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Antidepressant Medications And Cognitive Functioning In Major Depressive Disorder

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ANTIDEPRESSANT MEDICATIONS AND COGNITIVE FUNCTIONING IN MAJOR DEPRESSIVE DISORDER

by

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CHAPTER 1

INTRODUCTION

Individuals with Major Depressive Disorder (MDD) frequently experience cognitive decrements as part of the illness. Ironically, medications used to treat depression may have a positive effect on some aspects of cognition but may adversely affect others. Understanding the relative cognitive costs of medications is imperative for considering treatment of patients in a variety of circumstances. Cognitive side effect profiles of antidepressant medications for depression must be carefully distinguished from the adverse cognitive effects of depression per se. Unfortunately, few studies evaluating cognitive profiles of psychotropic medications directly compare unmedicated and medicated adults with clinically significant depression; those that do are generally troubled by methodological problems such as very small samples and mixed samples of medicated and unmedicated patients with depression.

One fundamental challenge in studying the effects of medications for depression is that psychotropic research is most frequently conducted on healthy adults. These methods are continually used despite evidence that side effect profiles based on non-depressed adults may not generalize to depressed adults, especially those with the most severe symptoms who are most likely to benefit from psychotropic treatment (Fournier et al., 2010; Kirsch et al., 2008). Until more is known about the beneficial and adverse effects of antidepressant medications on cognition among adults with clinical depression, research and clinical interventions cannot be formulated on sound empirical bases. Accordingly, the present study compares cognitive functioning profiles among unmedicated adults with MDD (uMDD), adults with MDD on therapeutic levels of antidepressant medications (mMDD), and healthy comparison (HC) participants.

Debilitating Symptoms of Depression

Major Depressive Disorder (MDD) is the most prevalent psychiatric disorder, with an estimated lifetime prevalence of 13 to 21% and an incidence rate of 5 to 7% in the United States (Kessler & Walters, 1998; Turner & Gil, 2002; Hasin et al., 2005; Alonso & Lépine, 2007; Kessler et al., 2005; Murphy et al., 2000). Within the framework of affective disruptions of the disease, individuals with MDD are also likely to experience impairments in several domains of cognitive functioning (Purcell et al., 1997; Porter et al., 2003; Ravnkilde et al., 2004). These affective and cognitive processing weaknesses may contribute to an increased risk for the alarming rates of suicide among people with depression. Currently, patients with MDD account for 60% of suicides in the United States each year (NIMH, 2009).

Individuals living with MDD experience hallmark symptoms of sadness and/or anhedonia, in addition to signs of withdrawal, fatigue, sleep disruption, anxiety, and decreased self-worth. These individuals may also face difficulties upholding responsibilities within the household and workplace, and struggle to establish and maintain close relationships (Godard, Grondin, Baruch & Lafleur, 2011; see Papakostas et al., 2004 for review). Many patients likely experience both state-specific cognitive effects from symptoms of a current episode as well as cumulative cognitive effects from chronic years with depression (Austin et al., 2001; Castaneda et al., 2008; Papakostas et al., 2004; Schmid et al., 2011). Furthermore, the effect of depression on certain cognitive domains (e.g., verbal memory) appears to be worse for individuals in recurrent episodes than for those experiencing a first episode (Fossati et al., 2004; Sweeney et al., 2000).

Debilitating Effects of Depression on Cognition

Among the debilitating psychological symptoms of depression are the demonstrated deficits in several domains of cognitive functioning. The field of neuropsychology has traditionally viewed depression as associated with potentially reversible cognitive deficits that can fade during episode remission or after treatment (Sobow et al., 2006; Burt et al., 1995). However, cognitive decrements during depression may not be as universal or reversible as once thought. First, not all individuals with depression exhibit symptoms of cognitive dysfunction. Furthermore, for the patients who do exhibit these decrements, cognitive difficulties in attention and executive functioning often remain during remission from depressive symptoms (Iverson et al., 2011, Paelecke-Habermann, Pohl, & Leplow, 2005; Weiland-Fiedler et al., 2004).

Despite the literature that consistently suggests that patients with depression endure cognitive deficits, there are inconsistencies in the breadth of affected areas. There is some consensus that, at minimum, the areas of executive functioning, psychomotor functioning, and memory are adversely affected during MDD (Egeland et al., 2005). Theories suggest that differences in cognitive functioning within the depressed population may vary as a function of cortisol levels, depressive subtype, ascertainment status (inpatient, outpatient, volunteer), severity and/or use of psychotropic medication.

A limited body of research suggests that patients who are successfully treated using selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCA) have better cognitive functioning than do their unmedicated counterparts (Gualtieri et al., 2006). A comparison of healthy adults and unmedicated depressed patients is therefore a strong method for examining cognitive deficits endured due to depression, in the absence of medication effects on cognitive functioning. Table 1 (see Appendix A) summarizes six studies that are the main sources of empirical information focused specifically on unmedicated adults with MDD. As

shown in the table, the literature evaluating cognitive functioning in unmedicated depressed adults is limited. The dearth of information on unmedicated adults with depression likely reflects that most patients are psychotropically treated without delay (i.e., prior to enrollment in research, especially longitudinal study). Furthermore, the few studies that include unmedicated depressed patients typically do not evaluate the group separately from medicated patients when examined in reference to a healthy comparison group. When unmedicated depressed patients are studied, they are too often combined with medicated depressed patients, therefore confounding the assessment of direct effects of depression on cognition with those associated with antidepressant drugs. In addition, late-phase studies of medication effects rarely include measures of cognitive functioning, as budgetary emphasis is placed on obtaining a large enough sample size to power studies to separate active from placebo antidepressant effects. Separately examining medicated and unmedicated groups would systematically separate the cognitive deficits experienced in depression not complicated by the use of the psychotropic medication treatments.

As indicated in Table 1, limited findings available suggest that healthy adults outperform unmedicated depressed patients in the areas of attention, inhibition, concentration, executive functioning, and psychomotor functioning (Porter et al., 2003; Grant et al., 2001; Den Hartog et al., 2003; Langenecker et al., 2007; Gualtieri et al., 2006; Bulshman et al., 2006). Findings in the areas of working memory, visuospatial memory and verbal learning memory, however, were more variable (Den Hartog et al., 2003; Grant et al., 2001; Gualtieri et al., 2006; Porter et al., 2003). Inconsistency across studies depending on the cognitive domain indicates potential methodological limitations. An important weakness of these studies is their use of small samples and that they neglect to provide effect sizes; therefore, concern about insufficient power clouds interpretation of null findings as evidence for equivalence of unmedicated depressed patients and

their healthy adult counterparts.

Potential Debilitating Effects of Antidepressant Medication on Cognition

The effects of antidepressant medications on cognition are an important, yet surprisingly understudied question. Moreover, the limited extant literature evaluating this question may be restricted because antidepressant effects on cognitive functioning has been conducted by producers of the pharmacological agents and infrequently by neuropsychologists. Because these evaluations are not typically conducted from a neuropsychological perspective that includes comprehensive assessment of cognitive domains of executive functioning, attention, concentration, psychomotor speed, working memory and verbal and visuospatial memory, a thorough understanding of cognitive effects of antidepressant medications remains unknown. Most studies of antidepressant side effects investigate safety and tolerability on small samples of healthy adults (e.g., 10-15 participants), completed as part of Phase I trials (Klein, 1991). Phase II trials aim to examine short-term safety and tolerability for patients with the disorder. These trials also typically employ small sample sizes and often work within the constraints of limited budgets. Finally, Phase III and IV studies incorporate thousands of patients during the cost-benefit analysis evaluation of the medication relative to placebo (Klein, 1991). These trials typically recruit samples too large to feasibly administer comprehensive neuropsychological assessments on all patients due to budgetary constraints.

Because most psychopharmacological studies are designed to assess only positive changes in symptoms of depression as a response to medication, the variability in patients' initial experiences of cognitive difficulties (e.g., absence or presence of cognitive problems) can mask the mild to moderate effects of the medications. Furthermore, the effects of medications make it difficult to measure the full variability of cognitive difficulties endured by patients with

depression. Therefore, there has historically been no place in the field of pharmacological studies to examine effects of changes to cognition in medicated depressed patients. Furthermore, pharmacological researchers have few financial or other incentives to investigate this problem.

Thus far, neuropsychological studies of healthy adults suggest deleterious cognitive and psychological effects from antidepressants with sedative, anticholinergic or histaminic components (Amado-Boccara et al., 1992; Hindmarch, 1997). Studies find that tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine-reuptake inhibitors (SNRIs) and other antidepressant medications have disparate effects on psychomotor speed as measured by reaction time, both between and within medication classes. Findings suggest that medications such as nomifensine, bupropion and desipramine produce improved psychomotor performance, whereas amitriptyline, dothiepin, and mianserin yield significant impairments in reaction time on a driving simulator task (Hindmarch, 1997). On the other hand, several antidepressants of varying types have been found to have no effect on cognitive performance in healthy control participants (e.g., cericlamine, fluvoxamine, bupropion, viloxazine, fluoxetine, and moclobemide). Lastly, a small group of antidepressants appear to have a positive effect on cognitive performance in healthy participants (e.g., nomifensine, midalcipran, zimeldine, lofepramine, paroxetine, sertraline; Amado-Boccara et al., 1992). These incongruent findings suggest that specific medications both within and between antidepressant classes may partially explain changes in neuropsychological functioning. It is important to consider, however, that because studies such as these include only healthy adults, the evaluation of cognitive functioning post medication use may be different for individuals with depression, as they have putatively much different brain chemistry.

Studies examining antidepressant effects in patients with MDD find that several specific

areas of neuropsychological functioning may improve during symptom reduction, including verbal declarative memory, for example (Gallagher et al., 2007). Contrastingly, other researchers propose that impairments in selective executive functions and working memory remain stable after clinical remission (Paelecke-Habermann, Pohl J & Leplow, 2005; Trichard et al., 1995). Others suggest that varied antidepressant medications with different neurotransmitter targets may have unique cognitive profiles of improvement indicators. For example, Levkovitz et al. (2002) proposed that SSRIs may be responsible for more improvements than TCAs in the memory and attention functioning of patients with depression. The study found that 6-week administration of fluoxetine yielded significant improvement in affective depressive symptoms, attention and verbal and visuospatial memory functioning when compared to baseline. Although psychological symptomatology also improved with a 6-week administration of desipramine, functioning in the domains of memory and attention were not examined (Levkovitz et al., 2002). Thus, continued research examining effects of antidepressant medications on specific cognitive domains of functioning is still needed.

Studying Antidepressant Medication in Healthy Adults and Depressed Patients

Although some research examines the effect of antidepressants on cognitive functioning of healthy adults (e.g., Fairweather et al., 1996; Siepmann et al., 2001), the application of this method to the real world use of psychotropic medications is relatively flawed. Antidepressants are meant to alter brain chemistry in patients experiencing symptomatology. In particular, the mechanism of action for SSRIs is, as its name suggests, to selectively block the reuptake of serotonin in the synapse. The mechanisms of TCAs work similar to the SSRIs but target blocking the reuptake of norepinephrine. A third group of antidepressant drugs acts generally on noradrenergic and serotoninergic neurons to enhance the synaptic transmission (Lenox & Frazer,

2002). Of special importance, some evidence indicates that antidepressants have different effects depending upon severity of depressive symptoms (Fournier et al., 2010; DeRubeis et al., 2012; Kirsch et al., 2008): Among patients with mild and moderate symptoms, benefits are negligible or nonexistent, whereas among patients with severe symptoms the benefits may be large. Similarly, given that brain chemistry is assumed to differ even more substantially between healthy adults and patients with MDD, medication intended to remediate neurochemical deficiencies in MDD may have different effects among patients than those demonstrated among healthy controls in pharmaceutical safety tests. Thus, it is possible that side effect profiles based on healthy adults may not generalize to depressed adults, especially those most likely to benefit from psychotropic treatment; adverse response to antidepressant medication experienced by healthy adults may result because the medications were not intended for their use.

If antidepressants truly improve brain functioning for areas involved in emotion processing and regulation in major depression, they may not have deleterious effects for patients (Amado-Boccara et al., 1992). Alternatively, patients with depression who do experience adverse cognitive and physical side effects from antidepressant medications may consider those worthwhile costs when compared to the broadly debilitating effects of depressive symptoms. For instance, Amin et al. (1980) found marked improvement in memory and attention but decrements in psychomotor functioning after a 4-week (75-225 mg) daily administration of imipramine to depressed patients. These improvements may be considered more beneficial than the adverse effects on functioning.

A small set of studies has attempted to address the effects of depression alone on cognition by evaluating unmedicated patients with MDD, using a design in which assessments were conducted within a week of medication initiation (i.e., Ravnkilde et al., 2002; Gohier et al.,

2009). Authors of these studies argue that effects of the antidepressants are not likely to be present within this first week. Therefore, these studies label patients as "unmedicated" and compare them to healthy participants and patients with depression who have been psychotropically medicated for longer periods of time. This method is problematic, however, as the first week of medication is often the time in which most side effects occur, and side effect onsets vary by medication (Tollefson, 1991; Stassen et al., 1993). Furthermore, initial onset of antidepressant-related symptom-reduction has been examined within one week of onset, as opposed to the traditionally viewed changes occurring at 6-8 weeks (Stahl, Nierenberg, & Gorman, 2001; Taylor et al., 2006). These side effects and unpredictable onset of medication effects may interfere with valid testing and result in different cognitive outcomes relative to the actual long term effects of medication compared to those that might be associated with initial side effects, placebo responding, and treatment response.

Studies Examining MDD With and Without Medication and its Effect on Cognition

Several problems undermine the extant literature of the effects of medication and depression, alone and together, on cognitive functioning. The effects of MDD on cognition and the effects of MDD plus antidepressant medications on cognition are essentially separate questions. Unfortunately, most studies are too underpowered to compare medicated and unmedicated groups. Small sample sizes and variability in medication type, dose, duration and compliance would make most of these studies weak tests of the hypothesis. These studies therefore combine groups of medicated and unmedicated patients with MDD together to enhance statistical power in comparisons to healthy adult participants.

Studies relevant to the cognitive effects of antidepressant medications include at least one group of depressed patients (i.e., medicated, or medicated and unmedicated) and a healthy

comparison group. Additionally, useable studies of this class must have specified whether depressed patients were medicated or unmedicated at the time of testing. Studies examining cognitive domains with only antidepressant-medicated patients are not of interest to this topic, because it is not possible to disentangle the effects of depression from those of medication.

Cognitive domains of interest in prior research for medicated and unmedicated patients span a broad range of areas including psychomotor and processing speed, attention, concentration, inhibition, working memory, and verbal and visuospatial memory. Most studies evaluated performance in more than one cognitive domain, which allows for the comparison of medication effects across various cognitive domains both within and between samples. The patterns reported in these studies have been helpful to compare to the present study.

Pertinence and Grading Relevance of Studies to the Research Question

The focus of the present study was to evaluate the unique effects of antidepressant medication on cognition apart from the effects of depression on cognition. As such, studies including all three groups (unmedicated MDD, medicated MDD and a healthy comparison group) for several cognitive domains are most pertinent to address this question. Unfortunately, there are surprisingly few studies that include all three groups in a well-characterized fashion that evaluate cognitive functioning and depression. In the absence of three-group comparisons, studies that include unmedicated MDD patients and those including recently medicated patients with MDD are used to infer the most comprehensive understanding of the literature. See Table 2 for study details and classification outlines.

Grade A Studies: Direct Evaluation of Medication Effects on Cognition in Depressed Subjects

In order to examine the usefulness and methodological strengths or weaknesses of past studies, the relevant literature is categorized and graded. *Grade-A* studies are of the highest

pertinence and the most methodologically sound to contribute to answering the research question. These studies separately compare patients with unmedicated MDD, medicated MDD and healthy comparison groups on cognitive domains of functioning.

Grade B Studies: Direct Evaluation of Depression and Medication Effects in Cognition in Depressed Subjects

Also relevant are Grade-B studies, which include a medicated MDD group compared to a healthy comparison group or a recently-medicated MDD group compared to a healthy comparison group. Though these studies offer some insights, many are problematic in classifying patients with recent medication onset as "unmedicated" in their analyses, as patients may begin to show side effects, intended effects of medications within the first week, including also placebo effects.

Grade C Studies: Indirect Evidence of the Effects of Medication or Depression on Cognition in Depressed Subjects

Grade-C studies are those that did not include ideal groups, but offered information about the effects of depression or psychotropic medication on cognitive domains of functioning. For instance, Grade-C studies included either only unmedicated patients (e.g., Bulmash et al., 2006; Grant et al., 2001; Porter et al., 2003) or participants tested pre-SSRI initiation and post-SSRI adherence (e.g., Wadsworth et al., 2005), among other methodologies.

Aims and Hypotheses:

Aim 1: Examine psychomotor and processing speed among patients with MDD on antidepressant medication compared to unmedicated patients and a healthy comparison group.

Rather consistent in the literature is the understanding that depressed patients experience robust deficits in psychomotor speed. Although few studies examine psychomotor speed using

direct cognitive measures from neuropsychological testing, several studies use observational measures, self-report measures of psychomotor retardation and agitation, and applied methods that parallel daily activities such as gait and driving simulation (Schrijvers, Hulstijn, & Sabbe, 2008). These studies evaluate both short-term and long-term effects of antidepressants. Although direct comparisons of gait and driving simulation tasks are not traditional neuropsychological measures, inferences can be drawn based on the improvements experienced by patients with depression in these areas. Several studies have found that patients taking medication experience improved gait performance (Bader et al., 1999; Lecrubier, 2006) and self-reported psychomotor improvements (Ferguson, 2002; Gattaz et al., 1995; Guelfi et al., 2001; Sechter et al., 1999; Stahl et al., 2002; Tollefson et al., 1996; Wheatley et al., 1998). Findings suggest that unmedicated depressed patients have slower reaction time relative to the healthy comparison group on computer tasks as well as in vivo driving manipulation, accuracy and speed tasks (Pier, Hulstijn, & Sabbe, 2004).

Limited findings from neuropsychological testing suggest that patients with MDD successfully treated with antidepressants perform better than untreated patients on the computer measures of psychomotor speed (Raoux et al., 1994; Sobin & Sackeim, 1997); however, measures such as Digit Symbol and Cancellation yield inconsistent results (Gorenstein et al., 2006, Ravindran et al., 1995). Findings to date on paper-and-pencil measures of psychomotor speed generally suggest that medicated depressed patients and healthy comparison participants outperform unmedicated depressed patients (Gualtieri et al., 2006; Raoux et al., 1994; Sobin & Sackeim, 1997; Tsourtos et al., 2002; Caligiuri & Ellwanger, 2000). Studies report few significant psychomotor deficits in depressed medicated patients (Austin et al., 1992, 1999). Because of the limited literature reports of motor deficits in medicated patients, it is difficult to

determine whether the psychomotor problems occurred prior to medication onset thereby suggesting successful response to antidepressants, or whether the patients are maintaining their previously functioning motor abilities.

Hypothesis 1: With findings indicating a small effect size for psychomotor speed based on medication status, it was not clear what to expect in the current study. It was predicted that antidepressants would positively influence psychomotor speed, such that healthy comparison participants and MDD patients taking antidepressants would outperform unmedicated MDD patients. It was also expected that there would be limited differences between medicated depressed patients and healthy comparison participants.

Aim 2: Examine attention and concentration among patients with MDD on antidepressant medication compared to unmedicated patients and a healthy comparison group.

Mixed and null findings in the domains of attention and concentration may partly reflect wide differences across studies in the measures used to assess these domains. For example, paper-and-pencil measures of attention have yielded minimal to no differences between patients with MDD and healthy comparison (Grant et al., 2001); however, studies employing more precise and sensitive computerized tasks tend to report such differences more frequently and in greater magnitude (Langenecker et al., 2007a; Porter et al., 2003). Specifically, in the areas of concentration and inhibitory control, unmedicated MDD patients make more errors of omission and commission than do healthy adults on continuous performance computer tasks (Langenecker et al., 2007a; Porter et al., 2003). A group of predominantly medicated patients also performed more poorly during computer tasks assessing attention and concentration than did the healthy comparison group (Langenecker et al., 2007b; Gualtieri et al., 2006). Unmedicated MDD patients also have poorer performance than healthy adults and medicated MDD patients on

inhibitory control measures (e.g., lure rejections) in computer tasks of sustained attention (Langenecker et al., 2005; Porter et al., 2003).

Hypothesis 2: Given prior findings suggesting superior performance in healthy adults compared to medicated and unmedicated depressed patients on sensitive measures of attention, concentration and inhibitory control, it was expected that medicated and unmedicated patients would perform significantly more poorly than the healthy comparison on measures of inhibitory control, with limited differences between the two depressed groups. Similarly, it was expected that the healthy comparison adults would outperform medicated and unmedicated MDD patients on computer measures of attention and concentration. Few studies have examined the performance of medicated depressed patients during paper-and-pencil measures of attention. Because it appears that psychotropically medicated and unmedicated patients do not significantly differ from each other overall in computer measures of attention and concentration, a similar pattern is expected for examiner-administered, non-computerized tasks. Here, both MDD groups were expected to underperform relative to the healthy comparison group.

Aim 3: Examine auditory and visuospatial learning and memory among patients with MDD on antidepressant medication compared to unmedicated patients and a healthy comparison group.

Findings regarding verbal list-learning performance are relatively inconsistent, with a number of studies suggesting that patients with MDD have equivalent performance to healthy adults in verbal list-learning tasks (Porter et al., 2003; Grant et al., 2001), and others suggesting poorer performance on immediate, short-delay free-recall and long-delay free-recall (Considine et al., 2011). Furthermore, studies suggest that MDD patients on SSRIs still have more difficulty in recalling words during semantic/story learning tasks than non-depressed adults (Ravnkilde et al., 2002; Vythilingham et al., 2004). Lastly, evidence suggests that verbal memory differs for

old and young depressed adults when compared to nondepressed adults. Specifically, young depressed adults exhibit poorer verbal memory than their similar aged healthy peers, despite intact processing speed, attention and executive functioning (Hermens et al., 2010).

The literature suggests that deficits in visuospatial memory functioning are associated with unmedicated depression. Some studies report that unmedicated patients with MDD perform significantly worse than nondepressed adults in recalling patterns on spatial and recognition tasks and for delayed trials on tasks requiring simultaneous matching and delayed matching to sample stimuli (Porter et al., 2003). Although few studies examine visuospatial memory among psychotropically medicated depressed patients, findings suggest no significant differences between unmedicated and medicated patients with depression on visuospatial memory tests. Both depressed groups have poorer performance on visuospatial memory and recall than healthy adults (Gualtieri, 2006; Langenecker et al., 2005).

Hypothesis 3: With inconsistent findings regarding verbal memory, significant differences in performance on verbal learning memory tasks between medicated patients and healthy comparison were not expected. Although little evidence exists, the limited research on antidepressants lead to the expectation of significantly stronger performance in healthy adults compared to unmedicated patients on verbal memory tasks. Regarding visuospatial memory, it was expected that differences between medicated and unmedicated depressed groups would not be significant; however, medicated and unmedicated patients would perform more poorly than would healthy the healthy comparison group.

Aim 4: Examine working memory among patients with MDD on antidepressant medication compared to unmedicated patients with MDD and a healthy comparison group.

Unmedicated patients with MDD perform significantly more poorly on tasks of working

memory in visual and verbal domains compared to the healthy comparison participants (Den Hartog, 2003; Gohier, 2009; Porter et al., 2003; Ravnikilde et al., 2002). The limited studies examining medication status indicate that both medicated and unmedicated depressed groups had difficulty in some tasks of set-shifting and working memory (e.g., Tower of London), but did not differ from each other (Purcell et al., 1997).

Hypothesis 4: It was expected that both medicated and unmedicated patients with MDD would perform significantly worse than the healthy comparison adults measures of working memory.

Aim 5: Examine executive functioning among patients with MDD on antidepressant medication compared to unmedicated patients and healthy comparison participants.

Studies of the influence of depression on executive functioning have yielded some mixed findings. This inconsistency may be because researchers have interpreted the construct differently, thus including different measurements. The literature, however, suggests that executive abilities such as planning, organizing, set-shifting and cognitive flexibility appear disturbed in patients with depression when compared to healthy adults (Grant et al., 2001, Porter et al., 2003; Wadsworth et al., 2005). Few studies have investigated differences in executive functioning between stable medicated and unmedicated MDD patient groups in comparison to the healthy comparison. Although evidence suggests that patients taking psychotropic medications will experience improvements in cognitive functioning as a whole, the limited research suggests that medicated and unmedicated patients maintain poorer performance than healthy adults on set-shifting tasks, but maintain similar planning abilities as one another (Purcell et al., 1997).

Hypothesis 5: This domain includes tests in which decision-making, planning, and organization are the key features of measures, such as performance on the Wisconsin Card Sort test (Grant &

Berg, 1948). Given prior findings, it was expected that patients with MDD would show worse executive functioning than healthy adults, with unmedicated patients showing the poorest functioning and patients on psychotropic medications demonstrating performance intermediate between the two other groups.

Aim 6: Conduct exploratory and illustrative analyses to examine differences between statistical methodologies to address empirically and/or theoretically meaningful relationships between age and education on neuropsychological function in depression.

Age and education have shown meaningful theoretical and empirical relationships to neuropsychological function; for example, these robust relationships are easily observed in normative data used to interpret the tests (e.g., Heaton, Grant, & Matthews, 1986; Heaton et al., 2003). Moreover, both of these demographic characteristics have been identified as having important theoretical and empirical relationships to neuropsychological function in studies of depression (e.g., Baune et al., 2012; Lam et al., 2013; Morimoto et al., 2012; Wight et al., 2002). A small body of research suggests that depression may have a disproportionate adverse effect with advancing age and low education (Andel, 2007; Compton, 2000; Wight et al., 2002). This issue is especially relevant to studies of depression and medication effects in depression; for example, age is likely confounded with years of illness and years on antidepressant medication, in addition to its robust relationship with general cognitive function. Similarly, given links between education and access to mental healthcare and utilization of mental health services, education is commonly confounded with treatment status and years of treatment. Thus, it is important to assess, if not account for, age and education in studies of neuropsychological function in depression.

Problems of systematically confounded variables are frequently observed in

observational research like the present study (Miller & Chapman, 2001). Experimental design relies on random assignment to groups; only with random assignment can a comparison group legitimately be labeled a "control group" (Tabachnick & Fidell, 2007; Guo & Fraser, 2010). In contrast, research on naturally occurring clinical phenomena, by its nature, often reflects selection bias and shows systematic differences in core characteristics that themselves could explain observed group differences. This problem of a systematic confounding variable is particularly grave when the group difference favors the hypothesis, and the characteristic that is systematically confounded with group status can itself explain the group difference. For instance, if a specific condition, such as depression, is hypothesized to have adverse effects on cognition as compared to another group, and the group with depression is also systematically older than its comparison group, it is not possible to compare the two groups directly. Because statistical attempts to remove or control for systematic confounding variables are viewed by some as difficult if not impossible (See Miller & Chapman, 2001 for review), the presence of such a confound is often considered a fatal flaw in a study. Efforts to understand and deal with this problem would therefore be very beneficial.

Hypothesis 6: As the present study was the first to compare various methods of accounting for highly related variables systematically confounded with neuropsychological performance in a depressed sample, empirically-based hypotheses were difficult to form. However, a conceptual understanding of each method offers insights from which theoretical hypotheses were created. Each method assessed the same phenomena, which provided the expectation that the pattern of results should be similar across the methods; however, different methods yield a range of effect sizes for depression status and antidepressant medications on neuropsychological function related to differences in the rigor, sensitivities, and technical aspects of the methods.

The primary goal of this aim was to compare and discuss the conceptual underpinnings of different statistical methods used to account for systematic covariates, so that a chosen methodology would be consistent with theoretical and logical assumptions required by it. Overall, it was expected that the methods would identify a relatively similar pattern of findings (e.g., domains identified). However, the sensitivity to identify specific measures that yield significant results may differ by methodology. The ability to compare and contrast these measures can offer some greater depth of understanding of sensitivity and strengths and weaknesses for a given approach.

Summary and Purpose

In all, the lack of research within the fields of pharmacology and neuropsychology examining the effects of antidepressant medications in depressed patients on specific cognitive domains such as attention, concentration, inhibition, executive functioning, psychomotor speed, working memory, and verbal and visuospatial memory inhibits our ability to inform patients comprehensively in their decisions to take antidepressant medications, or at the least provide cost-benefit tradeoffs. Accordingly, the current study investigated decrements and improvements in these areas of cognitive functioning among three groups: unmedicated patients with MDD, patients with MDD who were currently taking antidepressant medications for treatment of their symptoms, and nondepressed healthy adults. The main goal of the present study was to provide practitioners and consumers with new and useful information about the effects of antidepressant medications on cognitive functioning. This study also aimed to provide researchers with information to make informed decisions about the appropriate methodologies to use in accounting for covariates that are highly related to dependent variables but not the central point of interest.

CHAPTER 2

METHOD

Participants

Participants included 331 adults (117 men, 214 women): 178 adults with Major Depressive Disorder (89 taking antidepressant medications and 89 unmedicated) and 153 nondepressed healthy adults from research records of internal and externally funded protocols. Tables 3 and 4 present demographic information for the sample and depressed groups, respectively. As seen in Table 3, the participants ranged in age from 18 and 88 years old and ranged in education from 7 to 23 years. Table 4 indicates that, among participants with MDD, age of onset ranged from 3.0 – 60.0 years (M = 41.9, SD = 19.1). Severity of depressive symptoms as assessed by self-report on the Beck Depression Inventory-II (Beck et al., 1961) ranged from 0 - 50; the average endorsement (M = 23.8, SD = 12.9) corresponded to moderate depression. Clinician-rated severity of depressive symptoms as assessed by the Hamilton Depression Rating Scale (Hamilton, 1967) ranged from 0 to 41; the average endorsement (M = 15.6, SD = 8.0) also corresponded to the moderate depression range.

This was an archival study that combined deidentified records of multiple protocols, each of which was conducted and approved according to institutional review board (IRB) guidelines. Appendix B provides a copy of the Wayne State University IRB approval of the present study. Recruitment of MDD participants occurred through the University of Michigan Depression Center, University of Michigan Turner Geriatric Center, the Michigan Clinical Outcomes and Research Engines (MStrides) program, University of Michigan Clinical Studies (UM Engage), as well as community advertisement; recruitment of healthy comparison participants occurred through advertisements in the community and MStrides and UM Engage. Exclusionary criteria included contraindications for MRI, as the funded research project included an imaging

component; presence or history of psychotic symptoms, bipolar disorder, dementia, head injury, schizophrenia; history of ECT, or other medical conditions that are likely to affect cognition (e.g., epilepsy).

Measures

Determination of MDD status and psychiatric screening. All participants were administered the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) to screen out for history of psychiatric illness in the healthy comparison group and to confirm MDD status in depressed participants (First, Spitzer, & Gibbon, 1995). Depression severity was measured with the Hamilton Rating Scale for Depression–Second Edition (HDRS; Hamilton, 1967), Beck Depression Inventory–II (Beck, 1961) and SCID-I severity measures (First, Spitzer, & Gibbon, 1995).

Neuropsychological Tests. All eligible participants were administered a comprehensive battery of neuropsychological measures.

Controlled Oral Word Association Test (Benton, Sivan, Hamsher, Varney, & Spreen, 1994). The Controlled Oral Word Association Test (COWAT) is a word-list generation task that requires participants to produce as many words as possible beginning with a given letter of the within 1-minute trials (e.g., letters C, F, and L). COWA forms CFL and PRW were used, as they have been found to be equivalent in difficulty (Mitrushina, Boone, and D'Elia, 1999). The current study evaluates total valid words generated for the three trials. Successful completion of the COWAT requires phonemic fluency and cognitive initiation.

California Verbal Learning Test – 2nd Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000). The CVLT-II is a verbal list-learning task in which examinees are required to learn a list of 16 words presented verbally over five consecutive trials (List A). The words comprise

four semantic categories, read in a standardized, uncategorized order. Following the fifth trial of List A, participants are presented with a 16-item distracter list to recall immediately (List B). The participant is then asked to recall the original list of words without prompt Free (short-delay free recall, SDFR) and category-cued (short-delay cued recall, SDCR) trials of List A follow the immediate free recall of List B. After a 30-minute delay, List A is again assessed with free recall (long-delay free recall, LDFR) trials. Lastly, a forced-choice recognition trial contains the 16 target items from List A and 32 distracter items. During the recognition trial, the examiner orally presents each of the 48 items and the examinee indicates whether or not the item was included in List A. The current study examines Trial 1 words, which parallels digits forward as an index of simple attention; total words recalled over the five learning trials of List A, as an index of global learning, and LDFR as an index of verbal memory.

Trail Making Tests (Reitan & Wolfson, 1985). The Trail Making Test, parts A and B (TMT-A and TMT-B), is a two-part, timed, paper-and pencil measure with numeric and alpha-numeric sequencing tasks. In TMT-A, participants are instructed to connect circled numbers from 1 to 25 in numerical sequence as quickly and accurately as possible (i.e., 1-2-3). TMT-B requires participants to connect circled numbers and letters in sequence alternating between numbers and letters from 1 to 13 (i.e., 1-A-2-B-3-C). Successful completion of these tasks requires visual searching, psychomotor speed and agility, and attention. Successful completion of TMT-B also requires the ability to shift cognitive set, indicating cognitive flexibility (Spreen & Strauss, 1998). desRosiers and Kavanaugh (1987) developed alternate forms (TMT-C and TMT-D). Alternate-form reliability coefficients between TMT-A and TMT-C were .66 to .79, and .88 to .89 for TMT-B and TMT-D. The present study examines total time in seconds to complete each part of the test.

***Wisconsin Card Sort Test (Berg, 1948; Heaton et al., 1993*).** The Wisconsin Card Sort Test (WCST) requires novel problem-solving, and the abilities to shift and maintain cognitive set. Participants categorize 128 cards by visual characteristics of four key cards (i.e., color, form, and number). The examiner gives feedback to the participant as to whether the card was matched correctly to the standardized characteristic after each card is placed (e.g., "correct" or "incorrect"). The characteristic by which participants are to match the cards changes throughout the task. Successful completion of the WCST requires ability to shift cognitive sets and respond to examiner feedback in order to decipher the changing categorical rule. The current study evaluates perseverative errors.

Digit Span (Wechsler, 1997). The Wechsler Memory Scales- 3rd Edition, Digit Span (WMS-III, Digit Span) task is a two-part verbal measure of attention and working memory. In the first trial, Digits Forward, participants repeat number series of increasing length (beginning with two numbers, maximum nine numbers), immediately following the oral presentation of the series by the examiner. Digits Forward is widely used as an index of simple attention. In the second trial, Digits Backward, participants are directed to repeat numerical strings aloud in reverse order. This task involves both working memory and sequential processing. The present study examined total digits recalled for the forward trial and total digits recalled for the backward trial.

Purdue Pegboard (Tiffin, 1948). The Purdue Pegboard is a widely used timed test that measures visual-motor coordination via gross movement of arms, hands, and fingers in addition to fingertip dexterity. Trials assess differences in dominant and non-dominant hands, as well as bilateral coordinated movements. In the dominant and nondominant trials, participants use one hand to pick up one peg at a time and place it into the holes quickly as possible within 30

seconds, without skipping any holes. In the third trial, the participant completes the same process using both hands. Examinees must place the pegs into the holes simultaneously to receive credit for each peg. The three phases (dominant hand, nondominant hand, and both hands) may be repeated to calculate an average performance over several trials. The current study evaluates the total pegs placed on the dominant-hand.

Michigan Spatial Relation Test (Langenecker et al., 2005). The Michigan Spatial Relation Test (MSRT-10/35) assesses visual learning and memory. The task is an extension of the 7/24 Spatial Recall Test (Rao, Hammeke, & McQuillan, 1984) to a 10/35 on a 5 x 7 grid (Pattern A) in 10-second intervals. After each presentation participants are asked to reproduce the pattern by placing tokens onto a blank grid. Five learning trials are assessed with immediate recall. Following the fifth trial is a single interference trial that presents a distracter pattern for 10 seconds with assessment of immediate recall (Pattern B). The participant must then recall the original design without reviewing the stimulus (short-delay free recall). Long-delay free recall (MSRT-LDFR) is assessed following 20 - minute delay. Lastly, is a copy trial, in which the examinee is asked to reproduce the original design using a model. The current study will evaluate the global spatial learning score, as reflected in total correct over Trials 1 – 5 (MSRT-Total) and the long-delay free recall (MSRT-LDFR), an index of visuospatial memory.

Parametric Go/No-Go Task (Langenecker et al., 2005). The Parametric Go/No-Go (PGNG) Task is a computer-administered test of sustained, selective, and divided attention and inhibitory control. Participants are presented with a string of letters. In the “Go” task, examinees are directed to respond only to a prescribed set of target letters (e.g., x, y, and z) and not respond to all other stimuli. In the “No-Go” version, participants are directed to respond to one of three target letters only if they had just responded to either of the other two target letters. This task

requires participants to track the last target to which they responded and inhibit responding to a target letter on successive presentations. Successful completion of the "Go" portion of the test requires sustained attention and set maintenance through percent correct target trials for all three levels. The present study will evaluate participants' ability to complete the "No-Go" task requirements of cognitive flexibility by examining set-shifting, complex processing speed, and inhibitory control. Set-shifting will be measured through percent correct target trials on level 2 (Go Accuracy). Complex processing speed will be measured through based on response time skills exercised in level 1 (Go Reaction Time). Inhibitory control will be measured through percent correct on inhibitory trials for levels 2 and 3 (No-Go Accuracy).

Procedure

Participants completed informed consent procedures per Institutional Review Board guidelines. Potential participants were contacted by research assistants via phone and screened briefly for basic inclusion criteria. If phone-screening criteria were met, individuals were scheduled for in-person screening, in which they were administered a series of psychological and health screening measures by research assistants and psychologists. After completing the clinical interview, eligible participants were administered a battery of neuropsychological measures including paper-and-pencil and computer testing. Participants were paid for participation.

Statistical Analyses

Data for all test indices were converted to a common metric (z score), unadjusted for demographic characteristics, using normative expectations as specified in the test manuals. Tests with scoring rubrics that utilized demographic adjustments were set for all participants to correspond to reference group normative expectations (i.e., adult men age 25-44 years, with 12 years of education). In this manner, the effects of demographics can be assessed independently,

the indices can be directly compared, and a neuropsychological composite score reflecting overall functioning can be calculated using the mean z scores of the individual indices. Table 3 presents the indices for each test linked to the cognitive domains.

Descriptive statistics were conducted for the overall sample and diagnostic groups separately. Neuropsychological test data were examined by domain, using individual and domain composite measures, with a series of analysis of variance (ANOVA) followed by simple contrasts.

As age and education are often highly related to neuropsychological performance in general (Heaton, Grant, & Matthews, 1986; Heaton et al., 2003), and for patients with depression (e.g., Baune et al., 2012; Lam et al., 2013; Morimoto et al., 2012; Wight et al., 2002), the current study conducted exploratory analyses using several available statistical methods to address the relationship between age and education and neuropsychological functioning among unmedicated participants with MDD (uMDD), medicated participants with MDD (mMDD), and healthy comparison (HC) groups. These methods included: analysis of covariance (ANCOVA), matched-sample analysis, regression-residual method, and propensity scores analyses (PSA). A brief review of practical information about each method is presented next.

Analysis of Covariance Method. Analysis of Covariance (ANCOVA) is a direct extension of ANOVA, in which main effects and interactions of a model are assessed after the dependent variable has been adjusted in light of its relationship with covariates. Although it is often used to "control" for group differences on variables considered extraneous or nuisance in a research design, Miller and Chapman (2001) describe that the ANCOVA method was developed to increase power to test an independent variable by reducing within-group variance: When covariate(s) account for unexplained variance in a model, the error term is reduced. The core

assumptions of ANCOVA cited throughout the literature include conditional normality, homoscedasticity, independence of observations, linearity of regression, covariates are perfectly reliable and with homogeneous slopes, and equivalent covariate values between or among groups (Tabachnick & Fidell, 2007; Fleiss & Tanur, 1973). Thus, ANCOVA is an appropriate method when a covariate is related to the outcome but is randomly distributed across the group (i.e., the groups are equivalent on the covariate). Although controversial due to the frequent violation of its core assumptions (Fleiss & Tanur, 1973; Lord, 1967), ANCOVA is commonly used to address systematic confounds. The current study conducted the ANCOVA method for illustrative purposes to allow for the comparison of ANCOVA results with other methodologies used to manage systematic covariates.

Matched-samples Method. Presented with a design in which controlling or accounting for a characteristic is desired, many researchers opt to match their groups on such characteristic(s). There are several methods to match groups, including univariate matching and varied multivariate matching techniques. In any case, participants from separate groups are matched on the variable that is believed to be correlated with the dependent variable (Kirk, 2012). It is important to note that formal matched-samples method is not the same as "equivalent samples;" the latter simply means that the group differences on the characteristics are not statistically significant, which can reflect a combination of power associated with sample size and the magnitude of the difference. Depending on the research question of interest, researchers may employ one of several matching strategies; some of these techniques include nearest available metric matching, caliper matching, minimum distance metric matching, minimum distance circular matching, or discriminant matching (Cochran & Rubin, 1973). The most commonly used of these methods is minimum distance metric matching, in which participants

from separate groups are matched on all confounding variables according to a fixed rule; this is the matching method used for the current study, in which participants were paired to individuals in a comparison group using matching rules for age (± 5 years) and education (± 3 years).

Regression-residuals "Regression Line" Method. The Regression-residual method fits a regression line between the covariate(s) and the dependent variable using a criterion group (e.g., healthy comparison; Fleiss & Tanur, 1973). Predicted scores for other groups are generated using the formula weights from the criterion group; the predicted scores are then compared to actual scores to produce residuals. These residuals represent the effect of the dependent variable beyond that attributable to the effect of the covariate observed among the criterion sample (e.g., the differences on a neuropsychological index in excess of that due to age and education). Group contrasts (e.g., ANOVA or t test) can be conducted to examine the residuals.

Propensity Score Analysis Method. Propensity Score Analysis (PSA) estimates the probability that each participant is assigned to all groups by equating groups on identified covariates (Guo & Fraser, 2010). As such, PSA can be used to correct for selection bias in observational studies. Data were evaluated in pairwise contrasts using the Nearest Neighbor Matching for Average Treatment Effects (nnmatch). Nnmatch estimates the average treatment effect on the dependent variables of interest by matching cases in the treatment group to the healthy comparison group based on covariates of interest. A unique feature of this method is that individual observations in the healthy comparison group can be used as a match more than once in a single matching analysis (i.e., "matching with replacement;" Abadie et al., 2004). Another unique and desirable feature of nnmatch is that it allows for use of more than one match per case (i.e., "oversampling"). Thus, a single case in the treatment group could be matched to multiple nearest neighbor healthy comparison participants. Researchers can identify the number of

matches to be made per observation; the current study specified four matches, as recommended by Guo and Fraser (2010). The *Mahalanobis metric* was used as the weighting matrix to specify the relative weight to place on each variable in defining the nearest neighbor match. Essentially, the Mahalanobis metric assesses the distance between data points. The *bias-corrected estimator* was chosen for a regression-adjustment using the original matching variables, which adjusts the matches for the differences on the covariate using least squares on the matched observations (Abadie et al., 2004). A *robust* variance estimator was selected to allow for heteroscedasticity. The *average treatment effect* (ATE) was chosen to determine the average treatment effect for the population rather than the *average treatment effect for the treated* (ATT) group. Unlike the ATT that is estimated by averaging the within-pair differences to evaluate whether the treatment was beneficial for those who received the intervention, the ATE, examines for treatment effects by comparing groups who did and did not receive the treatment. This matching procedure creates a counterfactual outcome (i.e., a simulation of what would be the case if the matched conditions were true) to evaluate the overall effectiveness of the treatment implemented. Lastly, to maximize generalizability, the analyses specified estimation of the *population* variance rather than the sample variance.

CHAPTER 3

RESULTS

Descriptive statistics for demographic characteristics and neuropsychological tests descriptive statistics are presented in Table 3 for the three groups: unmedicated participants with MDD (uMDD), medicated participants with MDD (mMDD), and healthy comparison (HC). To facilitate comparisons across indices, all neuropsychological tests are reported in Z scores. The three groups differed on age, $F(2, 328) = 6.04$, $p = .003$; participants in the mMDD group were older than participants in the HC and uMDD groups, which did not differ. Education was not significantly different among the groups, $F(2,328) = 0.43$, $p = .651$.

Descriptive statistics for depression-related characteristics are presented in Table 4 for unmedicated and medicated depressed groups, including percentages of the mMDD group taking antidepressants from each medication class. Groups were equivalent for age of onset, $t(116) = 0.58$, $p = .563$. The effectiveness of antidepressants on depressive symptoms was assessed via the BDI-II and HDRS. Using the interpretive guidelines recommended by the test author (Beck, 1996), on average, both groups reported moderately severe symptoms of depression on the BDI-II. Similarly, using cutpoints recommended for the HDRS (Hamilton, 1960), clinicians rated both groups as having moderately severe depression. However, the uMDD group showed greater depression severity than did the mMDD group, on both the self-reported BDI-II, $t(163) = 3.68$, $p < .001$, Cohen's $d = 0.61$, and the clinician-rated HDRS, $t(167) = 4.00$, $p < .001$, Cohen's $d = 0.57$.

Group Contrasts Using Analysis of Variance

Analyses of Variance (ANOVA) were conducted to compare the three groups on all neuropsychological indices and cognitive domain composite scores. As seen in Table 6, the

ANOVAs indicated that performance among the groups was significantly different for measures of processing speed, attention, and some aspects of the learning and memory domain. However, the groups were generally equivalent on measures of working memory and executive functioning domains.

Post hoc analyses using simple contrasts indicated that the significant effects in *processing speed* abilities were driven by worse performance of the mMDD group as compared to the HC and uMDD groups. Effect sizes were interpreted according to guidelines presented by Cohen (1988), in which d = 0.20 reflects a small effect, d =0.50 reflects a medium effect, and $d \geq 0.80$ is large. As shown in Table 6, differences in the processing speed abilities revealed generally medium effect sizes (d = .32 – .57, median = .43) for mMDD participants compared to HC and uMDD groups. The most pronounced difference within the processing speed domain was seen in the uMDD and mMDD contrast effect size for Purdue Pegboard. The HC and uMDD groups were statistically equivalent in performance on all processing speed indices.

Post hoc analyses for the domain of *attention* revealed a similar pattern of significant effects driven by poorer performance of the mMDD group compared to HC and uMDD, with generally small to medium effect sizes (d = 0.28 – 0.51, median = 0.41). The most notable differences in attention abilities were seen in the uMDD and mMDD contrast. Lastly, significant differences were observed for the *learning-memory composite* and the verbal learning measure. Post hoc analyses for these measures of learning and memory again indicated significant effects driven by worse performance of the mMDD group compared to HC and uMDD groups. Differences in performance yielded small to medium effect sizes (d = 0.25 – 0.56, median = 0.36), with the most pronounced difference seen in the uMDD and mMDD contrast for the learning and memory composite. The HC and uMDD groups were equivalent in performance on

all attention and learning-memory indices.

Group Contrasts Accounting for Age and Education

ANOVAs provided the most common perspective of the effects of depression and medication status on neuropsychological performance; however, the groups differed significantly on age, with an older mMDD group than both the HC and uMDD groups. Furthermore, consistent with most samples, age was significantly correlated with the vast majority of cognitive performance measures, thereby identifying it as a confounding variable to group differences in neuropsychological performance (Table 7). The relationship between age and cognitive performance was especially high for psychomotor functioning, and verbal and visual learning and memory. In other words, it is possible that the group differences observed on the ANOVAs were driven, at least in part, by age and not group membership. Education was not significantly different across the groups and showed few significant correlations to neuropsychological performance in the total sample, but it showed small and significant correlations with a variety of the indices across the three separate groups.

For demonstrative and educational purposes, the following sections provide results from various methods used to address covariate analyses for age and education in group comparisons on the neuropsychological indices, organized from the most to least commonly used methods in the current literature: analysis of covariance (ANCOVA), matched-sample analysis, regression-residual method, and propensity scores. Consideration of advantages, disadvantages, and appropriateness of each method will be comprehensively addressed in the discussion. *The eager reader may wish to skip to Table 12, which compares results from each statistical methodology.*

Analysis of Covariance (ANCOVA). The use of ANCOVA would not normally be recommended for the present study due to the violation of core ANCOVA assumptions;

specifically, the independent variable, group membership, was related to the covariate of age, as the medicated patients with depression were significantly older than the other two groups. However, ANCOVA analyses were conducted on each of the neuropsychological indices using age and education as covariates for illustrative purposes. As shown in Table 8, the ANCOVA results are similar to those observed from unadjusted ANOVA, with significant differences seen in performance for *processing speed* and *attention* measures. Effect sizes were attenuated due to accounting for contributing effects of age and education. Differences in processing speed revealed medium effect sizes (d = 0.31 – 0.41) for mMDD compared to HC and uMDD groups. The largest effect size within the processing speed domain was seen in the HC and mMDD contrast. Post hoc analyses for attention revealed a similar pattern of significant effects driven by weaker performance of the mMDD group compared to HC and uMDD groups. Effect sizes were moderate (d = 0.32 – 0.44), with the most pronounced difference in attention abilities seen in the uMDD and mMDD contrast on Digit Span Forward. Due to the attenuation of group differences after accounting for age and education in ANCOVA, differences in learning and memory performance that were observed in the unadjusted ANOVAs were no longer significant. The groups remained equivalent on indices of working memory and executive functions, similar to the results of the ANOVA.

Matched-samples Analyses. Table 9a depicts the descriptive statistics for the Matched-samples groups on demographic characteristics and neuropsychological test performance measures. As expected, the sample size became smaller than for the alternative methods due to tailoring of groups to match participants according to the age and education rules. Despite the decrease in power associated with reduced sample size, the pattern of results was largely consistent with those observed for ANCOVA, with significant differences revealed in measures

of *processing speed* and *attention,* and statistically equivalent performances observed across the groups for *working memory* and *executive functioning* measures (Table 9b). With the exception of the Learning-Memory Composite, measures within the domain of *learning and memory* were equivalent across groups. Effect sizes from the Matched-samples t test analyses were attenuated as compared to ANOVA for the Learning-Memory Composite and a measure of attention (Digit Span Forward), but were strengthened for the Processing Speed Composite and Purdue Pegboard measure. Significant differences on the Processing Speed Composite revealed a medium effect size (d = 0.55), reflecting inferior performance of mMDD compared to HC. Small to medium effect sizes (d = 0.44 – 0.62) for mMDD compared to HC and uMDD groups were present on the Purdue Pegboard task. Although still yielding significantly different performance, t tests revealed attenuated effects on Digit Span Forward (d = .48) and Learning-Memory Composite (d = 0.39) from ANOVA, driven by weaker performance of the mMDD group compared to uMDD group and HC group, respectively.

Regression-residual Method. The Regression-residual method employed in the present study used the HC group as the criterion model of the relationship of the covariates age and education to the neuropsychological performance indices. Residual scores were generated for the uMDD and mMDD groups using the formula weights from the HC group to yield predicted scores that were then subtracted from actual scores (Fleiss & Tanur, 1973). Results for the Regression-residuals method are reported in Table 10, and revealed a similar pattern of findings to the Matched-samples methodology, with attenuated effect sizes compared to ANOVA results. The Regression-residual results had relatively equivalent effect sizes compared to ANCOVA and Matched-samples methodologies. Analyses also revealed equivalent performance across groups on measures of working memory and executive functions, and significant differences between

the groups on tasks of *processing speed* and *attention,* similar to results of the ANCOVA and Matched-samples methodologies. Regression-residual analyses yielded varied performance on learning and memory tasks.

Specifically, differences in the processing speed abilities were driven by worse performance for the mMDD group compared to HC and mMDD groups, with small effect sizes (d = 0.30 – 0.39). The most pronounced difference within the processing speed domain was seen in the HC and mMDD contrast for the Processing Speed Composite. Post hoc analyses within the attention domain revealed a similar pattern of significant effects driven by weaker performance of the mMDD group compared to HC and uMDD. Effect sizes were moderate (d = .34 – .39), with the most pronounced difference in attention abilities again seen in the uMDD and mMDD contrast on Digit Span Forward, with weaker mMDD performance. Lastly, the differences in performance on the Learning-Memory Composite was also driven by underperformance of mMDD participants compared to HC and uMDD, with small effect sizes (d = 0.34 – 0.35).

Propensity Score Method. Data for the Propensity Score method were evaluated in pairwise contrasts using the Nearest Neighbor Matching (nnmatch) for Average Treatment Effects (ATE). Results of the Propensity Score Matching Estimator analyses are presented in Table 11. Similar to previous methods, results from PSA showed significant differences in performance for uMDD compared to mMDD on *processing speed* and *attention*, and for HC versus mMDD for the Processing Speed Composite. Results for the *learning and memory* domain revealed significant differences in performance for the HC versus mMDD and uMDD versus mMDD groups on the Learning-Memory Composite. All groups had equivalent performances for *working memory* and *executive functioning* domains.

Differences in group performance on *processing speed abilities* were again indicative of

worse performance for the mMDD group compared to HC and uMDD groups, with effect sizes ranging from $d = 0.34 – 0.35$; the most prominent difference within the processing speed domain was for the Processing Speed Composite. The simple contrasts on measures of attention also showed worse performance of mMDD compared to HC and uMDD groups. Effect sizes varied from small to medium ($d = 0.22 – 0.58$), with the most pronounced difference in attention abilities again seen between the uMDD and mMDD groups on Digit Span Forward.

Summary of Group Comparisons

In sum, all the analyses yielded significant differences between HC versus mMDD groups and uMDD versus mMDD groups for *processing speed* and *attention* domains with medium effect sizes; analyses also revealed similar patterns for the *learning and memory* domain, but only for the composite score. All methods yielded statistically equivalent performances among the groups for *working memory* and *executive functioning*. The HC and uMDD groups performed equivalently for all domains regardless of the analysis type (Table 12).

In comparing the methods of covariate adjustment, the pattern of *significant* results across the methods used to account for age and education indicates that the ANOVA method liberally identified group differences and produced larger effect sizes compared to all age- and education- adjusted methods. The PSA and Matched-samples analyses typically produced the most conservative results in terms of frequency in yielding statistically significant differences.

With regard to effect sizes, the adjustment methods yielded generally similar results; however, examination of patterns across all results (independent of significance level) revealed a reduction in effect size for methods that accounted for age and education compared to the ANOVA results. The most notably attenuated effects, compared to unadjusted ANOVAs, were observed in the PSA method for the HC versus uMDD and HC versus mMDD contrasts and

Matched-samples method for the uMDD versus mMDD contrast. For results with significant group differences, the various methods were generally consistent in their pattern and range of effect sizes, with methods that accounted for covariates finding small to medium effects (*d* = 0.22 – 0.62). For HC-mMDD in *processing speed*, unadjusted d (i.e., ANOVA) = 0.5, whereas the average d across the methods adjusting for age and education was 0.4; for attention, unadjusted d = 0.4, and average adjusted d = 0.3; for learning-memory, unadjusted d = 0.5, average adjusted d = 0.4. For uMDD-mMDD comparisons in *processing speed*, unadjusted d = -0.4 (i.e., uMDD outperforming mMDD), whereas the average d across the methods adjusting for age and education was -0.2; for attention, unadjusted d = -0.5, and average adjusted d = -0.3; for learning-memory, unadjusted d = -0.6, average adjusted d = -0.4.

Occasions in which results diverged by method were also examined. Disparate results from the overall consensus of significant results occurred under a number of conditions: the Matched-samples method identified fewer significant differences than the other methods (likely due to reduced sample size or an idiosyncratic sampling of selected participants), the PSA method identified fewer significant group differences for the HC versus mMDD contrast, and all age- and education- adjusted methods identified fewer group differences compared to ANOVAs.

CHAPTER 4

DISCUSSION

The present study found that adults with MDD who were taking antidepressant medications generally performed more poorly on tasks of processing speed, attention, and the learning and memory composite compared to unmedicated adults with MDD and nondepressed healthy adults. This finding suggests that, although treatment with antidepressants was associated with substantial amelioration of affective symptoms of depression, patients on the medications may experience adverse cognitive complications distinct from depression. In fact, despite experiencing moderate to severe depressive symptoms, patients with MDD not taking antidepressant medications performed similarly to nondepressed healthy adults in several domains of neuropsychological functioning. Interestingly, the cognitive processes most disrupted by antidepressant medication included lower-level, fundamental processes. These findings diverge from prior studies, which identified differences in higher-order functioning (e.g., working memory, executive functioning, etc.) between healthy and depressed adults (Purcell et al., 1997; Gualtieri et al., 2006).

Although the literature has long demonstrated the need to consider age and education when examining neuropsychological performance in healthy and neurologically impaired adults (Heaton, Grant, & Matthews, 1986; & Heaton et al., 2003), the current study highlights the relevance of this issue when examining patients with depression. The importance of considering these characteristics is evident by the divergent findings from the unadjusted (i.e., simple ANOVA) versus age- and education- adjusted methods of comparing patients with and without MDD. The present study also highlights the importance of choosing the appropriate methodology with which to adjust for covariates, as the methods vary in the magnitude of effects, methodological strengths and weaknesses, and theoretical rationale. Lastly, and perhaps

of the utmost importance, is the current study's review of the appropriateness of using statistical methods to make adjustments and "control" for covariates; improperly using any of the "adjustment" methods when statistical assumptions are violated can misrepresent findings, often more liberally to the benefit of the research question.

Cognitive Impairment Associated with Depression and Antidepressant Medications

Conclusions regarding processing speed and attention performance are noteworthy, as findings from the present study are inconsistent with those of prior studies. Prior studies on processing speed indicate equivalent performance between medicated patients with MDD and healthy adults, with relative deficits in performance observed among unmedicated patients with MDD (Tsourtos et al., 2002; Gualtieri et al., 2006). However, limited findings suggest that MDD patients who are taking antidepressants may have psychomotor difficulties starting within the first month of antidepressant use (Amin et al., 1980). The literature on attention performance has reported superior ability among healthy adults as compared to patients with MDD, and equivalent performance among patients with MDD regardless of medication status (Gualtieri et al., 2006). The present study, however, found that individuals with MDD taking antidepressants performed worse than unmedicated patients and healthy adults in processing speed and attention, with equivalent performance between the latter two groups. One explanation for the incompatible findings with those of prior studies could be due to the varied effects of different antidepressant classes, as previous research indicates that decrements in psychomotor functioning occur more among patients with MDD taking TCAs than among those taking SSRIs (Elliot, 1998; Wadsworth et al., 2005). However, antidepressant subtype does not likely drive group differences in the present study because fewer than 6% of participants taking medications included TCA or MAOIs in the regimen; the vast majority were prescribed SSRI and SNRI

medications individually or in combination. Another possibility is that medications other than antidepressants prescribed for these participants were different in kind, quantity, or in combined effects for participants taking antidepressants as compared to those who were not. Patients requiring combinations of medication may be more intractable to treatment, and it would be difficult to tease apart the effects of multiple drugs and the psychiatric disturbance. Lastly, it is possible that the prior studies with which these findings clash were limited and flawed; they are few in number and reported on small samples of patients with depression (Tsourtos et al., 2002; Gualtieri et al., 2006).

Findings regarding the effects of MDD status and antidepressant status on verbal and visual learning and memory were varied. The diverse outcomes depended on the measure, modality (i.e., visual or verbal) and analysis method employed. Inconsistency of findings observed in the present study within the learning and memory domain appear to parallel the variations seen in the existing literature. In general, the understanding of learning and memory functioning from the limited research available suggests that healthy adults and unmedicated adults with MDD individuals perform equivalently (Gaultieri et al., 2005), with some studies suggesting poorer performance among medicated adults with MDD compared to healthy adults (Hermens et al., 2010; Sweeney et al., 2000). Findings did not support the hypothesis predicting stronger learning and memory performance in healthy adults and adults with MDD on antidepressants compared to unmedicated adults with MDD; in the present study, the medicated MDD group performed worse than did the unmedicated MDD and healthy comparison groups on verbal learning. In contrast to the hypothesis, equivalent performances were observed across the three groups on all other indices of learning and memory.

The findings for the cognitive domains of working memory and executive functioning

were also inconsistent with the hypotheses. Although these predictions were made from the insubstantial literature available on the topic, previous studies suggested that individuals with MDD would underperform compared to healthy adults on tasks of visual working memory (Purcell et al., 1997; Porter et al., 2003) and set-shifting components of executive functioning (Grant et al., 2001; Porter et al., 2003) and perform equivalently for executive functioning tasks of planning, verbal fluency, and cognitive flexibility (Purcell et al., 1997; Gualtieri et al., 2006; Porter et al., 2003) and verbal working memory (Gorenstein et al., 2006). However, both MDD groups in the present study performed equivalent to healthy adults on all indices of working memory and executive functioning. In addition to the potential explanations discussed for findings on the other cognitive domains, the contrasting findings in the literature and present study may result from the use of different measures to examine working memory and executive functioning domains, as these constructs are fairly complex and often interpreted differently by research teams.

Comparing Methods to Account for Group Differences on a Covariate: Strengths, Weaknesses, and Appropriate Uses of Adjustment Methodologies

This section will explore the strengths, weakness, and important aspects to consider when choosing a method to address systematic covariates.

Analysis of Covariance to Account for Group Differences on a Covariate. Analysis of covariance (ANCOVA) is an appropriate method when a covariate is related to the outcome but is randomly distributed across group (i.e., the groups are equivalent on the covariate). The ANCOVA approach offers the advantage of reducing error variance in models associated with extraneous characteristics when evaluating the relationship of group status to the dependent variable (Miller & Chapman, 2001 for review). However, researchers often fail to ensure that all

core assumptions of ANCOVA are met before proceeding with the analyses. Ironically, violation of the criterion that groups are equivalent on the covariate values between or among groups is frequently the *reason* that researchers adopt ANCOVA: Very often in observational research designs, groups differ on an important characteristic that is related to the outcome and could itself drive group differences on the outcome. Researchers wanting to "account" for the group difference on the characteristic use ANCOVA; however, this is not a valid use of ANCOVA because the covariate is not independent or distributed independently with respect to the treatment effect (see Miller & Chapman, 2001 for review). For instance, one cannot statistically remove the effect of anxiety from depression if the two phenomena are overlapping constructs because to do so would yield a distorted remnant of the construct of depression, much like removing all water from soup would yield a dehydrated remnant that lacks the essential character of soup (Miller & Chapman, 2001). In the same way, removing age or education from depression-medication status in the current study may obstruct illuminating information about characteristics of the groups by inadvertently removing their unique features. Lastly, the ANCOVA method is viewed in the technical literature as inappropriate unless the groups were determined by random assignment (Miller & Chapman, 2001).

Matched Sample to Account for Group Differences on a Covariate. The Matched-samples method works to directly address differences on an independent variable that are related to the outcome between groups. Although effective in eliminating significant differences on the covariate, the Matched-samples method often works at the cost of losing power associated with a reduced sample size, because not all participants will be matched. As demonstrated in the current study, the loss of sample size and power can be considerable and is idiosyncratic to the specific sample. Another drawback to the Matched-samples method is that it can be labor intensive to

identify the optimal set of cases that maximizes sample size, while keeping the magnitude of difference on the matched variable ecologically valid (i.e., not exceeding a meaningful difference on the characteristic). A third disadvantage of using the Matched-samples method is that the nature of the participants included in the sample may limit the ecological validity because many of the differences on the neutralized (matched) variable exist as part of the phenomenon. For example, in the present sample age of MDD onset is understandably related to current age, but it is also related to years of illness and treatment; thus, adjusting for age also removes effects associated with years of illness and years taking antidepressant medications, which might have cumulative adverse effects on cognition. Therefore, we have no way of knowing the extent to which deletions of unpaired cases made during the matching process may selectively limit the generalizability of the findings from the chosen portion of the sample.

Matching participants at the point of recruitment might be a better alternative, provided that no person from the smallest group to be recruited is turned away. The unmedicated and medicated depressed groups tend to be smaller and more difficulty to recruit than the healthy comparison group in depression research. Therefore, healthy adult participants would be selectively matched to the MDD groups at the point of recruitment to ensure a tight match between groups. As the present study was a pooling of many small studies, where cognitive testing was not the primary dependent variable, and medication status was not the primary recruitment criterion for MDD participants, having disproportionate ages in the mMDD groups could not be matched apriori.

Regression-residuals Method to Account for Group Differences on a Covariate. Regression-residual analysis is an appropriate method for analyses when between-group comparisons are required (Miller & Chapman, 2001). This method allows for direct comparison

of performance for several groups to the criterion group. According to Fleiss and Tanur (1973), Regression-residual analyses are ideally conducted when the criterion group is a random sample of the population of interest. Yet, most non-experimental, observational research does not have this luxury. Researchers have therefore established that Regression-residual analyses can be used appropriately if the criterion group has sufficient variability in the mean responses (Fleiss & Tanur, 1973). Another weakness to the Regression-residual method is that it may have a procedural artifact that the makes the method more vulnerable to random error. By definition, the criterion group is a perfect fit to the line and all other groups deviate from it. Random error in the fit of the criterion-group regression line can therefore produce false or exaggerated differences in the fit of the regression line for predicted results made for other groups (Miller & Chapman, 2001). In addition, non-linearity in the regression line may result in skewed variances from the regression line, resulting in an overly conservative estimate process.

Propensity Score Analysis to Account for Group Differences on a Covariate. The Propensity Score Analysis (PSA) is a method that is gaining momentum in the field of psychology, as it can handle heteroscedasticity and allows researchers to balance data when treatment assignment and imbedded demographic characteristics of treatment groups cannot be ignored in nonrandomized studies (Guo & Fraser, 2010). The matching estimators PSA can also be used to estimate treatment effects of samples and populations, as it can examine treatment effects of the treated group and/or compare groups on the effects of an intervention in the treated group to a group that did not receive the treatment. Another benefit of PSA, and the Nearest Neighbor (Nnmatch) procedure specifically, is that it includes the option to match with replacement, which allows individual values in the criterion group to serve as a match multiple times in a single matching analysis. When treatment and comparison groups differ greatly,

multiple-match comparison seems particularly advantageous. This option typically reduces bias because the average quality of the match improves; on the other hand, it increases variance in the estimator as compared to methods employing matching without replacement because it reduces the number of excluded cases used to create the counterfactual outcome (Smith & Todd, 2005).

Like any methodology, PSA has its disadvantages as well: For one, the quality of matching continuous covariates in PSA is limited by the quality of the available criterion group. Secondly, although PSA has the capability to examine the quality of match, the process is extensive and requires further expertise. The limited exposure of PSA in the fields of psychology and neuropsychology also makes findings of PSA difficult to communicate quickly and effectively.

Comparing Methods of Adjusting for Covariates. This study provides a sample of comparisons for the methodologies. In terms of *significance tests*, the PSA and matched-samples methods tended to yield the most conservative outcomes; this is an expected pattern with the matched-samples method due to diminished power from reduced sample size, but it likely reflects a stable characteristic of the PSA method. Because PSA sampled four cases as comparisons to each treatment case, the method is inherently less reactive to idiosyncratic characteristics of individual case matches and enhances stability of estimates. PSA is essentially a multidimensional and dynamic extension of the matched-samples method. Matched-samples method using minimum distance metric matching is effectively a unidimensional version of PSA, with the drawbacks of using one only match per case and consequently lowering power due to unmatched cases. As such, it would be more prone to random error than PSA.

In terms of *effect size estimates*, across a single performance index the effect sizes for the different statistical methods showed marked range, sometimes varying nearly half a standard

deviation; for example, the comparison of medicated MDD with healthy adults on learning-memory composite ranged from an inconsequential effect using PSA (d = .14) to a medium-large effect using matched-sample (d = .62). Over the entire set of comparisons, however, the average effects yielded by the methods were generally very similar. The matched-sample method was the most idiosyncratic, after ANOVA, tallying the most estimates as the largest effect and also the most estimates as the smallest effect. PSA tended to yield relatively conservative estimates overall but also did so in a narrower range as compared to the other methods, and it did not yield the smallest estimates most frequently.

Misusing ANCOVA is still wrong. Of note, the observation that ANCOVA yielded generally similar results to those observed by the other methods does not obviate the fact that the technique is theoretically incorrect under these circumstances (i.e., a covariate confounded with group status). In this instance, sample size was large, variance was equivalent in age, and mean and variance were equivalent in education. Were there to be more notable covariance differences across groups, one could expect ANCOVA to perform less well, and with more error. Further, with a smaller sample size and less statistical power than present in the current study, the methods may have yielded more a divergent than consistent pattern of findings. The difference in age between the healthy comparison adults and medicated patients with MDD was d = .33, slightly smaller than the effect of the healthy comparison group compared to the medicated patients with MDD on processing speed and attention composites. With smaller sample sizes, and larger age differences, the ANCOVA method cannot actually result in an overly conservative result.

Limitations and Future Research

Despite addressing difficult, yet real, issues in conducting research of neuropsychological

performance in depressed groups, the present study had several limitations. Firstly, the current study was observational and was restricted by its non-randomization to groups. The participants in the medicated depressed group likely represent more severely depressed individuals who were previously less responsive to treatment than the unmedicated group of individuals, which may reflect a real and meaningful sampling bias. Secondly, because the data were archival and compiled from several research projects, detailed medication information for all participants (e.g., dosage, recent changes in medication, time of day medication was taken relative to the evaluation, years on the medication, other medications in the regimen, etc.) was not collected and therefore could not be empirically considered as a possible influence on performance. Furthermore, participants were not recruited on the basis of antidepressant use or antidepressant class, therefore making it challenging to attain sufficient power to examine effects of medication class on performance. Another limitation of the present study was the high level of education of the sample, with a limited range of education. The participants also had good access to mental healthcare and were screened out for a recent history of substance abuse and dependence, which may not be representative of the general community of patients with depression. These characteristics potentially limit the generalizability of the findings. Lastly, because this was an illustrative study, numerous kinds of analyses were conducted to evaluate how to manage systematic confounds best, which inflates the probability of Type I error. It is important to note, however, that the pattern of findings across adjusted analyses was generally consistent.

Future research should examine the effects of antidepressant medication on cognition separate from the effects of depressive prospectively, as many of the limitations (e.g., collecting medication information) can be addressed during the recruitment and data collection process. Studies should include participants with MDD who represent a broad range of demographic

characteristics (e.g., education, race, etc.). In addition to recruiting participants with similar age and education, researchers may benefit from matching depressed groups by depression severity and years of medication treatment (although this may limit the sample size) to allow for a cleaner evaluation of the research question.

Conclusions

The findings of this study provide some initial support that antidepressant medications affect several areas of cognition, including processing speed, attention, and some areas of learning and memory. With regard to domain-specific hypotheses, the findings are generally not consistent with the existing literature. This deviance may be due to sample-specific characteristics (e.g., highly educated participants, length and types of treatment, selection biases inherent in medication status, etc.), as well as the small samples included in previous research studies on the topic. The present study also offers convincing evidence for the importance of appropriately attending to age and education, as it relates to neuropsychological functioning among individuals with major depressive disorder.

The present study is one of few in the literature to evaluate differences in cognitive functioning associated with depression status and medication status separately and simultaneously, comparing unmedicated adults with MDD to those taking antidepressant medications and to nondepressed healthy adults. The general literature on effectiveness of antidepressant medications suggests that medicated patients experience benefit in treatment for reduction of symptoms; however, a growing literature indicates that individuals with different subtypes and severity of depression have substantially different profiles of responsiveness to medication (Kirsch et al., 2008). It will be important to continue examining the importance of depression severity and depression subtypes on cognitive functioning. Findings indicate that,

although patients with MDD who take antidepressant medications experience improvement in their emotional symptoms, the side effects of such medications may yield adverse effects on attention and processing speed. It is important to pursue research on the ecological cost-benefit tradeoff of antidepressants in terms of the positive effects on mood and the detrimental effects on cognition. Furthermore, it is important for practitioners to communicate potential adverse cognitive effects, as they may disrupt job functioning and potentially increase risk in complex psychomotor activities such as driving. It may be the case that slowed processing speed is a bona fide reason to see educational and occupational accommodations, such as extra time to meet task requirements and deadlines. The present study highlights that antidepressant treatment is not without meaningful adverse consequence and therefore should not be overused or prescribed by default without careful consideration by providers and consumers.

APPENDIX A

Table 1. *Comparative findings of unmedicated patients with Major Depressive Disorder (uMDD) and Healthy Comparison (HC) participants organized by cognitive domain*

Domain	*Author*	*Year*	*uMDD (N)*	*HC (N)*	*Effects of Interest*
Psychomotor Functioning					
	Bulshman et al.	2006	18	29	HC > uMDD RT and number of crashes on driving simulation
	Porter et al.	2003	44	44	HC = uMDD DSST
	Grant et al.	2001	123	36	HC = uMDD TMT-A, CPT verbal and visual discriminative ability
	Gualtieri et al.	2006	38	69	HC = uMDD finger-tapping; HC > MDD CPT RT, DSST
Attention, Inhibition, and Concentration					
	Porter et al.	2003	44	44	HC = uMDD verbal fluency; HC > uMDD VCPT commission and omission errors
	Langenecker et al.	2007	20	22	HC > uMDD RT on CPT
	Grant et al.	2001	123	36	HC = uMDD TMT-A, DS, and CPT
	Gualtieri et al.	2006	38	69	HC > uMDD complex attention
Learning and Memory (Verbal and Visuospatial)					
	Porter et al.	2003	44	44	HC = uMDD RAVLT HC > uMDD RAVLT distractor list
	Gualtieri et al.	2006	38	69	HC = uMDD VBM area
Working Memory					
	Den Hartog et al.	2003	30	38	HC = uMDD MST-2, verbal fluency HC > uMDD MST-1
	Porter et al.	2003	44	44	HC > uMDD SWM errors
	Grant et al.	2001	123	36	HC > uMDD CANTAB SWM
Executive Functioning					
	Porter et al.	2003	44	44	HC > uMDD COWAT
	Grant et al.	2001	123	36	HC = uMDD TMT-B, category and verbal fluency; HC > MDD WCST
	Den Hartog et al.	2003	30	38	HC > uMDD Stroop

Note. X > Y = Group X performed *better* on the task than Group Y. uMDD = unmedicated MDD; HC = healthy comparison; COWAT= Controlled Oral Word Association Task; TMT-A/B = Trail Making Test-Part A/B; WCST = Wisconsin Card Sorting Task, VCPT = Vigil Continuous Performance Test; RT = Reaction Time; CPT = Continuous Performance Task; DS = Digit Span; DSST: Digit Symbol Substitution Task; MST = Memory Scanning Test; CANTAB = Cambridge Neuopsychological Test Automated Battery; SWM = Spatial Working Memory; RAVLT = Rey Auditory Verbal Learning Test

Table 2. *Studies organized by relevance to current study and cognitive domain*

Author (Year)	*Sample*	*Psychomotor Processing Speed*	*Attention, Inhibition, Concentration*	*Learning-Memory*	*Working Memory*	*Executive Functioning*
Grade A						
Purcell et al. (1997)	20 HC 8 uMDD 12 mMDD				HC > MDD ToL	HC = MDD planning task, ToL
Tsourtos et al. (2002)	20 HC 20 uMDD 19 mMDD	mMDD > uMDD, HC > uMDD, HC = mMDD RT computer task				
Gualtieri et al. (2006)	69 HC 38 uMDD 31 mMDD	HC = MDD finger tapping; HC > uMDD RT CPT, DS	HC > MDD CPT; HC > uMDD complex attention; mMDD > uMDD complex attention, vigilance	H = MDD visual/ verbal memory; HC = uMDD VBM area		HC > MDD Stroop errors, shifting attention; mMDD > uMDD, HC = mMDD cognitive flexibility
Grade B						
Gohier et al. (2009)	20 HC 20 mMDD	HC > mMDD TMT-A secs	HC > mMDD on Prose Distraction Task, TMT-A secs; HC = mMDD TMT-A errors			HC > mMDD Stroop color, HSC (Part 2), Modified 6 rule shifts, elements test simple dual task, TMT-B time & errors HC = mMDD MCST execution, PE & trials
Hermens et al. (2010)	17 HC 20mMDD			HC > mMDD RAVLT		HC > mMDD TMT-B
Sweeney et al. (2000)	51 HC 58 mMDD	HC = mMDD computer RT tests		HC > mMDD visual delayed	HC = mMDD SWM	HC = mMDD ID/ED attentional set-shifting

Author (Year)	*Sample*	*Psychomotor Processing Speed*	*Attention, Inhibition, Concentration*	*Learning-Memory*	*Working Memory*	*Executive Functioning*
				match to sample		
Ravnkilde et al. (2002)	49 HC 20 mMDD 20*mMDD	HC > mMDD TMT-A secs, DS	HC > mMDD DSF, Subtracting Serial 7s	49 HC 40 mMDD WMS-R VR I & II, WMS-R LM I & II, LVLT	HC > mMDD DSB	HC > mMDD Stroop, TMT-B secs, verbal fluency, WCST
Gorenstein et al. (2006)	31 HC 56 mMDD	HC = mMDD DS, RT, tapping, symbol coding, cancellation	mMDD = HC DSF	HC = mMDD = verbal recall	HC = mMDD DSB	
Grade C						
Wadsworth et al. (2005)	161 HC/MDD 17 SSRI	no detrimental effects in SSRI on motor speed	no detrimental effects in SSRI on speed of focus in attention	SSRI HC < SSRI MDD episodic memory, recog. memory, delayed recall; SSRI < nSSRI episodic memory, recog. memory, delayed recall		
Porter et al. (2003)	44 HC 44 uMDD	HC = uMDD on DS Substitution Task	HC > uMDD VCPT omission & comission errors,	HC = uMDD RAVLT; HC > uMDD RAVLT distract list	HC > uMDD SWM, interaction of level	HC = uMDD verbal fluency, HC > uMDD ToL
Grant et al. (2001)	36 HC 123 uMDD	HC = uMDD TMT-A secs, RT, discriminative ability on visual/verbal CPT	HC = uMDD on TMT-A, DS, CPT		HC > uMDD CANTAB SWM	HC = uMDD TMT-B, verbal & semantic fluency; HC > uMDD WCST

Author (Year)	*Sample*	*Psychomotor Processing Speed*	*Attention, Inhibition, Concentration*	*Learning-Memory*	*Working Memory*	*Executive Functioning*
Den Hartog et al. (2003)	38 HC 30 uMDD	HC = uMDD MST-2 and VFT secs 16–60; HC > uMDD on MST-1				HC > uMDD Stroop
Langenecker et al. (2007)	22 HC 20 uMDD	HC > uMDD RT on CPT				
Bulshman et al., (2007)	29 HC 18 uMDD	HC > uMDD steering RT, driving simulation crashes				
Meyer et al. (2006)	21 HC 21 mMDD	HC = mMDD finger tapping				
Naismith et al. (2002)	20 HC 47 mDD	HC > mMDD TMT-A & TMT-B secs				

Note. uMDD = unmedicated MDD; mMDD = medicated MDD; MDD = both MDD groups; HC = healthy comparison; *mMDD = recently medicated MDD; SSRI = on selective serotonin reuptake inhibitor; nSSRI = not on SSRI; ToL = Tower of London; RT = reaction time; DS = Digit Symbol; PE = perseverative errors; HSC = Hayling Sentence Completion; MCST = Modified Card Sorting Test; RAVLT = Rey Auditory Verbal Learning Test; ID/ED = Intradimensional/ Extradimensional; SWM = Spatial Working Memory; WCST = Wisconsin Card Sorting Test; DSF = Digit Span Forward; DSB = Digit Span Backward; WMS-R VR = Wechsler Memory Scale-Revised Visual Reproduction; WMS-R LM = WMS-R Logical Memory; LVLT = Luria Verbal Learning Test ; VCPT = vigil continuous performance tests; TMT = Trail Making Test (Parts A & B); CANTAB = Cambridge Neuropsychological Test Automated Battery; MST-1 = memory scanning test; VFT = Verbal Fluency Test

Table 3. Descriptive Statistics for Demographic Characteristics and Neuropsychological Tests: Healthy Comparison, Unmedicated MDD, and Medicated MDD Groups

	HC (n = 153)		uMDD (n = 89)		mMDD (n = 89)		
Variable	*M*	*(SD)*	*M*	*(SD)*	*M*	*(SD)*	*Range*
Age (years)	40.7	(19.9)	38.2	(16.1)	47. 5	(19.4)	18.0 – 88.0
Education (years)	15.7	(2.2)	15.5	(2.5)	15.8	(2.5)	7.0 – 23.0
Percent Women	58.8		61.8		77.5		
Psychomotor Speed Composite	-0.77	(0.94)	-0.87	(0.87)	-1.27	(0.99)	-4.87 – 1.24
Purdue Pegboard	-1.81	(1.24)	-1.72	(1.02)	-2.36	(1.21)	-5.39 – 1.51
Trails A	0.24	(0.69)	0.18	(0.74)	-0.14	(0.91)	-2.50 – 1.67
Go Reaction Time	-0.69	(1.35)	-0.90	(1.17)	-1.12	(1.34)	-5.00 – 1.88
Attention Composite	-0.06	(0.75)	0.01	(0.77)	-0.41	(0.87)	-2.40 – 2.70
Digit Span Forward	-0.74	(0.65)	0.58	(0.68)	-0.91	(0.56)	-1.89 – 1.44
CVLT-II Trial 1	0.62	(1.26)	0.55	(1.24)	0.06	(1.20)	-2.27 – 4.36
Go Accuracy	-0.23	(1.05)	-0.08	(1.02)	-0.28	(1.17)	-4.80 – 0.88
Learning-Memory Composite	0.39	(0.82)	0.43	(0.75)	-0.04	(0.92)	-2.64 – 1.89
CVLT-II Total 1-5	0.63	(0.90)	0.57	(0.90)	0.27	(1.14)	-2.49 – 2.33
CVLT-II Long Delay Free Recall	0.50	(0.83)	0.61	(0.77)	0.27	(1.01)	-2.21 – 1.44
MSRT Total 1-5	-0.06	(1.01)	-0.03	(0.96)	-0.32	(1.17)	-2.93 – 1.39
MSRT Long Delay Free Recall	-0.03	(1.04)	-0.15	(0.91)	-0.20	(1.06)	-2.94 – 0.75
Working Memory Composite	-0.45	(0.69)	0.43	(0.78)	-0.59	(0.71)	-2.58 – 1.50
Digit Span Backward	-1.23	(0.63)	-1.21	(0.68)	-1.41	(0.48)	-2.58 – 0.97
No- Go Accuracy	0.18	(0.79)	0.15	(0.88)	0.14	(0.86)	-2.20 – 1.50
Executive Functioning Composite	0.01	(0.75)	0.07	(0.63)	-0.14	(0.97)	-3.88 – 1.18
COWAT	0.18	(1.06)	0.31	(0.84)	0.20	(0.93)	-2.41 – 2.73
Trails B	0.39	(0.60)	0.35	(0.55)	0.17	(0.82)	-2.74 – 1.24
WCST Perseverative Errors	-0.54	(1.52)	-0.50	(1.39)	-0.90	(2.17)	-7.00 – 0.76

Note. uMDD = Unmedicated – Major Depressive Disorder group, mMDD = Medicated – Major Depressive Disorder group, CVLT = California Verbal Learning Test, MSRT = Michigan Spatial Relation Test, COWAT = Controlled Oral Word Association Test, WCST = Wisconsin Card Sorting Test. Tests expressed in Z scores standardized on a reference sample, age 25-44, education 12 years.

Table 4. *Descriptive Statistics for Depression-Related Characteristics for Unmedicated MDD (uMDD) and Medicated MDD (mMDD) Groups*

	uMDD (n = 89)		mMDD (n = 89)		
Variable	*M*	*(SD)*	*M*	*(SD)*	*Range*
MDD Age of Onset (years)	22.8	(16.1)	21. 4	(12.1)	3.0 – 60.0
Depression Symptoms					
Hamilton Depression Rating Scale	17.9	(7.3)	13.1	(8.3)	0.0 – 41.0
Beck Depression Inventory-II	27.0	(11.3)	19.8	(13.9)	0.0 – 50.0
Medication Classifications[1]					
SSRI (%)			60.6		
SNRI (%)			43.8		
TCA (%)			3.3		
MAOI (%)			2.2		
Other (%)			3.4		

Note. SSRI = Selective Serotonin Reuptake Inhibitor, SNRI = Serotonin Norepinephrine Reuptake Inhibitor, TCA = Tricyclic antidepressant, MAOI = Monoamine Oxidase Inhibitor.
1. Percent of participants taking *each* medication type (including overlap); 56.1% taking multiple classes of medications.

Table 5. *Indices of neuropsychological function organized by cognitive domain.*

Domain	*Index*
Psychomotor speed and dexterity:	
Purdue Pegboard	Pegs placed, dominant hand
Trail-Making Test-Part A	Seconds to complete
Parametric Go/No-Go	Mean response time (msec) to Go targets (Level 1)
Attention/Concentration:	
Digit Span Forward	Percentile
CVLT-II	Trial 1 words
Parametric Go/No-Go	Go percent correct (Level 1)
Learning and Memory:	
Auditory	
CVLT-II	Total words Trials 1 – 5
CVLT-II	Long-delay free recall (CVLT-LDFR)
Visuospatial	
MSRT	Total Trials 1 – 5 (MSRT-Total)
MSRT	long-delay free recall (MSRT-LDFR)
Working Memory:	
Digit Span Backward	Percentile
Parametric Go/No-Go	No-go mean percent correct (Levels 2 – 3)
Executive Functioning:	
COWAT	Total words (CFL, PRW)
WCST	Perseverative errors
Trail-Making Test-Part B	Seconds to complete

Note. CVLT-II = California Verbal Learning Test–II, LDFR = Long-delay free recall, MSRT = Michigan Spatial Relation Test, COWAT = Controlled Oral Word Association Test, WCST = Wisconsin Card Sorting Test.

Table 6. *Unadjusted ANOVA Group Comparisons for Neuropsychological Tests for Healthy Comparison, Unmedicated MDD and Medicated MDD Groups.*

Variable	M_{diff}	(SE_{diff})	*F or t*	*df*	*p*	*Cohen's d*
Processing Speed Composite			8.27	2, 325	< .001	
HC vs. uMDD	0.10	(0.12)	0.78	237	.437	0.10
HC vs. mMDD	0.50	(0.13)	3.89	238	.000	0.52
uMDD vs. mMDD	-0.40	(0.14)	2.88	175	.004	-0.43
Purdue Pegboard			7.33	2, 296	< .001	
HC vs. uMDD	-0.09	(0.16)	0.54	217	.587	-0.08
HC vs. mMDD	0.55	(0.17)	3.15	212	.002	0.44
uMDD vs. mMDD	-0.64	(0.17)	3.66	163	< .001	-0.57
Trails A			5.80	2, 270	.003	
HC vs. uMDD	0.06	(0.10)	0.58	200	.562	0.08
HC vs. mMDD	0.37	(0.12)	3.27	194	.001	0.48
uMDD vs. mMDD	-0.32	(0.14)	2.34	147	.021	-0.38
Go Reaction Time			2.63	2, 282	.074	
HC vs. uMDD	0.20	(0.18)	1.10	209	.272	0.16
HC vs. mMDD	0.43	(0.20)	2.20	206	.029	0.32
uMDD vs. mMDD	-0.23	(0.21)	1.10	149	.272	-0.18
Attention Composite			7.54	2, 328	.001	
HC vs. uMDD	-0.07	(0.10)	-0.68	240	.500	-0.09
HC vs. mMDD	0.35	(0.11)	3.29	240	.001	0.44
uMDD vs. mMDD	-0.42	(0.12)	3.39	176	.001	-0.51
Digit Span Forward			4.87	2, 270	.008	
HC vs. uMDD	0.15	(0.10)	-1.58	198	.115	-0.20
HC vs. mMDD	0.17	(0.09)	1.89	195	.060	0.28
uMDD vs. mMDD	-0.33	(0.10)	3.19	147	.002	-0.44
CVLT-II Trial 1			6.12	2, 323	.002	
HC vs. uMDD	0.07	(0.17)	0.39	236	.695	0.05
HC vs. mMDD	0.56	(0.17)	3.37	236	.001	0.45
uMDD vs. mMDD	-0.50	(0.18)	2.70	174	.008	-0.41
Go Accuracy			3.75	2, 282	.025	
HC vs. uMDD	-0.15	(0.15)	-1.04	209	.301	-0.15
HC vs. mMDD	0.35	(0.17)	1.98	206	.049	0.29
uMDD vs. mMDD	-0.50	(0.20)	2.46	131.1[a]	.015	-0.40
Learning-Memory Composite			9.35	2, 326	< .001	
HC vs. uMDD	-0.04	(0.11)	-0.39	238	.694	-0.05
HC vs. mMDD	0.43	(0.11)	3.74	239	< .001	0.50
uMDD vs. mMDD	-0.47	(0.13)	3.73	175	< .001	-0.56
CVLT-II Total 1-5			4.05	2, 323	.018	
HC vs. uMDD	0.05	(0.12)	0.43	236	.669	0.06
HC vs. mMDD	0.36	(0.13)	2.70	236	.007	0.36
uMDD vs. mMDD	-0.31	(0.15)	1.99	165.4[a]	.048	-0.30

(table continues)

Variable	M_{diff}	(SE_{diff})	*F or t*	*df*	*p*	*Cohen's d*
CVLT-II LDFR			3.41	2, 321	.553	
HC vs. uMDD	-0.11	(0.11)	-0.96	234	.340	-0.13
HC vs. mMDD	0.23	(0.12)	1.88	235	.061	0.25
uMDD vs. mMDD	-0.33	(0.14)	2.44	163.7[a]	.016	-0.37
MSRT Total 1-5			1.57	2, 221	.211	
HC vs. uMDD	-0.03	(0.18)	-0.15	147	.882	-0.03
HC vs. mMDD	0.26	(0.16)	1.56	176	.121	0.24
uMDD vs. mMDD	-0.28	(0.20)	1.38	119	.171	-0.26
MSRT LDFR			0.59	2, 220	.553	
HC vs. uMDD	-0.11	(0.18)	0.63	147	.528	-0.11
HC vs. mMDD	0.16	(0.16)	1.03	175	.303	0.16
uMDD vs. mMDD	-0.05	(0.19)	0.28	118	.781	-0.05
Working Memory Composite			1.05	2, 320	.350	
HC vs. uMDD	-0.07	(0.10)	0.73	234	.465	0.10
HC vs. mMDD	0.14	(0.09)	1.48	235	.140	0.20
uMDD vs. mMDD	-0.07	(0.11)	0.60	171	.552	-0.09
Digit Span Backward			0.08	2, 282	.071	
HC vs. uMDD	-0.01	(0.09)	-0.15	199	.878	-0.02
HC vs. mMDD	0.19	(0.09)	2.17	195	.031	0.23
uMDD vs. mMDD	-0.20	(0.10)	2.11	137.3[a]	.037	-0.34
No-Go Accuracy			0.08	2, 282	.921	
HC vs. uMDD	0.04	(0.12)	0.32	209	.752	0.04
HC vs. mMDD	0.04	(0.12)	0.36	206	.716	0.05
uMDD vs. mMDD	-0.01	(0.14)	0.04	149	.968	-0.01
Executive Function Composite			1.42	2, 281	.244	
HC vs. uMDD	-0.06	(-0.10)	-0.59	208	.555	-0.08
HC vs. mMDD	0.15	(0.12)	1.21	204	.227	0.18
uMDD vs. mMDD	-0.21	(0.13)	1.57	150	.119	-0.25
COWAT			0.48	2, 269	.617	
HC vs. uMDD	-0.13	(0.14)	-0.95	207	.345	-0.14
HC vs. mMDD	-0.02	(0.16)	-0.12	193	.903	-0.02
uMDD vs. mMDD	-0.11	(0.15)	0.77	138	.445	-0.13
Trails B			2.81	2, 270	.062	
HC vs. uMDD	0.04	(0.08)	0.53	199	.599	0.08
HC vs. mMDD	0.23	(0.10)	2.21	194	.028	0.33
uMDD vs. mMDD	-0.18	(0.11)	1.59	147	.114	-0.26
WCST Perseverative Errors				2, 245	.325	
HC vs. uMDD	-0.04	(0.22)	-0.19	190	.853	-0.03
HC vs. mMDD	0.36	(0.28)	1.27	174	.206	0.20
uMDD vs. mMDD	-0.40	(0.32)	1.21	188.8[a]	.231	-0.23

Note. CVLT = California Verbal Learning Test, MSRT = Michigan Spatial Relation Test, LDFR = Long Delay Free Recall, COWAT = Controlled Oral Word Association Test, WCST = Wisconsin Card Sorting Test. Tests expressed in Z scores standardized on a reference sample, age 25-44, education 12 years.

a. Levene's correction for heterogeneity of variance.

Table 7. *Descriptive Correlations: Age, Education, Depression Severity, and Neuropsychological Performance - All Participants* (*N* = 331)

	Age	Education	HDRS	BDI-II
1. Age	--	-.10	-.01	.02
2. Education		--	-.09	-.07
3. Hamilton Depression Rating Scale (HDRS)			--	.89**
4. Beck Depression Inventory-II (BDI-II)				--
5. *Processing Speed Composite*	-.42**	-.05	-.11	-.14*
6. Purdue Pegboard	-.50**	-.03	-.04	-.11
7. Trails A	-.44**	-.06	-.09	-.09
8. Go Reaction Time	-.37**	-.10	-.10	-.09
9. *Attention Composite*	-.43**	.05	-.05	-.05
10. Digit Span Forward	-.14*	.01	.02	-.02
11. CVLT-II Trial 1	-.39**	.05	-.08	-.08
12. Go Accuracy	-.39**	.04	-.02	-.03
13. *Learning-Memory Composite*	-.56**	.08	-.09	-.10
14. CVLT-II Total 1-5	-.48**	.11*	-.12*	-.12*
15. CVLT-II Long Delay Free Recall	-.45**	.11	-.07	-.08
16. MSRT Total 1-5	-.52**	-.02	-.09	-.07
17. MSRT Long Delay Free Recall	-.50**	-.01	-.11	-.09
18. *Working Memory Composite*	-.13*	-.07	-.06	-.05
19. Digit Span Backward	-.22**	-.02	-.01	-.07
20. No-Go Accuracy	-.02	-.06	-.05	.01
21. *Executive Functioning Composite*	-.44**	.03	-.01	-.01
22. COWAT	-.16**	.10	.02	.03
23. Trails B	-.52**	-.08	-.07	-.08
24. WCST Perseverative Errors	-.36**	.05	-.02	-.01
25. *Neuropsychological Composite*	-.51**	.07	-.10	-.13*

Note. HDRS = Hamilton Depression Rating Scale, BDI = Beck Depression Inventory, CVLT = California Verbal Learning Test, MSRT = Michigan Spatial Relation Test, COWAT = Controlled Oral Word Association Test, WCST = Wisconsin Card Sorting Test.
*$p < .05$, **$p < .01$ two-tailed

Table 8. *ANCOVA Method: Group Comparisons for Neuropsychological Tests for Healthy Comparison, Unmedicated MDD and Medicated MDD Groups Adjusted for Age and Education.*

Variable	M_{diff} [1]	(SE_{diff})	*F*	*df*	*p*	*Cohen's d*
Processing Speed Composite			4.65	2, 323	.010	
HC vs. uMDD	-0.15	(0.12)			.210	0.17
HC vs. mMDD	0.36	(0.12)			.003	0.41
uMDD vs. mMDD	-0.21	(0.13)			.113	-0.24
Purdue Pegboard			2.93	2, 294	.055	
HC vs. uMDD	-0.02	(0.14)			.866	-0.02
HC vs. mMDD	0.33	(0.15)			.030	0.31
uMDD vs. mMDD	-0.35	(0.17)			.035	-0.33
Trails A			2.65	2, 268	.072	
HC vs. uMDD	0.12	(0.10)			.227	0.17
HC vs. mMDD	0.24	(0.11)			.025	0.34
uMDD vs. mMDD	-0.12	(0.12)			.330	-0.16
Go Reaction Time			1.67	2, 284	.190	
HC vs. uMDD	0.25	(0.18)			.152	0.20
HC vs. mMDD	0.28	(0.18)			.119	0.23
uMDD vs. mMDD	-0.03	(0.20)			.891	-0.02
Attention Composite			3.69	2, 326	.026	
HC vs. uMDD	-0.03	(0.10)			.751	-0.04
HC vs. mMDD	0.23	(0.10)			.017	0.32
uMDD vs. mMDD	-0.26	(0.11)			.017	-0.36
Digit Span Forward			3.60	2, 268	.029	
HC vs. uMDD	-0.14	(0.09)			.129	-0.22
HC vs. mMDD	0.15	(0.10)			.127	0.23
uMDD vs. mMDD	-0.29	(0.11)			.008	-0.44
CVLT-II Trial 1			3.35	2, 321	.036	
HC vs. uMDD	0.12	(0.15)			.455	0.10
HC vs. mMDD	0.40	(0.16)			.010	0.35
uMDD vs. mMDD	-0.29	(0.18)			.104	-0.25
Go Accuracy			1.88	2, 280	.155	
HC vs. uMDD	-0.11	(0.15)			.461	-0.10
HC vs. mMDD	0.22	(0.16)			.157	0.20
uMDD vs. mMDD	-0.34	(0.18)			.059	-0.31
Learning-Memory Composite			4.59	2, 324	.011	
HC vs. uMDD	0.01	(0.93)			.968	0.00
HC vs. mMDD	0.27	(0.93)			.005	0.38
uMDD vs. mMDD	-0.26	(0.11)			.014	-0.37
CVLT-II Total 1-5			1.63	2, 321	.198	
HC vs. uMDD	0.10	(0.11)			.394	0.01
HC vs. mMDD	0.21	(0.12)			.074	0.24
uMDD vs. mMDD	-0.11	(0.13)			.403	-0.13

(table continues)

Variable	M_{diff}[1]	(SE_{diff})	*F*	*df*	*p*	*Cohen's d*
CVLT-II LDFR			0.96	2, 319	.085	
HC vs. uMDD	-0.06	(0.11)			.566	-0.08
HC vs. mMDD	0.10	(0.11)			.333	0.13
uMDD vs. mMDD	-0.16	(0.12)			-.174	-0.21
MSRT Total 1-5			0.88	2, 219	.418	
HC vs. uMDD	0.10	(0.16)			.557	-0.10
HC vs. mMDD	0.18	(0.14)			.189	0.20
uMDD vs. mMDD	-0.09	(0.17)			.612	-0.09
MSRT LDFR			1.04	2, 218	.354	
HC vs. uMDD	0.23	(0.16)			.153	0.25
HC vs. mMDD	0.09	(0.14)			.515	0.10
uMDD vs. mMDD	0.14	(0.17)			.412	0.15
Working Memory Composite			0.70	2, 318	.497	
HC vs. uMDD	0.09	(0.10)			.383	0.12
HC vs. mMDD	0.10	(0.10)			.293	0.14
uMDD vs. mMDD	-0.02	(0.11)			.868	-0.02
Digit Span Backward			1.18	2, 269	.310	
HC vs. uMDD	0.01	(0.09)			.916	-0.01
HC vs. mMDD	0.13	(0.09)			.143	0.22
uMDD vs. mMDD	-0.12	(0.10)			.224	-0.20
No-Go Accuracy			0.07	2, 280	.931	
HC vs. uMDD	0.04	(0.12)			.741	0.05
HC vs. mMDD	0.04	(0.12)			.776	0.04
uMDD vs. mMDD	-0.01	(0.14)			.972	-0.01
Executive Function Composite			0.01	2, 279	.993	
HC vs. uMDD	0.01	(0.10)			.908	-0.02
HC vs. mMDD	0.01	(0.11)			.944	0.01
uMDD vs. mMDD	0.01	(0.12)			.970	-0.01
COWAT			0.32	2, 287	.730	
HC vs. uMDD	-0.11	(0.14)			.443	-0.11
HC vs. mMDD	-0.07	(0.15)			.661	-0.07
[b]uMDD vs. mMDD	-0.04	(0.17)			.805	-0.04
Trails B			1.05	2, 288	.008	
HC vs. uMDD	0.11	(0.08)			.176	0.19
HC vs. mMDD	0.08	(0.09)			.343	0.14
uMDD vs. mMDD	0.03	(0.08)			.747	0.05
WCST Perseverative Errors			0.52	2, 243	.597	
HC vs. uMDD	0.85	(0.23)			.714	-0.05
HC vs. mMDD	0.26	(0.25)			.311	0.16
uMDD vs. mMDD	-0.17	(0.28)			.542	-0.11

Note. LDFR = Long Delay Free Recall, CVLT = California Verbal Learning Test, MSRT = Michigan Spatial Relation Test, COWAT = Controlled Oral Word Association Test, WCST = Wisconsin Card Sorting Test.

1. M_{diff} = Mean difference of *adjusted* means.

Table 9a. *Matched-Samples Method: Descriptive Statistics for Demographic Characteristics and Neuropsychological Tests for Healthy Comparison, Unmedicated MDD and Medicated MDD Groups.*

	Healthy Comparison v. uMDD				Healthy Comparison v. mMDD				uMDD v. mMDD			
	HC (n = 88)		uMDD (n = 88)		HC (n = 67)		mMDD (n = 67)		uMDD (n = 64)		mMDD (n = 64)	
Variable	*M*	*(SD)*	*M*	*(SD)*	*M*	*(SD)*	*M*	*(SD)*	*M*	*(SD)*	*M*	*(SD)*
Age	38.1	(16.2)	38.2	(16.2)	41.1	(16.9)	40.6	(16.2)	40.8	(16.7)	40.8	(17.0)
Education	15.6	(2.2)	15.4	(2.4)	16.0	(2.1)	16.2	(2.0)	15.9	(2.3)	16.0	(2.2)
Processing Speed Composite	-0.64	(0.87)	-0.87	(0.87)	-0.63	(0.78)	-1.07	(0.83)	-0.91	(0.92)	-1.08	(0.91)
Purdue Pegboard	-1.61	(1.05)	-1.74	(1.01)	-1.51	(0.97)	-2.15	(1.11)	-1.65	(0.99)	-2.13	(1.12)
Trails A	0.25	(0.68)	0.18	(0.74)	0.31	(0.69)	0.08	(0.76)	0.09	(0.77)	-0.03	(0.83)
Go Reaction Time	-0.62	(1.31)	-0.91	(1.18)	-0.66	(1.14)	-0.86	(1.26)	-1.04	(1.21)	-0.90	(1.34)
Attention Composite	-0.03	(0.72)	0.00	(0.76)	-0.04	(0.73)	-0.20	(0.81)	0.00	(0.79)	-0.23	(0.86)
Digit Span Forward	-0.68	(0.70)	-0.58	(0.68)	-0.66	(0.70)	-0.86	(0.56)	-0.58	(0.70)	-0.90	(0.55)
CVLT-II Trial 1	0.66	(1.06)	0.54	(1.23)	0.66	(1.14)	0.27	(1.18)	0.47	(1.17)	0.29	(1.20)
Go Accuracy	-0.24	(1.14)	-0.08	(1.03)	-0.32	(1.04)	-0.22	(1.22)	-0.07	(1.07)	-0.36	(1.38)
Learning-Memory Composite	0.50	(0.79)	0.43	(0.76)	0.48	(0.82)	0.16	(0.83)	0.43	(0.80)	0.20	(0.80)
CVLT-II Total 1-5	0.69	(0.83)	0.56	(0.90)	0.73	(0.84)	0.49	(1.05)	0.56	(0.91)	0.52	(1.02)
CVLT-II LDFR	0.57	(0.81)	0.60	(0.79)	0.52	(0.81)	0.44	(0.88)	0.63	(0.79)	0.50	(0.82)
MSRT Total 1-5	0.10	(0.92)	-0.01	(0.96)	0.01	(0.96)	-0.10	(1.07)	-0.04	(0.98)	-0.09	(1.09)
MSRT LDFR	0.11	(0.97)	-0.15	(0.92)	0.05	(0.95)	-0.04	(0.99)	-0.23	(0.98)	-0.04	(1.00)
Working Memory Composite	-0.51	(0.66)	-0.52	(0.78)	-0.47	(0.62)	-0.50	(0.70)	-0.56	(0.78)	-0.50	(0.76)
Digit Span Backward	-1.17	(0.68)	-1.21	(0.68)	-1.18	(0.69)	-1.34	(0.45)	-1.26	(0.65)	-1.34	(0.43)
No-Go Accuracy	0.14	(0.72)	0.16	(0.88)	0.25	(0.60)	0.26	(0.83)	0.14	(0.82)	0.23	(0.86)
Executive Function Composite	0.00	(0.78)	0.07	(0.63)	0.04	(0.80)	0.11	(0.67)	0.04	(0.62)	0.05	(0.74)
COWAT	0.09	(1.16)	0.31	(0.84)	0.13	(1.25)	0.35	(0.89)	0.28	(0.85)	0.33	(0.88)
Trails B	0.50	(0.52)	0.35	(0.55)	0.47	(0.56)	0.38	(0.60)	0.31	(0.55)	0.30	(0.72)
WCST Perseverative Errors	-0.54	(1.57)	-0.50	(1.39)	-0.44	(1.42)	-0.44	(1.61)	-0.50	(1.36)	-0.47	(1.54)

Note. uMDD = unmedicated MDD, mMDD = medicated MDD; CVLT = California Verbal Learning Test, MSRT = Michigan Spatial Relation Test, LDFR = Long Delay Free Recall, COWAT = Controlled Oral Word Association Test, WCST = Wisconsin Card Sorting Test. 1. Samples matched for age (± 5 years) and education (± 3 years); one pool of HC participants to match clinical groups.

Table 9b. *Matched-Samples[1] Method: Group Comparisons of Neuropsychological Tests for Healthy Comparison, Unmedicated MDD and Medicated MDD Groups.*

Variable	M_{diff}	(SE_{diff})	*t*	*df*	*p*	*Cohen's d*
Processing Speed Composite						
HC vs. uMDD	0.23	(0.13)	1.75	172	.082	0.26
HC vs. mMDD	0.44	(0.14)	3.17	131	.002	0.55
uMDD vs. mMDD	0.12	(0.16)	1.02	125	.312	0.13
Purdue Pegboard						
HC vs. uMDD	0.12	(0.16)	0.76	158	.452	-0.12
HC vs. mMDD	0.65	(0.19)	3.37	117	.001	0.62
uMDD vs. mMDD	0.42	(0.19)	2.43	116	.017	0.41
Trails A						
HC vs. uMDD	0.07	(0.12)	0.63	150	.527	0.10
HC vs. mMDD	0.23	(0.14)	1.66	107	.100	0.32
uMDD vs. mMDD	0.08	(0.15)	0.82	104	.415	0.10
Go Reaction Time						
HC vs. uMDD	0.29	(0.20)	1.43	148	.156	0.29
HC vs. mMDD	0.19	(0.23)	0.85	108	.397	0.16
uMDD vs. mMDD	-0.20	(0.24)	-0.54	106	.588	0.16
Attention Composite						
HC vs. uMDD	-0.03	(0.11)	-0.30	174	.763	-0.04
HC vs. mMDD	0.16	(0.13)	1.12	132	.237	0.20
uMDD vs. mMDD	0.20	(0.12)	1.58	126	.117	-0.24
Digit Span Forward						
HC vs. uMDD	-0.09	(0.11)	-0.83	149	.407	-0.13
HC vs. mMDD	0.20	(0.12)	1.63	107	.107	0.31
uMDD vs. mMDD	0.30	(0.12)	2.57	103	.012	-0.48
CVLT-II Trial 1						
HC vs. uMDD	0.12	(0.17)	0.69	172	.489	0.10
HC vs. mMDD	0.39	(0.20)	1.91	130	.059	0.33
uMDD vs. mMDD	0.16	(0.21)	0.82	125	.414	-0.13
Go Accuracy						
HC vs. uMDD	-0.16	(0.18)	-0.93	148	.356	-0.02
HC vs. mMDD	-0.10	(0.22)	-0.45	108	.652	-0.09
uMDD vs. mMDD	0.21	(0.22)	1.24	106	.217	-0.18
Learning-Memory Composite						
HC vs. uMDD	0.07	(0.12)	0.59	173	.557	0.09
HC vs. mMDD	0.32	(0.14)	2.25	132	.026	0.39
uMDD vs. mMDD	0.21	(0.14)	1.64	125	.103	-0.27
CVLT-II Total 1-5						
HC vs. uMDD	0.13	(0.13)	1.01	172	.312	0.15
HC vs. mMDD	0.24	(0.17)	1.47	130	.144	0.25
uMDD vs. mMDD	0.02	(0.17)	0.25	125	.806	-0.02

(table continues)

Variable	M_{diff}	(SE_{diff})	*t*	*df*	*p*	*Cohen's d*
CVLT-II LDFR						
HC vs. uMDD	-0.03	(0.12)	-0.24	171	.810	-0.04
HC vs. mMDD	0.08	(0.15)	0.33	130	.593	0.09
uMDD vs. mMDD	0.10	(0.14)	0.90	124	.370	-0.13
MSRT Total 1-5						
HC vs. uMDD	0.11	(0.19)	0.58	95	.563	0.12
HC vs. mMDD	0.11	(0.21)	0.54	96	.591	0.11
uMDD vs. mMDD	0.03	(0.23)	0.22	87	.826	-0.03
MSRT LDFR						
HC vs. uMDD	0.26	(0.19)	1.33	95	.188	0.27
HC vs. mMDD	0.08	(0.20)	0.42	95	.677	0.09
uMDD vs. mMDD	-0.19	(0.22)	-0.84	86	.403	0.19
Working Memory Composite						
HC vs. uMDD	0.01	(0.11)	0.11	169	.912	0.02
HC vs. mMDD	0.03	(0.12)	0.24	129	.807	0.04
uMDD vs. mMDD	-0.08	(0.14)	-0.49	121	.625	0.10
Digit Span Backward						
HC vs. uMDD	0.05	(0.11)	0.41	150	.682	-0.07
HC vs. mMDD	0.16	(0.11)	1.39	107	.166	0.27
uMDD vs. mMDD	0.07	(0.11)	0.74	104	.460	-0.11
No-Go Accuracy						
HC vs. uMDD	-0.02	(0.13)	-0.15	148	.879	0.02
HC vs. mMDD	-0.01	(0.14)	-0.08	108	.939	-0.01
uMDD vs. mMDD	-0.12	(0.16)	-0.57	106	.569	0.14
Executive Function Composite						
HC vs. uMDD	-0.07	(0.11)	-0.57	156	.567	-0.09
HC vs. mMDD	-0.08	(0.14)	-0.55	112	.583	-0.10
uMDD vs. mMDD	0.02	(0.13)	-0.03	106	.976	0.04
COWAT						
HC vs. uMDD	-0.22	(0.16)	-1.37	155	.172	-0.22
HC vs. mMDD	-0.21	(0.22)	-0.99	105	.326	-0.19
[b]uMDD vs. mMDD	-0.05	(0.18)	-0.28	99	.777	-0.07
Trails B						
HC vs. uMDD	0.16	(0.09)	1.80	150	.074	0.29
HC vs. mMDD	0.08	(0.11)	0.75	107	.456	0.14
uMDD vs. mMDD	0.05	(0.11)	0.08	104	.937	0.08
WCST Perseverative Errors						
HC vs. uMDD	-0.04	(0.25)	-0.16	142	.872	-0.03
HC vs. mMDD	0.01	(0.31)	0.20	95	.984	0.00
uMDD vs. mMDD	-0.03	(0.30)	-0.09	91	.927	0.02

Note. M_{diff} = Mean difference; HC = healthy comparison, uMDD = unmedicated MDD, mMDD = medicated MDD; CVLT = California Verbal Learning Test, MSRT = Michigan Spatial Relation Test, COWAT = Controlled Oral Word Association Test, WCST = Wisconsin Card Sorting Test. 1. Samples matched for age (±5 years) and education (± 3 years).

Table 10. *Regression Line Method[1]: Group Comparisons of Standardized Predicted-Residuals on Neuropsychological Tests Adjusted for Age and Education Based on Healthy Comparison Group*

Variable	M_{diff}	(SE_{diff})	*F or t*	*df*	*p*	*Cohen's d*
Processing Speed Composite			4.26	2, 325	.015	
HC vs. uMDD	0.14	(0.11)	1.26	237	.210	0.17
HC vs. mMDD	0.34	(0.12)	2.92	238	.004	0.39
uMDD vs. mMDD	0.20	(0.13)	1.45	175	.149	-0.22
Purdue Pegboard			2.94	2, 296	.054	
HC vs. uMDD	-0.02	(0.15)	-0.15	217	.878	-0.02
HC vs. mMDD	0.32	(0.15)	2.14	212	.034	0.30
uMDD vs. mMDD	0.34	(0.15)	2.20	163	.029	-0.34
Trails A			2.33	2, 270	.099	
HC vs. uMDD	0.13	(0.09)	1.37	200	.172	0.20
HC vs. mMDD	0.22	(0.10)	2.14	194	.034	0.32
uMDD vs. mMDD	0.09	(0.13)	0.71	147	.481	-0.12
Go Reaction Time			1.67	2, 282	.190	
HC vs. uMDD	0.25	(0.17)	1.46	209	.145	0.21
HC vs. mMDD	0.28	(0.18)	1.54	206	.126	0.22
uMDD vs. mMDD	0.03	(0.20)	0.13	149	.899	-0.02
Attention Composite			4.28	2, 328	.015	
HC vs. uMDD	0.04	(0.09)	-0.41	240	.684	-0.05
HC vs. mMDD	0.24	(0.10)	2.55	240	.011	0.34
uMDD vs. mMDD	0.28	(0.11)	2.52	176	.013	-0.38
Digit Span Forward			2.88	2, 270	.058	
HC vs. uMDD	-0.13	(0.10)	-1.37	198	.171	-0.20
HC vs. mMDD	0.12	(0.09)	1.31	195	.191	0.19
uMDD vs. mMDD	0.25	(0.11)	2.38	147	.018	-0.39
CVLT-II Trial 1			3.56	2, 323	.030	
HC vs. uMDD	0.11	(0.16)	0.72	236	.474	0.10
HC vs. mMDD	0.41	(0.15)	2.65	236	.009	0.35
uMDD vs. mMDD	0.30	(0.17)	1.75	174	.081	-0.26
Go Accuracy			2.53	2, 282	.082	
HC vs. uMDD	-0.12	(0.14)	-0.89	209	.374	-0.13
HC vs. mMDD	0.26	(0.16)	1.60	206	.111	0.23
uMDD vs. mMDD	0.38	(0.19)	2.06	131.1[a]	.041	-0.33
Learning-Memory Composite			4.93	2, 326	.008	
HC vs. uMDD	0.00	(0.09)	-0.01	238	.993	0.00
HC vs. mMDD	0.27	(0.09)	2.90	239	.004	0.39
uMDD vs. mMDD	0.27	(0.11)	2.55	175	.012	-0.38
CVLT-II Total 1-5			1.77	2, 323	.171	
HC vs. uMDD	0.09	(0.11)	0.88	236	.378	0.12
HC vs. mMDD	0.21	(0.11)	1.86	236	.065	0.25
uMDD vs. mMDD	0.12	(0.14)	0.88	165.4[a]	.381	-0.13

(table continues)

Variable	M_{diff}	(SE_{diff})	*F or t*	*df*	*p*	*Cohen's d*
CVLT-II LDFR			0.98	2, 321	.378	
HC vs. uMDD	-0.06	(0.10)	-0.63	234	.531	-0.08
HC vs. mMDD	0.10	(0.11)	0.95	235	.345	0.13
uMDD vs. mMDD	0.16	(0.13)	1.30	163.7[a]	.195	-0.20
MSRT Total 1-5			0.96	2, 221	.384	
HC vs. uMDD	0.07	(0.16)	0.45	147	.655	0.08
HC vs. mMDD	0.19	(0.14)	1.37	176	.174	0.21
uMDD vs. mMDD	0.12	(0.17)	0.70	119	.485	-0.13
MSRT LDFR			1.06	2, 220	.348	
HC vs. uMDD	0.23	(0.16)	1.45	147	.150	0.26
HC vs. mMDD	0.10	(0.14)	0.71	175	.477	0.11
uMDD vs. mMDD	-0.13	(0.16)	-0.79	118	.434	0.15
Working Memory Composite			0.57	2, 320	.567	
HC vs. uMDD	0.08	(0.10)	0.84	234	.403	0.11
HC vs. mMDD	0.09	(0.09)	0.96	235	.340	0.13
uMDD vs. mMDD	0.01	(0.11)	0.05	171	.963	-0.01
Digit Span Backward			0.87	2, 282	.419	
HC vs. uMDD	0.01	(0.09)	0.15	199	.884	0.02
HC vs. mMDD	0.11	(0.08)	1.35	195	.178	0.20
uMDD vs. mMDD	0.10	(0.10)	1.02	137.3[a]	.311	-0.17
No-Go Accuracy			0.07	2, 282	.931	
HC vs. uMDD	0.04	(0.12)	0.34	209	.734	0.05
HC vs. mMDD	0.03	(0.12)	0.29	206	.773	0.04
uMDD vs. mMDD	-0.01	(0.14)	-0.05	149	.964	0.01
Executive Function Composite			0.00	2, 281	.997	
HC vs. uMDD	0.01	(0.09)	0.08	208	.934	0.01
HC vs. mMDD	0.00	(0.11)	0.04	204	.968	0.01
uMDD vs. mMDD	-0.01	(0.12)	-0.03	150	.977	0.00
COWAT			0.36	2, 269	.695	
HC vs. uMDD	-0.12	(0.14)	-0.84	207	.400	-0.12
HC vs. mMDD	-0.05	(0.15)	-0.32	193	.752	-0.05
[b]uMDD vs. mMDD	0.07	(0.12)	0.46	138	.645	-0.08
Trails B			0.98	2, 270	.378	
HC vs. uMDD	-0.11	(0.07)	1.45	199	.149	0.21
HC vs. mMDD	0.08	(0.08)	0.93	194	.354	0.14
uMDD vs. mMDD	-0.03	(0.10)	-0.29	147	.769	0.05
WCST Perseverative Errors			0.50	2, 245	.610	
HC vs. uMDD	-0.09	(0.21)	0.41	190	.683	0.06
HC vs. mMDD	0.25	(0.25)	0.98	174	.330	0.16
uMDD vs. mMDD	0.16	(0.30)	0.54	188.8[a]	.588	-0.10

Note. HC = Healthy Control, uMDD = Unmedicated MDD, mMDD = Medicated MDD, CVLT = California Verbal Learning Test, MSRT = Michigan Spatial Relation Test, LDFR = Long Delay Free Recall, COWAT = Controlled Oral Word Association Test, WCST = Wisconsin Card Sorting Test. 1. Fleiss & Tanur, 1973.

Table 11. *Propensity Matching Estimators Method: Group Comparisons of Propensity Scores on Neuropsychological Tests Adjusted for Age and Education*

Variable	*Z*	*N*	*p*	*Cohen's d*
Processing Speed Composite				
HC vs. uMDD	-1.08	239	.278	0.14
HC vs. mMDD	-2.69	240	.007	0.35
uMDD vs. mMDD	-2.28	177	.023	-0.35
Purdue Pegboard				
HC vs. uMDD	0.43	219	.666	-0.06
HC vs. mMDD	-1.46	214	.143	0.20
uMDD vs. mMDD	-2.15	165	.032	-0.34
Trails A				
HC vs. uMDD	-0.61	201	.542	0.08
HC vs. mMDD	-1.65	196	.099	0.22
uMDD vs. mMDD	-0.74	149	.458	-0.11
Go Reaction Time				
HC vs. uMDD	-1.24	211	.214	0.17
HC vs. mMDD	-1.53	208	.127	0.21
uMDD vs. mMDD	-0.78	151	.434	-0.13
Attention Composite				
HC vs. uMDD	0.84	242	.403	-0.11
HC vs. mMDD	-1.88	242	.060	0.24
uMDD vs. mMDD	-2.31	178	.021	-0.35
Digit Span Forward				
HC vs. uMDD	1.77	201	.077	-0.25
HC vs. mMDD	-1.75	197	.080	0.25
uMDD vs. mMDD	-3.41	150	.001	-0.58
CVLT-II Trial 1				
HC vs. uMDD	-0.46	238	.645	0.06
HC vs. mMDD	-2.30	238	.022	0.22
uMDD vs. mMDD	-1.54	176	.123	-0.23
Go Accuracy				
HC vs. uMDD	-0.27	211	.787	0.04
HC vs. mMDD	-0.37	208	.714	0.05
uMDD vs. mMDD	-0.14	151	.892	-0.02
Learning-Memory Composite				
HC vs. uMDD	0.27	240	.790	-0.04
HC vs. mMDD	-2.55	241	.011	0.33
uMDD vs. mMDD	-2.45	177	.014	-0.38
CVLT-II Total 1-5				
HC vs. uMDD	-0.42	238	.674	0.05
HC vs. mMDD	-1.65	238	.099	0.22
uMDD vs. mMDD	-0.65	176	.517	-0.10

(table continues)

Variable		*Z*	*N*	*p*	*Cohen's d*
CVLT-II LDFR					
	HC vs. uMDD	0.75	236	.455	-0.10
	HC vs. mMDD	-0.97	237	.331	0.13
	uMDD vs. mMDD	-1.02	175	.309	-0.16
MSRT Total 1-5					
	HC vs. uMDD	0.16	149	.873	-0.02
	HC vs. mMDD	-0.73	178	.467	0.10
	uMDD vs. mMDD	-0.77	121	.440	-0.12
MSRT LDFR					
	HC vs. uMDD	-1.15	149	.252	0.15
	HC vs. mMDD	-0.25	177	.805	0.03
	uMDD vs. mMDD	0.51	120	.612	0.08
Working Memory Composite					
	HC vs. uMDD	-0.49	236	.624	0.06
	HC vs. mMDD	-0.90	237	.369	0.12
	uMDD vs. mMDD	-0.21	173	.834	-0.03
Digit Span Backward					
	HC vs. uMDD	-0.06	201	.954	0.01
	HC vs. mMDD	-1.72	197	.086	0.25
	uMDD vs. mMDD	-1.01	150	.313	-0.17
No-Go Accuracy					
	HC vs. uMDD	-0.29	211	.772	0.04
	HC vs. mMDD	-0.43	208	.664	0.06
	uMDD vs. mMDD	-0.17	151	.864	-0.03
Executive Function Composite					
	HC vs. uMDD	0.09	210	.929	-0.01
	HC vs. mMDD	-0.04	206	.967	0.01
	uMDD vs. mMDD	-0.24	152	.814	-0.04
COWAT					
	HC vs. uMDD	0.87	209	.387	-0.12
	HC vs. mMDD	0.47	195	.636	-0.07
	uMDD vs. mMDD	-0.12	140	.902	-0.02
Trails B					
	HC vs. uMDD	-0.84	201	.403	0.11
	HC vs. mMDD	0.22	196	.824	-0.03
	uMDD vs. mMDD	0.98	177	.329	0.15
WCST Perseverative Errors					
	HC vs. uMDD	-0.33	192	.742	0.05
	HC vs. mMDD	-1.30	176	.192	0.20
	uMDD vs. mMDD	-1.11	128	.267	-0.20

Note. HC = Healthy Control, uMDD = Unmedicated MDD, mMDD = Medicated MDD, CVLT = California Verbal Learning Test, MSRT = Michigan Spatial Relation Test, LDFR = Long Delay Free Recall, COWAT = Controlled Oral Word Association Test, WCST = Wisconsin Card Sorting Test.

Table 12. *Group Comparisons on Neuropsychological Tests for Healthy Controls, Unmedicated MDD and Medicated MDD: Unadjusted ANOVA, and Age- and Education-Adjusted ANCOVA, Matched Sample, Regression Line, and Propensity Score Methods.*

		ANOVA		*ANCOVA*		*Matched Sample*		*Regression Line*		*Propensity Score*	
Variable	*df*[1]	*p*	*Cohen's d*	*p*	*Cohen's d*	*p*	*Cohen's d*	*p*	*Cohen's d*	*p*	*Cohen's d*
Processing Speed Composite	2, 325	.00		.01		--		.02		--	
HC vs. uMDD	237	.44	0.10	.21	0.17	.08	0.26	.21	0.17	.28	0.14
HC vs. mMDD	238	.00	0.52	.00	0.41	.00	0.55	.00	0.39	.01	0.35
uMDD vs. mMDD	175	.00	-0.43	.11	-0.24	.31	0.13	.15	-0.22	.02	-0.35
Purdue Pegboard	2, 296	.00		.06		--		.05		--	
HC vs. uMDD	217	.59	-0.08	.87	-0.02	.45	-0.12	.88	-0.02	.67	-0.06
HC vs. mMDD	212	.00	0.44	.03	0.31	.00	0.62	.03	0.30	.14	0.20
uMDD vs. mMDD	163	.00	-0.57	.04	-0.33	.02	0.41	.03	-0.34	.03	-0.34
Trails A	2, 270	.00		.07		--		.10		--	
HC vs. uMDD	200	.56	0.08	.23	0.17	.53	0.10	.17	0.20	.54	0.08
HC vs. mMDD	194	.00	0.48	.03	0.34	.10	0.32	.03	0.32	.10	0.22
uMDD vs. mMDD	147	.02	-0.38	.33	-0.16	.42	0.10	.48	-0.12	.46	-0.11
Go Reaction Time	2, 282	.07		.19		--		.19		--	
HC vs. uMDD	209	.27	0.16	.15	0.20	.16	0.29	.15	0.21	.21	0.17
HC vs. mMDD	206	.03	0.32	.12	0.23	.40	0.16	.13	0.22	.13	0.21
uMDD vs. mMDD	149	.27	-0.18	.89	-0.02	.59	0.16	.90	-0.02	.43	-0.13
Attention Composite	2, 328	.00		.03		--		.02		--	
HC vs. uMDD	240	.50	-0.09	.75	-0.04	.76	-0.04	.68	-0.05	.40	-0.11
HC vs. mMDD	240	.00	0.44	.02	0.32	.24	0.20	.01	0.34	.06	0.24
uMDD vs. mMDD	176	.00	-0.51	.02	-0.36	.12	-0.24	.01	-0.38	.02	-0.35
Digit Span Forward	2, 270	.01		.03		--		.06		--	
HC vs. uMDD	198	.12	-0.20	.13	-0.22	.41	-0.13	.17	-0.20	.08	-0.25
HC vs. mMDD	195	.06	0.28	.13	0.23	.11	0.31	.19	0.19	.08	0.25
uMDD vs. mMDD	147	.00	-0.44	.01	-0.44	.01	-0.48	.02	-0.39	.00	-0.58
CVLT-II Trial 1	2, 323	.00		.04		--		.03		--	
HC vs. uMDD	236	.70	0.05	.46	0.10	.49	0.10	.47	0.10	.65	0.06
HC vs. mMDD	236	.00	0.45	.01	0.35	.06	0.33	.01	0.35	.02	0.22
uMDD vs. mMDD	174	.01	-0.41	.10	-0.25	.41	-0.13	.08	-0.26	.12	-0.23

		ANOVA		*ANCOVA*		*Matched Sample*		*Regression Line*		*Propensity Score*	
Variable	*df*[1]	*p*	*Cohen's d*	*p*	*Cohen's d*	*p*	*Cohen's d*	*p*	*Cohen's d*	*p*	*Cohen's d*
Go Accuracy	2, 282	.03		.16		--		.08		--	
HC vs. uMDD	209	.30	-0.15	.46	-0.10	.36	-0.02	.37	-0.13	.79	0.04
HC vs. mMDD	206	.05	0.29	.16	0.20	.65	-0.09	.11	0.23	.71	0.05
uMDD vs. mMDD	131.1[a]	.02	-0.40	.06	-0.31	.22	-0.18	.04	-0.33	.89	-0.02
Learning-Memory Composite	2, 326	.00		.01		--		.01		--	
HC vs. uMDD	238	.69	-0.05	.97	0.00	.56	0.09	.99	0.00	.79	-0.04
HC vs. mMDD	239	.00	0.50	.01	0.38	.03	0.39	.00	0.39	.01	0.33
uMDD vs. mMDD	175	.00	-0.56	.01	-0.37	.10	-0.27	.01	-0.38	.01	-0.38
CVLT-II Total 1-5	2, 323	.02		.20		--		.17		--	
HC vs. uMDD	236	.67	0.06	.39	0.01	.31	0.15	.38	0.12	.67	0.05
HC vs. mMDD	236	.01	0.36	.07	0.24	.14	0.25	.07	0.25	.10	0.22
uMDD vs. mMDD	165.4[a]	.05	-0.30	.40	-0.13	.81	-0.02	.38	-0.13	.52	-0.10
CVLT-II LDFR	2, 321	.55		.09		--		.38		--	
HC vs. uMDD	234	.34	-0.13	.57	-0.08	.81	-0.04	.53	-0.08	.46	-0.10
HC vs. mMDD	235	.06	0.25	.33	0.13	.59	0.09	.35	0.13	.33	0.13
uMDD vs. mMDD	163.7[a]	.02	-0.37	.17	-0.21	.37	-0.13	.20	-0.20	.31	-0.16
MSRT Total 1-5	2, 221	.21		.42		--		.38		--	
HC vs. uMDD	147	.88	-0.03	.56	-0.10	.56	0.12	.66	0.08	.87	-0.02
HC vs. mMDD	176	.12	0.24	.19	0.20	.59	0.11	.17	0.21	.47	0.10
uMDD vs. mMDD	119	.17	-0.26	.61	-0.09	.83	-0.03	.49	-0.13	.44	-0.12
MSRT LDFR	2, 220	.55		.35		--		.35		--	
[b]HC vs. uMDD	147	.53	-0.11	.15	0.25	.19	0.27	.15	0.26	.25	0.15
[b]HC vs. mMDD	175	.30	0.16	.52	0.10	.68	0.09	.48	0.11	.81	0.03
[b]uMDD vs. mMDD	118	.78	-0.05	.41	0.15	.40	0.19	.43	0.15	.61	0.08
Working Memory Composite	2, 320	.35		.50		--		.57		--	
HC vs. uMDD	234	.47	0.10	.38	0.12	.91	0.02	.40	0.11	.62	0.06
HC vs. mMDD	235	.14	0.20	.29	0.14	.81	0.04	.34	0.13	.37	0.12
uMDD vs. mMDD	171	.55	-0.09	.87	-0.02	.63	0.10	.96	-0.01	.83	-0.03

		ANOVA		*ANCOVA*		*Matched Sample*		*Regression Line*		*Propensity Score*	
Variable	*df*[1]	*p*	*Cohen's d*	*p*	*Cohen's d*	*p*	*Cohen's d*	*p*	*Cohen's d*	*p*	*Cohen's d*
Digit Span Backward	2, 282	.07		.31		--		.42		--	
HC vs. uMDD	199	.88	-0.02	.92	-0.01	.68	-0.07	.88	0.02	.95	0.01
HC vs. mMDD	195	.03	0.23	.14	0.22	.17	0.27	.18	0.20	.09	0.25
uMDD vs. mMDD	137.3[a]	.04	-0.34	.22	-0.20	.46	-0.11	.31	-0.17	.31	-0.17
No- Go Accuracy	2, 282										
HC vs. uMDD	209	.75	0.04	.74	0.05	.88	0.02	.73	0.05	.77	0.04
HC vs. mMDD	206	.72	0.05	.78	0.04	.94	-0.01	.77	0.04	.66	0.06
uMDD vs. mMDD	149	.97	-0.01	.97	-0.01	.57	0.14	.96	0.01	.86	-0.03
Executive Function Composite	2, 281	.24		.99		--		.99		--	
HC vs. uMDD	208	.56	-0.08	.91	-0.02	.57	-0.09	.93	0.01	.93	-0.01
HC vs. mMDD	204	.23	0.18	.94	0.01	.58	-0.10	.97	0.01	.97	0.01
uMDD vs. mMDD	150	.12	-0.25	.97	-0.01	.98	0.04	.98	0.00	.81	-0.04
COWAT	2, 269	.62		.73		--		.70		--	
HC vs. uMDD	207	.35	-0.14	.44	-0.11	.17	-0.22	.40	-0.12	.39	-0.12
HC vs. mMDD	193	.90	-0.02	.66	-0.07	.33	-0.19	.75	-0.05	.64	-0.07
uMDD vs. mMDD	138	.45	-0.13	.81	-0.04	.78	-0.07	.65	-0.08	.90	-0.02
Trails B	2, 270	.06		.01		--		.38		--	
HC vs. uMDD	199	.60	0.08	.18	0.19	.07	0.29	.15	0.21	.40	0.11
HC vs. mMDD	194	.03	0.33	.34	0.14	.46	0.14	.35	0.14	.82	-0.03
uMDD vs. mMDD	147	.11	-0.26	.75	0.05	.94	0.08	.77	0.05	.33	0.15
WCST Perseverative Errors	2, 245	.33		.60		--		.61		--	
HC vs. uMDD	190	.85	-0.03	.71	-0.05	.87	-0.03	.68	0.06	.74	0.05
HC vs. mMDD	174	.21	0.20	.31	0.16	.98	0.00	.33	0.16	.19	0.20
uMDD vs. mMDD	188.8[a]	.23	-0.23	.54	-0.11	.93	0.02	.59	-0.10	.27	-0.20

Note. HC = Healthy Controls, uMDD = unmedicated MDD, mMDD = medicated MDD; CVLT = California Verbal Learning Test, MSRT = Michigan Spatial Relation Test, COWAT = Controlled Oral Word Association Test, WCST = Wisconsin Card Sorting Test. a. Levene's correction for heterogeneity of variance. *df* = degrees of freedom for ANOVA or t test. Matched-sample analyses *df* varied by contrast pair: HC-uMDD (176), HC-mMDD (134), uMDD-mMDD (126).

APPENDIX B

WAYNE STATE UNIVERSITY

IRB Administration Office
87 East Canfield, Second Floor
Detroit, Michigan 48201
Phone: (313) 577-1628
FAX: (313) 993-7122
http://irb.wayne.edu

CONCURRENCE OF EXEMPTION

To: Rachel Kay
Psychology

From: Dr. Scott Millis
Chairperson, Behavioral Institutional Review Board (B3)

Date: April 30, 2013

RE:

IRB #:	046913B3X
Protocol Title:	Antidepressant Medications and Coginitve Functioning in Major Depressive Disorder (MDD)
Sponsor:	Psychology
Protocol #:	1304011941

The above-referenced protocol has been reviewed and found to qualify for **Exemption** according to paragraph #4 of the Department of Health and Human Services Code of Federal Regulations [45 CFR 46.101(b)].

- Protocol Summary Form (received in the IRB Office 4/18/2013)
- Revised Protocol (received in the IRB Office 4/18/2013)

This proposal has not been evaluated for scientific merit, except to weigh the risk to the human subjects in relation to the potential benefits.

- Exempt protocols do not require annual review by the IRB.
- All changes or amendments to the above-referenced protocol require review and approval by the IRB **BEFORE** implementation.
- Adverse Reactions/Unexpected Events (AR/UE) must be submitted on the appropriate form within the timeframe specified in the IRB Administration Office Policy (http://irb.wayne.edu/policies-human-research.php).

NOTE: Forms should be downloaded from the IRB Administration Office website http://irb.wayne.edu at each use.

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ABSTRACT

ANTIDEPRESSANT MEDICATIONS AND COGNITIVE FUNCTIONING IN MAJOR DEPRESSIVE DISORDER

by

Rachel E. Kay

August 2013

Advisor: Dr. Lisa J. Rapport

Major: Psychology (Clinical)

Degree: Master of Arts

Individuals with Major Depressive Disorder (MDD) frequently experience cognitive decrements in addition to mood impairments. Ironically, antidepressant medications used to treat depression may have adverse effects on cognitive functioning. It is imperative to understand the relative cognitive costs of antidepressants when considering the treatment of MDD patients. Furthermore, observational studies of depression are challenged by problems of systematically confounded variables. Researchers are often faced with difficulties in managing this issue and opt to either ignore the problem, alter their sample, or use inappropriate statistical methods (e.g., Analysis of Covariance) due to a limited understanding of acceptable solutions. It is important to provide researchers with the access to general knowledge of methods to manage systematic covariates in order to aid in effective and appropriate decision-making.

Participants included 178 adults with MDD (89 unmedicated-uMDD, 89 medicated-mMDD) and 153 healthy comparison (HC) adults who were evaluated for performance in several domains of cognition. The three groups were significantly different on age (mMDD

group was oldest) but equivalent on education. The MDD groups were equivalent in years of illness, differed on depression severity (uMDD more severe than mMDD).

Univariate analyses of variance (ANOVAs) indicated that performance among the groups was significantly different for measures of processing speed, attention, and some aspects of the learning and memory domain. However, the groups were generally equivalent on measures of working memory and executive functioning domains. Post hoc analyses using simple contrasts indicated that the significant were generally driven by worse performance for mMDD groups compared to uMDD and HCs. Exploratory analyses accounting for age and education included Analysis of Covariance (ANCOVA), Matched-samples, Regression-residuals, and Propensity Score Analysis (PSA). Overall, the pattern of findings was constant across methods, with relatively stable effect sizes for significant results. However, effect sizes for general (significant and non-significant) results varied by method.

Antidepressants used to treat MDD improve dispositional symptoms of depression but have adverse effects on some areas of cognition. Comparing the effect sizes may be useful to clinicians and researchers in distinguishing cognitive effects of medication separately from those associated with MDD. Furthermore, employing the proper methods to address systematic confounds (e.g., age and education) are essential to maintain sound research and to promote effective antidepressant treatment. Statistical solutions that are theoretically acceptable to use in order to address systematic covariates are discussed. Both the beneficial effects on depressive symptoms and adverse effects on cognition should be considered by practitioners and consumers when making treatment decisions.

AUTOBIOGRAPHICAL STATEMENT

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Education

In progress	**Graduate Student** Wayne State University, Detroit, Michigan Major: Clinical Psychology Minor: Neuropsychology
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Research Experience

2010 – present	***Graduate Research Assistant*** Lisa J. Rapport, Ph.D. Department of Psychology, Wayne State University Detroit, Michigan
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Memberships and Affiliations

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