent MDEs or one MDE performed similarly on measures of executive function used in the current investigation which implies that the number of depressive episodes alone does not impact executive function.

To further explore the relation between recurrent depression and neurocognitive function, the total number of MDEs and the individual neurocognitive variables were correlated. These analyses revealed no significant relationships between the number of MDEs and any of the 24 neuropsychological variables. This suggests that the performance on the neuropsychological measures was not related to the number of depressive episodes. Similar findings were reported in two studies (Fossati et al., 2001; Markela-Lerenc et al., 2006) that examined the interaction between the number of MDEs

and neurocognitive measures. In a study of 23 depressed patients by Markela-Lerenc et al. (2006), no significant correlation was found between the number of depressive episodes (M = 1.7, SD = 1.6) and performance on the Stroop test. Also, in a study of 22 depressed patients, no significant correlation was found between the number of MDEs (M = 2.2, SD = 2.0) and performance on the California Card Sort Test (CCST, Fossati et al., 2001), which is now called the DKEFS-Sorting Test. Thus, it may be possible that the number of depressive episodes does not increase neurotoxic effects as posited by Burt et al. (2000). Rather, as found in the current investigation, one MDE may have the same neurocognitive impact as two or more, although due to a small sample of patients with single episode depression (N = 7), the results must be interpreted cautiously.

Neurocognitive Profile of Atypical Depression

To date, there is no published information regarding the neurocognitive functioning of patients with atypical depression. Atypical depression has been suggested to be different from typical depression due to the presence of less common symptoms such as mood reactivity, hyperphagia, hypersomnia, leaden paralysis, and interpersonal sensitivity (APA, 1994; Quitkin & Davies, 2004). Moreover, atypical depression has been associated with HPA axis hypoactivity, diminished corticotropin-releasing hormone, and poor response to tricyclic antidepressants (Heit et al., 1997; Nierenberg et al., 1998). Due to these depressive symptomatic and physiological differences, it was hypothesized that patients with atypical depression would differ in terms of neurcognitive functioning from those with typical depression.

Seven of the 82 unipolar depressed patients met DSM-IV criteria (APA, 1994) for atypical depression based on the SCID-I interview. No significant differences in terms of

socio-demographic and clinical characteristics were found between the atypical and typical depressed groups. However, the atypical group relative to the typical group was slightly younger, had an earlier age of onset of the first psychiatric illness, and an earlier age of onset of the current depressive episode, which is consistent with previous reports (Stewart, Bruder, McGrath, & Quitkin, 2003).

Focusing on depression severity, due to the inability of the $HRSD_{24}$ to assess atypical items, the six-item HRSD (Bech et al., 1975) was used to measure depression severity. The $HRSD_6$ consists of six items from the $HRSD_{24}$, those items being: 1 (Depressed Mood), 2 (Guilt), 7 (Anhedonia), 8 (Psychomotor Retardation), 10 (Psychic Anxiety), and 13 (Decreased Energy). The $HRSD_6$ was significantly correlated with the $HRSD_{24}$ ($r = .616$, $p < .0001$) and allowed for the comparison of depression severity between the atypical and typical patients while eliminating the potential confound of reverse neurovegetative (e.g., insomnia, decreased appetite) items that could affect the overall depressive symptom severity level based on the $HRSD_{24}$ (Hooper & Bakish, 2000). The depressive severity measures (i.e., $HRSD_6$, the $IDS\text{-}SR_{30}$, $HRSD_{24}$) did not significantly differ between the two groups, suggesting both groups had similar depression severity levels. Prior research (i.e., Henkel et al., 2004) assumed atypical depression was less severe than typical depression. However, that conclusion was reached in a less depressed, outpatient sample, whereas this study focused on severely depressed patients who were referred for ECT. The current results substantiate the assumption of Quitkin and Davies (2004) that atypical depression may be as severe as typical depression.

Regarding neurocognitive functioning, there were only four differences between groups that reached significance, and all were from the same verbal memory test. Specifically, the atypical group correctly recalled more words over five learning trials, recalled more words on immediate and delayed recall trials, and showed better recognition discrimination on the RAVLT. No other significant differences were found between groups on any other neurocognitive measures. However, the atypical group produced more words on the COWAT, took less time on Part B of the Trail Making Test, and had a higher score on the Stroop. It may be possible that atypical depression does not affect neuropsychological performance in the same manner as does typical depression. For example, Austin et al. (1999) found that depressed patients with melancholia, compared to depressed patients without melancholia, recalled fewer words on the delayed recall trial, learned fewer words over the five trials, and recognized fewer words on the RAVLT. No differences between groups were found on other neuropsychological tests including the Trail Making Test, WCST, and verbal fluency. The findings of Austin et al. (1999) and the current results suggest that some aspects of neuropsychological performance may be affected by depression subtype.

The significant difference between groups on the RAVLT begs the question as to why patients with atypical depression performed better than patients with typical depression. Patients with depression have been found to perform poorly on the RAVLT suggesting that this test, even relative to other memory tests, is particularly sensitive to the effects of depression. For example, relative to other neuropsychological tests (i.e., Trail Making Test, WCST), the RAVLT had the largest effect size related to depression

(Zakzanis et al., 1999). However, depression severity cannot account for these differences, as both groups had similar severity levels.

Although motivation was not measured in this study, it may be plausible that motivational factors may have influenced results. The typical depressed group may have been in a low mood during the time of testing, and may also have had diurnal variation with mood worsening in the morning. The low mood state could have decreased motivation and effortful processing of information (Farrin et al., 2003) which could have interfered with encoding of information during the five learning trials, resulting in fewer recalled words on the immediate and delayed recall trials. Due to the atypical symptom mood reactivity, the atypical group may not have been in a low mood state at the time of testing. Also, the atypical group may have had diurnal variation with mood worsening in the evening (Gold & Chrousos, 2002). Since the neurocognitive battery and the depression severity measures were administered in the morning, the typical group may have been at a disadvantage relative to the atypical group. However, if motivation and diurnal variation were the reasons for the difference between the performance on the RAVLT of the two groups, then other cognitive performance differences would likely have been also seen. Since no other significant neurocognitive differences were found between the two groups, motivation and diurnal variation do not likely account for the differences found between the groups on the RAVLT.

Although not measured in this study, physiological variables may have also influenced RAVLT performance differences between the groups. Specifically, patients with typical depression tend to have HPA axis hyperarousal, whereas patients with atypical depression tend to have HPA axis hypoarousal (Gold & Chrousos, 2002). HPA

axis hyperactivity has been associated with decreased memory (Lupien, Gillin, & Hauger, 1999; Newcomer et al., 1999). However, research by Zobel et al. (2004) failed to show an association between changes in cortisol response and performance on the RAVLT ($r = .098$). If differences in HPA axis activity contributed to the differences between the groups performance on the RAVLT, the other neuropsychological test variables might have been expected to show differences as well, though this was not this case. This suggests that HPA axis activity may contribute to, but does not fully account for group differences in neurocognitive function.

A possible reason for the mixed neurocognitive findings between the typical and atypical groups may be explained by the sample size. The atypical group was quite small, which could have resulted in a Type II error and significant differences may have gone undetected. Also, due to multiple comparisons, the differences found on the RAVLT may have been due to a Type I error, suggesting the results need to be interpreted with caution. For example, using a conservative approach and adjusting by using Bonferroni correction, a p-value range of $p = .0004$ to $p = .00008$ would be needed for significance. However, the purpose of this exploratory analysis was to generate hypotheses for future testing; thus, using a Bonferroni correction would have been too restrictive. The preliminary results suggests that patients with atypical or typical depression may differ in terms of verbal memory, with the former group showing better performance than the latter.

Depressive Episode Length and Neurocognitive Function

To date, the relationship between depressive episode length and neurocognitive functioning has received limited attention. Two studies that examined measures of

attention and executive functioning found mixed results. Markela-Lerenc et al. (2006) studied the performance of 23 depressed patients on the Stroop. The mean depressive episode length for the sample was 52.6 (SD = 60.4) months and the mean number of depressive episodes was 1.7 (SD = 1.6). No significant correlations were found between performance on the Stroop interference trial (color-word) and depressive episode length, depression severity level, or number of MDEs. The current study also found no relationship between the duration of the depressive episode and performance on the Stroop, which suggests that duration of the depressive episode does not affect performance on the Stroop. In a previous examination of 22 depressed patients' performance on executive function measures, negative associations were found with depressive episode length (Fossati, Ergis, & Allilaire, 2001). The mean duration of the depressive episodes was 8.97 (SD = 8.10) months, and the mean number of MDEs was 2.2 (SD = 1.99). The mean duration of depressive episodes, although not statistically significant, was found to be negatively associated ($r = -0.37$, $p = .08$) with the number of attempted sorts on the CCST (Delis et al., 1992). The results of the present study also suggested no association between the number of attempted sorts on the CCST/DKEFS Sorting test and the duration of depressive episode.

Data on depressive episode length in the current study were available for only 18 patients. The length of the depressive episode (in weeks: M = 75.2, SD = 147.3, Median = 22.0) was negatively correlated with immediate recall of the RAVLT ($r = -.491$, $p = .039$) and the WRAT-3 reading subtest ($r = -.575$, $p = .013$). That is, the longer the depressive episode length, the fewer words immediately recalled on the RAVLT or correctly read on the WRAT-3 reading subtest. However, depressive episode length was

not associated with other neurocognitive variables, age ($r = -.298$, $p = .230$), or education ($r = .060$, $p = .818$). It is unclear why depressive episode length was related to the RAVLT immediate recall trial and the WRAT-3 reading test. The relationship between episode duration and the RAVLT may be due to the sensitivity of the RAVLT in depression. For example, the immediate recall trial of the RAVLT had the largest effect size (–1.77) relative to other neurocognitive variables in the meta analysis by Zakzanis et al. (1999). However, if sensitivity of the RAVLT was the reason for the negative association, then negative associations would have been expected between other RAVLT variables and episode duration.

The relationship of depression duration and neurocognitive performance was also explored in study by Reischies and Neu (2000). This study included patients with minor depression, bipolar depression, and schizoaffective disorder, and the neuropsychological battery included tests similar to the measures in this study such as the RAVLT, COWAT, Trail Making Test, and the MMSE. No significant associations were found between the duration of the depressive episode and the neurocognitive measures. While both the current study and that of Reischies and Neu (2000) showed similar findings, the studies differed methodologically, specifically regarding the patient sample and test variables. In this study, depression episode length was evaluated only in those patients with unipolar MDD, whereas in Reischies and Neu's (2000) study, the patient sample included four separate DSM-IV diagnostic categories. Having a heterogeneous group could increase the variability in neuropsychological performance. Although patients with bipolar or unipolar depression may not vary in terms of neurocognitive performance (Osuji & Cullum, 2005), patients with depression differ from those patients with schizoaffective

disorder, as the latter group tends to show more executive dysfunction than the former (Goldstein, Shemansky, & Allen, 2005). Thus, having a group of patients with different psychiatric diagnoses makes it difficult to determine what factors are contributing to the cognitive functioning of the group. Furthermore, when exploring neurcognitive performance, Reischies and Neu (2000) did not examine the immediate recall trial of the RAVLT, their analyses only focused on the delayed recall trial. By not examining the immediate recall trial of the RAVLT and by including a heterogeneous patient group, the comparison of this current study with that of Reischies and Neu (2000) is limited.

Focusing on the reading subtest of the WRAT-3, the negative association with MDE duration, as well as depression severity, was unexpected. The reading subtest of the WRAT tends to be a relatively easy task that involves sight-word reading (Henderson, 1987); moreover, reading performance has been found to be unaffected by depression (Crawford, Besson, Parker, Sutherland, & Keen, 1987). Most importantly, the finding of a relationship between the WRAT-3 and episode length could be spurious due to the limited data available for episode duration (N = 18) as well as the large variability in episode duration within those 18 patients. For example, the distribution of data was positively skewed due to three patients with very lengthy episodes (i.e., 156 to 624 weeks), compared with a mean of 25 weeks (range: 5 – 78) for the remainder of subjects. When these three patients were removed from the analyses, episode duration no longer correlated with the IDS-SR_{30} ($r = -.134$, $p = .647$), RAVLT immediate recall trial ($r = .034$, $p = .903$), or the reading subtest of the WRAT-3 ($r = .278$, $p = .316$).

Depressive episode length was also found to be positively correlated to the IDS-SR_{30}, but not to the $HRSD_{24}$. The reason for this is unclear but could be due to the way

depression severity was assessed as well as the depressive symptoms measured by each instrument. The IDS-SR_{30} is a self report measure and the patients may have responded to the symptoms differently than they responded to the clinician-assessed $HRSD_{24}$. For example, the questions on the IDS-SR_{30} and the $HRSD_{24}$ are phrased differently and as such the patient may have endorsed a symptom on one measure but not the other. Domken et al. (1994) reported a 30% discordant rate between patient- and clinician-rated depression severity assessments, with a slight trend for patients to overate their level of severity. When controlling for depression severity, the authors found that the variable of low self esteem, as rated by patients, contributed to the discrepant results between the patients and the clinicians (1994).

It can also be argued that the IDS-SR_{30} and the $HRSD_{24}$ assess different depressive symptoms. For example, the IDS-SR_{30} contains atypical symptoms (i.e., hypersomnia, hyperphagia) and symptoms related to concentration, irritability, and pain (Rush et al., 1996). By measuring depressive items consistent with the DSM-IV depressive symptoms, the IDS-SR_{30} provides a comprehensive assessment of depressive symptomatology that may relate to depressive clinical characteristics (Rush et al., 1996). However, focusing on clinical measures, Rush et al. (1987) examined the IDS-C_{30} and the IDS-SR_{30} in three groups of depressed outpatients including endogenous, nonendogenous, and dysthymic depression, and found that the nonendogenous and dysthymic groups tended to rate their depression severity higher than did the clinician. However, the length of the depressive episode did not significantly correlate with either the self-report or clinician-rated measure (1987).

Psychometrically, the findings of the associations between the WRAT-3 reading subtest, IDS-SR_{30}, and duration of the depressive episode need to be interpreted with caution. Due to multiple correlations with a small sample size, the possibility of making a Type I error was high. The significant correlations may be due to chance and thus may not be reliable. For instance, if being conservative and using a Bonferroni correction, the p-value required for significance would range from p = .0001 to p = .00002. All in all, the findings of the relationship between episode duration, the WRAT-3 reading test, and the RAVLT immediate recall trial probably are not reliable. For example, when the three outliers were removed from the analyses, episode length was no longer associated with depression severity, the RAVLT, or the WRAT-3. Further studies with more accounts of depressive episode duration are needed to better understand the relationship between episode duration and neurocognitive function.

Based on these preliminary findings, future research may provide additional information concerning the relationship between depressive episode length and depression severity as well as the impact on neurocognitive functioning. To provide thorough information, the depressive episode should be defined in terms of duration, severity, and quality of depressive symptomatology. Future research may want to include a clinical instrument that has both a self- and clinician-rated version (i.e., IDS-SR_{30} and IDS-C_{30}) to control for depression symptom reporting method and depression symptom content. Also, future studies may want to include patients with a full range of depression severity scores. This information could have been useful in this study as it would have helped determine if the association between clinician rated and patient rated depression severity and episode duration resulted from a difference in item content or because of the

method of rating (i.e., clinician). Further, utilizing a thorough clinical instrument that assesses many depressive symptoms would allow for a comprehensive exploration of the relationship between depressive episode length and depressive symptoms. The patient population in this study was a severely depressed inpatient sample with a score of 21 or greater on the $HRSD_{24}$. Allowing the inclusion of patients with any depression severity score could show if the association of depression severity and episode length applied to mild, moderate, and severe depression severity scores.

Limitations

This study had four main limitations, including (a) small sample size for certain analyses, (b) limited racial composition, (c) no data regarding concurrent Axis I disorders, and (d) use of neuropsychological measures without corresponding standardized scores.

For certain analyses, the sample sizes were small and the results must be considered tentative. The atypical and single episode groups both consisted of seven participants, and the exploratory analyses examining the relationship of depressive episode length to neurocognitive function consisted of eighteen patients. Having a small sample size increases the possibility of making a Type II error. However, the percentage of participants with atypical depression in this study is consistent with other investigations (Quitkin et al., 1993; Stewart et al., 2005). Of interest, this is one of the first studies to document psychotic symptoms in patients with atypical depression. This is an area that requires further study, as a majority of published data for patients with atypical depression consisted of outpatient samples. Because of recruitment of patients only in outpatient settings, there could have been a sampling bias that limited the

inclusion of atypical depressed patients with psychotic features. If atypical depressed patients present with psychosis, then perhaps psychosis may be a moderator of depression, as noted in the DSM-IV (APA, 1994) versus a depressive subtype as argued by Schatzberg et al. (2000, 1992).

The second limitation of this study concerns racial composition. The majority (93.8%) of patients in this study were Caucasian. This may decrease the external validity of this study's findings to persons of other ethnicities, as there may be variability in neuropsychological performance by different sociodemographic/ethnic groups (Lezak et al., 2004 p. 312, Heaton, 2004). Thus, the findings of this study may not be representative of the cognitive differences between depressed patients of other ethnic backgrounds and may only apply to those depressed inpatients who are predominantly Caucasian. However, the racial composition of the sample (93.8% Caucasian) is comparable to that of persons referred for ECT. For instance, in a nationwide study utilizing admissions data from 913 community hospitals, 63% of 2,191 patients were Caucasian and 3% were African American (Olfson, Marcus, Sackeim, Thompson, & Pincus, 1998). This was also supported in a retrospective study of 17, 914 participants in which it was found that Caucasians were more likely (68% versus 32%, odds ratio = 4.71) to receive ECT than African Americans (Breakey & Dunn, 2004).

The third limitation is that this study did not have data regarding concurrent Axis I psychiatric disorders. This information is important, as it could help explain and account for the interaction between the depressive subtypes and neurocognitive functioning. For example, anxiety spectrum disorders (e.g., generalized anxiety disorder, obsessive-compulsive disorder) have been found to interfere with memory (Shackman et

al., 2006), attention (Fertuck et al., 2006), and executive function in some reports (Eysenck, Payne, & Derakshan, 2005). Given the high comorbidity (59.2%) between MDD and anxiety (Kessler et al., 2003), it may be possible that anxiety could have influenced certain results of this study (i.e., atypical versus typical depression); however, this study was not able to substantiate the affects of anxiety. However, a number of studies have found no relationship between anxiety and neuropsychological test performance (Temple, Horner, & Taylor, 2004; Waldstein, Ryan, Jennings, & Muldoon, 1997). Thus, the potential influence of this factor in the current sample is unknown, although the finding of generally normal neurocognitive performances would seem to argue against anxiety as playing a significant role in the results.

Lastly, a potential minor limitation of the present study was that certain neurocognitive measures utilized did not have normative data for the purpose of converting raw scores into standard scores. For instance, the alternate versions of Part B of the Trail Making Test and the DKEFS Sorting test (due to the alternate administration procedures) lacked normative data. Normative data are helpful for neurocognitive measures as they can adjust raw scores for factors such as age or education that may interact with neurocognitive functioning. For example, healthy older adults relative to younger adults have been found to show cognitive slowing and decreases in aspects of memory (Tarbuck & Paykel, 1995). This is important as the single episode group was significantly older than the recurrent group, and although not significant, age differences were noted between the psychotic and non-psychotic group. Yet, when analyzing the available normative data adjusted scores (i.e., RAVLT), no main differences were found from the analyses of the raw data. Finding no differences between the use of raw or

standard scores in this study suggests that the raw scores provided reliable estimates of performance for comparisons.

While this investigation had respective limitations, it also had significant strengths, including a homogenous, severe, unipolar depressed group, data regarding depressive subtypes, and utilization of a comprehensive neuropsychological battery. These strengths ensured high internal validity, which increases the confidence of the findings.

The sample in this study consisted of depressed patients referred for ECT, which underscores that this sample was severely depressed. There is a dearth of information regarding the neuropsychological performance of severely depressed patients (Sackeim et al., 1992); thus, this study provides vital information regarding the effects of the most severe of depressions on neurocognitive function. Moreover, this study was strengthened by dividing the depressed group into subgroups of distinct depressive subtypes based on research diagnostic criteria. Grouping all depressed patients together may enhance the variance of test performance and not allow for discerning differences between subtypes of depression (Kizilbash et al., 2002; Veiel, 1997). For example, Porter et al. (2003) found that significant differences between depressed patients and a control group were no longer significant after excluding depressed patients with melancholia. Thus, depressive subtypes may influence test performance and it may be beneficial to examine depressive subtypes to help account for differences in neuropsychological performance across studies. Also, this study benefited from utilizing a comprehensive neuropsychological battery that measured many neurocognitive domains including memory and learning, executive function, attention, and psychomotor speed.

The high internal validity of this study was further enhanced due to the administration of the clinical and neuropsychological measures by trained and certified clinical raters and psychometrists. This allowed for consistency among the four centers enrolling patients by standardizing administration procedures, interviewing techniques, symptom ratings, and scoring methods. Overall, this study maximized internal validity by defining a priori depression severity, depressive subtypes, and clinical and neuropsychological administration and scoring procedures which limited subjective clinical bias and increased research objectivity. Thus, the findings of the current study are considered to be sound and valid.

Conclusion

The principle focus of this study was to assess and characterize the interaction between neurocognitive functioning and unipolar major depressive disorder. Numerous depression variables were examined, including depression severity, number of depressive episodes and episode duration, atypical and typical depressive symptoms, as well as the presence or absence of psychotic features. A comprehensive neuropsychological battery allowed for the assessment of global cognitive functioning, attention, learning and memory (both verbal and visual), verbal fluency, psychomotor speed, and executive function.

Depression severity was expected to have an inverse relationship with global cognitive functioning and executive function; however, no relationship between the magnitude of depression severity and global cognitive function or executive function was found. This suggests that the severity of the depressive episode is not systematically related to the degree of cognitive difficulties in patients with MDD.

Differences in neuropsychological performance were expected between the depressive subtypes. However, the findings of this study were mixed. Exploring the presence of psychosis showed that patients with psychotic depression performed similarly to patients without psychosis. Unexpectedly, psychosis did not impact the cognitive domain of executive function in this study.

To date, this is one of the first investigations to characterize the neurocognitive functioning of patients with atypical depression. This exploration found no significant neurocognitive differences between the groups, except on a test of verbal memory, in which the atypical group showed better performance. This is also one of the first reported observations of psychosis in patients with atypical depression. Future studies should examine the neurocognitive function of larger groups of atypical depressed patients to determine if these findings are replicable. Also, future research may want to examine the clinical similarities and differences between atypical and typical depression with psychotic features. This would aid in understanding whether psychosis is a moderator of depressive subtypes or if it is a distinct subtype.

Clinical characteristics of depression such as the number of depressive episodes and episode length were not found to be related to neurocognitive impairment. Contrary to prediction, patients with recurrent depression showed no neurocognitive differences from patients with single episode depression, and there was no significant association between the number of depressive episodes and neurocognitive performance. Regarding depressive episode duration, the length of the depressive episode was found to be negatively related to only a few cognitive test scores. This suggests that the depressive episode duration may only affect a small number of neurocognitive variables and may not

be related to overall neuropsychological performance. Although the correlations were moderate in strength, these associations may have been found by chance and require further study.

Overall, most depressive characteristics examined were not found to be related to neurocognitive functioning in this sample of severely depressed patients. Although this was unexpected, the findings of study are considered to be valid. The study had significant internal validity, classification of diagnoses based on research diagnostic criteria, and utilization of comprehensive clinical and neuropsychological batteries administered by trained and certified clinical raters and psychometrists. Future research is warranted to examine the interactions between depressive clinical characteristics, depressive subtypes, and neurocognitive functioning, as nonlinear relationships within subgroups are possible. To optimize future research, studies should consider utilizing large sample sizes, standardized adjusted neurocognitive scores, hospitalized and non-hospitalized patients, and clinical measures that contain both a patient self-report and clinician rated versions, which will allow for a further increase in internal validity thereby providing a more elegant examination of complex interactions.

CHAPTER 6

TABLES

Table 1

Socio-demographic Characteristics of the Sample

Characteristic	Total Sample (N = 145)	Unipolar MDD (N = 82)
Age (M±SD)	52.3 (15.5)	52.0 (15.3)
Gender (%)		
Female	67.8	61.3
Race (%)		
Caucasian	87.9	93.8
African American	7.4	6.2
Other	4.7	--
Education (M±SD)	13.9 (2.7)	14.3 (2.6)
Handedness (%)		
Right	90.6	89.0
Left	8.2	8.5
Ambidextrous	1.2	2.4
Employment Status (%)		
Employed	22.5	23.0
Unemployed	13.0	15.4
Retired	24.6	23.1
Disability	22.5	21.8
Other	17.3	16.7
Marital Status (%)		
Married	59.4	55.1
Never Married	13.8	19.2
Divorced	12.3	16.7
Other	14.5	9.0

Table 2

Clinical Characteristics of the Sample

Characteristic	Total Sample (N = 145)	Unipolar MDD (N = 82)
Depressive Type		
Unipolar	78.2	100
Bipolar	21.8	--
Psychotic Features (%)	22.0	17.3
Melancholic Features (%)	79.5	80.2
Atypical Features (%)	7.9	8.6
Recurrent Depression (%)	93.0	91.5
Number of MDEs	4.0 (4.4)	3.8 (4.3)
Number of Psychiatric Hospitalizations	3.1 (2.5)	3.0 (2.6)
Age of onset of first psychiatric illness[1]	30.1 (19.0)	29.8 (20.0)
Age of onset of current MDE	52.2 (15.6)	51.1 (15.7)
Depression Severity		
$HRSD_{24}$	34.7 (7.2)	33.5 (7.9)
$IDS\text{-}SR_{30}$	45.6 (12.1)	46.0 (12.3)

[1]age of onset of first psychiatric illness was based on patient self report during SCID interview. First psychiatric illness included any psychiatric illness

MDE=Major Depressive Episode
$HRSD_{24}$=24-item Hamilton Rating Scale for Depression
$IDS\text{-}SR_{30}$=30-item Inventory of Depressive Symptomatology

Table 3

Neuropsychological Raw Scores

Measure	Total Sample[1] (N = 145)	Unipolar MDD[2] (N = 82)	Normal
MMSE[3]	26.7 (2.8)	27.4 (1.9)	24-30
RAVLT[4]			
Total List A	40.0 (11.9)	42.8 (10.9)	56.1 (8.7)
Total List B	4.4 (1.8)	4.9 (1.6)	6.9 (2.5)
Immediate Recall	7.4 (3.7)	8.0 (3.9)	11.7 (3.0)
Delayed Recall	6.5 (3.9)	6.8 (4.1)	11.3 (3.0)
Recognition	11.4 (3.0)	11.6 (3.1)	13.8 (1.8)
Discrimination	8.9 (4.7)	9.7 (4.2)	--
Retention (%)	61.8 (28.4)	60.3 (30.8)	--
Complex Figure Test[5]			
Copy	29.5 (6.5)	31.3 (4.7)	32.8 (3.1)
Immediate Recall	14.6 (7.9)	16.1 (8.1)	20.3 (7.4)
Delayed Recall	13.7 (8.0)	14.9 (7.9)	19.2 (7.3)
COWAT[6]	33.1 (13.4)	35.0 (13.6)	33-41
Category Fluency[6]	13.5 (4.7)	14.0 (4.8)	16-20
Trail Making Test[6]			
Part A	48.2 (45.7)	38.7 (21.1)	25-38
Part B	116.2 (79.0)	103.6 (63.5)	64-104
Stroop[7]			
Word	85.1 (18.6)	88.8 (18.9)	105.4 (15.6)
Color	58.0 (15.2)	61.7 (14.9)	76.2 (11.1)
Color-Word	29.8 (10.5)	32.2 (10.5)	46.8 (8.6)
DKEFS Sorting Test[8]			
Free Sort	13.2 (6.8)	15.0 (6.0)	--
Correct Sort	3.5 (1.7)	3.9 (1.5)	4.5-4.6
Verbal Sort	1.5 (0.7)	1.7 (0.7)	3.1
Perceptual Sort	2.0 (1.4)	2.3 (1.4)	5.9
WRAT-3 Reading[9]	98.7 (13.8)	98.9 (15.2)	90-109
Global Cognitive Index	0.0 (2.8)	0.0 (2.8)	--

[1]Total sample includes patients with bipolar or unipolar major depressive disorder and a score of 22 or greater on the MMSE

[2]Unipolar sample includes those patients with unipolar major depressive disorder and MMSE scores $\geq$ 24
[3]MMSE normative data provided from the Mini-Mental™ State Examination User's Guide. (Folstein, Folstein, McHugh, & Fanjiang, 2001)
[4]RAVLT normative data provided from the RAVLT manual (Schmidt, 1996)
[5]Complex Figure Test normative data provided from Fastenau et al. (1999)
[6]COWAT, Category Fluency, and Trail Making Test Parts A and B normative data provided from Heaton et al. (2004)
[7]Stroop normative data provided from Chafetz & Matthews (2004)
[8]DKEFS normative data provided from the DKEFS manual (Delis et al., 2001)
[9]WRAT-3 reading test (standard score) normative data provided from the WRAT-3 manual (Wilkinson, 1993)

MMSE=Mini Mental State Examination
RAVLT=Rey Auditory Verbal Learning Test
COWAT=Controlled Oral Word Association Test
DKEFS Sorting Test=Delis-Kaplan Executive Function System Sorting Test
WRAT-3 Reading Test=Wide Range Achievement Test-3rd Edition Reading Test

Table 4

Demographic Adjusted Neuropsychological Scores

Measure	Unipolar MDD[1] (N = 82)
MMSE[2]	43.0 (12.0)
RAVLT[3]	
Total List A	44.2 (11.2)
Total List B	46.5 (8.6)
Immediate Recall	43.5 (13.1)
Delayed Recall	40.0 (13.3)
Recognition	33.4 (22.5)
Discrimination	--
Retention	--
Complex Figure Test[4]	
Copy	--
Immediate Recall	41.7 (14.6)
Delayed Recall	38.8 (13.5)
COWAT[5]	44.5 (13.0)
Category Fluency[5]	41.4 (11.5)
Trail Making Test[5]	
Part A	43.5 (11.6)
Part B (original version)	43.1 (11.4)
Stroop[6]	
Word	40.2 (12.1)
Color	38.8 (10.9)
Color-Word	43.0 (8.3)
DKEFS Sorting Test	
Free Sort	--
Correct Sort	--
Verbal Sort	--
Perceptual Sort	--
WRAT-3 Reading[7]	98.9 (15.2)
Global Cognitive Index	--

[1]Unipolar sample includes those patients with unipolar major depressive disorder and MMSE scores $\geq$ 24

[2]MMSE normative data provided from the Mini-Mental™ State Examination User's Guide. (Folstein et al., 2001)
[3]RAVLT normative data provided from the RAVLT manual (Schmidt, 1996)
[4]Complex Figure Test normative data provided from Fastenau et al. (1999)
[5]COWAT, Category Fluency, and Trail Making Test Parts A and B normative data provided from Heaton et al. (2004)
[6]Stroop normative data provided from Chafetz & Matthews (2004)
[7]WRAT-3 reading test (standard score) normative data provided from the WRAT-3 manual (Wilkinson, 1993)

MMSE=Mini Mental State Examination
RAVLT=Rey Auditory Verbal Learning Test
COWAT=Controlled Oral Word Association Test
DKEFS Sorting Test=Delis-Kaplan Executive Function System Sorting Test
WRAT-3 Reading Test=Wide Range Achievement Test-3rd Edition Reading Test

Table 5

Pearson Product-Moment Correlations for Depression Severity and Global Cognitive Functioning in Patients with Unipolar Depression and MMSE scores 24 or Greater

Measure	$HRSD_{24}$	$IDS\text{-}SR_{30}$	GCI	WRAT	MMSE
$HRSD_{24}$	--				
$IDS\text{-}SR_{30}$	.584*	--			
GCI	.158	.181	--		
WRAT	-.005	-.277**	.341****	--	
MMSE	-.009	.003	.350***	.400*	--

HRSD24=24-item Hamilton Rating Scale for Depression
IDS-SR30=30-item Inventory of Depressive Symptomatology
GCI=Global Cognitive Index
WRAT= Wide Range Achievement Test-3rd Edition, Reading Subtest (standard score)
MMSE=Mini-Mental State Examination

*p<.0001, **p=.027, ***p=.004, ****p=.005

Table 6

Pearson Product-Moment Correlations for Depression Severity and Global Cognitive Functioning in Total Sample[1]

Measure	$HRSD_{24}$	$IDS\text{-}SR_{30}$	GCI	WRAT	MMSE
$HRSD_{24}$	--				
$IDS\text{-}SR_{30}$	.490**	--			
GCI	.126	.245*	--		
WRAT	.069	-.190	.314**	--	
MMSE	-.031	.052	.472**	.415**	--

[1]Total sample includes patient with unipolar or bipolar depression and a score of 22 or greater on the MMSE

HRSD24=24-item Hamilton Rating Scale for Depression
IDS-SR30=30-item Inventory of Depressive Symptomatology
GCI=Global Cognitive Index
WRAT= Wide Range Achievement Test-3rd Edition, Reading Subtest (standard score)
MMSE=Mini-Mental State Examination

*p=.017, **p<.0001

Table 7

Prediction of Depression Severity Using Multiple Regression[1]

	Total R^2	Df	F	P	ß	P
Model 1	.23	5, 59	4.61	.001		
RAVLT Total List A					.117	.56
RAVLT Immediate Recall					.022	.92
RAVLT Recognition					.201	.24
Trail Making Test Part A					-.273	.05
WRAT-3 Reading					-.369	.005
Model 2	.25	3, 59	7.68	<.0001		
WRAT-3 Reading					-.339	.004
Trail Making Test Part A					-.326	.006
RAVLT Recognition					.273	.020

[1]Depression severity was measured using the 30-item Inventory of Depressive Symptomatology-Self Report

RAVLT=Rey Auditory Verbal Learning Test
WRAT= Wide Range Achievement Test-3rd Edition, Reading Subtest (standard score)

Table 8

Socio-demographic Characteristics between Depressed Patients with and without Psychosis

Characteristic	Psychotic (N = 14)	Non-Psychotic (N = 67)	P-Value
Age (M±SD)	44.6 (11.7)	53.4 (15.8)	.052
Gender (%)			.065
Male	61.5	34.3	
Female	38.5	65.7	
Race (%)			.814
Caucasian	92.3	94.0	
African American	7.7	6.0	
Education (M±SD)	14.0 (2.7)	14.3 (2.6)	.69
Handedness (%)			.728
Right	85.7	89.6	
Left	14.3	7.5	
Ambidextrous	0.0	3.0	
Employment Status (%)			.767
Employed	21.4	23.5	
Unemployed	28.6	12.5	
Retired	7.1	26.6	
Disability	28.6	20.3	
Other	14.2	15.7	
Marital Status (%)			.495
Married	42.9	57.8	
Never Married	35.7	15.6	
Divorced	14.3	17.2	
Other	7.1	9.4	

Table 9

Clinical Characteristics between Depressed Patients with and without Psychosis

Characteristic	Psychotic (N = 14)	Non-Psychotic (N = 67)	P-Value
Recurrent Depression (%)	78.6	94.0	.095
Number of MDEs	1.8 (1.5)	4.2 (4.6)	.148
Number of Psychiatric Hospitalizations	2.6 (1.6)	3.1 (2.8)	.541
Age of onset of first psychiatric illness	31.3 (19.1)	29.5 (20.5)	.793
Age of onset of current MDE	43.9 (11.4)	52.7 (16.2)	.057
Depression Severity			
$HRSD_{24}$	35.0 (7.5)	33.9 (6.9)	.577
$IDS\text{-}SR_{30}$	46.9 (12.5)	45.9 (12.4)	.811

MDE=Major Depressive Episode
$HRSD_{24}$=24-item Hamilton Rating Scale for Depression
$IDS\text{-}SR_{30}$=30-item Inventory of Depressive Symptomatology

Table 10

Neuropsychological Score Comparisons between Psychotic and Non-Psychotic Depressed Patients[1]

Measure	Psychotic (N = 14)	Non-Psychotic (N = 67)	P-value
MMSE	26.7 (1.5)	27.5 (1.9)	.145
RAVLT			
Total List A	40.1 (13.1)	43.5 (10.5)	.331
Total List B	4.9 (1.6)	4.9 (1.6)	.960
Immediate Recall	5.8 (4.4)	8.4 (3.7)	.031
Delayed Recall	5.3 (4.4)	7.0 (4.0)	.168
Recognition	11.0 (3.2)	11.6 (3.1)	.530
Discrimination	9.2 (4.8)	9.7 (4.1)	.697
Retention (%)	44.8 (36.5)	62.5 (29.0)	.078
Complex Figure Test			
Copy	30.4 (5.9)	31.4 (4.5)	.512
Immediate Recall	14.8 (10.9)	16.1 (7.3)	.596
Delayed Recall	11.8 (9.1)	15.2 (7.4)	.190
COWAT	34.7 (13.0)	35.2 (13.9)	.912
Category Fluency	14.7 (6.1)	13.7 (6.1)	.533
Trail Making Test			
Part A	37.6 (11.1)	39.1 (22.8)	.829
Part B	109.0 (54.3)	102.9 (66.0)	.764
Stroop			
Word	85.5 (21.4)	89.5 (18.7)	.519
Color	56.4 (12.6)	62.5 (15.2)	.213
Color-Word	29.6 (6.9)	32.7 (11.0)	.370
DKEFS Sorting Test			
Free Sort	15.4 (6.3)	14.9 (6.0)	.809
Correct Sort	4.0 (1.7)	3.9 (1.5)	.845
Verbal Sort	1.7 (0.5)	1.7 (0.7)	.888
Perceptual Sort	2.3 (1.5)	2.2 (1.4)	.882
Global Cognitive Impairment	-1.2 (3.2)	0.1 (2.6)	.170
WRAT-3 Reading	92.7 (27.4)	100.2 (10.9)	.097

[1]Mean±SD unless otherwise noted

MMSE=Mini Mental State Examination
RAVLT=Rey Auditory Verbal Learning Test
COWAT=Controlled Oral Word Association Test
DKEFS Sorting Test=Delis-Kaplan Executive Function System Sorting Test
WRAT-3 Reading Test=Wide Range Achievement Test-3rd Edition Reading Test (standard score)

Table 11

Standardized Coefficients and Correlations of Predictor Variables to Psychotic Features

Predictors	Correlation Coefficients	Standardized Coefficients
RAVLT Total List A	.34	-.37
RAVLT Immediate Recall	.76	1.43
RAVLT Recognition	.32	-.34
Trail Making Test Part A	.12	.50
WRAT-3 Reading	.41	.21

RAVLT = Rey Auditory and Verbal Learning Test
WRAT-3 = Wide Range Achievement Test, 3rd Edition (standard score)

Table 12

Socio-demographic Characteristics between Recurrent and Single Episode Depressed Patients

Characteristic	Recurrent (N = 75)	Single Episode (N = 7)	P-Value
Age (M±SD)	50.8 (15.0)	64.9 (14.4)	.019
Gender (%)			.421
Male	37.0	57.1	
Female	63.0	42.9	
Race (%)			1.0
Caucasian	93.2	100.0	
African American	6.8	0.0	
Education (M±SD)	14.3 (2.6)	14.1 (2.7)	.879
Handedness (%)			.258
Right	90.7	41.4	
Left	6.7	28.6	
Ambidextrous	2.7	0.0	
Employment Status (%)			.374
Employed	22.5	28.6	
Unemployed	15.5	14.3	
Retired	19.7	57.1	
Disability	23.9	0.0	
Other	18.3	0.0	
Marital Status (%)			.554
Married	57.7	28.6	
Never Married	18.3	28.6	
Divorced	15.5	28.6	
Other	8.4	14.3	

Table 13

Clinical Characteristics between Recurrent and Single Episode Depressed Patients

Characteristic	Recurrent (N = 75)	Single Episode (N = 7)	P-Value	P-Value[1]
Psychosis (%)	14.9	42.9	.095	--
Number of MDEs	4.4 (4.3)	--	--	--
Number of Psychiatric Hospitalizations	3.2 (2.7)	0.9 (0.7)	.023	--
Age of onset of first psychiatric illness	26.1 (16.7)	64.4 (14.8)	<.0001	--
Age of onset of current MDE	49.8 (15.3)	64.4 (14.8)	.018	--
Depression Severity				
$HRSD_{24}$	34.1 (7.0)	33.5 (7.8)	.820	.541
$IDS\text{-}SR_{30}$	46.4 (11.7)	42.2 (18.1)	.425	.779

[1]covaried for age

MDE=Major Depressive Episode
$HRSD_{24}$=24-item Hamilton Rating Scale for Depression
$IDS\text{-}SR_{30}$=30-item Inventory of Depressive Symptomatology

Table 14

Neuropsychological Score Comparisons between Recurrent and Single Episode Depressed Patients[1]

Measure	Recurrent (N = 75)	Single Episode (N = 7)	P-value	P-Value[2]
MMSE	27.4 (1.8)	27.0 (2.2)	.552	.702
RAVLT				
Total List A	43.3 (10.6)	37.0 (13.6)	.174	.800
Total List B	4.9 (1.6)	5.5 (1.6)	.342	.063
Immediate Recall	8.1 (3.9)	6.2 (3.9)	.232	.647
Delayed Recall	6.9 (4.0)	6.0 (4.6)	.626	.888
Recognition	11.6 (3.1)	11.3 (3.0)	.849	.686
Discrimination	9.8 (4.1)	8.0 (5.4)	.314	.946
Retention (%)	60.8 (29.7)	55.8 (44.3)	.711	.970
Complex Figure Test				
Copy	31.51 (4.7)	28.7 (3.5)	.155	.211
Immediate Recall	16.4 (8.0)	12.3 (9.1)	.238	.754
Delayed Recall	15.2 (7.8)	11.2 (9.0)	.234	.735
COWAT	35.3 (13.8)	32.4 (12.5)	.600	.769
Category Fluency	14.1 (4.6)	12.6 (6.3)	.422	.729
Trail Making Test				
Part A	36.8 (17.2)	56.7 (38.5)	.017	.119
Part B	101.7 (60.4)	121.6 (92.3)	.435	.606
Stroop				
Word	88.6 (18.9)	90.7 (18.8)	.798	.278
Color	62.3 (15.0)	55.7 (13.6)	.301	.891
Color-Word	32.9 (10.2)	25.7 (11.3)	.107	.631
DKEFS Sorting Test				
Free Sort	14.9 (6.1)	16.2 (6.0)	.636	.188
Correct Sort	3.9 (1.6)	4.2 (1.6)	.694	.202
Verbal Sort	1.7 (0.7)	1.8 (0.8)	.557	.231
Perceptual Sort	2.2 (1.4)	2.3 (1.4)	.879	.423
Global Cognitive Impairment	0.1 (2.7)	-1.1 (3.3)	.305	.917
WRAT-3 Reading	98.6 (15.8)	102.4 (6.4)	.525	.730

[1]Mean±SD
[2]covaried for age

MMSE=Mini Mental State Examination
RAVLT=Rey Auditory Verbal Learning Test
COWAT=Controlled Oral Word Association Test
DKEFS Sorting Test=Delis-Kaplan Executive Function System Sorting Test
WRAT-3 Reading=Wide Range Achievement Test-3rd Edition Reading Test (standard score)

Table 15

Socio-demographic Characteristics between Atypical and Non-Atypical Depressed Patients

Characteristic	Atypical (N = 7)	Non-Atypical (N= 74)	P-Value
Age (M±SD)	44.1 (10.0)	52.7 (15.7)	.164
Gender (%)			.399
Male	16.7	39.7	
Female	83.3	60.3	
Race (%)			1.00
Caucasian	100.0	93.2	
African American	0.0	6.8	
Education (M±SD)	14.6 (2.1)	14.2 (2.6)	.742
Handedness (%)			.685
Right	100.0	87.8	
Left	0.0	9.5	
Ambidextrous	0.0	2.7	
Employment Status (%)			.609
Employed	28.6	22.9	
Unemployed	28.6	12.9	
Retired	0.0	25.7	
Disability	28.6	21.4	
Other	14.3	17.0	
Marital Status (%)			.524
Married	42.9	55.7	
Never Married	42.9	17.1	
Divorced	14.3	17.1	
Other	0.0	10.0	

Table 16

Clinical Characteristics between Atypical and Non-Atypical Depressed Patients

Characteristic	Atypical (N = 7)	Non-Atypical (N = 74)	P-Value
Psychosis (%)	28.6	15.1	.592
Number of MDEs	4.7 (3.1)	3.8 (4.4)	.732
Number of Psychiatric Hospitalizations	3.3 (2.1)	3.0 (2.7)	.797
Age of onset of first psychiatric illness	19.2 (12.2)	30.4 (20.3)	.188
Age of onset of current MDE	44.1 (10.0)	51.7 (16.2)	.233
Depression Severity			
$HRSD_{24}$	31.1 (6.4)	34.5 (7.0)	.235
$HRSD_{6}$	12.4 (1.0)	13.1 (2.3)	.428
$IDS\text{-}SR_{30}$	46.6 (15.9)	46.2 (12.2)	.943

MDE=Major Depressive Episode
$HRSD_{24}$=24-item Hamilton Rating Scale for Depression
$HRSD_{6}$=6-item Hamilton Rating Scale for Depression (Item 1 (Depressed Mood), Item 2 (Guilt), Item 7 (Anhedonia), Item 8 (Psychomotor Retardation), Item 10 (Psychic Anxiety), and Item 13(Decreased Energy))
$IDS\text{-}SR_{30}$=30-item Inventory of Depressive Symptomatology

Table 17

Neuropsychological Score Comparisons between Atypical and Non-Atypical Depressed Patients[1]

Measure	Atypical (N = 7)	Non-Atypical (N = 74)	P-value
MMSE	27.7 (2.0)	27.4 (1.9)	.676
RAVLT			
Total List A	54.4 (8.2)	41.8 (10.5)	.003
Total List B	5.3 (1.3)	4.9 (1.7)	.507
Immediate Recall	10.9 (3.2)	7.8 (3.8)	.042
Delayed Recall	10.4 (4.3)	6.4 (3.9)	.013
Recognition	13.4 (2.5)	11.4 (3.1)	.104
Discrimination	12.9 (2.4)	9.4 (4.3)	.038
Retention (%)	76.4 (28.5)	58.9 (30.9)	.155
Complex Figure Test			
Copy	33.9 (2.1)	31.0 (4.8)	.123
Immediate Recall	17.4 (5.4)	15.8 (8.3)	.619
Delayed Recall	14.9 (7.4)	14.8 (8.1)	.993
COWAT	41.6 (19.1)	34.3 (13.0)	.186
Category Fluency	15.7 (4.8)	13.7 (4.7)	.274
Trail Making Test			
Part A	33.0 (12.8)	39.5 (21.9)	.447
Part B	76.7 (23.0)	107.2 (66.0)	.232
Stroop			
Word	99.6 (15.9)	87.2 (18.9)	.100
Color	70.9 (12.3)	60.6 (15.0)	.086
Color-Word	36.0 (9.0)	31.9 (10.7)	.330
DKEFS Sorting Test			
Free Sort	13.9 (7.5)	15.2 (5.9)	.593
Correct Sort	3.6 (1.9)	4.0 (1.5)	.530
Verbal Sort	1.7 (0.5)	1.7 (0.7)	.863
Perceptual Sort	1.9 (1.8)	2.3 (1.4)	.431
Global Cognitive Impairment	1.1 (2.1)	-0.1 (2.9)	.303
WRAT-3 Reading	100.3 (7.6)	98.6 (15.8)	.779

[1]Mean±SD unless otherwise noted

MMSE=Mini Mental State Examination
RAVLT=Rey Auditory Verbal Learning Test
COWAT=Controlled Oral Word Association Test
DKEFS Sorting Test=Delis-Kaplan Executive Function System Sorting Test
WRAT-3 Reading=Wide Range Achievement Test-3rd Edition Reading Test (standard score)

Table 18

Pearson Product-Moment Correlations for Current Depressive Episode Length[1] and Cognitive Functioning in Patients with Unipolar Depression[2]

Measure	Length of Depressive Episode
MMSE	-.340
RAVLT	
Total List A	-.240
Total List B	.169
Immediate Recall	-.491*
Delayed Recall	-.304
Recognition	-.047
Discrimination	-.320
Retention (%)	-.367
Complex Figure Test	
Copy	-.007
Immediate Recall	-.217
Delayed Recall	-.018
COWAT	-.373
Category Fluency	-.146
Trail Making Test	
Part A	-.023
Part B	.210
Stroop	
Word	.087
Color	.008
Color-Word	.091
DKEFS Sorting Test	
Free Sort	-.023
Correct Sort	.040
Verbal Sort	-.197
Perceptual Sort	.097
WRAT-3 Reading	-.575**
Global Cognitive Index	-.070

[1]N=18

[2]MMSE score $\geq$ 24

MMSE=Mini Mental State Examination
RAVLT=Rey Auditory Verbal Learning Test
COWAT=Controlled Oral Word Association Test
DKEFS Sorting Test=Delis-Kaplan Executive Function System Sorting Test
WRAT-3 Reading Test=Wide Range Achievement Test-3rd Edition Reading Test (standard score)

*p=.039, **P=.013

Table 19

Pearson Product-Moment Correlations for Current Depressive Episode Length[1] and Depression Severity in Patients with Unipolar Depression[2]

Measure	Length of Depressive Episode
$HRSD_{24}$	.142
$IDS\text{-}SR_{30}$	.539*

[1]N=18
[2]MMSE score $\geq$ 24

$HRSD_{24}$=24-item Hamilton Rating Scale for Depression
$IDS\text{-}SR_{30}$=30-item Inventory of Depressive Symptomatology

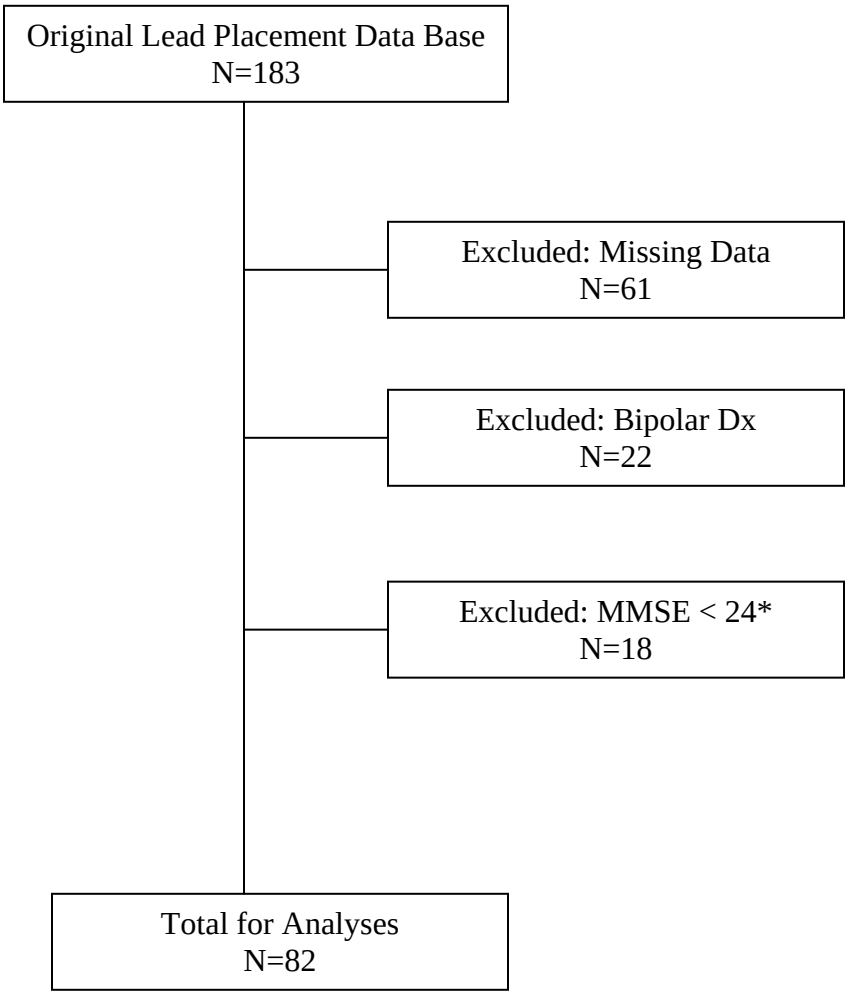
*p=.025

CHAPTER 7

FIGURES

Figure 1

Schematic of Data



*An MMSE score of 23 or less has been suggested to be indicative of pseudodementia or dementia (Lockwood et al., 2000).

Figure 2

Neurocognitive Domains Assessed

Domain	**Measure**
Global Cognitive Function	Mini Mental State Examination Global Cognitive Impairment Scale WRAT-3 Reading Test
Executive Function	Trail Making Test Part B DKEFS Sorting Test Stroop COWAT Category Fluency
Learning and Memory	RAVLT Complex Figure Test
Attention	Trail Making Test Part A Stroop
Psychomotor Speed	Trail Making Test Part A

Figure 3

The Global Cognitive Index (GCI)

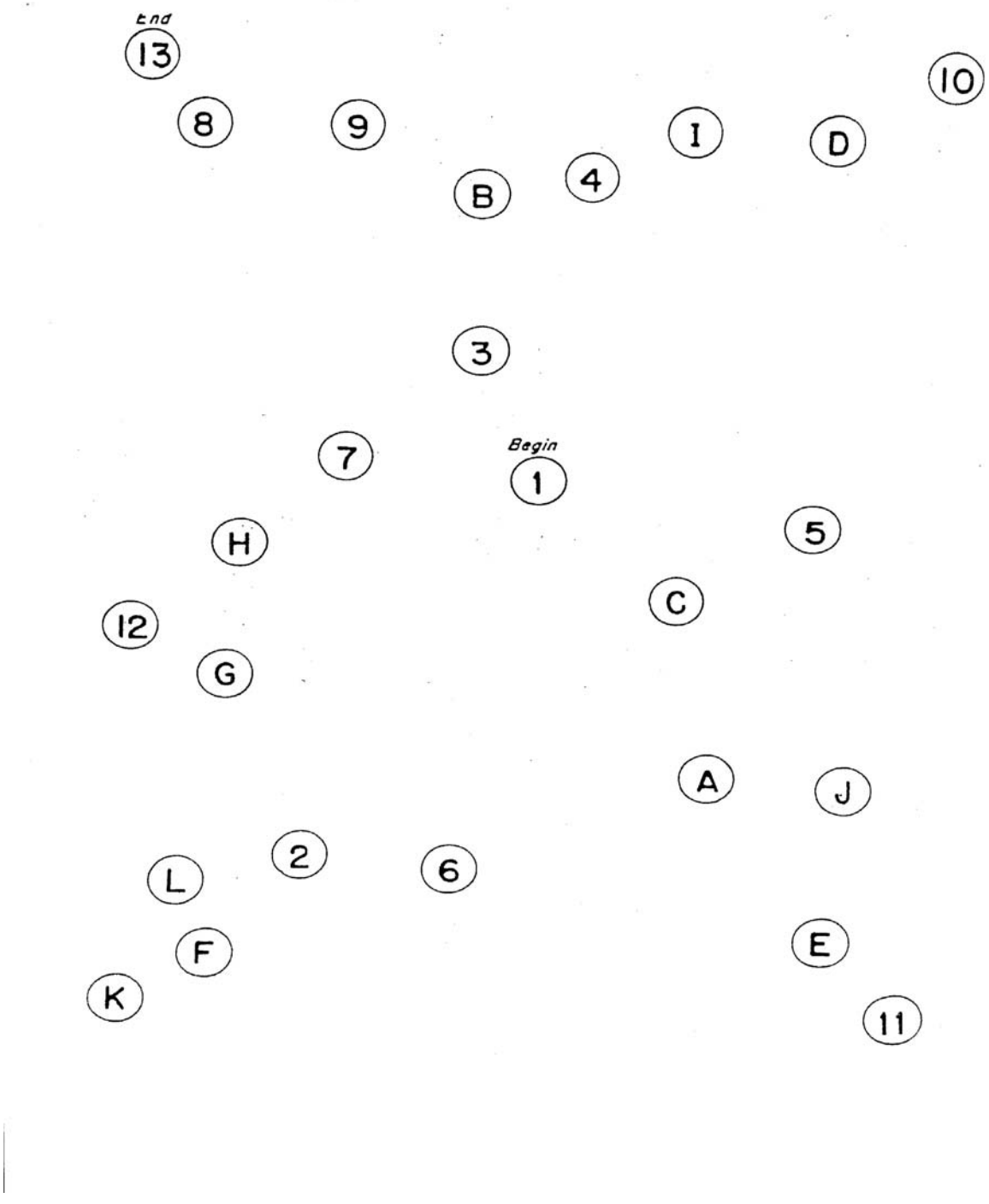
The Global Cognitive Index (GCI) consists of the following neuropsychological measures:

Test	**Min Raw Score**	**Max Raw Score**
RAVLT-Delay	0	15
CCST-Correct Sort	0	8
Rey-O-Delay	0	36
Stroop-CW	0	100
Grand Total	0	189

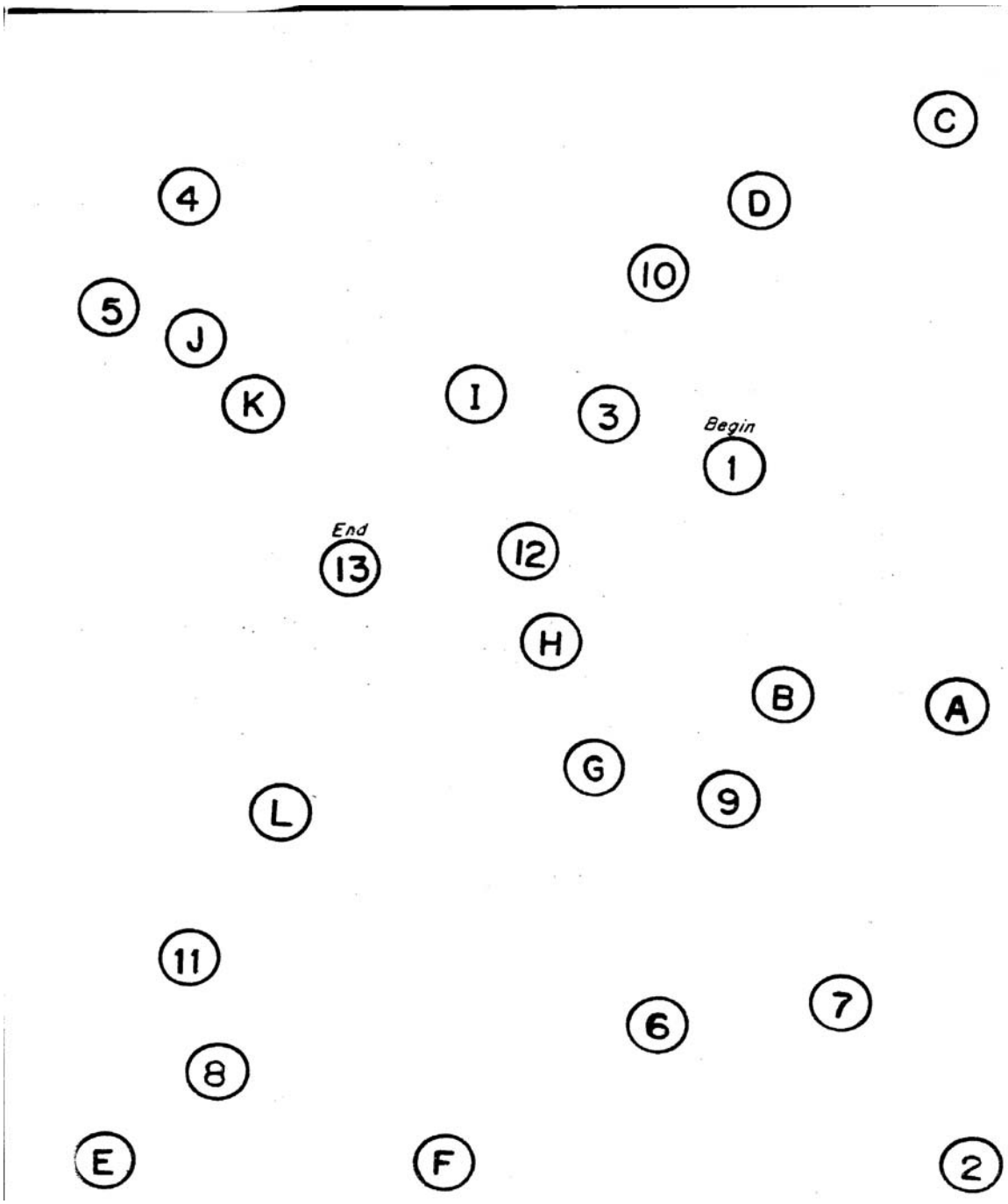
The z-scores of each individual test are summed to create a grand z-score which constitutes the GCI. The grand total raw score is then be converted into a z-score.

Appendix A: Original and Alternate Versions of the Trail Making Test Part B

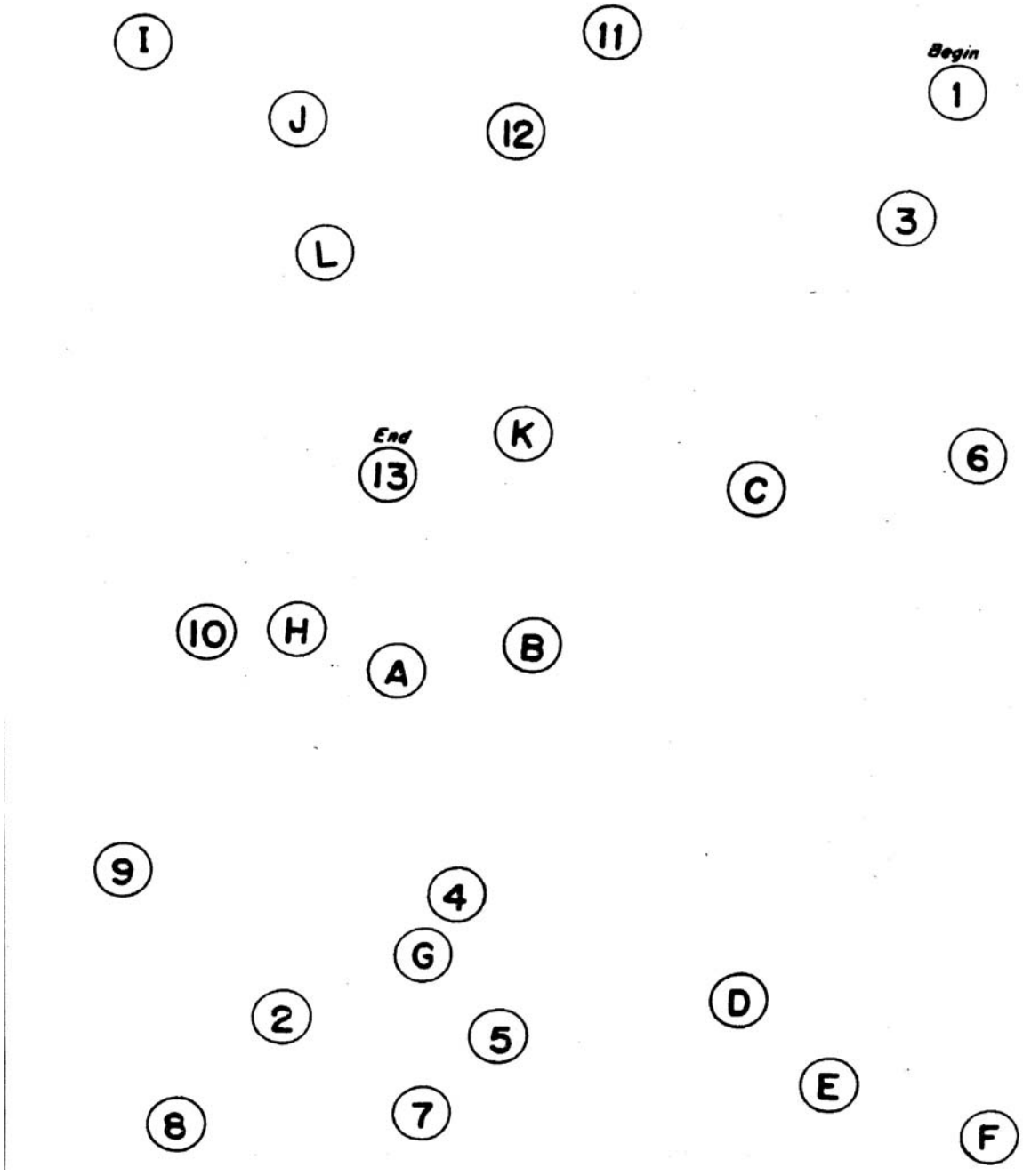
Trail Making Test Form B - Original Version



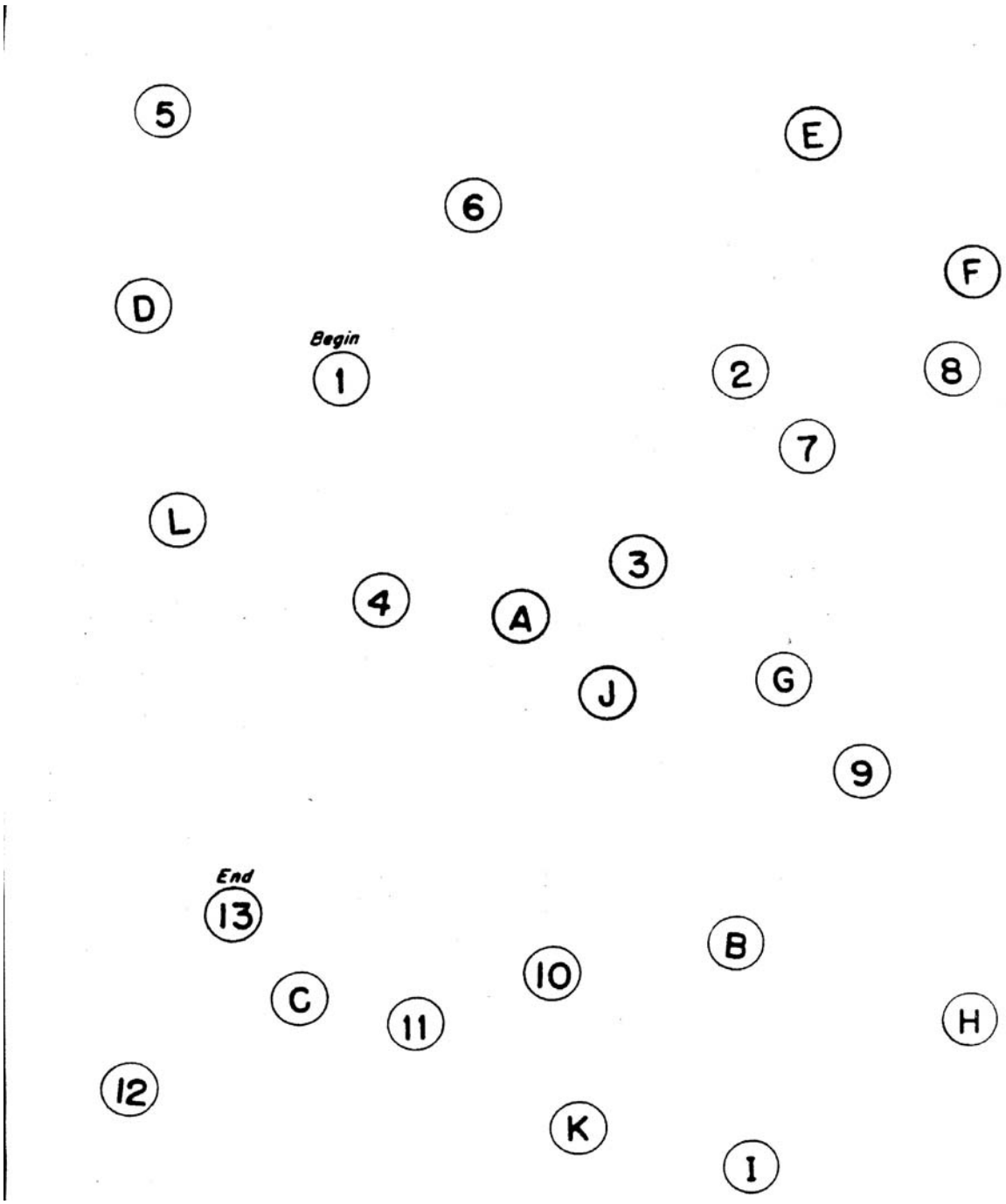
Trail Making Test Part B – Alternate Version 1



Trail Making Test Part B – Alternate Version 2



Trail Making Test Part B – Alternate Version 3



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