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Neuropsychological Indicators of Preclinical Alzheimer's Disease Among Depressed Older Adults

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NEUROPSYCHOLOGICAL INDICATORS OF PRECLINICAL ALZHEIMER’S DISEASE
AMONG DEPRESSED OLDER ADULTS

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Depression and Alzheimer’s disease (AD) occur frequently in geriatric patients, but it is difficult to identify which depressed patients are in the preclinical AD phase due to the overlapping cognitive impairment in depression and AD. Based on data from 120 depressed patients who were dementia-free and completed a range of neuropsychological tests at baseline, we predicted that measures of temporal lobe function (area affected most in early AD), but not frontal lobe function, would distinguish older depressed patients who developed AD from those who did not develop AD. We found the domain of temporal lobe function was associated with AD to a greater extent than frontal lobe function in a structural equation model (SEM). Individual tests of temporal lobe function, including Logical Memory and Word List Learning were most predictive of AD status and had the highest sensitivity in logistic regression models. At least a one standard deviation on these tests in relation to scores derived for the population based on age and education should alert the clinician to the possibility of preclinical AD and warrant closer follow-up.
CHAPTER ONE

INTRODUCTION

Depression and Alzheimer’s disease (AD) are frequently seen conditions in geriatric patients. Not only are depressed elderly patients at greater risk for AD than healthy controls, but the disorders can be difficult to distinguish, particularly in the initial stages of AD because of the overlapping symptoms of AD and depression (Pfennig, Littman, & Bauer, 2007). Most depressed older adults show some cognitive deficits that can be mischaracterized as preclinical AD; however, most of these symptoms remit when the depression remits. On the other hand, for some patients, the cognitive symptoms actually represent the preclinical phase of AD, the period between AD onset and subsequent diagnosis, during which underlying disease processes may have already begun, but cognitive impairment is not severe enough to meet the criteria of AD. The challenge for geriatric practitioners is determining whether cognitive impairment in depression can be ameliorated by treatment for depression or whether cognitive impairment reflects underlying brain pathology associated with preclinical AD, in which both the depression and cognitive impairment would need to be addressed.

Early diagnosis of AD is important because patients might benefit from cognition-enhancing or disease-modifying drugs currently under development. It is generally assumed that treatment will have the greatest efficacy in delaying symptoms early in the course of AD before further irreversible brain damage has occurred (Gauthier, 2005). Not only is it important to identify and treat AD early in its course, but early recognition and treatment of depression in subjects who are not demented may also improve their prognosis (Kupfer, Frank, & Perel, 1989). The current longitudinal study attempted to identify neuropsychological tests that differentiated depressed patients with preclinical AD from depressed patients who did not develop AD.

1.1 Alzheimer’s Disease

AD is the most prevalent type of dementia, accounting for two-thirds of dementia cases (Hendrie, 1998), and was the focus of the current study. Among community dwelling adults age 65 and older, the prevalence of probable AD is 10.3% (Evans et al., 1989). However, as the number of elderly persons rises due to the aging of the baby boomer generation, the annual number of AD cases is expected to increase dramatically, from an estimated 5.1 million older Americans in 2010 to over 11 million in 2050 (Alzheimer’s Association, 2011).
AD is characterized by insidious onset and gradual decline in memory and mental abilities. The cause of AD is not altogether clear; however, evidence from structural and functional imaging reveals that advanced AD is characterized by neurofibrillary tangles, neuritic plaques, and loss of neurons and synapses. Neuropsychological evaluation is considered the most sensitive way to identify cognitive deficits in preclinical AD (Tuokko, Kristjansson, & Miller, 1995; Wright & Persad, 2007).

Non-AD dementias can present clinically similar to AD; however, the underlying causes (e.g., stroke, head injury, infection) involve different neurological mechanisms. For example, in the case of an individual who has a stroke, behavioral and cognitive problems that emerge reflect damage to the brain region where the stroke occurred. Thus, neuropsychological tests that identify preclinical AD may differ from those that identify non-AD dementias. However, it is important to note that much of the research in the area of neuropsychological indicators relates to dementia in general and not preclinical AD specifically. Thus, research on AD as well as dementia in general was reviewed when relevant.

1.2 Rationale for Studying Depressed Older Adults with Possible Preclinical AD

The current study was based on a sample of depressed older adults (age 60+) who were identified as not having dementia at baseline (though preclinical cognitive impairment may have been present and not measured) and who were followed over time to determine if AD occurred. As discussed below, we examined depressed individuals for two reasons: 1) depressed patients are at higher risk for developing AD, and thus, we were more likely to detect AD in this population than in healthy controls, 2) central to the present investigation, depressed elderly patients often present with cognitive deficits, and it is difficult to distinguish those elderly depressed patients with cognitive impairment that will remit along with the depression from those with cognitive impairments that persist and represent an underlying AD syndrome.

1.2.1 Relationship between Depression and AD

Depression is frequently associated with subsequent AD. Two meta-analyses of case-control and prospective studies found depression or depressive symptoms predicted subsequent cognitive decline and AD (Jorm, 2001; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). In addition, based on data from the current study, Steffens and colleagues (2004) found that compared to a control group of older adults with no history of depression, the risk of developing dementia over ten years was much higher among older adults with a history of depression.
Several theories have been suggested to account for the association between depression and AD. Jorm (2001) summarized the most viable explanations: 1) depression increases risk for AD by damage to the hippocampus via a glucocorticoid cascade (Sapolsky, Krey, & McEwan, 1986), and 2) depression is an early prodrome of dementia. Both explanations have received empirical support, and some suggest the relationship may be due to a combination of both factors (Andreescu et al., 2008).

According to the glucocorticoid cascade hypothesis proposed by Sapolsky (1996), depression and chronic stressors are associated with prolonged activation of the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis involves the hypothalamus, pituitary, and adrenal glands. In response to stress, the hypothalamus releases vasopressin and corticotropin-releasing hormone which, in turn, stimulate the pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH then stimulates the adrenal gland to release corticosteroids such as cortisol. Long-term exposure to stress during a depressive episode and the resulting prolonged high levels of cortisol are associated with cell death and shrinking of the hippocampus (McEwen, 1999), an area of the temporal lobe associated with learning and memory and damaged early in the course of AD.

Similar to the glucocorticoid cascade hypothesis, the prodrome hypothesis also predicts smaller hippocampal volumes as a marker of neuronal loss among depressed patients (Andreescu et al., 2008). However, the prodrome hypothesis diverges from the glucocorticoid cascade hypothesis in that it predicts a subgroup of subjects develops late-life depression as an early symptom of underlying pathological changes in AD (Brommelhoff et al., 2009) rather than serving as a risk factor for AD. Support for the prodrome hypothesis comes from studies of late-onset depression in which development of AD occurs shortly after the detection of depression (Brommelhoff et al., 2009; van Reekum et al., 1999).

Although there have been inconsistent findings regarding the mechanism of the relationship between depression and AD (i.e., glucocorticoid cascade versus prodrome hypothesis), there is empirical support for a relationship between depression and temporal lobe (e.g., hippocampal) volume loss. A meta-analysis of twelve studies of unipolar depression found an eight percent reduction in left hippocampal volume size and ten percent reduction in right hippocampal volume size among depressed patients relative to controls (Videbech & Ravnkilde, 2004). Smaller hippocampal volume is also associated with dementia. In the current sample,
researchers found smaller hippocampal volumes among depressed patients increased risk of later dementia (Steffens et al., 2007). Supporting the glucocorticoid cascade hypothesis, depressed people have high circulating levels of glucocorticoids through HPA dysregulation (Sapolsky, 1996), and HPA dysregulation and decreased hippocampal volumes are associated with cognitive decline in studies in humans and rodents (Lupien et al., 1998). Thus, depressed patients with temporal lobe damage may be at greatest risk for AD.

1.2.2 Overlapping Symptoms in Depression and AD

Not only are depressed patients at higher risk for AD, but it is also difficult to distinguish the two disorders due to their overlapping symptoms. Depression is associated with cognitive deficits that resemble AD, and historically, the term “depressive pseudodementia” was used to describe these memory problems. In fact, up to 32% of patients referred for dementia evaluations actually suffer from depression and not dementia (Marin, Sewell, & Schlechter, 2002). Unlike neuropsychological impairment in AD, neuropsychological impairment in depression in general may remit after successful treatment. Because differential diagnosis of depression and AD at baseline is difficult, many studies investigating indicators of preclinical AD among older adults have excluded subjects with depression and focused on non-depressed elderly. As a result, few studies have attempted to identify cognitive measures that differentiate depressed older adults with preclinical AD from depressed older adults without preclinical AD.

1.3 Neuropsychological Characteristics of AD

A main goal of the current study was to identify neuropsychological tests that detected individuals who have preclinical AD who present for treatment for depression. Importantly, to identify tests that indicate preclinical AD, we determined areas of the brain affected by AD. It should be noted that there are neuropsychological tests sensitive to early changes in cognition in preclinical AD among non-depressed individuals, but these tests may not be useful in discriminating depression from preclinical AD. Nonetheless, knowledge of early cognitive deficits in AD among non-depressed individuals may be informative to the current study.

1.3.1 Neuropsychological Deficits in AD Post-Diagnosis

Volume loss, plaques, and tangles in limbic areas (e.g., entorhinal cortex, hippocampus, and amygdala of the medial temporal lobe) can be detected at the earliest stages of AD (Braak & Braak, 1991). Not surprisingly, subtle declines in delayed recall and episodic memory tasks, which are associated with these structures, occur early in the manifestation of AD. For example,
the patient has difficulty encoding and storing new information, as well as recalling the information later (Lezak, Howieson, & Loring, 2004). As AD progresses, the syndrome is characterized by semantic memory impairment (i.e., memory of meanings and concept relationships often measured by verbal fluency or confrontation naming), associated with damage to the lateral temporal lobe (Levy, Bailey, & Squire, 2004). In addition, there are problems with executive functions of planning, flexibility, and abstract thinking, as well as language and visuospatial abilities as the disease progresses to the frontal and parietal lobes (Bondi et al., 2008). Primary sensory and motor cortices are spared until severe stages (Bondi et al., 2008), and simple attention span tasks are usually not impaired (Lezak et al., 2004).

1.3.2 Neuropsychological Deficits in Preclinical AD

Amyloid accumulation, significant neural dysfunction, and cell death occur well in advance of clinical diagnosis of AD (Wierenga & Bondi, 2007), but there is less consensus about specific areas of cognitive impairment pre-diagnosis. In the preclinical period, structural and functional imaging studies identified anatomical changes in the temporal lobe most often, although structural changes and decreased blood flow in other brain regions have also been identified, including frontal and parietal lobes, and the posterior cingulate of the “limbic lobe” (Backman, 2009; Bondi et al., 2008; Twamley, Ropacki, & Bondi, 2006). Thus, it may be that many possible brain regions are susceptible earlier in AD than previously thought (Twamley et al., 2006).

Given the impairment identified by structural and functioning imaging in multiple brain regions in preclinical AD, it is not surprising that studies have found a range of neuropsychological deficits appear before diagnosis. Research suggests that neuropsychological deficits are evident up to fourteen years before diagnosis (Amieva et al., 2008), although the range and type of deficits tend to vary across studies, likely due to variations in follow-up periods and the limited variety of tests administered. Importantly, there is agreement that one area consistently impaired in preclinical AD is episodic memory, which is related to the temporal lobe area. In this regard, deficits on tests of verbal and nonverbal delayed recall of new information are most consistently characteristic of the group that progresses to AD (Small, Fratiglioni, Viitanen, Winblad, & Backman, 2000). These episodic memory deficits in preclinical AD are not surprising given that episodic memory is associated with the area of the brain, the medial temporal lobe, first impaired once AD has been diagnosed (Braak & Braak, 1991).
Other temporal lobe areas of neuropsychological impairment (as well as frontal lobe areas) in preclinical AD were identified in a recent meta-analysis (Backman, 2009) and review (Twamley et al., 2006). In addition to large effects for episodic memory, impairments in semantic memory, processing speed, executive functioning, and global cognitive functioning were also noted. Results from individual studies are also consistent with these findings. For example, deficits associated with temporal lobe damage (i.e., episodic memory, semantic memory, and orientation), in addition to some deficits associated with frontal lobe dysfunction (i.e., processing speed and executive functioning/working memory) are related to the development of AD in many prospective studies (Ingles, Boulton, Fisk, & Rockwood, 2007; Jones, Tranel, Benton, & Paulton, 1992; Sacuiu, Sjogren, Johansson, Gustafson, & Skoog, 2005).

On the other hand, frontal lobe areas that do not appear to be impacted in preclinical AD (but may be impacted by depression in general) include short-term or immediate memory (Backman, Small, & Fratiglioni, 2001; Backman, Jones, Berger, Laukka, & Small, 2005; Backman, 2009), as well as sensory and motor abilities (Arnaiz & Almkvist, 2003). It is important to note that tests that successfully differentiate preclinical AD from healthy controls may not necessarily differentiate these outcomes in depressed patients due to similarities in cognitive impairment seen in depression and preclinical AD.

1.4 Neuropsychological Characteristics of Late Life Depression (With or Without Preclinical AD)

Elderly depressed patients present with cognitive impairment that may or may not indicate preclinical AD. Documented cognitive difficulties among older depressed patients relative to non-depressed controls are found in the areas of episodic memory, semantic memory, attention, short-term memory, processing speed, executive functioning/working memory, and visuospatial ability in meta-analytic (Christensen, Griffiths, Mackinnon, & Jacomb, 1997) and cross-sectional studies (Austin, Mitchell, & Goodwin, 2001; Pfennig et al., 2007; Reischies & Neu, 2000). As described in further detail below, there is considerable overlap in cognitive deficits in depressed elderly and preclinical AD in domains associated with the frontal (i.e., processing speed and executive functioning/working memory), as well as, temporal lobes (i.e., episodic memory and semantic memory). However, as we will argue, the temporal lobe area is most prominently disturbed in preclinical AD. There are also areas of cognitive functioning impaired in depression in general but not preclinical AD, including short-term or immediate
memory. Measures tapping areas impaired solely due to mechanisms associated with the depressive episode might not adequately distinguish depressed patients with and without preclinical AD.

1.4.1 Frontal Lobe Measures

First, depressed older adults in general (without preclinical AD) are impaired on frontal lobe tasks measuring attention, short-term memory, processing speed, and executive functioning/working memory relative to healthy controls (Nebes et al., 2000). Neuroimaging studies reveal disruption of the basal ganglia and fronto-striatal pathways caused by white-matter hyperintensities contributes to the development of late life depression (Lin, Kuo, Chiang, Chen, & Chen, 2006), results in deficits in emotion and mood (Steffens & Potter, 2008), and underlies these cognitive abilities (Butters et al., 2000). These abilities generally improve after treatment of depression, even in studies where other cognitive abilities such as episodic memory may not improve (Butters et al., 2000; Devanand et al., 2003), which suggests impairment in short-term memory, processing speed and executive functioning/working memory would not be predictive of preclinical AD among depressed patients. For example, improvement in depression is associated with increased scores on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) digit symbol subtest, a measure of processing speed (Devanand et al., 2003).

There is also evidence that deficits associated with frontal lobe dysfunction may impact older depressed patients’ performance on other cognitive tasks. For example, processing speed and executive functioning mediate episodic memory and visuospatial deficits in depression (Nebes et al., 2000). Thus, the mechanism of reversible episodic memory deficits in depression in general may differ from that of stable episodic memory deficits in preclinical AD. It is important to note that depressed individuals who have preclinical AD may show some improvement in cognitive tasks after the depression remits, making differential diagnosis more difficult; however, the underlying AD progresses.

1.4.2 Temporal Lobe Measures

As we will argue, we expected temporal lobe function to most likely be disrupted in preclinical AD. As stated above, however, depressed older adults in general may also be impaired on measures of temporal lobe function (e.g., episodic and semantic memory tasks) relative to healthy controls. Often times, these impairments are largely due to (i.e., fully mediated by) the secondary effects of attention, motivation, and processing speed (Nebes et al.,
2000). On the other hand, depression may be associated with temporal lobe impairment that is not explained by attention, motivation, and processing deficits, does not improve after treatment (Butters et al., 2000; Devanand et al., 2003), and may be indicative of structural changes that represent underlying AD. In fact, among patients with AD but not depression, statistically removing the effects of processing speed does not fully attenuate the effect of impaired episodic memory in the prediction of AD (Sliwinski & Buschke, 1997). According to the glucocorticoid cascade hypothesis, those depressed patients with impairments indicative of temporal lobe dysfunction (via atrophy to the hippocampus, as described above) at baseline above and beyond the effects of motivation, attention, and frontal lobe impairment should be at greatest risk for developing AD.

1.5 Neuropsychological Deficits Indicative of Preclinical AD in Depressed Older Adults

To date, most research on depression and AD has focused on distinguishing the two cross-sectionally once AD is severe in clinical course. There is a lack of studies relating neuropsychological tests at baseline to follow-up diagnoses of AD among depressed individuals. The few studies that have been conducted in this area have found particular cognitive characteristics may help differentiate depressed subjects who are predisposed to developing AD from those who are not, though results are not always consistent. Currently, there is no consensus as to which neuropsychological tests are most indicative of preclinical AD.

Critical to the present investigation, some studies have attempted to identify depressed individuals who are in the preclinical AD phase. First, studies show tests of global cognitive functioning at baseline are helpful in predicting new cases of dementia. In one study, depressed inpatients with cognitive impairment determined by Mini Mental Status Examination (MMSE) scores less than 24 at admission had higher rates of any dementia after discharge than depressed subjects without cognitive impairment (Alexopoulos, Meyers, Young, Mattis, & Kakuma, 1993). However, as we discuss below in the method section, the depressed patients in the current study were required to have a MMSE score of 25 or higher and, thus, a global scale of cognitive functioning may not be a useful assessment for this sample of depressed patients. Nonetheless, using data from which the current study is based, Steffens and colleagues (2007) found in proportional hazards analyses controlling for age, sex, education, and depression severity that a lower overall MMSE score at baseline was associated with reduced time to any dementia onset.
However, these two studies examined a single measure of global cognitive functioning, the MMSE, which is made up of indicators of various cognitive abilities, and they focused on development of any dementia rather than AD specifically. Findings of general deficits on global measures of cognitive functioning may be limited in their usefulness in depressed patients. Specifically, it is difficult to determine which area of cognitive functioning is most impaired in preclinical AD with depression to facilitate differential diagnosis. If there is a particular area of cognitive functioning indicative of preclinical AD among depressed individuals, there may be more sensitive neuropsychological tests specific to the impaired area.

A third study utilized a number of neuropsychological tests in addition to the MMSE in a sample of 116 depressed patients at a large hospital (Halloran et al., 1999). Although global cognitive scores were lower in those patients who received a later diagnosis of any dementia, there were no baseline differences on specific measures such as delayed word recall, the digit symbol substitution test of the WAIS-R, immediate and delayed story recall, picture recognition, or the National Adult Reading Test. However, methodological limitations may have led to these results. In this regard, although subjects did not have a DSM diagnosis of dementia at baseline, baseline MMSE scores ranged from 12 to 30, suggesting some subjects were already experiencing considerable cognitive difficulties, but nonetheless, were not excluded from the study. As a result, some subjects may already have been in an advanced dementia phase. Additionally, subjects were only followed up on average for two years, which may not have identified subjects who would later develop dementia.

Jean and colleagues (2005) utilized a longer follow-up period (7.5 years on average) to assess depressed patients at a day hospital on subscales of the MMSE and Dementia Rating Scale at baseline. Patients who developed any dementia had lower scores on attention and memory subscales, and those who met criteria for AD in particular had lower scores on the MMSE orientation items. However, many subjects were lost to follow-up (only 44 of 191 initial subjects were followed-up), and the attrition in the study limits the generalizability of the results. Furthermore, as in the previous study, one limitation is that some subjects had low MMSE scores suggestive of significant cognitive impairment at baseline.

In a fifth study, Visser and colleagues (2000) assessed non-demented patients at a memory clinic on several neuropsychological tests at baseline and over five years later for AD. They excluded at baseline subjects with dementia or MMSE scores less than 24. Overall,
depressed and non-depressed subjects who developed AD were impaired on measures of fluency and time on a memory scanning task, which the authors define as executive functions associated with the frontal lobe, as well as delayed recall, an episodic memory task associated with the temporal lobe. However, among depressed subjects in particular, poorer delayed recall scores distinguished those who developed AD at follow-up. Although the executive functioning tasks were found to be impaired among the depressed group relative to the non-depressed control group at baseline, importantly, these measures were not predictive of AD among depressed subjects. Thus, episodic memory (a temporal lobe function) in particular predicted new cases of AD among the depressed subjects.

Based on the results of this handful of studies, it is expected that the best approach for identifying depressed persons in the preclinical AD phase is to show the presence of temporal lobe impairment (e.g., episodic memory, semantic memory, or orientation) that is not explained by other cognitive deficits such as those associated with frontal lobe impairment (e.g., short-term memory, processing speed and executive functioning/working memory) associated with depressed elders in general and which may remit after the depression remits.

1.6 Current Study

The current study used previously collected data from the Neurocognitive Outcomes of Depression in the Elderly (NCODE) study (Steffens et al., 2004), a NIMH-supported study at Duke University Medical Center in Durham, North Carolina. Recruitment began in 1997 and continues to the present. Participants were elderly depressed individuals (age 60+) without dementia for whom a wide array of neuropsychological tests was obtained at baseline and who were assessed each year for AD over at least 2.5 years. The current study had three aims.

1.6.1 Aim 1: Theoretical Model

First, we formulated a theoretical structural equation model (SEM) of two specific domains of neuropsychological deficits that identified depressed individuals who develop AD over time. A strength of SEM is the ability to construct latent variables that are not measured directly, but are estimated in the model from several observed variables, each of which is thought to “tap into” the latent variable. This allowed the structural relations between latent variables to be estimated. We developed a latent construct of temporal lobe function derived from several measures (episodic memory, semantic memory, orientation) assessed at baseline which we predicted would be strongly related to AD status more than 2.5
years later. We also developed a latent construct of *frontal lobe function* derived from measures (short-term memory, processing speed, executive functioning/working memory) thought to identify deficits in cognition among depressed individuals in general. We predicted that this latent construct would have a *weaker* association to AD status.

### 1.6.2 Aim 2: Practical Model

Because results of the theoretical model may not have direct clinical utility, we also tested a practical model of individual neuropsychological tests at baseline most likely to predict AD status. We accomplished this aim using a hierarchical logistic regression analysis with AD status at follow-up as the dependent variable and included as predictors a number of tests of temporal lobe and frontal lobe dysfunction at baseline. Given the relatively intact short-term memory function in preclinical AD, as well as the overlapping cognitive impairment seen in depression in general and AD in the areas of executive functioning and processing speed, we predicted that poorer performance on temporal lobe tests at baseline (above and beyond frontal lobe tests of short-term memory, processing speed, or executive functioning/working memory) would be associated with a later diagnosis of AD. Tests of temporal lobe function included the Wechsler Memory Scale-Revised (WMS-R) Logical Memory Delayed Recall subtest, Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) Word List Learning subtest, CERAD Constructional Praxis Delayed Recall subtest, CERAD Category Fluency, CERAD Boston Naming Test, MMSE delayed recall items, and MMSE orientation items.

### 1.6.3 Aim 3: Predictive Accuracy

Based on the results of the two previous analyses described above, we hoped to identify in an overall model domains of cognitive functioning, as well as individual neuropsychological tests, most predictive of new cases of AD. To further aid in clinical utility, a final aim was to evaluate the individual predictive accuracy (sensitivity, specificity, positive predictive value, and negative predictive value) of the three tests that were the strongest predictors of AD status in the overall logistic regression analysis. We accomplished this third aim by running three separate logistic regression analyses, selecting each neuropsychological test as a predictor variable and AD status as the dependent variable while controlling for covariates.
CHAPTER TWO

METHOD

2.1 Participants

Our sample consisted of depressed patients enrolled in the Neurocognitive Outcomes of Depression in the Elderly (NCODE) study, a study of adults age 60 and older at Duke University Medical Center, beginning in 1997. Participants were referred from primary care physicians, psychotherapists, or psychiatrists at Duke or in the community.

At baseline participants were excluded from the NCODE study if they met criteria for a primary diagnosis of another major Axis I psychiatric disorder that may have affected neurological functioning (e.g., bipolar disorder, schizophrenia, schizoaffective disorder, substance abuse), endorsed history of alcohol or substance use problems, were diagnosed with a primary neurological condition (e.g., stroke, seizure disorder, Parkinson’s disease), or were coping with other factors/conditions that may affect neuropsychological performance (e.g., barbiturate or hypnotic use, major medical illness with cognitive sequelae, significant sensory or motor limitations). Participants were also excluded from the NCODE study if they met criteria for dementia at baseline (as assessed by MMSE, psychiatric interviews and physician notes). Those with psychotic depression or comorbid anxiety disorders were included in the NCODE study as long as the geriatric psychiatrist deemed major depression to be the primary psychiatric disorder.

There were 152 individuals who met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for current major depression at baseline and received neuropsychological testing at baseline. Among these participants, as illustrated in Figure 1, there were 124 individuals who were followed up for at least 2.5 years (and selected for inclusion in the current study). However, we should note that among those followed for at least 2.5 years, several participants were followed for a longer period of time.

2.2 Baseline Depression Assessment

At baseline a geriatric psychiatrist diagnosed depression based on 1) a clinical interview, 2) the Duke Depression Evaluation Schedule (DDES), a validated research tool, and 3) a number of standardized clinical assessments, including the Montgomery Asberg Depression Rating Scale.
Trained interviewers administered the DDES, a computer-assisted structured interview that included the Diagnostic Interview Survey (DIS) which allows for an assessment of DSM-IV current and lifetime Major Depression and history of depression. Items on the DIS paralleled symptom criteria for DSM-IV diagnosis of depression. It fully specified all questions and probes to be used, and it was accompanied by a set of computer programs that made diagnoses on the basis of analysis of symptom scores. The DIS has been used in a set of epidemiological studies sponsored by the NIMH Center for Epidemiological Studies. Its accuracy has been evaluated in a test-retest design (Robins, Helzer, Croughan, Williams, & Spitzer, 1981). It has been found to have good validity and reliability for participants of all ages (Robins, Helzer, Croughan, & Ratcliff, 1981) and is widely used in research in aging populations (see, for example, Beekman et al., 2000).

2.3 Baseline Cognitive Screening to Rule out Dementia

In addition to assessing for depression, at baseline a geriatric psychiatrist examined each participant, reviewed the participant’s medical records and results of the DIS assessment, and consulted with the referring physician to determine whether the participant had dementia. Participants with significant cognitive impairment at baseline were excluded from the NCODE study due to the focus on predictors of preclinical AD. Additionally, at baseline all participants were administered the MMSE (Folstein, Folstein, & McHugh, 1975), an objective measure of global cognitive functioning used extensively in epidemiologic research of older adults. Scores range from 0 to 30, with higher scores indicative of better cognitive functioning; a score below 25 is generally indicative of cognitive impairment. Depressed participants with initial MMSE scores less than 25 were followed through an 8-week phase of treatment to determine if cognition improved as the depression improved (e.g. MMSE of 25 or greater). Individuals whose MMSE scores remained below 25 were not followed longitudinally in the NCODE study, as these individuals were already experiencing cognitive difficulties potentially indicative of dementia.

2.4 Clinical Follow-Up of Depressed Subjects

The NCODE study operates in a naturalistic treatment milieu using a treatment algorithm established by the Duke Affective Disorders program. Treatment modalities included antidepressant medication, electroconvulsive therapy, and individual and group cognitive-behavioral therapy. Although data identifying current treatment for each participant are not
available, the majority of the participants received a selective serotonin reuptake inhibitor
(SSRI). A history of past treatments was assessed during the DDES. Fourteen reported having
ECT, twelve reported having taken lithium, and 89 reported having taken antidepressant
medication in the past.

2.5 AD Diagnosis

Based on follow-up evaluations over time, a subsample of participants possibly having
cognitive problems indicative of the onset of AD was reviewed by a consensus diagnostic
conference. Participants were selected into this subsample for further follow-up if the geriatric
psychiatrist suspected dementia or clinically significant cognitive decline, if the participant was
given a neuropsychological diagnosis consistent with dementia or cognitive impairment after
review of the most recent neuropsychological data, or if a neurological consultation resulted in a
diagnosis of dementia or cognitive impairment. This subsample was then reviewed by a yearly
consensus panel. Therefore, participants who have not been selected to be reviewed by the
consensus diagnostic conference are those whose study geriatric psychiatrist has not identified a
cognitive problem after a complete review of the most recent records.

The subsample of participants identified as potentially exhibiting AD or dementia was
reviewed by the consensus panel of experts in dementia, including three geriatric psychiatrists, a
cognitive neuroscientist, one to two neuropsychologists specializing in memory disorders, and a
neurologist specializing in memory disorders. Panel members reviewed initial and most recent
depression study notes, most recent neuropsychological testing, and neurological consultations
when available. The National Institute of Neurological and Communicative Disorders and Stroke
(NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA, now
known as the Alzheimer's Association) established the most commonly used NINCDS-ADRDA
Alzheimer's criteria for diagnosis (McKhann et al., 1984). Panel members used these criteria for
diagnoses of probable and possible AD (See Table 1) or other dementia (Roman et al., 1993).
These criteria require that the presence of cognitive impairment and a suspected dementia
syndrome be confirmed by neuropsychological testing for a clinical diagnosis of possible or
probable AD. Cognitive impairment had to be demonstrated in at least one of eight domains:
memory, language, perceptual skills, attention, constructive abilities, orientation, problem
solving and functional abilities. These criteria have shown good reliability and validity (Blacker
et al., 1994). In addition, subsyndromal AD was defined as early or prodromal stages of AD and
included functional impairment in one or more cognitive domains. As shown in Figure 1, participants \((n=4)\) who developed dementias other than AD (e.g., vascular, subcortical, Pick’s disease, Lewy Body) were excluded from the current analyses. The dependent variable was coded 1 (probable, possible, or subsyndromal AD) or 0 (no dementia).

Any participant whose case was not reviewed at a consensus diagnostic conference or was not assigned a dementia diagnosis was coded 0 (non-AD case). Given that there was some attrition, we included data from only those participants who were followed up at least 2.5 years.

2.6 Neuropsychological Test Battery

The neuropsychological test battery was administered to depressed participants at baseline while still symptomatic and then annually regardless of depression status. It consisted of a brief screening battery for dementia, the CERAD, supplemented by additional measures that correspond to several domains of cognitive functioning to enhance detection of early dementia (See Table 2). This battery was designed for efficient neurocognitive evaluation of geriatric patients and has now been successfully employed in clinical and epidemiological settings (Tschanz et al., 2000). For the current study, we examined tests known to be associated with preclinical AD, and eliminated measures not impaired in preclinical AD (e.g., tests sensitive to sensory and motor abilities). When both recognition and recall forms of a test were given, we chose recall due to evidence that recall is impaired to a greater extent than recognition in preclinical AD (Backman, 2009). Testing was administered by a trained psychometric technician supervised by a licensed clinical neuropsychologist and took approximately 60 minutes. To minimize possible fatigue effects, subjects received a five minute rest period after 20 minutes of testing.

Cicchetti (1994) provided recommendations for the clinically acceptable level of internal consistency reliability: Tests with reliabilities below .70 are unreliable, those between .70 and .79 are fair, those between .80 and .89 are good, and those above .90 are excellent. Cicchetti and Sparrow (1981) provided recommendations for acceptable levels of interrater reliability: Below .40 is poor, between .40 and .59 is fair, between .60 and .74 is good, and between .75 and 1.00 is excellent.

2.6.1 Measures of Temporal Lobe Function
Episodic Memory. Episodic memory includes recall of specific events and experiences and is impaired in preclinical AD. Lesions of the left temporal lobe disrupt verbal memory, and lesions of the right temporal lobe disrupt nonverbal memory (Lezak et al., 2004).

WMS-R Logical Memory Delayed Recall. Logical Memory Delayed Recall assessed delayed verbal memory and involved two orally presented narratives (Wechsler, 1987). The subject was asked to repeat as many details from the narratives as possible, first for an immediate recall trial, and second for a 30-minute delayed recall trial. Subjects were awarded one point for each correctly recalled detail. Interrater reliability coefficients are excellent at above .95 (Wechsler, 1987), and internal consistency reliability estimates are fair at .75 (Wechsler, 1987). Scores on the delayed recall trial range from 0-50. Performance is associated with activation of the medial and left temporal lobe (Ragland, Coleman, Gur, Glahn, & Gur, 2000), and declines in scores are associated with atrophy of the left medial temporal lobe (McDonald et al., 2010). Furthermore, lower scores predict preclinical AD among older adults (Elias et al., 2000; Howieson et al., 1997).

CERAD Word List Learning Delayed Recall. Word List Learning Delayed Recall assessed learning ability for new verbal information (Morris et al., 1989). Ten nouns were simultaneously read aloud by the examiner and shown from a booklet one at a time for two seconds to ensure that the subject understood each word. The same ten words were presented in a different order for three trials. The number of correctly recalled words after a ten minute delay filled with a nonverbal distracter task was recorded. One point was given for each correctly recalled word, and scores range from 0-10. Interrater reliability has been reported as high at 1.0 (Morris et al., 1989). This test accurately detects mild AD (Karrasch et al., 2005; Welsh et al., 1991) and is associated with reduced volume (Mortimer, Gosche, Riley, Markesbery, & Snowdon, 2004) and greater neurochemical abnormalities (Ackl et al., 2005) of the hippocampus.

CERAD Constructional Praxis Delayed Recall. Constructional Praxis Delayed Recall measured nonverbal memory. This subtest was not included in the initial CERAD battery, and reliability information is not reported. Participants were asked to draw the four geometric figures from the CERAD Constructional Praxis test approximately four minutes after their initial drawings (Yuspeh et al., 1998). Subjects were awarded one point for each detail correctly drawn, and scores range from 0-11. This test accurately distinguishes AD patients from controls.
(Karrasch et al., 2005) and is associated with reduced gray matter of the temporal cortex (Dos Santos et al., 2011).

**MMSE delayed recall items.** Participants were asked to recall three words (apple, table, and penny) they were told earlier in the examination and awarded one point for each correctly recalled word (range 0-3; Folstein et al., 1975). Internal consistency reliability has been reported as fair at $\alpha = 0.765$ (Shigemori, Ohgi, Okuyama, Shimura, & Schneider, 2010). Scores predict the development of AD (Small et al., 1997; Small et al., 2000), and performance is associated with activation of the medial temporal cortex (Ushijima et al., 2002).

**Semantic Memory.** Semantic memory refers to what is learned as knowledge. Semantic disruptions in preclinical AD appear in verbal fluency, or the ability to produce words in uninterrupted strings. Effective verbal fluency requires intact semantic store for supplying a knowledge base of words, plus an effective search process to access and retrieve this information (Chertkow & Bub, 1990). Confrontation naming, or the ability to pull out the correct word at will, is also a form of semantic memory impaired in preclinical AD. The temporal lobe (e.g., perirhinal cortex) is associated with semantic errors and retrieval of semantic information, and the hippocampus in particular is a component of the network of visual confrontation naming (Sawrie et al., 2000).

**CERAD Category Fluency.** Subjects were asked to generate words that belonged to a specific category (i.e., animals). The total score was calculated by summing the number of words the subject produced each 15 seconds. Perseverations (repetitions of the same word), and losses of set (productions of words that were not animals) were not counted. Interrater reliability has been reported as high at above .90 (Morris et al., 1989). Category fluency has been established as a useful tool for differentiating mild AD from normal aging (Karrasch et al., 2005) and staging the level of dementia (Welsh et al., 1991) and is associated with neurochemical abnormalities in the hippocampus (Ackl et al., 2005).

**CERAD Boston Naming Test.** The Boston Naming Test (BNT) is a measure of confrontation naming ability (Kaplan, Goodglass, & Weintraub, 1978) that contains five high, medium, and low frequency items from the original BNT. The examiner presented subjects with a series of black and white drawings and asked them to provide the name of the object. Ten seconds were allowed for each picture. The subject was prompted if he or she provided an ambiguous answer (e.g., “is there another name for that?”). Each correct response was given one
point (range 0-15). Interrater reliability is high, reported at above .90 (Morris et al., 1989).
Scores on the BNT predict AD (Karrasch et al., 2005) and preclinical AD among older adults
(Howieson et al., 1997) and are associated with temporal lobe volume (Wilson et al., 1996).
Declines in scores are related to temporal lobe volume loss over time (McDonald et al., 2010).

**Orientation.** Orientation refers to the awareness of self in relation to one’s surroundings.
Both temporal and spatial disorientation in AD are related to the degeneration (i.e.,
neurofibrillary tangle densities) of pathways linking the hippocampus with the superior parietal
and posterior cingulate cortex in the right hemisphere (Giannakopoulos et al., 2000).
Spatial orientation was assessed with the MMSE orientation items (Folstein et al., 1975)
by asking for the state, county, city, floor of building, and address. Temporal orientation was
assessed by asking for the year, season, date, day of week, month. Responses to each question
were coded 1 (correct) or 0 (incorrect) and then summed (range 0-10). Internal consistency has
been reported as fair at α=0.734 (Shigemori et al., 2010). MMSE orientation scores predict
preclinical AD among older depressed patients (Jean et al., 2005) and new cases of AD among
non-depressed patients (Small et al., 1997). Poorer scores are associated with reduced activation
of the parietal cortex and hippocampus (Ushijimi et al., 2002).

### 2.6.2 Measures of Frontal Lobe Function

**Short-Term Memory.** Short term (immediate) memory refers to the capacity for holding
a small amount of information in mind in an active, readily available state for a short period of
time and can be thought of as simple, immediate span of attention, or how much information can
be grasped at once (Lezak et al., 2004). Short-term memory is associated with the dorsolateral
prefrontal cortex of the frontal lobe and is affected in depression but not preclinical AD.

The Benton Visual Retention Test (BVRT; Benton, 1974) is an un-timed test measuring
immediate visual memory and involved reproducing ten visual designs one at a time on paper
from memory. Each design was shown for ten seconds, and the patient was asked to draw the
design immediately after removing the stimulus. Results were scored by form, shape, patterns,
and arrangement on the paper (correct/incorrect) and range from 0-10. Internal reliability has
been reported as fair at .79 (Steck, Beer, Frey, Frühschütz, & Körner, 1990), and interrater
reliability was reported as excellent at above .95 (Dougherty et al., 2003; Swan, Morrison, &
Eslinger, 1990). BVRT scores predict conversion to AD in some (Kawas et al., 2003) but not all
(Galvin et al., 2005; Ingles et al., 2007) studies, and lower scores are associated with smaller orbital frontal cortex volume (Steffens, McQuoid, Welsh-Bohmer, & Krishnan, 2003).

**Processing Speed.** Processing speed is the ability to automatically and fluently perform cognitive tasks, especially when high mental efficiency is required. Processing speed is associated with activity in the prefrontal cortex of the frontal lobe (Rypma et al., 2006) and is impaired in preclinical AD.

The Symbol Digit Modalities Test assessed attention, processing speed, and incidental memory. Participants used a key showing nine number and symbol pairs to write a series of numbers matching their corresponding symbols (Smith, 1982). The total number of correct responses within 90 seconds was recorded, with a maximum score of 110. Internal and interrater reliability information is not reported, likely because it is a timed task (Strauss, Sherman, & Spreen, 2006). Scores predict conversion to AD (Fleisher et al., 2007).

**Executive Functioning/Working Memory.** The domain of executive functioning is broadly defined across studies, but generally includes higher-order cognitive processes like attentional control, planning, working memory, performance monitoring, and mental flexibility. Working memory requires people to hold information in mind while performing a mental operation on it via executive processes (such as decision making and attentional control); thus, in the current study we considered working memory tasks to fall under the domain of executive functioning. Executive functions and working memory involve different regions of the frontal lobes, prefrontal cortex, and subcortical structures and are impacted in mild AD. The dorsal prefrontal cortex in particular is critical for the allocation of attentional resources during working memory tasks (Koechlin, Basso, Pietrini, Panzer, & Grafman, 1999).

**Trail Making Test Part B – Part A.** The Trail Making Test is part of the Halstead-Reitan Test Battery. Part A required patients to quickly connect numbered circles ranging from 1-25 scattered on a page in sequence, whereas Part B assessed attention, visuomotor processing speed, and mental flexibility by requiring patients to connect circles in alternating numerical (1-13) and alphabetical (A-L) sequences (Reitan & Wolfson, 1985). If an error was made, the examiner pointed it out for correction and had the patient return to and continue from the correct location while the clock remained running. Completion time in seconds was recorded with a maximum of 300 seconds. Alternate form reliability estimates for Part A range from .89 to .95 (Charter, Adkins, Alekoumbides, & Seacat, 1987), and interrater reliability has been reported as excellent.
at .94 (Fals-Stewart, 1991). For Part B, alternate form reliability estimates range from .92 to .94 (Charter et al., 1987), and interrater reliability has been reported as excellent at .90 (Fals-Stewart, 1991). We computed the difference in seconds on Parts B and A, which is thought to minimize the influence of visuomotor tracking on Part B performance and to be a purer measure of executive functioning and working memory (Strauss et al., 2006). Declines in scores are associated with atrophy of the left and right frontal regions (McDonald et al., 2010).

**WAIS-R Digit Span Backward.** Digit Span Backward (Wechsler, 1981) is a test of working memory and mental tracking which involved presenting a series of digits out loud at a rate of one per second. The participant was then asked to repeat the digits in backward order. Scores range from 0-14. Internal consistency and interrater reliability have not been reported (Wechsler, 1981). Scores on Digit Span Backward are associated with preclinical AD in some but not all (Elias et al., 2000; Howieson et al., 1997) studies, and performance is associated with activation of the lateral frontal cortex (Owen, 2000).

**Ascending Digit Span.** Ascending Digit Span was modeled after the Digit Ordering Test. The examiner read a series of numbers and asked the subject to reorder the numbers in ascending order from smallest to largest (Sair, Welsh-Bohmer, Wagner, & Steffens, 2006). In this study, participants were read lists ranging from 2-8 numbers and allowed a maximum of two tries at each level. The task was stopped if the subject made two errors at a given level or completed eight digits correctly. Scores range from 0-14. Reliability information has not yet been reported.

**MMSE attention and calculation item.** Participants were asked to spell “world” backwards and awarded one point for every correct letter (range 0-5; Folstein et al., 1975). Errors were assigned consistent with the CERAD scoring method based on deletions, additions, transpositions, and misplacements. Internal consistency reliability has been reported as fair at $\alpha=0.752$ (Shigemori et al., 2010). Performance is associated with activation of the frontal cortex (Ushijimi et al., 2002). AD patients perform worse than controls on this item (Hohl, Grundman, Salmon, Thomas, & Thal, 1999); however, it is unclear whether poor performance is indicative of preclinical AD (Small et al., 1997).

### 2.7 Control Variables

Variables associated with poorer cognitive functioning or AD including advancing age (Kawas & Katzman, 1999), fewer years of education (Ott et al., 1995), non-Caucasian race (Sachs-Ericsson & Blazer, 2005), and female gender (Fratiglioni, 1997) were assessed at
baseline and controlled for in logistic regression analyses. In addition, we controlled for indicators of depression severity from the DDES including age of depression onset, number of depressive episodes, and number of current DSM-IV depressive symptoms on the DIS.

2.8 Explanatory Variables

In addition to neuropsychological tests, we also determined whether the following variables discriminated AD and non-AD groups using ANOVA and chi-square analyses: number of years followed-up, self-rated physical health on a 1-4 scale, self-reported health problems (asthma, diabetes, heart trouble, hypertension, arthritis, stroke, cancer, emphysema, ulcer, hardening of arteries, anemia), self-rated stress over the past six months (on a 1-6 scale), number of stressful life events reported over the past year, seven item activities of daily living (ADL) scale (Chronbach’s α = .802), nine item independent activities of daily living (IADL) scale (Chronbach’s α = .903), and a subjective social support scale derived from prior factor analysis (Koenig et al., 1993) of the Duke Social Support Index (e.g., feeling useful, listened to, understood, satisfied with relationships, etc.; Chronbach’s α previously reported as .79; Hays, Steffens, Flint, Bosworth, & George, 2001).

2.9 Data Analytic Plan

2.9.1 Aim 1: Theoretical Model

We used SEM in Mplus (Muthén & Muthén, 2004) to relate baseline scores on neuropsychological tests to AD status over the follow-up period (See Figure 2). The first latent predictor variable, temporal lobe function, was comprised of neuropsychological tests at baseline hypothesized to be strongly related to AD status at follow-up. These included episodic memory tests (WMS-R Logical Memory Delayed Recall, CERAD Word List Learning, CERAD Constructional Praxis Delayed Recall, MMSE delayed recall items), semantic memory tests (CERAD Category Fluency, CERAD Boston Naming Test), and orientation (MMSE orientation items). The second latent predictor variable, frontal lobe function, was comprised of neuropsychological tests at baseline generally associated with deficits among depressed patients but not hypothesized to be strongly related to AD status at follow-up among depressed patients. These included short-term memory tests (Benton Visual Retention Test), processing speed tests (Symbol Digit Modalities Test) and executive functioning/working memory tests (Trail Making Test Part B – Part A, WAIS-R Digit Span Backward, Ascending Digit Span, MMSE attention/calculation item).
Given the wide range of neuropsychological impairment in preclinical AD, we expected all of the neuropsychological measures would be related to AD status to some extent; however, we expected certain measures to be better predictors than others. Thus, recommendations about effect size interpretation (Kline, 2005) are as follows: Standardized path coefficients with absolute values less than .10 indicated a small effect, around .30 indicated a medium effect, and greater than or equal to .50 indicated a large effect. We expected the standardized structure coefficient of temporal lobe function would be greater than frontal lobe function. To statistically compare the strength of the structure coefficients to AD status, we ran the model a second time constraining the structure coefficients to be equal and examined results from a one degree of freedom chi-square difference test comparing the two models. If the chi-square difference test was significant, we could conclude one path was statistically greater than the other.

Power Analysis. Using guidelines from MacCallum and colleagues (1996) for a post-hoc power analysis of overall model fit, for a test of not close fit, the null hypothesis is that the fit is not excellent or close, and power is the probability of rejecting the null hypothesis. With 70 degrees of freedom and a sample size of 100 for a test of not close fit, power is 0.33; with a sample size of 200, power increases to 0.74. With 80 degrees of freedom and a sample size of 100, power is 0.36; with a sample size of 200, power increases to 0.79. Therefore, power for the overall model in the current study (N=120) with 75 degrees of freedom ranged between 0.33 and 0.79.

Model Fit. To evaluate model fit, we used the following indices: \( \chi^2 \) goodness of fit, \( \chi^2/df \), the Comparative Fit Index (CFI), the Tucker-Lewis Index (TLI), and the root-mean-square error of approximation (RMSEA). Models with non-significant \( \chi^2 \) are good fitting models. Models with \( \chi^2/df \) values less than two are good fitting models, between two and three are considered modestly fitting models, and values greater than three are poor fitting models. CFI and TLI values at or above .95 are considered indicators of good fit. Models with RMSEA values equal to or less than .05 indicate good fit.

2.9.2 Aim 2: Practical Model
Hierarchical logistic regression in SPSS Predictive Analytics Software (PASW) version 18 was used to predict accuracy of conversion to AD based on individual neuropsychological tests. Logistic regression does not make assumptions concerning distribution of scores for predictor variables. However, it is sensitive to high correlations among the predictor variables.
and outliers. As is consistent with other studies predicting conversion to AD (Tierney et al., 1996; Tierney, Yao, Kiss, & McDowell, 2005), we examined intercorrelations on test scores in our battery to eliminate variables with correlations of more than 0.80 to reduce multicollinearity. We then entered the predictors in a planned manner. Demographic variables (e.g., age, sex, race, education) and indicators of depression severity (i.e., age of onset, number of episodes, and number of current depressive symptoms) were entered first. Next, those test related to AD status in our theoretical model, which we predicted would be temporal lobe tests, were entered, followed by frontal lobe tests. To reduce the number of parameters to estimate, we selected the neuropsychological tests with the three highest loadings on each latent variable (temporal and frontal lobe function) for this analysis. Entering the variables in this planned manner allowed us to examine whether the addition of the frontal lobe tests attenuated the effect of the temporal lobe tests in predicting AD status.

Variables that contributed significantly to the predictive ability of the model had a significant Wald test. We expected temporal lobe tests to be associated with AD status to a greater extent than frontal lobe tests. Standardized regression coefficients were used to compare the relative strength of the relationship between the independent variables and dependent variable in a single sample when the independent variables are measured on different scales (Menard, 2010). Regression coefficients standardized on both the independent and dependent variable were not provided directly in PASW, but calculated based on the following formula (Menard, 2010) where $\beta$ is the standardized regression coefficient, $b$ is the unstandardized regression coefficient, $sX$ is the standard deviation of the predictor variable, $sY$ is the estimated standard deviation of predicted values of logit ($Y$), and $R$ is the square root of the explained variance: $\beta = (b)(sX)/sY = (b)(sX)(R)/s\text{logit}(Y)$. The interpretation of this standardized regression coefficient is “a one standard deviation difference in the independent variable is associated with an ‘$X$’ standard deviation difference in the dependent variable, logit($Y$), or the logged odds.”

Sample size calculation for logistic regression is a complex problem, but based on the work of Peduzzi and colleagues (1996) for an apriori power analysis, there should be at least five “cases” per independent variable. Where “$p$” is the smallest of the proportions of negative or positive cases in the population and “$k$” the number of independent variables, the minimum number of cases to include is: $N = 5k/p$. Based on our sample size of 120, our seven covariates
and six neuropsychological tests (thirteen predictors), and the proportion of cases who developed AD in our sample (12.5%), 520 subjects would have been required apriori. Thus, we would not have adequate power apriori for a small to medium effect and would require a large effect to detect statistically significant differences. This limitation should be kept in mind.

2.9.3 Aim 3: Predictive Accuracy

To determine the neuropsychological tests with the greatest clinical utility, we evaluated the predictive accuracy of the individual neuropsychological tests used in Aim 2. We ran a separate logistic regression analysis with each test as an independent variable predicting AD status while controlling for covariates. Predictive accuracy was determined by the sensitivity, specificity, positive predictive value, and negative predictive value of the individual models, with good measures maximizing these values. The sensitivity of the model was the percentage of the sample that developed AD that was accurately identified by the model (true positives). The specificity of the model was the percentage of the sample that did not develop AD that was correctly identified by the model (true negatives). The positive predictive value was the percentage cases that the model classified as developing AD that was actually observed in the sample as having AD. The negative predictive value was the percentage of cases predicted by the model not to develop AD that were observed to not develop AD.

We examined the predictive value of the neuropsychological tests using logistic regression analyses rather than analyses based on cut-scores or published norms because our sample was predominantly Caucasian, highly educated, and varied in age, and thus, cut scores established for this population alone would not be particularly useful. Furthermore, the sample consisted of depressed patients, who would have lower baseline scores on neuropsychological tests compared to same-age healthy controls due to cognitive impairment associated with depression in general (Steffens et al., 2004). Thus, the distribution of test scores in the current sample may not be best characterized with cut scores or norms based on other populations. However, because an aim of the current study was to aid clinicians in early diagnosis of AD, we reported the mean and standard deviation of each test score for the preclinical AD group and the dementia-free group, which may be a useful starting point for subsequent research in developing clinical guidelines for depressed patients.

2.9.4 Attrition
Because participants dropped out of the study over time, we compared participants who were followed-up over the 2.5+ year time-frame to participants who were not followed-up on key variables (age, sex, education, race, cognitive functioning, depression severity, etc.) at baseline to determine if there appeared to be differential attrition that may have affected results.
CHAPTER THREE

RESULTS

3.1 Descriptive Statistics

Participants in the sample for the current study (N=120) were 68 years old on average and highly educated (14 years on average; see Table 3). The majority were female and Caucasian. Participants were followed-up seven years on average. On average, participants had suffered their first depressive episode in mid-life (44 years old) and had experienced seven depressive episodes over their lifetime.

3.2 Explanatory Variables

We wished to determine if there were variables other than the neuropsychological tests that discriminated the group that developed AD from the dementia-free group (see Table 3). The AD group was more likely to suffer anemia, but no other health variables distinguished the two groups. However, the analysis of anemia was based on only two participants, making an assessment of the contribution of anemia to AD status somewhat unreliable. The two groups did not differ on number of years followed-up, self-rated physical health, ADLs, IADLs, stressful life events, or subjective social support.

In terms of previous treatment for depression, there were no significant differences in global cognitive functioning at baseline between those who had received ECT in the past (M=28.07, SD=1.59) and those who had not received ECT (M=28.85, SD=1.58), F(1, 107)=2.99, p=.087. There was no difference between those who had received ECT and those who had not received ECT in the percentage who developed AD, 14.3% versus 11.6%, respectively, $\chi^2(1, N=109) = 0.085$, $p=.770$.

3.3 Aim 1: Theoretical Model

3.3.1 Missing Data

Some data on some of the neuropsychological tests at baseline were missing (See Table 3). Missing data was handled using full-information maximum-likelihood (FIML), a model-based approached to account for missing data in which an estimated covariance matrix is generated and is the default method in Mplus.
3.3.2 Model Fit
Adequacy of model fit was determined by several indices. The $\chi^2$ goodness of fit was significant, indicating poor model fit. However, $\chi^2$ is strongly affected by sample size. Thus, $\chi^2/df$ (1.37), which is less sensitive to small samples sizes, indicated good fit. The value of the TLI for the model was .945, indicating model fit was moderate to good. The value of the CFI for the model was .955, and RMSEA for the model was .056, indicating good fit. Therefore, according to the majority of indices, model fit was good.

3.3.3 Interpretation of Structure Coefficients
Standardized SEM results are displayed in Figure 2, and significance levels are displayed in Table 4. All latent variable (temporal lobe function and frontal lobe function) loadings were significant. For temporal lobe function, the standardized loadings with the highest absolute values were WMS-R Logical Memory Delayed Recall, CERAD Constructional Praxis Delayed Recall, and CERAD Word List Learning, respectively, all measures of episodic memory. Loadings are interpreted as follows: a one unit increase in the latent variable causes an x increase in the indicator. For example, a one unit increase in temporal lobe function caused a 0.762 increase in WMS-R Logical Memory Delayed Recall. For frontal lobe function, the standardized loadings with the highest absolute values were the Benton Visual Retention Test, the Symbol Digit Modalities Test, and Trail Making Test Part B - Part A, respectively. The residual variances of the indicators were all significant, which suggests that there was unique variance in the indicators not fully accounted for by the latent variables.

As would be expected, the latent construct temporal lobe function was positively correlated with the latent construct frontal lobe function. As we had predicted, both temporal and frontal lobe functions at baseline were significantly associated with AD status at follow-up such that lower cognitive functioning was related to a diagnosis of AD. Importantly, as predicted, the standardized structure coefficient of temporal lobe function (-0.366, medium effect) was greater than that of frontal lobe function (-0.248, small to medium effect).

3.3.4 Chi-Square Difference Test
To assess whether temporal lobe function was associated with AD to a greater extent than frontal lobe function, we compared the $\chi^2$ values obtained from the original model ($\chi^2 = 103.123, df=75$) with a model in which the structure coefficients to AD status from the latent variables were constrained ($\chi^2 = 106.953, df=76$). This resulted in a $\chi^2$ value of 3.83 with one degree of
freedom. This $\chi^2$ value was only slightly lower than the critical value in the $\chi^2$ distribution table for a one degree of freedom test at the .05 significance level ($\chi^2 = 3.84$). Thus, consistent with the main hypotheses of the project, we can conclude that the unconstrained model is a marginally better fit to the data, such that the temporal lobe function latent construct is associated with AD status to a greater extent than the frontal lobe function latent construct.

### 3.4 Aim 2: Practical Model

Prior to running the logistic regression analysis, we examined intercorrelations on test scores in our battery (See Table 5). No correlations had an absolute value greater than .80, so no neuropsychological tests were removed from the analysis on the basis of multicollinearity.

Results from the hierarchical logistic regression analysis are displayed in Table 6. The step one model (demographic and depression severity variables) was statistically significant, indicating the model was able to distinguish between those who developed AD and those who remained dementia-free. Only two predictors, increasing age and, interestingly, fewer current depressive symptoms made a unique, statistically significant contribution to the model. For each additional year in age, participants were 1.195 times more likely to develop AD, controlling for all other variables in the model. For each additional current depressive symptom, participants were 0.647 times less likely to develop AD, controlling for all other variables in the model.

The step two model (addition of temporal lobe tests) was statistically significant, and the additional variables distinguished who would develop AD over and above the variables in step one, $\chi^2(3, N=108) = 9.806, p = .020$. The model as a whole explained between 24.8% (Cox and Snell $R^2$) and 51.4% (Nagelkerke $R^2$) of the variance in AD status. Of note, only one of the temporal lobe tests, WMS-R Logical Memory Delayed Recall, made a statistically significant contribution to the model. For every additional point on this test, participants were 0.806 times less likely to develop AD, controlling for all other variables in the model. On average, the mean of those participants who developed AD was almost one $SD$ below the mean for the dementia-free patients.

The step three model (addition of frontal lobe tests) was statistically significant, but not over and above the step two model, $\chi^2(3, N=108) = 2.241, p = .524$. The model explained between 26.3% (Cox and Snell $R^2$) and 54.6% (Nagelkerke $R^2$) of the variance in AD status. None of the frontal lobe tests made a statistically significant contribution to the model. With the addition of the frontal lobe tests, WMS-R Logical Memory Delayed Recall remained marginally
significant. Standardized regression coefficients for the neuropsychological measures appear in Table 7. For the step three model with all variables included, the predictor with the highest standardized regression coefficient was WMS-R Logical Memory Delayed Recall, a temporal lobe test. For every one standard deviation increase in scores on Logical Memory, the logged odds of developing AD decreased by 0.443 standard deviation units, while controlling for all other variables in the model.

In addition to calculating standardized regression coefficients for the step three model with all variables included, we also computed standardized coefficients based on models with the single neuropsychological test predicting AD status (see Table 7). As predicted, the three temporal lobe tests (CERAD Word List Learning Delayed Recall, WMS-R Logical Memory Delayed Recall, and CERAD Constructional Praxis Delayed Recall, respectively) emerged as the standardized predictors with the highest absolute values. For those with AD, their mean score on Word List Learning and Constructional Praxis was about three-fourths of a SD below the mean for the dementia-free patients.

### 3.5 Aim 3: Predictive Accuracy

Predictive accuracy statistics were computed for the six neuropsychological tests used in the hierarchical logistic regression analysis and are shown in Table 8. Two of the temporal lobe tests (WMS-R Logical Memory Delayed Recall and CERAD Word List Learning) had the highest sensitivity values. For example, Logical Memory was able to correctly classify 47% of the participants who developed AD. Specificity values for all models were high; all models correctly identified all or nearly all of the participants who did not develop AD. The positive predictive value was highest for the Symbol Digit Modalities test, followed by CERAD Word List Learning and WMS-R Logical Memory Delayed Recall. For the CERAD Word List Learning model, of participants predicted to have AD, the model correctly identified 83% of them. Negative predictive values, or the percentage of cases predicted by the model as dementia-free that were observed to be dementia-free, were all high, ranging from 90% to 93%.

To give some clinical guidance, in Table 3 we identified the mean of the scores on each test for the group who developed AD compared to the group who did not develop AD. Additionally, in Table 9 we provided normative data from healthy subjects of similar age and education level as our sample for each of the neuropsychological tests used in the logistic regression analyses. For the majority of tests, the depressed patients in the current sample scored
lower than the healthy normative sample. The preclinical AD patients in the current sample scored lower than both the normative sample and depressed patients on all tests.

3.6 Attrition

As shown in Figure 1, there were 28 participants who were excluded from the current study due to inadequate follow-up period. Participants who were not followed up had fewer years of education, 12.5 (SD=3.2) versus 14.0 (SD=2.8), $F(1,150) = 5.96, p=.016$. They also had poorer cognitive functioning at baseline as assessed by the MMSE, 27.6 (SD=2.2) versus 28.5 (SD=2.0), $F(1,150) = 4.92, p=.028$. There were no differences in age, sex, race, or depression severity. Thus, these excluded participants may have been more likely to be exhibiting preclinical AD at baseline, and their inclusion may have provided further power for testing the models.
A body of literature has shown that depressed older adults (e.g., over 60) who currently show no overt clinical indications of dementia are nonetheless at particularly high risk for Alzheimer’s disease (AD). It may be that depression produces neurological changes over time that lead to heightened risk for AD (e.g., glucocorticoid cascade leading to atrophy in the hippocampus) or that depression among older adults is a consequence of the neurological changes in the preclinical stage of AD (e.g., prodrome hypothesis). Identifying which depressed patients are in the early stages of AD is challenging for clinicians due to overlapping cognitive impairment characteristic of both depression and AD. Though there are no “cures” at this time, to optimize treatment it is essential to identify patients in the preclinical AD phase before further irreversible brain damage has occurred.

The purpose of the current study was to identify domains of cognitive functioning and neuropsychological tests impaired during the preclinical AD phase among depressed older patients so that a more consistent procedure could be developed in the future to differentiate older adults with depression and depression-related cognitive impairment from those with depression and preclinical AD. At baseline a large battery of neuropsychological tests tapping functions associated with different areas of the brain was administered to 120 depressed subjects age 60 and older who were followed-up 2.5 years or more for the development of AD. As is consistent with the area of the brain most vulnerable in early AD, we predicted tests of temporal lobe function (assessed as both a latent construct in a structural equation model [SEM] and as individual tests in logistic regression analyses) would best predict AD outcome compared to neuropsychological tests associated with other areas of the brain such as the frontal lobe. This was the first study, to our knowledge, to assess the relationship between domains of cognitive functioning and AD using SEM.

As predicted, impaired temporal lobe function was associated with the development of AD over time to a greater extent than frontal lobe function in SEM. Examination of the loadings on the latent variables and then follow-up analyses with logistic regression showed that tests of episodic memory (associated with the temporal lobe), in particular the Wechsler Memory Scale-Revised (WMS-R) Logical Memory Delayed Recall subtest and the Consortium to Establish a
Registry for Alzheimer’s Disease (CERAD) Word List Learning Delayed Recall subtest, were the strongest predictors of the development of AD. For example, in logistic regression models, these tests had the largest standardized regression coefficients. Of most clinical relevance, these episodic memory tests (WMS-R Logical Memory and CERAD Word List Learning) also had the highest sensitivity for detecting AD in logistic regression models.

Our findings are consistent with other research in the field on depressed elders. Specifically, results that episodic memory impairment is associated with preclinical AD in our sample are consistent with the findings of Visser and colleagues (2005) and the cognitive functions known to be first impaired in AD, which are poor learning and deficient memory encoding. The formation of long-term memory is dependent on medial temporal lobe structures, which consist of the hippocampus, the entorhinal, perirhinal, and parahippocampal cortices. Atrophy of the entorhinal cortex and hippocampus has significant prognostic value in detecting subjects with progressive mild cognitive impairment (Tapiola et al., 2008). Thus, detection of temporal lobe deficits, in particular, those functions tapping episodic memory, is critical for the early identification of AD among depressed patients.

We predicted temporal lobe tests would be associated with AD to a greater extent than observed deficits in frontal lobe tests due to the reversible impairment in frontal lobe function seen in depression in general. Though our results were consistent with our hypothesis, we were also aware that individuals in the preclinical AD phase would likely score lower across most neuropsychological tests. In this regard, we found using SEM that impairment in frontal lobe function was associated with AD to some extent (but to a lesser extent than temporal lobe function). There is evidence suggesting that AD is a somewhat heterogeneous disorder which may imply multiple causal pathways such that some AD patients will have disproportionate frontal lobe impairments on neuropsychological tests (Johnson, Head, Kim, Starr, & Cotman, 1999). Thus, some depressed older adults with preclinical AD will manifest degraded performance on tests other than temporal lobe function. In addition, some patients present with mixed pathology (e.g., they may have preclinical AD and neurological damage related to vascular disease or stroke) in which tests of frontal and temporal lobe functioning are impacted (Bastos-Leite et al., 2007), which may explain our findings that both temporal lobe and frontal lobe tests are predictive of AD.
We performed logistic regression analyses to determine which tests had the most clinical utility in identifying preclinical AD. We found that WMS-R Logical Memory Delayed Recall was predictive of AD status above and beyond other neuropsychological tests and had the highest sensitivity. Patients who later developed AD scored eight points lower (about one $SD$) on average at baseline than patients who remained dementia-free in our sample. CERAD Word List Learning, another indicator of temporal lobe function, had the next highest sensitivity for detection of AD. Preclinical AD patients scored more than one $SD$ lower than the healthy normative sample on the Word List Learning subtest. It would be of great importance to replicate these findings in a less educated and more diverse population across different age groups, and the extent to which these findings are stable across different populations would be of great clinical relevance.

Although a test of episodic memory with the next highest loading on the temporal lobe function latent variable, CERAD Constructional Praxis Delayed Recall was not significantly related to AD in logistic regression analyses. Although impaired visual episodic memory has been shown to be impaired in other studies of preclinical AD (Guarch, Marcos, Salamero, Gasto, & Blesa, 2008), we found only measures of verbal episodic memory in the current study were associated with AD. One possibility to account for this finding is that the depressed patients in the current study may have had particularly poor performance on this subtest, which has a large motor component and requires sustained effort on the part of the depressed patient. These additional skills are not required on the verbal episodic memory tests in our battery and are often impaired among depressed patients in general (Austin et al., 2001). Thus, it is possible that the performance of the depressed patients in general was too similar to the preclinical AD patients’ performance to detect differences on this particular subtest.

Another possibility that must be considered to account for the greater sensitivity of some tests is that the properties of the tests themselves may have impacted our findings. Specifically, changes in cognitive function should appear earlier for tests with absence of ceiling effects and high reliability (Chapman & Chapman, 1973). First, it is possible that some of our baseline tests were not sensitive enough to detect subtle changes in cognitive functioning occurring during the preclinical AD phase because of ceiling effects. The MMSE is one test known to suffer from ceiling effects (Ihl, Frolich, Dierks, Martin, & Maurer, 1992). Indeed, in the current sample, the only tests in our battery that had significant negative skew (i.e., skewness value less than -2)
were the MMSE subtests. Second, our finding that temporal lobe tests were associated with AD to a greater extent than frontal lobe tests may have been an artifact of having more reliable measures rather than the area of the brain thought to be impaired. However, in review of the literature of these tests, there was no apparent superiority of the temporal lobe tests. Although we cannot confirm the theory that temporal lobe function is initially affected more than frontal lobe functioning, importantly, the current study was able to identify at least two tests of episodic memory associated with the temporal lobe that may be useful in identifying preclinical AD.

Despite some depressed individuals having several other risk factors for AD, some individuals developed AD and others did not. There are many factors that contribute to the development of AD. In addition to examining the predictive value of neuropsychological tests, we also examined whether other psychosocial variables would predict the development of AD. As is consistent with other studies (Kawas & Katzman, 1999), advancing age was related to AD status in ANOVA and logistic regression analyses. Interestingly, having more years of education was associated with AD status. Importantly, patients with more years of education were more likely to remain in the study longer, which would allow sufficient time for the development of AD among those with more education. Additionally, our sample consisted of highly educated individuals. Thus, we likely did not have a stable estimate of the relationship of education to AD. We do know, however, that based on the concept of cognitive reserve (Stern, 2002), individuals with more education are less likely to show signs of AD at earlier stages compared to their less educated peers. Reserve refers to the brain’s ability to tolerate the effects of dementia pathology. Educational experiences may increase ability to cope with advancing AD by providing a cognitive reserve against the clinical expression of initial cognitive problems but may be less protective of the initial depressive symptoms. Those with higher levels of education may need to be followed longer in order for dementia to be identified.

Interestingly, having fewer depressive symptoms at baseline was associated with greater likelihood of AD in logistic regression analyses. However, in our analysis of AD outcome (using ANOVA) we did not find number of depressive symptoms differed between AD and non-AD individuals. It may be that the severity of the depressive symptoms was so high at baseline in general that inadequate variability led to these findings. We were examining this relationship among a sample of depressed subjects who were experiencing more than six depressive symptoms at baseline on average. One other consideration that is important for further
investigation is that the prodrome hypothesis, which accounts for the relationship between depression and subsequent cognitive decline, may explain in great part our results that those individuals who were less severely ill with depression (i.e., fewer symptoms and later age of onset) were more likely to develop AD. The prodrome hypothesis posits that those individuals with late-onset depression (who also should have a less severe depression course than those with early-onset depression) may be suffering neurological changes and cognitive deficits associated with preclinical AD that also give rise to depressive symptoms (Janssen et al., 2007). Thus, in late-onset depression, mild depressive symptoms may first appear in late adulthood and co-occur as part of prodromal neurological changes in AD. It may also be the case that those individuals in the early stages of AD were beginning to experience some cognitive deficits and developed mild depressive symptoms in reaction to their early cognitive losses (Jorm, 2001).

4.1 Limitations

As with any study, there were several limitations to the present investigation, in addition to those mentioned above. Our sample consisted mostly of highly educated, Caucasian participants. There is evidence to suggest that higher levels of education are associated with higher scores on the CERAD battery (Unverzagt et al., 1996) used in the current study through educational strategies learned in the process of engaging in more highly complicated tasks. This is relevant to the cognitive reserve theory. Therefore, it would be important to determine if our results generalized to a less educated and more diverse population. In order for this study’s findings to have practical implications, future research should examine neuropsychological predictors of AD among more diverse samples and strive to generate applicable norms and cut-scores across age groups. Clearly this would be a major undertaking.

We must also consider that treatment may have affected outcomes. Depressed patients in the study underwent naturalistic treatment for depression, and another limitation is that we did not have current treatment data. However, 14 participants reported having received ECT in the past. There is some evidence to suggest that ECT impairs cognitive functioning, though cognitive deficits are not long-lasting or only for events close in time to ECT (Devanand, Dwork, Hutchingson, Bolwig, & Sackeim, 1994). Importantly, in our sample there were no significant differences in global cognitive functioning at baseline between those who had received ECT in the past and those who had not received ECT. In addition, there is no conclusive evidence that ECT induces structural changes to the brain (Devanand et al., 1994). Among our sample, there
was no difference between those who had received ECT and those who had not received ECT in the percentage who developed AD.

As stated earlier, apriori power to detect effects was low for some analyses, particularly the overall logistic regression analysis employed for the practical model. However, we did find significant effects for a temporal lobe test (WMS-R Logical Memory Delayed Recall) and several covariates, as discussed above. Nonetheless, we cannot rule out the possibility that we may have found an effect in the logistic regression analyses for more of the frontal lobe function tests had we been able to obtain data from more patients, and thus, increased our sample size.

Finally, participants with missing data or those excluded due to inadequate follow-up time had fewer years of education and lower global cognitive functioning scores at baseline. These characteristics have been associated with greater risk for AD. Thus, we may have been more likely to detect AD among some of the patients who were excluded, which reduces diagnostic accuracy and restricts the generalizability of our results to this population.

4.2 Conclusions

Our results have implications for early recognition and treatment of AD among depressed older adults. Clinicians often face a diagnostic quandary when an older depressed patient presents with cognitive impairment. In order to distinguish preclinical AD from reversible cognitive impairment seen in depression, clinicians may consider administering tests of episodic memory that indicate temporal lobe damage, in particular, the WMS-R Logical Memory Delayed Recall subtest and the CERAD Word List Learning subtest. At least one SD below the mean on these tests in relation to the scores derived for the population based on age and education should alert the clinician to the possibility of preclinical AD, and subsequent testing should be conducted to gauge the patient’s status.
# APPENDIX A

## TABLE 1

Table 1: Diagnostic criteria for Alzheimer’s disease diagnoses in the NCODE study.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable Alzheimer’s disease</td>
<td>Dementia has been established by clinical and neuropsychological examination, cognitive impairments are progressive and present in two or more areas of cognition, the onset of deficits has been between the ages of 40 and 90 years, there is an absence of other diseases capable of producing a dementia syndrome$^a$</td>
</tr>
<tr>
<td>Possible Alzheimer’s disease</td>
<td>There is a dementia syndrome with an atypical onset, presentation or progression and without a known etiology; but no co-morbid diseases capable of producing dementia are believed to be the origin of it$^a$</td>
</tr>
<tr>
<td>Subsyndromal Alzheimer’s disease</td>
<td>Functional impairment or impairment in one or more cognitive domains that is clinically suggestive of the early stages of AD</td>
</tr>
</tbody>
</table>

$^a$Criteria are from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)
## APPENDIX B

### TABLE 2

Table 2: NCODE study neuropsychological test battery.

<table>
<thead>
<tr>
<th>Test</th>
<th>Cognitive Domain</th>
<th>Inclusion in Current Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascending Digit Span</td>
<td>Working memory</td>
<td>Yes</td>
</tr>
<tr>
<td>Benton Visual Retention Test</td>
<td>Visual short-term memory</td>
<td>Yes</td>
</tr>
<tr>
<td>CERAD Boston Naming Test</td>
<td>Confrontation naming</td>
<td>Yes</td>
</tr>
<tr>
<td>CERAD Category Fluency</td>
<td>Semantic fluency</td>
<td>Yes</td>
</tr>
<tr>
<td>CERAD Constructional Praxis</td>
<td>Constructional praxis</td>
<td>No</td>
</tr>
<tr>
<td>CERAD Constructional Praxis Delayed Recall</td>
<td>Nonverbal delayed memory</td>
<td>Yes</td>
</tr>
<tr>
<td>CERAD Constructional Praxis Delayed Recognition</td>
<td>Nonverbal delayed memory</td>
<td>No</td>
</tr>
<tr>
<td>CERAD Word List Learning</td>
<td>Delayed verbal memory</td>
<td>Yes</td>
</tr>
<tr>
<td>Controlled Oral Word Association</td>
<td>Lexical fluency</td>
<td>Yes</td>
</tr>
<tr>
<td>Mini-Mental Status Examination</td>
<td>Global cognitive function</td>
<td>Yes</td>
</tr>
<tr>
<td>Shipley Vocabulary Test</td>
<td>Verbal functioning</td>
<td>No</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test</td>
<td>Processing speed</td>
<td>Yes</td>
</tr>
<tr>
<td>Trail Making Test</td>
<td>Processing speed, Working memory</td>
<td>Yes</td>
</tr>
<tr>
<td>WAIS-R Digit Span</td>
<td>Short-term memory, Working memory</td>
<td>Yes</td>
</tr>
<tr>
<td>WMS-R Logical Memory Delayed Recall</td>
<td>Delayed verbal memory</td>
<td>Yes</td>
</tr>
<tr>
<td>WMS-R Logical Memory Immediate Recall</td>
<td>Immediate verbal memory</td>
<td>No</td>
</tr>
</tbody>
</table>
## APPENDIX C

### TABLE 3

Table 3: Key variables at baseline reported for overall sample and by Alzheimer’s disease status.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>AD (n=15)</th>
<th>Dementia (n=105)</th>
<th>Total (N=120)</th>
<th>F or $\chi^2$ p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>120</td>
<td>11 (73.3%)</td>
<td>66 (62.9%)</td>
<td>77 (64.2%)</td>
<td>$\chi^2(1, N=120) = 0.63$</td>
</tr>
<tr>
<td>Age</td>
<td>120</td>
<td>74.2 (8.0)</td>
<td>67.4 (6.1)</td>
<td>68.2 (6.7)</td>
<td>F (1,118) = 15.30</td>
</tr>
<tr>
<td>Race</td>
<td>120</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>0 (0%)</td>
<td>2 (1.9%)</td>
<td>2 (1.7%)</td>
<td>$\chi^2(3, N=120) = 3.87$</td>
</tr>
<tr>
<td>African</td>
<td>3</td>
<td>2 (19.0%)</td>
<td>7 (6.7%)</td>
<td>10 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>American</td>
<td>12</td>
<td>12 (80.0%)</td>
<td>91 (86.7%)</td>
<td>103 (85.8%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>0</td>
<td>0 (0%)</td>
<td>5 (4.8%)</td>
<td>5 (4.2%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years of education</td>
<td>120</td>
<td>13.8 (3.9)</td>
<td>14.2 (2.5)</td>
<td>14.2 (2.7)</td>
<td>F (1,118) = 0.33</td>
</tr>
<tr>
<td><strong>Depression Severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first episode</td>
<td>119</td>
<td>53.4 (24.4)</td>
<td>42.7 (19.1)</td>
<td>44.0 (20.1)</td>
<td>F (1,117) = 3.83</td>
</tr>
<tr>
<td>Number of episodes</td>
<td>118</td>
<td>3.2 (2.4)</td>
<td>7.5 (16.3)</td>
<td>7.0 (15.4)</td>
<td>F (1,116) = 1.05</td>
</tr>
<tr>
<td>Number of DSM-IV symptoms</td>
<td>120</td>
<td>5.5 (2.6)</td>
<td>6.3 (2.4)</td>
<td>6.2 (2.4)</td>
<td>F (1,118) = 1.58</td>
</tr>
<tr>
<td>Variable</td>
<td>n</td>
<td>AD  (n=15)</td>
<td>Dementia  (n=105)</td>
<td>Total  (N=120)</td>
<td>F or $\chi^2$</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------</td>
<td>------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td><strong>Neuropsychological Tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMS-R$^a$ Logical Memory</td>
<td>118</td>
<td>12.9 (9.5)</td>
<td>21.1 (9.0)</td>
<td>20.0 (9.4)</td>
<td>F (1,116) =</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.56</td>
</tr>
<tr>
<td>CERAD$^b$ Word List Learning</td>
<td>120</td>
<td>4.5 (3.0)</td>
<td>6.3 (2.1)</td>
<td>6.1 (2.3)</td>
<td>F (1,118) =</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.13</td>
</tr>
<tr>
<td>CERAD$^b$ Constructional Praxis Delayed Recall</td>
<td>120</td>
<td>6.0 (3.0)</td>
<td>8.1 (2.4)</td>
<td>7.9 (2.6)</td>
<td>F (1,118) =</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.66</td>
</tr>
<tr>
<td>MMSE$^c$ Orientation Items</td>
<td>120</td>
<td>2.0 (1.1)</td>
<td>2.7 (0.6)</td>
<td>2.6 (0.7)</td>
<td>F (1,118) =</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.37</td>
</tr>
<tr>
<td>CERAD$^b$ Category Fluency</td>
<td>120</td>
<td>14.3 (7.1)</td>
<td>16.1 (4.9)</td>
<td>15.9 (5.3)</td>
<td>F (1,118) =</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.50</td>
</tr>
<tr>
<td>CERAD$^b$ Boston Naming Test</td>
<td>120</td>
<td>13.5 (1.2)</td>
<td>13.9 (1.5)</td>
<td>13.9 (1.5)</td>
<td>F (1,118) =</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>MMSE$^c$ Orientation Items</td>
<td>120</td>
<td>8.4 (1.8)</td>
<td>9.5 (0.7)</td>
<td>9.4 (1.0)</td>
<td>F (1,118) =</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18.99</td>
</tr>
<tr>
<td>Variable</td>
<td>n</td>
<td>AD (n=15)</td>
<td>Dementia (n=105)</td>
<td>Total (N=120)</td>
<td>F or $\chi^2$</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------</td>
<td>-----------</td>
<td>-----------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Benton Visual Retention Test</td>
<td>118</td>
<td>4.1 (2.3)</td>
<td>5.5 (2.2)</td>
<td>5.3 (2.3)</td>
<td>F (1,116) = 4.55</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test</td>
<td>116</td>
<td>30.0 (14.5)</td>
<td>36.7 (10.9)</td>
<td>35.9 (11.5)</td>
<td>F (1,114) = 4.23</td>
</tr>
<tr>
<td>Trail Making Test Part B – Part A</td>
<td>113</td>
<td>98.0 (66.7)</td>
<td>89.2 (65.2)</td>
<td>90.1 (65.1)</td>
<td>F (1,111) = 0.20</td>
</tr>
<tr>
<td>WAIS-R$^d$ Digit Span Backward</td>
<td>103</td>
<td>5.7 (2.0)</td>
<td>6.9 (2.4)</td>
<td>6.8 (2.4)</td>
<td>F (1,101) = 3.10</td>
</tr>
<tr>
<td>Ascending Digit Span</td>
<td>103</td>
<td>6.5 (3.3)</td>
<td>8.3 (2.6)</td>
<td>8.1 (2.7)</td>
<td>F (1,101) = 5.37</td>
</tr>
<tr>
<td>MMSE$^c$ Attention and Calculation Item</td>
<td>120</td>
<td>4.5 (1.1)</td>
<td>4.8 (0.7)</td>
<td>4.8 (0.7)</td>
<td>F (1,118) = 2.85</td>
</tr>
<tr>
<td>MMSE$^c$ total score</td>
<td>120</td>
<td>27.5 (3.4)</td>
<td>28.7 (1.6)</td>
<td>28.6 (1.9)</td>
<td>F (1,118) = 5.23</td>
</tr>
<tr>
<td>Explanatory Variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of years in study</td>
<td>120</td>
<td>6.6 (2.8)</td>
<td>7.2 (2.6)</td>
<td>7.1 (2.6)</td>
<td>F (1,118) = 0.56</td>
</tr>
<tr>
<td>Self-rated physical health</td>
<td>120</td>
<td>2.4 (0.9)</td>
<td>2.4 (0.9)</td>
<td>2.4 (0.9)</td>
<td>F (1,118) = 0.01</td>
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<tr>
<td>Asthma</td>
<td>120</td>
<td>0 (0%)</td>
<td>7 (6.7%)</td>
<td>7 (5.8%)</td>
<td>$\chi^2$ (1, N=120) = 1.06</td>
</tr>
<tr>
<td>Diabetes</td>
<td>120</td>
<td>1 (6.7%)</td>
<td>8 (7.6%)</td>
<td>9 (7.5%)</td>
<td>$\chi^2$ (1, N=120) = 0.02</td>
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</table>

\(\chi^2\): Chi-square test.
<table>
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<th>Variable</th>
<th>$n$</th>
<th>AD (n=15)</th>
<th>Dementia (n=105)</th>
<th>Total (N=120)</th>
<th>$F$ or $\chi^2$</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Heart trouble</td>
<td>120</td>
<td>3 (20.0%)</td>
<td>19 (18.1%)</td>
<td>22 (18.3%)</td>
<td>$\chi^2(1, N=120)$</td>
<td>.858</td>
</tr>
<tr>
<td>Hypertension</td>
<td>120</td>
<td>7 (46.7%)</td>
<td>45 (42.9%)</td>
<td>52 (43.3%)</td>
<td>$\chi^2(1, N=120)$</td>
<td>.781</td>
</tr>
<tr>
<td>Arthritis</td>
<td>119</td>
<td>9 (64.3%)</td>
<td>57 (54.3%)</td>
<td>66 (55.5%)</td>
<td>$\chi^2(1, N=120)$</td>
<td>.479</td>
</tr>
<tr>
<td>Stroke</td>
<td>120</td>
<td>1 (6.7%)</td>
<td>6 (5.7%)</td>
<td>7 (5.8%)</td>
<td>$\chi^2(1, N=120)$</td>
<td>.883</td>
</tr>
<tr>
<td>Cancer</td>
<td>120</td>
<td>0 (0%)</td>
<td>5 (4.8%)</td>
<td>5 (4.2%)</td>
<td>$\chi^2(1, N=120)$</td>
<td>.388</td>
</tr>
<tr>
<td>Emphysema</td>
<td>120</td>
<td>0 (0%)</td>
<td>8 (7.6%)</td>
<td>8 (6.7%)</td>
<td>$\chi^2(1, N=120)$</td>
<td>.268</td>
</tr>
<tr>
<td>Ulcer</td>
<td>120</td>
<td>1 (6.7%)</td>
<td>6 (5.7%)</td>
<td>7 (5.8%)</td>
<td>$\chi^2(1, N=120)$</td>
<td>.883</td>
</tr>
<tr>
<td>Hardening of arteries</td>
<td>116</td>
<td>1 (7.7%)</td>
<td>15 (14.6%)</td>
<td>16 (13.8%)</td>
<td>$\chi^2(1, N=116)$</td>
<td>.498</td>
</tr>
<tr>
<td>Anemia</td>
<td>120</td>
<td>2 (13.3%)</td>
<td>0 (0%)</td>
<td>2 (1.7%)</td>
<td>$\chi^2(1, N=120)$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td>120</td>
<td>0.7 (1.3)</td>
<td>0.5 (1.4)</td>
<td>0.5 (1.4)</td>
<td>$F(1,118) = 0.24$</td>
<td>.629</td>
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<tr>
<td>Independent activities of daily living</td>
<td>120</td>
<td>4.0 (5.7)</td>
<td>3.3 (4.2)</td>
<td>3.4 (4.4)</td>
<td>$F(1,118) = 0.33$</td>
<td>.566</td>
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<tr>
<td>Self-rated stress</td>
<td>120</td>
<td>5.8 (2.2)</td>
<td>7.0 (2.1)</td>
<td>6.8 (2.2)</td>
<td>$F(1,118) = 3.74$</td>
<td>.056</td>
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<tr>
<td>Variable</td>
<td>n</td>
<td>AD (n=15)</td>
<td>Dementia (n=105)</td>
<td>Total (N=120)</td>
<td>F or χ²</td>
<td>p-value</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----</td>
<td>-----------</td>
<td>------------------</td>
<td>---------------</td>
<td>---------</td>
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</tr>
<tr>
<td>Number of stressful events</td>
<td>119</td>
<td>2.5 (1.2)</td>
<td>2.7 (1.8)</td>
<td>2.7 (1.7)</td>
<td>F (1,117) = 0.24</td>
<td>.624</td>
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<td>Subjective social support</td>
<td>118</td>
<td>22.4 (4.0)</td>
<td>22.7 (4.4)</td>
<td>22.7 (4.3)</td>
<td>F (1,116) = 0.07</td>
<td>.796</td>
</tr>
</tbody>
</table>

*a* Wechsler Memory Scale-Revised  
*b* Consortium to Establish a Registry for Alzheimer’s Disease  
*c* Mini-Mental Status Examination  
*d* Wechsler Adult Intelligence Scale-Revised
## APPENDIX D

### TABLE 4

Table 4: Results from structural equation theoretical model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standardized Estimate</th>
<th>Standard Error</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Temporal Lobe Function Loadings</strong></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>WMS-R&lt;sup&gt;a&lt;/sup&gt; Logical Memory Delayed Recall</td>
<td>0.762</td>
<td>0.046</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CERAD&lt;sup&gt;b&lt;/sup&gt; Word List Learning Delayed Recall</td>
<td>0.684</td>
<td>0.055</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CERAD&lt;sup&gt;b&lt;/sup&gt; Constructional Praxis Delayed Recall</td>
<td>0.739</td>
<td>0.047</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MMSE&lt;sup&gt;c&lt;/sup&gt; Delayed Recall Items</td>
<td>0.650</td>
<td>0.059</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CERAD&lt;sup&gt;b&lt;/sup&gt; Category Fluency</td>
<td>0.681</td>
<td>0.055</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CERAD&lt;sup&gt;b&lt;/sup&gt; Boston Naming Test</td>
<td>0.556</td>
<td>0.069</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MMSE&lt;sup&gt;c&lt;/sup&gt; Orientation Items</td>
<td>0.553</td>
<td>0.069</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Frontal Lobe Function Loadings</strong></td>
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<td></td>
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<tr>
<td>Benton Visual Retention Test</td>
<td>0.813</td>
<td>0.039</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Trail Making Test Part B – Part A</td>
<td>-0.753</td>
<td>0.051</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test</td>
<td>0.810</td>
<td>0.039</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>WAIS-R&lt;sup&gt;d&lt;/sup&gt; Digit Span Backward</td>
<td>0.614</td>
<td>0.066</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ascending Digit Span</td>
<td>0.644</td>
<td>0.063</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MMSE&lt;sup&gt;c&lt;/sup&gt; Attention and Calculation Item</td>
<td>0.351</td>
<td>0.086</td>
<td>&lt;.001</td>
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<tr>
<td><strong>Temporal Lobe Function on Alzheimer’s Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.366</td>
<td>0.087</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td><strong>Frontal Lobe Function on Alzheimer’s Disease</strong></td>
<td></td>
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</tr>
<tr>
<td>-0.248</td>
<td>0.093</td>
<td>0.012</td>
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<tr>
<td><strong>Correlation of Temporal and Frontal Lobe Function</strong></td>
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<td>&lt;.001</td>
</tr>
<tr>
<td>Parameter</td>
<td>Standardized Estimate</td>
<td>Standard Error</td>
<td>p-value</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------------------------</td>
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<tr>
<td>Residual Variances</td>
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<tr>
<td>WMS-R(^a) Logical Memory Delayed Recall</td>
<td>0.420</td>
<td>0.070</td>
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<tr>
<td>CERAD(^b) Word List Learning Delayed Recall</td>
<td>0.532</td>
<td>0.075</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CERAD(^b) Constructional Praxis Delayed Recall</td>
<td>0.454</td>
<td>0.070</td>
<td>&lt;.001</td>
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<tr>
<td>MMSE(^c) Delayed Recall Items</td>
<td>0.577</td>
<td>0.076</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CERAD(^b) Category Fluency</td>
<td>0.537</td>
<td>0.075</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CERAD(^b) Boston Naming Test</td>
<td>0.691</td>
<td>0.076</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MMSE(^c) Orientation Items</td>
<td>0.694</td>
<td>0.076</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Benton Visual Retention Test</td>
<td>0.339</td>
<td>0.063</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test</td>
<td>0.343</td>
<td>0.063</td>
<td>&lt;.001</td>
</tr>
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<td>Trail Making Test Part B – Part A</td>
<td>0.433</td>
<td>0.077</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>WAIS-R(^d) Digit Span Backward</td>
<td>0.623</td>
<td>0.081</td>
<td>&lt;.001</td>
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<tr>
<td>Ascending Digit Span</td>
<td>0.585</td>
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<tr>
<td>MMSE(^c) Attention and Calculation Item</td>
<td>0.877</td>
<td>0.060</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

\(^{a}\)Wechsler Memory Scale-Revised  
\(^{b}\)Consortium to Establish a Registry for Alzheimer’s Disease  
\(^{c}\)Mini-Mental Status Examination  
\(^{d}\)Wechsler Adult Intelligence Scale-Revised
## APPENDIX E

### Table 5

Table 5: Correlations among neuropsychological tests at baseline.

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<tr>
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<th>2</th>
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<th>4</th>
<th>5</th>
<th>6</th>
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<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
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</thead>
<tbody>
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<td>1. WMS-R&lt;sup&gt;a&lt;/sup&gt; Logical Memory Delayed Recall</td>
<td>1</td>
<td>.573**</td>
<td>.588**</td>
<td>.441**</td>
<td>.506**</td>
<td>.390**</td>
<td>.341**</td>
<td>.518**</td>
<td>.544**</td>
<td>-</td>
<td>.456**</td>
<td>.448**</td>
<td>.163</td>
</tr>
<tr>
<td>2. CERAD&lt;sup&gt;b&lt;/sup&gt; Word List Learning Delayed Recall</td>
<td>.573**</td>
<td>1</td>
<td>.483**</td>
<td>.528**</td>
<td>.383**</td>
<td>.410**</td>
<td>.423**</td>
<td>.398**</td>
<td>.552**</td>
<td>-.319*</td>
<td>.455**</td>
<td>.378**</td>
<td>.190*</td>
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<td>3. CERAD&lt;sup&gt;b&lt;/sup&gt; Constructional Praxis Delayed Recall</td>
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<td>.483**</td>
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<td>.486**</td>
<td>.453**</td>
<td>.327**</td>
<td>.473**</td>
<td>.629**</td>
<td>.496**</td>
<td>-</td>
<td>.407**</td>
<td>.401**</td>
<td>.301*</td>
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<td>.528**</td>
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<td>.455**</td>
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<td>.455**</td>
<td>.431**</td>
<td>.468**</td>
<td>-.261*</td>
<td>.337**</td>
<td>.388**</td>
<td>.219*</td>
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<td>5. CERAD&lt;sup&gt;b&lt;/sup&gt; Category Fluency</td>
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<td>.383**</td>
<td>.453**</td>
<td>.455**</td>
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<td>.464**</td>
<td>.329**</td>
<td>.549**</td>
<td>.616**</td>
<td>-</td>
<td>.373**</td>
<td>.493**</td>
<td>.153</td>
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<td>6. CERAD&lt;sup&gt;b&lt;/sup&gt; Boston Naming Test</td>
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<td>.410**</td>
<td>.327**</td>
<td>.278**</td>
<td>.464**</td>
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<td>.283**</td>
<td>.458**</td>
<td>.478**</td>
<td>-</td>
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<td>.361**</td>
<td>.137</td>
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<td>5</td>
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<td>7</td>
<td>8</td>
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<td>.341**</td>
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<td>.445**</td>
<td>.329**</td>
<td>.283*</td>
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<td>.351**</td>
<td>- .233</td>
<td>.303*</td>
<td>.275**</td>
<td>.313**</td>
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<td>8. Benton Visual Retention Test</td>
<td>.518**</td>
<td>.398**</td>
<td>.629**</td>
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<td>.549**</td>
<td>.458**</td>
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<td>.552**</td>
<td>.496**</td>
<td>.468**</td>
<td>.616**</td>
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<td>.641**</td>
<td>1</td>
<td>-</td>
<td>.431**</td>
<td>.497**</td>
<td>.212*</td>
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<td>10. Trail Making Test Part B-Part A</td>
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<td>-</td>
<td>-.261*</td>
<td>-</td>
<td>-</td>
<td>-.233*</td>
<td>-.584**</td>
<td>-</td>
<td>1</td>
<td>-.368**</td>
<td>-.330*</td>
<td>-.239*</td>
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<td>11. WAIS-R\textsuperscript{d} Digit Span Backward</td>
<td>.490**</td>
<td>.407**</td>
<td>.485**</td>
<td>.406**</td>
<td>-</td>
<td>-</td>
<td>-.233*</td>
<td>-.584**</td>
<td>-</td>
<td>1</td>
<td>-.368**</td>
<td>-.330*</td>
<td>-.239*</td>
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<td>12. Ascending Digit Span</td>
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<td>.455**</td>
<td>.407**</td>
<td>.337**</td>
<td>.373**</td>
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<td>-</td>
<td>.368**</td>
<td>.524**</td>
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<td>13. MMSE\textsuperscript{c} Attention/Calculation Item</td>
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<td>.378**</td>
<td>.401**</td>
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<td>.493**</td>
<td>.361**</td>
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<td>.543**</td>
<td>.497**</td>
<td>- .330*</td>
<td>.524**</td>
<td>1</td>
<td>.191</td>
</tr>
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\textsuperscript{a}Wechsler Memory Scale-Revised  
\textsuperscript{b}Consortium to Establish a Registry for Alzheimer’s Disease  
\textsuperscript{c}Mini-Mental Status Examination  
\textsuperscript{d}Wechsler Adult Intelligence Scale-Revised  

Note: Significant at the .01 level**; Significant at the .05 level*
## APPENDIX F

### TABLE 6

Table 6: Hierarchical logistic regression analysis predicting Alzheimer’s disease status.

<table>
<thead>
<tr>
<th>Variable</th>
<th>b</th>
<th>Standard Error</th>
<th>Wald</th>
<th>df</th>
<th>p</th>
<th>Odds Ratio</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td>0.883</td>
<td>0.886</td>
<td>0.993</td>
<td>1</td>
<td>.319</td>
<td>2.418</td>
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<tr>
<td>Age</td>
<td>0.178</td>
<td>0.064</td>
<td>7.654</td>
<td>1</td>
<td>.006</td>
<td>1.195</td>
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<tr>
<td>Race</td>
<td>-0.311</td>
<td>1.074</td>
<td>0.084</td>
<td>1</td>
<td>.772</td>
<td>0.733</td>
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<tr>
<td>Education</td>
<td>0.278</td>
<td>0.162</td>
<td>2.940</td>
<td>1</td>
<td>.086</td>
<td>1.321</td>
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<td>Age of depression onset</td>
<td>0.021</td>
<td>0.026</td>
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<td>Number of depressive episodes</td>
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<td>0.146</td>
<td>1</td>
<td>.703</td>
<td>0.979</td>
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<tr>
<td>Number of current depressive symptoms</td>
<td>-0.436</td>
<td>0.177</td>
<td>6.028</td>
<td>1</td>
<td>.014</td>
<td>0.647</td>
</tr>
</tbody>
</table>

**Step 1**

\( \chi^2(7, N=108) = 20.97, p = .004 \)

<table>
<thead>
<tr>
<th>Variable</th>
<th>b</th>
<th>Standard Error</th>
<th>Wald</th>
<th>df</th>
<th>p</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.362</td>
<td>0.993</td>
<td>0.133</td>
<td>1</td>
<td>.715</td>
<td>1.437</td>
</tr>
<tr>
<td>Age</td>
<td>0.167</td>
<td>0.079</td>
<td>4.509</td>
<td>1</td>
<td>.034</td>
<td>1.182</td>
</tr>
<tr>
<td>Race</td>
<td>0.844</td>
<td>1.367</td>
<td>0.384</td>
<td>1</td>
<td>.537</td>
<td>2.325</td>
</tr>
<tr>
<td>Education</td>
<td>0.534</td>
<td>.225</td>
<td>5.615</td>
<td>1</td>
<td>.018</td>
<td>1.706</td>
</tr>
<tr>
<td>Age of depression onset</td>
<td>0.008</td>
<td>0.029</td>
<td>0.080</td>
<td>1</td>
<td>.777</td>
<td>1.008</td>
</tr>
<tr>
<td>Number of depressive episodes</td>
<td>-0.028</td>
<td>0.087</td>
<td>0.106</td>
<td>1</td>
<td>.744</td>
<td>0.972</td>
</tr>
<tr>
<td>Number of current depressive symptoms</td>
<td>-0.715</td>
<td>0.242</td>
<td>8.728</td>
<td>1</td>
<td>.003</td>
<td>0.489</td>
</tr>
<tr>
<td>WMS-R(^a) Logical Memory Delayed Recall</td>
<td>-0.216</td>
<td>0.104</td>
<td>4.278</td>
<td>1</td>
<td>.039</td>
<td>0.806</td>
</tr>
<tr>
<td>CERAD(^b) Word List Learning Delayed Recall</td>
<td>0.163</td>
<td>0.251</td>
<td>0.422</td>
<td>1</td>
<td>.516</td>
<td>1.177</td>
</tr>
<tr>
<td>CERAD(^b) Constructional Praxis Delayed Recall</td>
<td>-0.047</td>
<td>0.254</td>
<td>0.034</td>
<td>1</td>
<td>.853</td>
<td>0.954</td>
</tr>
</tbody>
</table>

**Step 2**

\( \chi^2(10, N=108) = 30.778, p = .001 \)
<table>
<thead>
<tr>
<th>Variable</th>
<th>b</th>
<th>Standard Error</th>
<th>Wald</th>
<th>df</th>
<th>p</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.130</td>
<td>1.033</td>
<td>0.016</td>
<td>1</td>
<td>.900</td>
<td>1.139</td>
</tr>
<tr>
<td>Age</td>
<td>0.206</td>
<td>0.102</td>
<td>4.088</td>
<td>1</td>
<td>.043</td>
<td>1.229</td>
</tr>
<tr>
<td>Race</td>
<td>1.195</td>
<td>1.539</td>
<td>0.603</td>
<td>1</td>
<td>.437</td>
<td>3.304</td>
</tr>
<tr>
<td>Education</td>
<td>0.792</td>
<td>0.345</td>
<td>5.269</td>
<td>1</td>
<td>.022</td>
<td>2.209</td>
</tr>
<tr>
<td>Age of depression onset</td>
<td>0.013</td>
<td>0.034</td>
<td>0.150</td>
<td>1</td>
<td>.698</td>
<td>1.013</td>
</tr>
<tr>
<td>Number of depressive episodes</td>
<td>-0.038</td>
<td>0.119</td>
<td>0.103</td>
<td>1</td>
<td>.748</td>
<td>0.962</td>
</tr>
<tr>
<td>Number of current depressive episodes</td>
<td>-0.767</td>
<td>0.274</td>
<td>7.816</td>
<td>1</td>
<td>.005</td>
<td>0.464</td>
</tr>
<tr>
<td>WMS-R&lt;sup&gt;a&lt;/sup&gt; Logical Memory Delayed Recall</td>
<td>-0.225</td>
<td>0.118</td>
<td>3.650</td>
<td>1</td>
<td>.056</td>
<td>0.798</td>
</tr>
<tr>
<td>CERAD&lt;sup&gt;b&lt;/sup&gt; Word List Learning Delayed Recall</td>
<td>0.174</td>
<td>0.275</td>
<td>0.397</td>
<td>1</td>
<td>.528</td>
<td>1.190</td>
</tr>
<tr>
<td>CERAD&lt;sup&gt;b&lt;/sup&gt; Constructional Praxis Delayed Recall</td>
<td>-0.089</td>
<td>0.257</td>
<td>0.121</td>
<td>1</td>
<td>.728</td>
<td>.915</td>
</tr>
<tr>
<td>Benton Visual Retention Test</td>
<td>-0.314</td>
<td>0.382</td>
<td>0.675</td>
<td>1</td>
<td>.411</td>
<td>0.730</td>
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<tr>
<td>Symbol Digit Modalities Test</td>
<td>0.068</td>
<td>0.087</td>
<td>0.618</td>
<td>1</td>
<td>.432</td>
<td>1.070</td>
</tr>
<tr>
<td>Trail Making Test Part B-Part A</td>
<td>0.008</td>
<td>0.009</td>
<td>0.833</td>
<td>1</td>
<td>.361</td>
<td>1.009</td>
</tr>
</tbody>
</table>

<sup>a</sup>Wechsler Memory Scale-Revised

<sup>b</sup>Consortium to Establish a Registry for Alzheimer’s Disease

---

**TABLE 6 - CONTINUED**

\[ \chi^2(13, N=108) = 33.019, p = 0.002 \]
## APPENDIX G

### TABLE 7

Table 7: Calculation of standardized regression coefficients predicting Alzheimer’s disease status

<table>
<thead>
<tr>
<th>Variable</th>
<th>$S_x$</th>
<th>$b$</th>
<th>$R$</th>
<th>$S_{yPred}$</th>
<th>$\beta$</th>
<th>$b$</th>
<th>$R$</th>
<th>$S_{yPred}$</th>
<th>$\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMS-R&lt;sup&gt;a&lt;/sup&gt; Logical Memory Delayed Recall</td>
<td>9.423</td>
<td>-0.225</td>
<td>.646</td>
<td>3.09</td>
<td>-0.443</td>
<td>-0.098</td>
<td>.324</td>
<td>0.923</td>
<td>-0.324</td>
</tr>
<tr>
<td>CERAD&lt;sup&gt;b&lt;/sup&gt; Word List Learning Delayed Recall</td>
<td>2.313</td>
<td>0.174</td>
<td>.646</td>
<td>3.09</td>
<td>0.084</td>
<td>-0.340</td>
<td>.326</td>
<td>0.787</td>
<td>-0.326</td>
</tr>
<tr>
<td>CERAD&lt;sup&gt;b&lt;/sup&gt; Constructional Praxis Delayed Recall</td>
<td>2.564</td>
<td>-0.089</td>
<td>.646</td>
<td>3.09</td>
<td>-0.048</td>
<td>-0.289</td>
<td>.284</td>
<td>0.741</td>
<td>-0.284</td>
</tr>
<tr>
<td>Benton Visual Retention Test</td>
<td>2.269</td>
<td>-0.314</td>
<td>.646</td>
<td>3.09</td>
<td>-0.149</td>
<td>-0.255</td>
<td>.194</td>
<td>0.579</td>
<td>-0.194</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test</td>
<td>11.515</td>
<td>0.068</td>
<td>.646</td>
<td>3.09</td>
<td>0.164</td>
<td>-0.052</td>
<td>.232</td>
<td>0.599</td>
<td>-0.232</td>
</tr>
<tr>
<td>Trail Making Test Part B-Part A</td>
<td>65.119</td>
<td>0.008</td>
<td>.646</td>
<td>3.09</td>
<td>0.109</td>
<td>0.002</td>
<td>.039</td>
<td>0.130</td>
<td>0.039</td>
</tr>
</tbody>
</table>

<sup>a</sup>Wechsler Memory Scale-Revised  
<sup>b</sup>Consortium to Establish a Registry for Alzheimer’s Disease
APPENDIX H

TABLE 8

Table 8: Predictive accuracy of logistic regression models with individual neuropsychological tests.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMS-R&lt;sup&gt;a&lt;/sup&gt; Logical Memory Delayed Recall</td>
<td>46.7</td>
<td>98.0</td>
<td>77.8</td>
<td>92.5</td>
</tr>
<tr>
<td>CERAD&lt;sup&gt;b&lt;/sup&gt; Word List Learning Delayed Recall</td>
<td>33.0</td>
<td>99.0</td>
<td>83.3</td>
<td>91.0</td>
</tr>
<tr>
<td>CERAD&lt;sup&gt;b&lt;/sup&gt; Constructional Praxis Delayed Recall</td>
<td>26.7</td>
<td>97.1</td>
<td>57.1</td>
<td>90.0</td>
</tr>
<tr>
<td>Benton Visual Retention Test</td>
<td>21.4</td>
<td>99.0</td>
<td>75.0</td>
<td>90.2</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test</td>
<td>28.6</td>
<td>100</td>
<td>100</td>
<td>90.9</td>
</tr>
<tr>
<td>Trail Making Test Part B-Part A</td>
<td>25.0</td>
<td>99.0</td>
<td>75.0</td>
<td>91.6</td>
</tr>
</tbody>
</table>

<sup>a</sup> Wechsler Memory Scale-Revised

<sup>b</sup> Consortium to Establish a Registry for Alzheimer’s Disease
## APPENDIX I

### TABLE 9

Table 9: Comparison of Alzheimer’s disease and no dementia group averages to neuropsychological test normative data

<table>
<thead>
<tr>
<th>Test</th>
<th>Current Study</th>
<th>Normative Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AD</td>
<td>No Dementia</td>
</tr>
<tr>
<td>WMS-R\textsuperscript{a} Logical Memory Delayed Recall</td>
<td>12.9 (9.5)</td>
<td>21.1 (9.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CERAD\textsuperscript{b} Word List Learning Delayed Recall</td>
<td>4.5 (3.0)</td>
<td>6.3 (2.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CERAD\textsuperscript{b} Constructional Praxis Delayed Recall</td>
<td>6.0 (3.0)</td>
<td>8.1 (2.4)</td>
</tr>
<tr>
<td>Benton Visual Retention Test</td>
<td>4.1 (2.3)</td>
<td>5.5 (2.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Current Study</td>
<td>Normative Data</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------</td>
<td>----------------</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>No Dementia</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test</td>
<td>30.0</td>
<td>36.7</td>
</tr>
<tr>
<td></td>
<td>(14.5)</td>
<td>(10.9)</td>
</tr>
<tr>
<td></td>
<td>Med = 39.0</td>
<td>66-75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Making Test Part B-Part</td>
<td>98.0</td>
<td>89.2</td>
</tr>
<tr>
<td>A</td>
<td>(66.7)</td>
<td>(65.2)</td>
</tr>
<tr>
<td></td>
<td>Med = 61.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>45.8</td>
<td></td>
</tr>
</tbody>
</table>

*a* Wechsler Memory Scale-Revised

*b* Consortium to Establish a Registry for Alzheimer’s Disease

Note: Mean and standard deviation are reported unless otherwise noted.
APPENDIX J

FIGURE 1

Depressed Participants with Neuropsychological Testing at Baseline ($n=152$)

Followed-Up 2.5+ Years ($n=124$)

AD ($n=15$)

No Dementia ($n=105$)

Followed-Up Less Than 2.5 Years ($n=28$)

Other Dementia ($n=4$)

Figure 1: Flowchart of participants enrolled in NCODE study.
APPENDIX K

FIGURE 2

Figure 2: Results from theoretical structural equation model: Association of temporal lobe and frontal lobe domains at baseline to Alzheimer’s disease status at follow-up.
APPENDIX L

INSTITUTIONAL REVIEW BOARD APPROVAL LETTER

Office of the Vice President For Research
Human Subjects Committee
Tallahassee, Florida 32306-2742
(850) 644-8673, FAX (850) 644-4392

APPROVAL MEMORANDUM

Date: 5/25/2011

To: Nicole Collins

Address: Department of Psychology
Dept.: PSYCHOLOGY DEPARTMENT

From: Thomas L. Jacobson, Chair

Re: Use of Human Subjects in Research
Neuropsychological Indicators of Preclinical Alzheimer's Disease among Depressed Older Adults

The application that you submitted to this office in regard to the use of human subjects in the proposal referenced above have been reviewed by the Secretary, the Chair, and one member of the Human Subjects Committee. Your project is determined to be Expedited per 45 CFR Â§ 46.110(7) and has been approved by an expedited review process.

The Human Subjects Committee has not evaluated your proposal for scientific merit, except to weigh the risk to the human participants and the aspects of the proposal related to potential risk
and benefit. This approval does not replace any departmental or other approvals, which may be required.

If you submitted a proposed consent form with your application, the approved stamped consent form is attached to this approval notice. Only the stamped version of the consent form may be used in recruiting research subjects.

If the project has not been completed by 5/23/2012 you must request a renewal of approval for continuation of the project. As a courtesy, a renewal notice will be sent to you prior to your expiration date; however, it is your responsibility as the Principal Investigator to timely request renewal of your approval from the Committee.

You are advised that any change in protocol for this project must be reviewed and approved by the Committee prior to implementation of the proposed change in the protocol. A protocol change/amendment form is required to be submitted for approval by the Committee. In addition, federal regulations require that the Principal Investigator promptly report, in writing any unanticipated problems or adverse events involving risks to research subjects or others.

By copy of this memorandum, the Chair of your department and/or your major professor is reminded that he/she is responsible for being informed concerning research projects involving human subjects in the department, and should review protocols as often as needed to insure that the project is being conducted in compliance with our institution and with DHHS regulations.

This institution has an Assurance on file with the Office for Human Research Protection. The Assurance Number is FWA00000168/IRB number IRB00000446.

Cc: Natalie Sachs-Ericsson, Advisor
HSC No. 2011.6357
REFERENCES


BIOGRAPHICAL SKETCH

Education

2007-Present   Florida State University; Tallahassee, FL
               Ph.D., Clinical Psychology (Expected 2014)
               Major Professor: Natalie Sachs-Ericsson, Ph.D.

2003-2007   University of North Carolina at Chapel Hill; Chapel Hill, NC
              B.A., Psychology

Honors and Awards

Southern Gerontological Society Student Paper Award, First Place ($250), April 2011
Congress of Graduate Students (COGS) Presentation Grant ($300), 2008-2010
Dean’s List, University of North Carolina at Chapel Hill, 2003-2007

Publications


**Published Abstracts**


**Presentations**


Related Experience

Research

2010-Present  Graduate Research Assistant

College of Medicine, Florida State University; Tallahassee, FL

FSU Weight Management Program

Supervisor: Gareth Dutton, PhD

Activities: Serve as group therapist for a year-long group cognitive-behavioral weight loss intervention; Recruit participants by phone; Conduct in-person baseline and follow-up assessments; Design surveys; Create, manage, and clean project databases; Generate ideas for research projects; Run analyses in SPSS; Supervise undergraduate and bridge medical students assisting with project.

2009-2010  Data Manager

Department of Psychology, Florida State University; Tallahassee, FL

Anxiety-Based Smoking Treatment Project

Supervisor: Mary Gerend, PhD

Activities: Cleaned and managed SPSS and Excel databases; Created coding schemes for qualitative data; Analyzed data and reported findings to research team; Generated ideas for research projects; Prepared manuscripts.

2004-2007  Student Research Assistant

Cecil G. Sheps Center for Health Services Research

Program on Aging, Disability, and Long-Term Care; Chapel Hill, NC
Supervisors: Philip Sloane, MD, MPH & Sheryl Zimmerman, PhD

Activities: Involved in project conception through writing IRB applications, creating consent forms, designing measures, and managing databases; Participated in data collection phase by recruiting subjects, obtaining consent, and conducting interviews with older adults and their direct care providers in person and by phone. Edited data, scored clock drawings administered as screens for dementia, and created a scoring system for qualitative data; Cleaned and analyzed data using SAS; Drafted and edited abstracts, literature reviews, and sections of papers for publication; Maintained project websites.

2006-2007 Undergraduate Research Assistant
Department of Psychology, University of North Carolina at Chapel Hill
Peer Relations Lab
Supervisor: Mitchell Prinstein, PhD

Activities: Conducted lab visits involving assessment of and social interaction tasks with pairs of adolescent participants; Explained consent and study procedures to participants and their parents; Transcribed videotapes of participant interactions; Attended weekly lab meetings.

Clinical

2008-2010 Psychological Trainee
Florida State University Psychology Clinic; Tallahassee, FL
Supervisors: N. Brad Schmidt, PhD, Thomas Joiner, PhD, Donald Kerr, PhD, & Jeanette Taylor, PhD

Activities: Provided individual outpatient therapy and assessment (intellectual functioning, learning disability, ADHD, work clearance, and autism spectrum) for adults and children from the local community, with an emphasis on empirically-supported interventions; Conducted diagnostic interviews, interpreted personality profiles (e.g., MMPI-2) and symptom scales (e.g., Beck Depression Inventory), and provided feedback regarding diagnoses.

2008-2009 Psychology Intern
Apalachee Center, Inc.
PATH Crisis Stabilization Unit, Eastside Psychiatric Hospital, Short-Term Residential Treatment Unit, and Primary Care Center/Detox Unit; Tallahassee, FL
Supervisors: Kristee Treadwell, PhD & Jay Reeve, PhD
Activities: Administered intake interviews and led group (process and content focused) and individual therapy with clients of various cultural and socioeconomic backgrounds with severe mental illness undergoing inpatient hospitalization for crisis stabilization or detox.

2008-2009  
**Psychology Department Practicum Student**  
*Florida State Hospital; Chattahoochee, FL*  
**Supervisor:** C. Wayne Anderson, PhD  
**Activities:** Conducted individual and group therapy with individuals suffering from severe depressive and psychotic disorders and undergoing long-term hospitalization; Provided competency education to individuals designated “incompetent to proceed” to trial; Administered and interpreted intellectual and neuropsychological assessments.

**Teaching**  
2009-2010  
**Teaching Assistant**  
*Department of Psychology, Florida State University; Tallahassee, FL*  
**Research Methods Lab (Undergraduate course)**  
**Supervisor:** Walter Boot, PhD  
**Activities:** Served as instructor for two lab sections of undergraduate research methods course for psychology majors; Instructed students on how to conduct a research project and input and analyze data using SPSS; Graded all assignments and provided feedback to students.

Spring 2007  
**Recitation Leader**  
*Department of Psychology, University of North Carolina at Chapel Hill*  
**Psychology 101 (Introduction to Psychology)**  
**Supervisor:** Beth Jordan, PhD  
**Activities:** Led discussions and group activities as a supplement to the lecture course for two weekly, one-hour recitation sections for students enrolled in Psychology 101.