COGNITIVE AND NEUROPSYCHIATRIC INDICATORS OF ADAPTIVE

FUNCTION IN ALZHEIMER'S DISEASE

A Dissertation

by

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disease that causes cognitive impairment, neuropsychiatric symptoms, and reduced adaptive function. In particular, reduced adaptive function can present challenges to patient safety and wellness, and is associated with reduced patient quality-of-life. Unfortunately, such declines typically do not manifest until much later in the disease course. Therefore, it may be useful to identify alternative indicators of potential adaptive function decline. Cognitive function and neuropsychiatric symptoms, which have been shown to be associated with adaptive function, may be such indicators, particularly given their presentation earlier in the disease course. The present study used hierarchical linear regression to explore associations between cognitive, neuropsychiatric, and adaptive function indicators of AD. Analyses were completed using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI; $N = 332$). Results indicated that baseline cognitive and neuropsychiatric indictors were indeed associated with adaptive function at baseline, 12, and 24 months follow-up. Future research is needed to corroborate this finding, which may have significant clinical implications for treatment planning.

DEDICATION

"If you want to go quickly, go alone. If you want to go far, go together."

–African Proverb

I would be remiss to not thank my beloved family, whose consistent support and encouragement enabled and empowered me not only to pursue graduate schooling but power through it, especially during those moments when that felt and seemed nearly impossible. My parents Azfar and Shahnaz, whose dreams for me have always been limitless, my sisters Samira, Saima, and Farina, and my extended family: you were my first friends, my first teachers, my first community. This has only been possible because of you.

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CHAPTER I

INTRODUCTION AND LITERATURE REVIEW

Epidemiology

Alzheimer's disease (AD) is a progressive neurodegenerative disease that causes cognitive impairment, neuropsychiatric symptoms, and reduced adaptive function. With the rapid growth of the older adult (65 years and older) population over the last fifty years, AD has become one of the most pressing health concerns in the United States. AD affects more than 5 million American adults, almost two thirds of whom are women (Alzheimer's Association, 2018). However, because the disorder is considerably underdiagnosed and underreported, these may be gross underestimates of the actual number of Americans living with AD. A new case of AD is diagnosed approximately every 66 seconds (Alzheimer's Association, 2018), and more than 480,000 older Americans were projected to be diagnosed with AD in 2018 alone.

AD is currently the sixth leading cause of death in the United States (Alzheimer's Association, 2018; Xu, Murphy, Kochanek, & Bastian, 2016). Of the top ten causes, it is the only one that cannot be prevented, cured, or slowed (Alzheimer's Association, 2018). Indeed, deaths from AD increased 123% between 2000 and 2015 (Miniño, Arias, Kochanek, Murphy, & Smith, 2002; Murphy, Xu, Kochanek, Curtin, & Arias, 2017). In comparison, deaths from other major causes, such as stroke or heart disease, have decreased by at least 10% each (Miniño et al., 2002; Murphy et al., 2017). The average AD patient will live for approximately 4 to 10 years following diagnosis (Alzheimer's Association, 2018; Brookmeyer, Corrada, Curriero, & Kawas, 2002; Cummings & Cole,

2002), although this estimate can vary in light of other factors, such as comorbid conditions and age at time of diagnosis (Brookmeyer et al., 2002).

Economic Impacts

The adverse impacts of AD on the individual patient are very apparent, but there are equally tremendous societal impacts to be considered as well. Regarding economic impacts, AD can be extremely costly to manage. By the end of 2018, the direct costs of caring for American AD patients exceeded $275 billion, more than half of was sustained by the federal government through Medicare and Medicaid (Alzheimer's Association, 2018). In addition to direct treatments costs, AD can have a modest impact on the national labor force, largely due to significant caregiving demands that can result in absenteeism or compromised productivity (Kubendran, DeVol, & Chatterjee, 2016). However, lost productivity due to earlier-onset AD can also be observed, as younger patients are forced to leave the work force prior to retirement age. For example, the cost of lost productivity for working-age AD patients is estimated to exceed $6 billion for African American patients alone (Gaskin, LaVeist, & Richard, 2013). This cost is likely to be considerably higher when considering patients across all racial or ethnic groups.

Individual families also bear an enormous financial burden when it comes to managing AD. Currently, there are projected to be more than 16 million informal caregivers of AD patients in the United States alone (Alzheimer's Association, 2018). Approximately 1 out of 4 caregivers spends at least 36 hours weekly caring for an AD patient (American Psychological Association, 2006), which equates to roughly 32% of their total waking hours in a given week. Often, caregiving obligations take time away

from work (Alzheimer's Association, 2018), leading to lost wages and a decrease in income. Expenses directly related to care provision exceed an average of $10,000 annually per family (Alzheimer's Association, 2018; Rainville, Skufca, & Mehegan, 2016). This is a considerably concerning figure, given that more than 40% of caregivers have an annual household income of $50,000 or less (Alzheimer's Association, 2018).

Neuropathology, Etiology, and Risk Factors

Although the exact etiology of AD remains unknown, evidence suggests that AD pathology is linked to abnormal deposits of proteins in the brain. These protein deposits form amyloid plaques and neurofibrillary tau tangles in and around neurons (National Institutes on Aging, 2016). As previously healthy neurons become diseased, they cease functioning, lose synaptic connections with surrounding neurons, and die (National Institutes on Aging, 2016). Progressive neuronal death results in atrophy, or shrinkage, of vital brain structures, leading to impairments in processes regulated by those structures, including cognitive, behavioral, emotional, and adaptive functions. AD pathology is also associated with inflammation in the brain, although it is unclear if this inflammation causes or is caused by the disorder itself (Wyss-Coray & Rogers, 2012), as well as decreased glucose metabolism in affected areas (Perrin, Fagan, & Holtzman, 2009; Shivamurthy, Tahari, Marcus, & Subramaniam, 2015).

Evidence from histological (Braak & Del Tredici, 2012; Gómez-Isla et al., 1996) and imaging (Moreno et al., 2007; Whitwell et al., 2007) studies suggests that AD-related pathological changes first begin in the entorhinal cortex (Khan et al., 2013). Located in the medial temporal lobe, the entorhinal cortex serves as a central processing

point for memory and navigation, as well as the primary interface between the hippocampus and neocortex. The entorhinal cortex-hippocampus system is largely responsible for memory formation, consolidation, and optimization (Preston & Eichenbaum, 2013). From the entorhinal cortex, progressive cell death spreads to other areas of the temporal lobe, such as the hippocampus, which has a major role in learning and memory (Anand & Dhikav, 2012).

Plaques and tangles continue to radiate outwards to additional areas of the brain (Arriagada, Growdon, Hedley-Whyte, & Hyman, 1992), such as the frontal lobe. Damage to the frontal lobe can result in difficulties with more complex cognitive processes, such as planning (Godefroy, 2003), decision-making (de Mendonça, Ribeiro, Guerreiro, & Garcia, 2004), and problem-solving (Godefroy, 2003). Neuropathology in the parietal and occipital lobes can cause impaired integration of sensory information and declines in visual processing, respectively. In tandem with noticeable cognitive changes, emotional disturbances and motor impairments can arise following neuronal death in the amygdala, cerebellum, thalamus (Hopper & Vogel, 1976).

It is difficult to attribute the development of AD to one specific causal factor, except in the case of specific genetic mutations. In the case of genetic mutations, there are genes from three relevant proteins to consider: amyloid precursor protein (APP), presenilin 1, and presenilin 2. Individuals who inherit mutations to the APP or presenilin 1 genes will inevitably go on to develop AD. Individuals who inherit a mutation to the presenilin 2 gene have a 95% chance of eventually developing AD (Goldman et al.,

2011). There are additional genes currently being investigated for ties to AD

development, including the Apolipoprotein E (APOE)-e4 gene. Unlike inheritance of

APP, presenilin 1, and presenilin 2 protein gene mutations, inheritance of the APOE-e4

allele does not guarantee or nearly guarantee eventual AD development (Loy, Schofield,

Turner, & Kwok, 2014). However, individuals who inherit one copy of the e4 allele are

three times as likely to develop AD compared to individuals who do not inherit the e4

allele (Holtzman, Herz, & Bu, 2012). Those with two copies of the e4 allele can be 8 to

12 times as likely to develop AD compared to their normal counterparts (Holtzman et

al., 2012; Loy et al., 2014).

Aside from cases caused by genetic mutation, most cases of AD develop from a

combination of risk factors; as such, incidence and progression of AD can vary widely

among patients. Risk factors that are commonly discussed in the literature include non-

modifiable factors, such as age or family history, and modifiable factors, such as

physical activity, social engagement, and diet. Many of these risk factors are associated

with comorbid conditions, such as cardiovascular disease or diabetes, which are

themselves hypothesized to be risk factors for eventual AD development. Individuals

can reduce their risk of developing AD or at least delay onset of symptoms by attending

to these factors, but there is currently no way of preventing the disease entirely.

Classification and Characterization

As a progressive disorder, the clinical presentation of AD is constantly changing

as the severity of the disease intensifies. The spectrum of disease severity can be roughly

delineated into a sequence of qualitative descriptors that reflect increasingly problematic

impairments. At one end of the continuum are cognitively normal, healthy individuals. Some of these individuals may go on to develop AD, although the initial neuropathological changes may precede actual diagnosis by as many as 20 years (Alzheimer's Association, 2018). This relatively symptom-free period is known as the preclinical state (Dubois et al., 2010). The preclinical state can be further divided into the asymptomatic at-risk state and the presymptomatic state (Dubois et al., 2010). Individuals in the asymptomatic at-risk state are cognitively normal and functionally independent but for whom there is in vivo evidence of AD-related pathology in the brain, as indicated by amyloid or tau biomarkers (Dubois et al., 2010). Individuals in the presymptomatic state also appear symptom-free but carry a genetic mutation that will predispose them to eventually developing AD (Dubois et al., 2010).

Many individuals on the AD trajectory eventually move from the preclinical state to the prodromal stage, also known as the "pre-dementia" stage of AD. Individuals in this stage exhibit memory loss or other mild cognitive impairments, but these symptoms generally do not interfere with functional activities and therefore do not yet warrant a diagnosis of dementia (Dubois et al., 2010). There is, however, in vivo biomarker evidence of AD-related pathology in the brain. The prodromal stage includes individuals who are diagnosed with Mild Cognitive Impairment (MCI) and is a related but distinct diagnostic descriptor. Patients with MCI exhibit similar levels of cognitive impairment to prodromal AD patients but do not have in vivo biomarker-indicated evidence of AD-related pathology (Dubois et al., 2010). MCI patients' symptoms could be attributable to

AD or to another etiology entirely. In comparison, patients in the prodromal AD stage will likely go on to develop full-blown Alzheimer's disease dementia (ADD).

The preclinical and prodromal stages of AD are of particular interest for researchers and clinicians due to the potential for early intervention, which has important clinical and research implications. In the absence of a cure, early intervention is necessary in order to optimize patient prognosis. Several studies have found that early intervention can have several important impacts on patients' overall quality-of-life. Nonpharmacological interventions, which may result in slowed disease progression (Olazarán et al., 2010), are likely to be more effective at lower levels of disease severity, thereby necessitating early diagnosis. Early diagnosis has also been shown to be associated with decreased subsequent mortality (Bruandet et al., 2009). Regarding clinical trials, identifying individuals with preclinical or prodromal AD can facilitate enrollment of participants for more robust longitudinal studies, which are vital for studying the progression of the disease over time.

Early diagnosis can also yield tremendous economic benefits (Hay & Ernst, 1987). For example, Barnett and colleagues (2014) demonstrated through health economics modelling that early intervention can significantly increase the cost-effectiveness of treatment, with the Alzheimer's Association projecting as much as $7.9 trillion in cumulative savings (Alzheimer's Association, 2018). Given the previously described economic burden of AD, such savings can be hugely impactful at the individual and national levels.

Rates of conversion from one stage to the next are somewhat variables across studies for a number of reasons. Perhaps most importantly, the AD trajectory is not necessarily linear, and there is considerable heterogeneity among individual patients, based on comorbid conditions, environmental factors, and family history. Nonetheless, estimates for conversion rates have been generated, most often for the transition from MCI to ADD. Estimates range from 10% to 50% (Bowen et al., 1997; Geslani, Tierney, Herrmann, & Szalai, 2005; Petersen et al., 1995; Schmidtke & Hermeneit, 2008), depending largely on methodological limitations of this type of research, including variability in operationalizing measures, follow-up time, and sample size (Dawe, Procter, & Philpot, 1992; Petersen et al., 1999).

AD can be described as typical, atypical, or mixed (Dubois et al., 2010). Typical AD is the most common clinical phenotype of AD and is characterized by early but persistent deficits in episodic memory, followed by additional impairments in other cognitive domains, including language, executive function, and visuospatial reasoning. Patients with typical AD are also positive for one or more in-vivo biomarkers of AD pathology. In contrast, atypical AD is comprised of less common and less well characterized clinical phenotypes, wherein episodic memory deficits are not necessarily the first impairments to be observed. Rather, these syndromes can include various progressive aphasias, frontal variant AD, and posterior cortical atrophy. The diagnosis of AD is supported by in-vivo evidence of amyloidosis in the brain or cerebrospinal fluid (CSF). Lastly, patients with mixed AD fully fulfill the diagnostic criteria for typical AD

but also present with clinical and biomarker evidence of other comorbid disorders, such as cerebrovascular disease or Lewy body disease.

AD can also be subdivided into severity stages that reflect the degree to which patients are impaired. These stages are mild, moderate, and severe. Severity stages can be characterized by different constellations of cognitive and behavioral symptoms. For example, individuals who are in the mild range are generally oriented to person and place but may have occasional difficulty orienting to time. They exhibit "benign forgetfulness" and need occasional assistance to engage in community and personal affairs completely independently. At the opposite end of the spectrum, individuals who are in the severe range are likely disoriented to both time and place, exhibit severe memory loss, and are so impaired that they cannot engage in virtually any community or personal affairs, even with assistance.

In tandem with observable cognitive and functional declines, significant neuropathological changes can arise across the severity spectrum. Patients in the severe range of AD severity have significantly atrophied brains compared to their normal counterparts (Fox & Schott, 2004; Jack et al., 1997), both at the individual structure and whole brain levels. One area of the brain where atrophy is particularly noticeable is the hippocampus. Differential hippocampal atrophy rates are so striking that they have been used diagnostically to track AD over time in multiple clinical studies (Mueller, Schuff, Yaffe, Madison, Miller, & Weiner, 2010). Patients with MCI or prodromal AD tend to exhibit 10 to 15% hippocampal volume loss, whereas patients with mild AD exhibit 15 to 30% (Frisoni, Fox, Jack, Scheltens, & Thompson, 2010). In the moderate range of

disease severity, the hippocampal atrophy rate can jump to as high as 50% (Dhikav & Anand, 2011). In addition to observable atrophy, increasingly dense amyloid (Braak & Braak, 1991) and tau (Cope et al., 2018) deposits can also be observed among patients who progress along the severity continuum. Declines in glucose metabolism also characterize increasing AD severity (Shivamurthy et al., 2015).

Cognitive Dysfunction

Although AD can manifest across a diverse array of symptoms, cognitive dysfunction is often considered the hallmark symptom of AD. Cognitive dysfunction can be reflected in impairments in memory, language, visuospatial reasoning, attention, and executive function. Impaired memory is perhaps the most recognizable and most frequently occurring of the cognitive symptoms, particularly earlier in the disease course (U.S. Department of Health & Human Services, 2016). This early manifestation of memory impairments distinguishes AD from other dementing conditions where memory impairments are not typically the first to be observed, such as vascular dementia and dementia with Lewy bodies (Alzheimer's Association, 2018). Examples of early memory impairments include difficulty remembering recent conversations, familiar names, and experienced events (Alzheimer's Association, 2018).

AD can also be characterized by deficits in language, which manifest as impairments in speaking, reading, and writing abilities (McKhann et al., 2011). Language deficits are common among AD patients and can present early in the disease course (Taler & Phillips, 2008). Examples of such deficits include word-finding difficulty, loss of verbal fluency, and poor comprehension of both written and spoken

language (Ferris & Farlow, 2013). These deficits worsen as the disease progresses; by the severe stage, speech is often limited to echolalia or verbal stereotypy (Ferris & Farlow, 2013).

Visuospatial reasoning abilities are also affected by AD (Meguro, Shimada, Someya, Horikawa, & Yamadori, 2001; Mendez, Mendez, Martin, Smyth, & Whitehouse, 1990). Visuospatial reasoning is a complex higher-order cognitive ability that encompasses several lower-level abilities, but broadly refers to the ability to identify, process, and interpret visual and spatial relationships among objects (Kolb & Whishaw, 1985; Owens, 2014; Pinel, 1993). Deficits in visuospatial reasoning that are typical of AD can manifest as difficulties with visual memory or visual attention (Meguro et al., 2001; Rizzo, Anderson, Dawson, Myers, & Ball, 2000). Visuospatial reasoning underlies several important functional abilities as well; patients who exhibit these deficits often have difficulty driving or navigating new and unfamiliar environments.

Declines in attention and concentration are another symptom of cognitive dysfunction observed among AD patients (McKhann et al., 2011), with some speculation that attentional deficits may arise early in the disease course along with memory impairments (Perry & Hodges, 1999). Like the other cognitive domains described, attention is a broad construct that encompasses multiple lower-level processes, including selective attention, sustained attention, and divided attention (Perry & Hodges, 1999). Problems with attention can manifest as poor concentration, distractibility, and

confusion while performing routine tasks. Attentional deficits often overlap with and are considered in tandem with executive function impairments, described below.

Executive function impairments (otherwise known as executive dysfunction) are recognized less often but can develop secondary to AD-related pathology nonetheless (Collette, Van der Linden, & Salmon, 1999). Executive function is a cognitive domain that includes but is not limited to abilities for concept formation, mental manipulation of information, planning, and decision-making (Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1993; Lafleche & Albert, 1995). Because executive function is associated with higher-order top-down processes, impairments in this domain can be especially problematic for patients and their caregivers. Examples of functional challenges that stem from executive dysfunction include difficulty selecting clothing appropriate for the weather or planning and preparing meals (Patterson, Mack, Geldmacher, &Whitehouse, 1996).

Regarding etiology, memory impairments are thought to stem from neuronal death in the entorhinal cortex and the hippocampus (U.S. Department of Health and Human Services, 2017), both of which are neuroanatomical structures in the temporal lobe of the brain (Collie & Maruff, 2000). The implication of medial temporal lobe areas in memory impairments has been demonstrated by a number of lesion, functional neuroimaging, and animal studies (Collie & Maruff, 2000). The neuropathology observed in the temporal lobe includes atrophy of specific structures as well as accumulation of plaques and tangles (Price & Morris, 1999). Specifically, episodic

memory, or the ability to remember past experiences, seems to become compromised due to temporal lobe pathology.

There are multiple areas of the brain that have a critical role in language abilities, including Broca's area in the left frontal lobe (Grodzinsky, 2000), Wernicke's area in the left temporal lobe, and the angular gyrus in the parietal lobe (Caplan, 1994; Seghier, 2013). Given the relatively wide distribution of language processing function across the brain, it can be inferred that declines in language likely originate from pathology in multiple brain areas, largely dependent on the nature of the impairment. Furthermore, given the association of language with memory and executive function (Taler & Phillips, 2008), declines in language may arise secondary to neuropathology in areas associated with these functions, such as the hippocampal-entorhinal system and the frontal lobe.

The neuroanatomical correlates of visuospatial deficits are often described in terms of hemispheric asymmetry, with the relevant pathology thought to manifest in the right hemisphere (Benton, Sivan, deS Hamsher, & Spreen, 1983; Caine & Hodges, 2001). Specifically, neuropathology in the right parietal lobe appears to correlate to various visuospatial deficits (Foster et al., 1983), including difficulty with perceptual classification (Warrington & Taylor, 1973) mental rotation (Butters & Barton, 1970), and mental reconstruction (Butters & Barton, 1970). It should be noted that variability of visuospatial deficits has been suggested to be reflective of heterogeneity in associated neuropathology, and not necessarily a progressive nature of the disease course (Kurylo, Corkin, Rizzo, & Growdon, 1996).

Declines in attention and concentration have been attributed to pathology in basal forebrain cholinergic system (Lawrence & Sahakian, 1995), as well as the prefrontal cortex, thalamus, and the parietal lobe (Lawrence & Sahakian, 1995), areas that are associated with spatial and sustained attention (Coull, 1994; Posner & Dehaene, 1994). Because attention as a cognitive function is broad (i.e. sustained versus divided, verbal versus visual), attentional deficits can stem from pathology in areas of the brain that are less obviously related to attention alone, as is the case with many of the cognitive impairments observed in AD.

Executive dysfunction is often associated with neuropathology in the frontal lobe (Bruen, McGeown, Shanks, & Venneri, 2008; Buckner, 2004; Elliott, 2003; Lyketsos et al., 2011; Tekin & Cummings, 2002) and corticostriatal circuits (Elliott, 2003). Again, these causal relationships have been demonstrated through various neuroimaging studies, as well as neuropsychological studies of patients with various neurological disorders, including multiple systems atrophy, progressive supranuclear palsy, Huntington's disease, and Parkinson's disease (Lawrence et al., 1996; Robbins et al., 1994; Taylor, Saint-Cyr, & Lang, 1986). In AD specifically, frontal lobe dysfunction has been shown to be associated with anosognosia (Michon, Deweer, Pillon, Agid, & Dubois, 1994), the inability to perceive or understand one's own illness.

Although these cognitive functions are thought to be maintained in different areas of the brain, they are inherently all interconnected. Deficits in these functions often span multiple domains (Perry & Hodges, 1999); for example, many patients exhibit declines in visual memory or verbal attention. Due to the interconnectedness of the

neural pathways that underlie memory, visuospatial reasoning, language, attention, and

executive function, as well as the interrelatedness of these processes in performing

various functional tasks, it is difficult to isolate the specific causal pathways that explain

how individual impairments arise (Baudic et al., 2006).

Neuropsychiatric Symptoms

In addition to cognitive impairment, between 50-90% of AD patients are

estimated to develop neuropsychiatric symptoms (Peters et al., 2015; Nowrangi,

Lyketsos, & Rosenberg, 2015). In general, the prevalence and severity of these

symptoms intensifies parallel to an advancing dementia course (Canevelli et al., 2013;

Geda et al., 2008). Neuropsychiatric symptoms commonly observed among AD patients

can be generally grouped into three categories: behavioral disturbances, psychotic

symptoms, and affective symptoms. Behavioral disturbances include aberrant motor

behavior, changes in appetite, and sleep disturbances/nighttime behaviors. Psychotic

symptoms primarily consist of hallucinations and delusions. Affective symptoms include

feelings of depression, anxiety, and apathy.

Patients may present with different constellations of symptoms, based on

comorbid conditions and their stage in the disease process. For example, symptoms of

depression and anxiety have been reported to be predictive of conversion from mild

cognitive impairment to AD (Gallagher et al., 2011; Palmer et al., 2007); apathy has also

been reported to present early in the disease course (Alzheimer's Association, 2018). In

contrast, hallucinations and delusions are more likely to be observed at a higher level of

AD severity (Fuller, Choudhury, Lowe, & Balsis, 2019). Estimated prevalence rates of

individual neuropsychiatric symptoms within the AD population vary, but evidence suggests that symptoms of apathy or indifference are some of the most frequently reported (Fauth & Gibbons, 2014; Mega, Cummings, Fiorello, & Gornbein, 1996). Agitation, anxiety, and irritability (Fauth & Gibbons, 2014; Mega, Cummings, Fiorello, & Gornbein, 1996) are also commonly observed neuropsychiatric symptoms among AD patients.

Neuropsychiatric symptoms can result from a diverse array of etiologies, but many of them, such as depression, apathy, and delusions, have been linked to neuropathology in the frontal lobe (Bruen, McGeown, Shanks, & Venneri, 2008; Hirono et al., 1998; Tekin & Cummings, 2002). Specifically, the cholinergic hypothesis of neuropsychiatric symptom development in AD is one that has been considered for several decades. This hypothesis, which broadly posits that acetylcholine deficits or dysfunction cause neuropsychiatric symptoms (Terry & Buccafusco, 2003), has been largely supported from clinical studies of the effectiveness of cholinergic drugs for ameliorating neuropsychiatric symptoms (Cummings & Back, 1998; Levy, Cummings, & Kahn-Rose, 1999).

The relevance of neuropsychiatric symptoms in AD is not to be underestimated. Incidence of neuropsychiatric symptoms has been associated with accelerated progression through severity stages. In one study, 85% of MCI patients with depression (a commonly observed neuropsychiatric symptom) converted to AD, where as 32% of MCI patients without depression converted to AD (Modrego & Ferrández, 2004). Furthermore, dementia appeared earlier in the depressed patients than in their non-

depressed counterparts (Modrego & Ferrández, 2004). In another study, anxiety was found to be associated with accelerated progression from MCI to AD (Visser et al., 2000).

In addition to potentially aggravating disease progression, neuropsychiatric symptoms are also known for being considerably troubling for caregivers (Allegri et al., 2006; Kaufer et al., 1998; Rabins, Mace, & Lucas; 1982). Kaufer and colleagues (1998) found that agitation, dysphoria, irritability, delusions, and apathy were the symptoms most often reported to be severely distressing to caregivers. A study from Allegri and colleagues (2006) identified delusions, hallucinations, restlessness, anxiety, euphoria, disinhibition, unusual motor behavior, sleep disturbances, and appetite alterations as predictive of caregiver distress. This presumably causal relationship between neuropsychiatric symptoms and caregiver distress is important because elevated caregiver distress can have several negative consequences for both caregivers and patients.

Adaptive Function

Declines in adaptive function, though less emphasized than cognitive impairment, is perhaps one of the most problematic aspects of AD. Adaptive function refers to an individual's ability to complete basic and instrumental activities of daily living. Examples of basic activities of daily living (also known as physical self-maintenance skills) include bathing, dressing, grooming, feeding, and toileting. In comparison, instrumental activities of daily living refers to more complex, multi-step processes, such as household chores, shopping, preparing meals, transportation,

managing financial and legal affairs, and answering the telephone. Declines in adaptive function have long been associated with dementia broadly and can help characterize AD progression specifically (Reisberg et al., 2001), in comparison to other dementing conditions.

Adaptive function declines generally worsen in concordance with increasing disease severity. Referring back to the previously described stages of AD severity, individuals in the normal to mild range are generally able to complete most basic and instrumental activities of daily living independently. As patients progress through the severity spectrum from mild to moderate and then to severe, they increasingly require assistance from a caregiver to complete adaptive function tasks. Patterns of adaptive function declines vary across patients, but difficulty completing instrumental activities of daily living often precedes difficulty competing basic activities of daily living (Gélinas, Gauthier, McIntyre, & Gauthier, 1999), perhaps due to the more complex, cognitively demanding nature of instrumental activities and the more learned, routine nature of basic activities (Weintraub, 1986).

Adaptive function declines can be very distressing for AD patients and their caregivers. There is ample evidence to suggest that reduced functional independence is associated with reduced quality-of-life for patients and increased subjective distress for their caregivers (Clyburn, Stones, Hadjistavropoulos, & Tuokko, 2000; Mioshi et al., 2007; Vitaliano, Russo, Young, Teri, & Maiuro, 1991). For patients, declines in adaptive function can be depressing as patients slowly lose their functional independence (Borell, 1996; Teri, 1997), which can have negative downstream effects on mood, motivation,

and consequently, ability to do other tasks for which capacity is still intact (Borell, 1996). For caregivers, having to assist patients with more activities of daily living can cause considerable strain (Alzheimer's Association, 2018; Clyburn et al., 2000). The literature is rich with information about the negative effects of increased caregiver strain, including poorer mental and physical health outcomes and financial burden (Alzheimer's Association, 2018; Ernst & Hay, 1994).

If declines in adaptive function are associated with reduced patient quality-of-life and caregiver distress, it follows then that preservation of adaptive function may be a positive mitigator of reduced quality-of-life and caregiver distress. This preservation can have further positive downstream effects on patient prognosis. In other words, patients who are able to maintain adaptive function abilities for longer are likely to retain a subjective sense of independence and self-efficacy (Clare, 2002). This can promote positive mood and motivation (Andersen, Wittrup-Jensen, Lolk, Andersen, & Kragh-Sørensen, 2004), which may in turn be protective against further cognitive decline (Ostir, Markides, Black, & Goodwin, 2000). Logsdon and colleagues (1999) found, for example, that AD patients who self-reported higher levels of functional independence also reported better quality-of-life. Preserving adaptive function abilities for as long as possible may also help reduce caregiver burnout (Vitaliano et al., 1991), as caregivers have more time to adjust to (and prepare for) gradually increasing caregiving demands.

It is nearly impossible to attribute the development of adaptive function impairments to just one source (Gélinas et al., 1999). Results from several studies suggest that such impairments can be partially attributed to cognitive declines:

specifically, executive dysfunction and memory declines (Marshall et al., 2011). The association between executive dysfunction or memory impairments and adaptive function impairments is robust and can even be observed among older adults who presumably do not have AD (Jefferson, Paul, Ozonoff, & Cohen, 2006). For patients who do go on to develop AD, the relationship can manifest as early as the prodromal stage (Martyr & Clare, 2012). This relationship is rather intuitive, particularly for instrumental activities of daily living, which often require multiple higher-level cognitive abilities.

Cognitive deficits alone, however, do not explain adaptive function declines (Borell, 1996; Gélinas et al., 1999; Weintraub, 1996). According to a study from Reed, Jagust, and Seab (1989), cognitive deficit only explained roughly one third of the variance in adaptive function. This suggests that there are other factors that likely impact adaptive function abilities in AD patients. Results from several studies have demonstrated an association between neuropsychiatric symptoms and adaptive function declines, with the general finding that patients with more neuropsychiatric symptoms are generally less functionally independent (Allegri et al., 2006; Lyketsos et al., 2011). It is important to note here that neuropsychiatric symptoms are hypothesized to be related somewhat to cognitive decline. Therefore, it is difficult to discern whether or not neuropsychiatric symptoms and cognitive deficits operate independently or, more likely, if they interact to produce adaptive function declines.

Assessing Adaptive Function

Assessment and characterization of adaptive function in AD patients has many important clinical implications, mostly in regard to treatment planning. Measuring current status, as well as tracking changes over time, can alert clinicians and caregivers to the need for additional or changes to existing support services (Borell, 1996; Weintraub, 1986). Implementing structural supports for AD patients who are functionally dependent can be costly and tedious. Caregivers who are alerted earlier to the potential for decline can prepare for these changes further in advance. Furthermore, adaptive function status has been shown to be associated with institutionalization (Borell, 1996); timely characterization can prevent premature institutionalization, which can be a significant financial burden for care providers (Alzheimer's Association, 2018). Also, understanding the impacts of adaptive function declines on caregivers can help clinicians tailor interventions and support resources for caregivers' specific needs, particularly as they change over time.

Additionally, measuring patients' adaptive function declines may yield a more externally valid reflection of their overall AD-related impairments. In other words, demonstrating "below average" performance on a task of graphomotor transcription may provide some information about general processing speed, but it likely provides more information about the ability to perform that specific cognitive test, which is not necessarily based in everyday functioning (Burgess et al., 2006). In comparison, difficulty completing an instrumental activity of daily living, such as financial

management, may be more relevant to everyday functioning (Burgess et al., 2006), both in the workplace and at home.

Because adaptive function impairments often do not manifest until later in the disease course, it may be useful to identify alternate indicators of potential decline that are detectable earlier in the disease and likely preclude adaptive function impairments. Cognitive impairments and neuropsychiatric symptoms may function as earlier indicators of future adaptive function declines. Additionally, cognitive impairments, specifically, can be assessed using neuropsychological instruments that do not require self or informant report. Although there are a handful of adaptive function measures that are used in clinical practice and research, the large majority are structured questionnaires that rely on self or informant report. Very few task-based instruments have been developed, and not all adaptive function tasks (such as toileting or bathing) can be easily simulated for assessment. Having a psychometrically robust proxy for assessing adaptive function would be useful for monitoring current status and anticipating future declines.

Predicting Adaptive Function

There has been some investigation of various predictors of adaptive function impairments in AD patients. However, such studies have been limited in number and have resulted in somewhat mixed findings. Additionally, these studies often use relatively small samples, and follow-up studies using larger samples have not been conducted. Furthermore, the majority of studies are cross-sectional in nature; very few studies include data beyond 12 months follow-up. Consequently, the mechanism through

which potentially causal relationships between these predictors and adaptive function impairments manifests remains unclear.

Interestingly, these three potential areas of impairment have not all been considered collectively. Specifically, the degree to which cognitive impairments and neuropsychiatric symptoms account for variance in adaptive function impairments has not been examined. Furthermore, this set of predictors has not been considered longitudinally within a cohort of patients across the AD severity spectrum. Given the prevalence of impairments in all three areas and salient impacts on both patient quality-of-life and caregiver distress, consideration of the potential interrelatedness of these three constructs is warranted.

Present Study

Despite promising preliminary findings, this area of the literature is still wanting for more recent and robust data to support the hypothesis that cognitive impairments, neuropsychiatric symptoms, and adaptive function are all associated. In particular, previous work that examines individual relationships among these three areas of impairment has largely been cross-sectional; longitudinal examination of these constructs is limited.

The purpose of this retrospective study was to determine the extent to which performance on measures of cognitive function, as well as neuropsychiatric symptoms, accounted for unique variance in adaptive function ability. We also examined if caregiver distress correlated to patient adaptive function.

To address gaps in the existing literature, we examined these relationships longitudinally within a cohort of patients across the AD severity spectrum. To isolate the effects of cognitive impairments, neuropsychiatric symptoms, and caregiver distress on adaptive function, we controlled for various demographic and clinical variables associated with AD severity. We used outcome data from 12 and 24 months follow-up, which allowed us to track the relationships between the predictors and adaptive function over time. We hypothesized the following:

1) Performance on measures of cognitive function would account for variance in adaptive function.

2) Neuropsychiatric symptoms would account for variance in adaptive function.

3) Caregiver distress in response to neuropsychiatric symptoms would be associated with patient adaptive function.

CHAPTER II

METHODS

Data used in the preparation of these studies was obtained from the Alzheimer's
Disease Neuroimaging Initiative (ADNI) database, adni.loni.usc.edu. The ADNI was
launched in 2003 as a public-private partnership. The initial goal of ADNI was to recruit
800 participants, but ADNI has been followed by two other initiatives, ADNI-GO and
ADNI-2. To date, these three protocols have been used to recruit over 1500 adults, ages
55 to 90, to participate in research. The sample consists of older adults who are
cognitively healthy, those with early or late MCI, and those with AD. Demographic
information and clinical data that was used for this study were downloaded from the
ADNI data repository (adni.loni.usc.edu) on May 28, 2014. Data for the proceeding
analyses came from individuals who completed baseline and follow-up assessments and
had complete data for key cognitive, neuropsychiatric, and neuroimaging variables
described below.

Participants

The analyses for the present study used data from baseline, 12, and 24 months
follow-up from participants enrolled in ADNI-2. Demographic data, including age,
gender, education level, and ethnicity was mined for each participant. Baseline diagnosis
was also recorded. In this dataset, baseline diagnoses represented a range of cognitive
impairment, from cognitively normal through MCI to presumed AD. Cognitively normal
participants were included to capture potential conversion to MCI/prodromal AD or full-

blown AD, thereby reflecting the larger continuum of normal cognitive aging to dementia.

Participants were excluded from the ADNI if they had a premorbid history of significant neurologic disease (including multi-infarct dementia and subdural hematoma), as well as various neuropsychiatric disorders such as major depressive disorder, schizophrenia, and bipolar disorder. Participants were excluded from our analyses based on missing or incomplete baseline or follow-up data for variables of interest. Following an iterative filtering process, a final sample of $N = 332$ was designated.

Measures

As part of standard ADNI procedures, all participants completed neuropsychological and neuropsychiatric assessments and neuroimaging on a regular basis. For this study, we used data from baseline (0 months), 12, and 24 months follow-up. The procedures used for each of these domains are briefly described below (full description online at adni.loni.usc.edu).

Neuropsychological Battery

The ADNI neuropsychological battery includes 16 metrics from 6 measures that can be mapped on to four cognitive domains: memory, language, visuospatial reasoning, and executive function/processing speed (Park et al., 2012). Table 1 illustrates the organization of these metrics by cognitive domain. Scores from these measures were used in subsequent analyses. Administration procedures for each measure are described below.

Memory

Auditory-verbal memory is assessed in the ADNI using the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964), Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog; Rosen, Mohs, & Davis, 1984) Word Recall subtest, and the ADAS-cog Recognition subtest.

For the RAVLT, participants are read a list of 15 unrelated words and then asked to repeat as many of the words as possible immediately after. There are 5 learning trials followed by a distractor trial featuring 15 completely different words. Participants then complete an immediate recall trial, during which they must avoid confabulation with the distractor trial. Following a 30-minute delay, participants are asked to recall as many of the original 15 words as possible. They then complete a forced-choice recognition trial. For our analyses, the following RAVLT metrics were used: learning (trial 5 – trial 1), short delay recall, long delay recall, and recognition.

The ADAS-cog Word Recall subtest is similar to the RAVLT, in that participants must encode and recall a designated list of words. Participants are shown a list of 10 high-frequency, high-imagery nouns. They are asked to read each word aloud and remember it. If the participant cannot read the word or is slow, the examiner can say the word aloud and have the participant repeat it. After presentation of the 10 words, participants are asked to recall as many of the words as possible. Two more learning trials are completed in this fashion. After a 5-minute delay, participants are asked to recall as many of the words as possible. The short and long delay recall scores, calculated out of a maximum of 10 possible correct, were used.

On the Recognition subtest, participants are first shown a list of 12 words, presented one at a time, that are printed in block letters on white cards. They are then asked to identify the stimulus words, mixed in with distractor words, during a recognition trial. Participants complete three trials. The average number of correctly recognized words across all three trials, out of a maximum of 12 possible correct, was used in the analyses.

Language

Language is assessed in the ADNI using a Verbal Fluency Test (Harrison, Buxton, Husain, & Wise, 2000), the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983), and the ADAS-cog Naming subtest.

During the Verbal Fluency Test, participants are asked to name as many different animals as they can in one minute. The number of correct, distinct responses is the final score that was used for the analyses.

The Boston Naming Test is a measure of confrontational naming ability. Participants are presented with 30 line drawings of objects that range from low to high-frequency and are given up to 20 seconds to correctly identify the depicted object. Semantic and phonemic cues are provided if the participant has difficulty recognizing the object or retrieving the correct name. The total number of correct responses produced without cueing, out of a maximum of 30 possible correct, is the score that was used in the analyses.

The ADAS-cog Naming subtest is different from the Boston Naming Test in that participants are asked to name 12 actual objects, as well as all 5 fingers. The total

number of correctly named items, out of a maximum of 17 possible correct, was the score that was used in the analyses.

Visuospatial Reasoning

Visuospatial reasoning is assessed in the ADNI using the Clock Drawing Test (CDT) and the ADAS-cog Construction subtest.

For the Clock Drawing Test, participants are first asked to draw a clock face with the hands set to 11:10. If the clock is drawn incorrectly, the examiner then demonstrates how to draw the clock face and then asks the participant to recreate the drawing. The spontaneous drawing and copy scores, out of a maximum of 15 possible points, were both used in the analyses.

For the ADAS-cog Construction subtest, participants are asked to copy four geometric figures; total score, out of a maximum of four possible correct, was used in the analyses.

Executive Function/Processing Speed

Executive function/processing speed is assessed in the ADNI using the Trail-Making Test (TMT; Reitan, 1958; Reitan & Wolfson, 1985) and the ADAS-cog Number Cancellation subtest.

During the Trail-Making Test, participants must connect numbered or lettered circles in ascending order as quickly as possible. Parts A and B depend on visuomotor and perceptual-scanning skills and assess processing speed. However, Part B also requires cognitive flexibility as participants must shift sets from numbers to letters and

therefore more directly reflects executive function. Participants are scored on completion time in seconds. Completion times were used in the analyses.

During the ADAS-cog Number Cancellation subtest, participants must systematically identify and cross out two target numbers randomly embedded among several lines of other numbers within 45 seconds. Participants are scored on total number of correctly identified targets, but omission and commission errors are also noted. Total score (i.e., number of correctly identified targets) was used in the analyses.

Global Cognitive Status

Several neuropsychological measures of global and specific cognitive functions are used in AD research. One of the clinician-administered measures used in the ADNI is the ADAS-cog, select subtests from which have been described previously. The ADAS-cog consists of 11 tasks measuring disturbances of memory, language, praxis, and attention. ADAS-cog scores are reported as errors made out of 70 points total (i.e. higher scores correspond to more compromised cognitive status). Total error score, out of a maximum of 70, was used in the analyses.

Severity Staging

Screening and staging measures are also included in the ADNI repository. One of the most commonly used staging measures is the Clinical Dementia Rating (CDR; Morris, 1993), a semi-structured, informant-report measure of six cognitive and functional domains that are related to AD and other dementias. These areas are: Memory, Orientation, Judgement and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. Ratings for each domain are computed through an

algorithm to generate a global score, which ranges from 0 to 3. A CDR score of 0

corresponds to "Normal" functioning or no AD. A score of 0.5 indicates "Very Mild

Dementia". A score of 1 indicates "Mild Dementia". A score of 2 indicates "Moderate

Dementia" and a score of 3 indicates "Severe Dementia".

In the ADNI database, CDR Sum of Boxes (CDR-SOB) scores are used, as they

are considered to provide more measurement variance and information than do global

scores (O'Bryant et al., 2008). CDR-SOB scores are derived from summing domain

scores and range from 0 to 18. A CDR-SOB score of 0 corresponds to "Normal"

functioning or no AD. Scores of 0.5 to 2.5 correspond to "questionable impairment".

Scores of 3.0 to 4.0 correspond to "Very Mild Dementia". Scores of 4.5 to 9.0

correspond to "Mild Dementia". Scores of 9.5 to 15.5 correspond to "moderate

Dementia", and scores of 16.0 to 18.0 correspond to "Severe Dementia". CDR-SOB

scores were used to characterize the sample.

Neuroimaging

To isolate the influence of cognitive function on adaptive function, we controlled

for other relevant baseline variables, such as neuroimaging. Structural magnetic

resonance imaging (MRI) scans enable volumetric measurements of the entire brain as

well as specific neuroanatomical regions, which can indicate patterns of volumetric

changes and brain atrophy associated with AD. For this study, we examined and

controlled for MRI volumes (cubic millimeters) of the whole brain and four temporal

lobe sub-regions hypothesized to be implicated in the neurodegenerative component of

AD pathology: the entorhinal cortex, hippocampus, the middle temporal gyrus, and the fusiform gyrus (Cai et al., 2015; Convit et al., 2000; Du et al., 2001).

In addition to structural MRI, fluorodeoxyglucose-positron emission tomography (FDG-PET) is commonly used to assess brain health. Namely, FDG-PET scans illustrate cerebral glucose metabolic activity, which is an index of neuronal and synaptic function (Shivamurthy et al., 2015). Glucose hypometabolism is a robust indicator of the type of neurodegeneration that is associated with AD; thus, it is considered to be a crucial diagnostic biomarker. For this study, we examined and controlled for FDG-PET uptake values. In the ADNI dataset, FDG-PET values are a composite metric derived from averaging scans of three regions-of-interest: angular, temporal, and posterior cingulate cortices. Lower FDG-PET uptake values correspond to higher probability of AD.

Neuropsychiatric Symptoms

The Neuropsychiatric Inventory (NPI; Cummings, 1997) is administered to participants' caregivers to assess the presence, frequency, and severity of 12 neuropsychiatric symptoms: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep disturbances, and disordered appetite/eating. On this measure, presence is scored on a binary scale ("yes" or "no"). Frequency is rated on a four-point scale as follows: 1 for "rarely", 2 for "sometimes", 3 for "often", and 4 for "very often". Severity is rated on a three-point scale as follows: 1 for "mild", 2 for "moderate", and 3 for "severe". An NPI domain score can be calculated by multiplying the frequency rating by the severity rating for a particular domain

(symptom) (Cummings, 1997); the maximum NPI domain score is 12. A total NPI score can be calculated by adding all 12 of the domain scores together (Cummings, 1997); the maximum total NPI score is 144. The total score was used in the analyses.

Adaptive Function

The Functional Assessment Questionnaire (FAQ; Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982) is an informant-report measure of social function and instrumental activities of daily living. Informants are asked to rate the participant's ability to complete 10 different functional activities using a 0 to 3 point scoring system. A score of 0 is given if the participant's ability is normal, or if the participant has never completed the activity in the past but could reasonably do so now. A score of 1 is given if the patient has difficulty completing the activity but can do so independently, or if the participant has never completed the activity in the past and would have difficulty doing so now. A score of 2 is given if the participant requires assistance completing the activity, and a score of 3 is given if the participant is totally dependent. A total FAQ score, ranging from 0 to 30, is calculated by adding the ratings for the 10 individual items. A cut-score of 9 or higher is used to infer that the participant is exhibiting functional, and potentially cognitive, impairments. Total FAQ scores were used in the analyses.

It should be noted that for baseline measures, raw total FAQ scores were used as the outcome variable. At 12 months follow-up, however, residualized FAQ scores were used as the outcome variable in order to control for variance in baseline FAQ score.

Residualized FAQ scores were also used at 24 months follow-up, again to control for variance in baseline and 12 months follow-up FAQ scores.

The Everyday Cognition Scale (ECog; Farias et al., 2008) is a self and informant-report brief questionnaire assessing participants' ability to perform normal everyday tasks, in comparison to activity levels 10 years prior. Six domains are assessed using 39 items: Everyday Memory, Everyday Language, Everyday Visuospatial Abilities, Everyday Planning, Everyday Organization, and Everyday Divided Attention. Ratings for each item are given on a 4-point scale. A score of 1 is given if the participant exhibits no change in ability level or actually performs better than 10 years ago. A score of 2 is given if the participant occasionally performs the task worse but not all of the time. A score of 3 is given if the participant consistently performs the task a little worse than 10 years ago, and a score of 4 indicates that the participant performs the task much worse than 10 years ago. Total scores are derived by dividing the sum of ratings by the number of items completed; thus, total scores range from 1 to 4. Total ECog scores from both participants and informants were used in the analyses.

It should be noted that for baseline measures, raw total Ecog scores were used as the outcome variable. At 12 months follow-up, however, residualized Ecog scores were used as the outcome variable in order to control for variance in baseline Ecog score. Residualized Ecog scores were also used at 24 months follow-up, again to control for variance in baseline and 12 months follow-up Ecog scores.

Caregiver Distress

The Neuropsychiatric Inventory is also administered to caregivers to assess their

subjective levels of distress in response to patients' neuropsychiatric symptoms.

Caregivers are asked to rate their own distress levels on a six-point scale as follows: 0

for "not at all", 1 for "minimally distressing", 2 for "mildly distressing", 3 for

"moderately distressing", 4 for "severely distressing", and 5 for "very severely or

extremely distressing". For this study, we calculated a total caregiver distress score by

summing distress ratings across all endorsed symptoms in order to capture variance in

both intensity and breadth of caregiver distress. The total distress score was used in the

analyses.

Data Analyses

Preliminary Analyses

SPSS Statistics 25.0 (IBM Corporation, 2017) was used to perform all analyses

in this study. To characterize the sample of patients, we generated descriptive statistics

for baseline demographic, cognitive, and clinical variables. To explore the potential

relationships among baseline scores for cognitive function, neuropsychiatric symptoms,

caregiver distress, and adaptive function, Pearson product-moment correlation

coefficients (Pearson's *r*) were generated.

In the next part of the analyses, we used one-way ANOVA to examine the effects

of categorical participant demographic variables on baseline adaptive function, using *p* <

0.05 as the significance threshold. Pearson product-moment correlation coefficients

(Pearson's *r*) were generated between the continuous participant demographic variables and baseline adaptive function. We again used $p < 0.05$ as the significance threshold.

Main Analyses

Hierarchical linear regression was used to determine if baseline performance on neuropsychological measures of cognitive function, as well as neuropsychiatric symptoms, accounted for unique variance in patient adaptive function at baseline, 12, and 24 months follow-up, after controlling for key demographic and clinical variables. Categorical demographic variables were dummy-coded prior to the regression analyses. We also generated Pearson's *r* correlation coefficients between caregiver distress scores and adaptive function (FAQ and Ecog scores).

In the first part of the analyses, we generated hierarchical liner regression models, with each model consisting of six steps. Patient demographics (age, gender, and education level) were entered in step one of the regression model. Baseline diagnosis was entered in step two. Baseline MRI volumes were entered in step three. Baseline FDG-PET was entered in step four. Baseline neuropsychiatric symptoms were entered in step five. Baseline neuropsychological test performance was entered as a set of predictors in step six.

This model was replicated three times, using total FAQ score as the outcome variable at each of the three time points (baseline, 12, and 24 months follow-up). Specifically, residualized FAQ scores were used for 12 and 24 months follow-up. We replicated this model an additional six times using self and informant-report Ecog scores from baseline, 12, and 24 months follow-up. Again, residualized Ecog scores were used

for 12 and 24 months follow-up. In this part of the analyses, we generated 54 regression equations divided into 9 models.

We generated nine additional models, wherein all predictors were entered as described above, except neuropsychological test performance was entered in step five and neuropsychiatric symptoms were entered as a set of predictors in step six. Again, we used FAQ and Ecog scores from baseline, 12, and 24 months follow-up (residualized). In total, we generated 108 regression equations divided into 18 hierarchical models in this part of the analyses.

CHAPTER III

RESULTS

Sample Characteristics

The analyses for the present study used baseline data from 332 participants (151 female, 46%) enrolled in ADNI-2. At baseline, participants were an average of 72.28 years old ($SD = 6.71$), with ages ranging from 55 to 90. Participants were also highly educated ($M = 16.44$, $SD = 2.58$ years), with all participants having completed at least the 11th grade. The majority identified their race as white ($n = 310$, 93%); other races represented included black or African American ($n = 11$, 3%), Asian ($n = 7$, 1%), and Hawaiian/Pacific Islander ($n = 1$, 0.3%). Regarding marital status, the majority of participants were married at the time of the baseline assessment ($n = 247$, 74%). Thirty-six (11%) were widowed, 35 (11%) were divorced, and 14 (4%) were never married.

Baseline diagnoses represented a range of cognitive impairment; 132 (40%) were cognitively normal or had subjective memory decline and 185 (56%) had MCI. Fifteen participants (5%) had presumed Alzheimer's dementia at baseline. We included the cognitively normal (CN) participants in order to capture possible conversion in diagnostic status over the course of the analyses. Mean total CDR-SOB score was 1.04 ($SD = 1.23$), which falls in the "questionable impairment" range. Mean total ADAS-cog score was 8.36 ($SD = 4.54$). Mean total NPI score was 3.04 ($SD = 5.70$) and mean total caregiver distress rating across the 12 neuropsychiatric symptoms assessed was 1.90 ($SD = 3.43$). Mean total FAQ score was 2.21 ($SD = 3.98$). Mean total Ecog self-report score was 1.63 ($SD = 0.51$) and mean total Ecog informant-report score was 1.57 ($SD = 0.64$).

Neuropsychological Test Performance

Baseline neuropsychological test performance was characterized for the sample

and is described below, as well as in Table 2, organized by associated cognitive domain:

Memory

At baseline, mean performance on the RAVLT was as follows: 5.02 words (SD =

2.66) for learning, 6.93 words (SD = 4.17) for short delay recall, 5.56 words (SD = 4.45)

for long delay recall and 11.61 words (SD = 3.18) for recognition. Mean performance on

the ADAS-cog was 3.83 words (SD = 1.54) for short delay recall, 4.46 words (SD =

2.68) for long delay recall, and 2.98 words (SD = 2.40) for recognition.

Language

At baseline, mean performance on the VFT was 19.46 animals (SD = 5.22)

generated. Mean performance on the BNT was 27.05 objects (SD = 2.96) correctly

named. Mean performance on the ADAS-cog Naming subtest was 0.12 (SD = 0.35).

Visuospatial Reasoning

At baseline, mean performance on the CDT was 4.5 points (SD = 0.81) for

spontaneous drawing and 4.78 points (SD = 0.55) for copy. Mean performance on the

ADAS-cog Construction subtest was 0.46 points (SD = 0.56).

Executive Function/Processing Speed

At baseline, mean performance on the TMT was 36.24 seconds (SD = 16.22) for

Part A and 95.70 seconds (SD = 55.03) for Part B. Mean performance on the ADAS-cog

Cancellation subtest was 0.48 correct responses (SD = 0.77).

Neuropsychiatric Symptoms and Caregiver Distress

Neuropsychiatric symptoms and associated caregiver distress were characterized for the sample at baseline. At baseline, the mean total NPI score was 3.04 ($SD = 5.70$), and the highest observed total NPI score was 43. Regarding symptom frequency, the most frequently endorsed symptom at baseline was depression/dysphoria ($n = 64$, 19%), followed by irritability/lability ($n = 58$, 18%), and sleep disturbance ($n = 50$, 15%). All neuropsychiatric symptoms were endorsed by at least one caregiver at baseline. The mean symptom severity rating at baseline was 0.11 ($SD = 0.19$). At baseline, four symptoms were rated by at least one caregiver as markedly severe: delusions, disinhibition, sleep disturbance, and disordered appetite/eating.

Regarding caregiver distress related to neuropsychiatric symptoms, the mean distress rating was 0.16 ($SD = 0.29$). Mean total distress rating score was 1.90 ($SD = 3.43$), and the highest observed total distress rating score was 17. At baseline, four symptoms were described by at least one caregiver as very severely or extremely distressing: anxiety, irritability/lability, sleep disturbance, and disordered appetite/eating.

Patient Variables and Adaptive Function

One-way analysis of variance (ANOVA) was used to examine the effects of categorical patient demographic variables (gender, marital status, race, and baseline diagnosis) on baseline adaptive function (FAQ and Ecog). Baseline adaptive function was found to significantly differ across baseline diagnoses ($p < 0.05$); the remaining variables were found not to significantly affect baseline adaptive function. Post hoc comparisons using the Tukey Honestly Significant Different (HSD) test revealed that

baseline adaptive function ability was significantly lower for patients with baseline diagnoses of MCI or AD compared to cognitively normal patients or patients with subjective memory complaints. Results from the ANOVA analyses are presented in Tables 3a through 3c.

Pearson product-moment correlation coefficients (Pearson's r) were generated between continuous patient demographic and clinical variables (age, education level, baseline neuroimaging, and baseline ADAS-cog score) and baseline adaptive function (FAQ and Ecog [patient and informant]). Baseline FAQ score was significantly correlated with patient's education level ($r = -0.14$; $p < 0.01$), baseline ADAS-cog score ($r = 0.51$; $p < 0.01$), baseline FDG-PET ($r = -0.39$; $p < 0.01$), baseline whole brain volume ($r = -0.13$; $p < 0.05$), and all four baseline temporal lobe volumes ($p < 0.05$). Baseline Ecog (self) score was significantly correlated with age ($r = -0.12$; $p < 0.05$), baseline ADAS-cog score ($r = 0.32$; $p < 0.01$), baseline FDG-PET ($r = -0.22$; $p < 0.01$), and all four baseline temporal lobe volumes ($p < 0.05$). Baseline Ecog (informant) score was significantly correlated with patient's education level ($r = -0.14$; $p < 0.05$), baseline ADAS-cog score ($r = 0.52$; $p < 0.01$), baseline FDG-PET ($r = -0.40$, $p < 0.01$), baseline whole brain volume ($r = -0.11$, $p < 0.05$), and all four baseline temporal lobe volumes ($p < 0.05$). Tables 4 lists the correlations described above.

Pearson's r correlation coefficients were also generated between baseline caregiver distress and baseline adaptive function. Baseline caregiver distress was significantly correlated with baseline FAQ and Ecog scores ($p < 0.01$). Furthermore, baseline caregiver distress was significantly correlated with FAQ and Ecog scores at

both 12 and 24 months follow-up ($p < 0.01$). Tables 5a through 5c list the correlations described above.

Predicting Adaptive Function from Neuropsychological Test Performance

Hierarchical linear regression was used to predict adaptive function from baseline neuropsychological test performance. Entering baseline neuropsychological test performance as a predictor significantly improved the model when baseline FAQ score was used as the outcome variable ($p < 0.01$). This suggests that variance in baseline neuropsychological test performance accounts for unique variance in baseline adaptive function ability, as measured by the FAQ, over and above other indicators of AD. At baseline, performance on the following individual metrics were significant predictors within the collective set of predictors: RAVLT Short Delay ($\beta = 0.170$; $p < 0.05$), RAVLT Recognition ($\beta = $ -0.123; $p < 0.05$), Clock Drawing ($\beta = $ -0.102; $p < 0.05$), and ADAS-cog Cancellation ($\beta = 0.151$; $p < 0.01$).

Furthermore, entering baseline neuropsychological test performance as a predictor significantly improved the model when residualized FAQ scores from 12 months follow-up was used as the outcome variable ($p < 0.01$). This suggests that variance in baseline neuropsychological test performance accounts for unique variance in adaptive function ability at 12 months follow-up, as measured by the FAQ, even after controlling for adaptive function ability at baseline. At 12 months follow-up, performance on the following individual metrics were significant predictors within the collective set of predictors: BNT ($\beta = 0.175$; $p < 0.01$), ADAS-cog Naming ($\beta = 0.198$; p

< 0.01), Clock Copy (β = -0.143; $p < 0.05$), and ADAS-cog Cancellation (β = -0.172; $p < 0.05$).

Entering baseline neuropsychological test performance as a predictor also significantly improved the model when residualized FAQ scores from 24 months follow-up was used as the outcome variable ($p < 0.01$). This suggests that variance in baseline neuropsychological test performance accounts for unique variance in adaptive function ability at 24 months follow-up, as measured by the FAQ, even after controlling for adaptive function ability at both baseline and 12 months follow-up. At 24 months follow-up, performance on the following individual metrics were significant predictors within the collective set of predictors: ADAS-cog Long Delay (β = 0.248; $p < 0.01$), BNT (β = -0.275; $p < 0.01$), and Trails A (β = -0.152; $p < 0.05$). Results of these regression analyses are presented in Tables 6a through 6c.

Entering baseline neuropsychological test performance as a predictor did not significantly improve the model when baseline Ecog (self) score was used as the outcome variable ($p > 0.05$). Entering baseline neuropsychological test performance as a predictor also did not significantly improve the model when residualized Ecog (self) scores from 12 or 24 months follow-up were used as the outcome variables ($p > 0.05$). Results of these regression analyses are presented in Tables 7a through 7c.

Entering baseline neuropsychological test performance as a predictor significantly improved the model when baseline Ecog (informant) score was used as the outcome variable ($p < 0.01$). This suggests that variance in baseline neuropsychological test performance accounts for unique variance in baseline adaptive function ability, as

measured by the Ecog (informant), over and above other indicators of AD. At baseline, performance on the following individual metrics were significant predictors within the collective set of predictors: RAVLT Short Delay ($\beta = 0.181$; $p < 0.05$), RAVLT Long Delay ($\beta = -0.220$; $p < 0.05$), ADAS-cog Short Delay ($\beta = -0.137$; $p < 0.05$), ADAS-cog Long Delay ($\beta = 0.200$; $p < 0.01$), BNT ($\beta = 0.091$; $p < 0.05$), and Clock Copy ($\beta = -0.114$; $p < 0.01$).

Entering baseline neuropsychological test performance as a predictor did not significantly improve the model when residualized Ecog (informant) score from 12 months follow-up was used as the outcome variable ($p > 0.05$).

However, entering neuropsychological test performance as predictor did significantly improve the model when the score from 24 months follow-up was used as the outcome variable ($p < 0.05$). This suggests that variance in baseline neuropsychological test performance accounts for unique variance in adaptive function at 24 months follow-up, as measured by the Ecog (informant), even after controlling for adaptive function ability at both baseline and 12 months follow-up. At 24 months follow-up, performance on the following individual metrics were significant predictors within the collective set of predictors: ADAS-cog Short Delay ($\beta = 0.176$; $p < 0.05$), BNT ($\beta = -0.160$; $p < 0.05$), and ADAS-cog Cancellation ($\beta = 0.141$; $p < 0.05$). Results of these regression analyses are presented in Tables 8a through 8c.

Predicting Adaptive Function from Neuropsychiatric Symptoms

Hierarchical linear regression was used to predict adaptive function from baseline neuropsychiatric symptoms. Entering baseline neuropsychiatric symptoms as a

predictor significantly improved the model when baseline FAQ score was used as the outcome variable ($p < 0.01$). This suggests that variance in baseline neuropsychiatric symptoms accounts for unique variance in baseline adaptive function ability, as measured by the FAQ, over and above other indicators of AD. At baseline, the following individual neuropsychiatric symptoms were significant predictors within the collective set of predictors: Delusions ($\beta = 0.094$; $p < 0.05$), Hallucinations ($\beta = 0.088$; $p < 0.05$), Agitation/Aggression ($\beta = 0.179$; $p < 0.01$), Depression/Dysphoria ($\beta = 0.131$; $p < 0.01$), Elation/Euphoria ($\beta = 0.145$; $p < 0.01$), Apathy/Indifference ($\beta = 0.222$; $p < 0.01$), and Disordered Appetite/Eating ($\beta = 0.099$; $p < 0.05$).

Furthermore, entering baseline neuropsychiatric symptoms as a predictor significantly improved the model when residualized FAQ score from 12 months follow-up was used as the outcome variable ($p < 0.01$). This suggests that variance in baseline neuropsychiatric symptoms accounts for unique variance in adaptive function ability at 12 months follow-up, as measured by the FAQ, even after controlling for adaptive function ability at baseline. At 12 months follow-up, the following individual neuropsychiatric symptoms were significant predictors within the collective set of predictors: Hallucinations ($\beta = 0.153$; $p < 0.01$), Agitation/Aggression ($\beta = -0.121$; $p < 0.05$), Depression/Dysphoria Hallucinations ($\beta = -0.124$; $p < 0.05$), Elation/Euphoria ($\beta = -0.241$; $p < 0.01$), Irritability/Lability ($\beta = 0.138$; $p < 0.05$), and Disordered Appetite/Eating ($\beta = 0.117$; $p < 0.05$).

Entering baseline neuropsychiatric symptoms as a predictor also improved the model when residualized FAQ score from 24 months follow-up was used as the outcome

variable ($p < 0.01$). This suggests that variance in baseline neuropsychiatric symptoms accounts for unique variance in adaptive function ability at 24 months follow-up, as measured by the FAQ, even after controlling for adaptive function ability at baseline and 12 months follow-up. At 24 months follow-up, the following individual neuropsychiatric symptoms were significant predictors within the collective set of predictors: Elation/Euphoria ($\beta = 0.237$; $p < 0.01$) and Aberrant Motor Behavior ($\beta = -0.145$; $p < 0.01$). Results of these regression analyses are presented in Tables 9a through 9c.

Entering baseline neuropsychiatric symptoms as a predictor significantly improved the model when baseline Ecog (self) score was used as the outcome variable ($p < 0.01$). This suggests that variance in baseline neuropsychiatric symptoms accounts for unique variance in baseline adaptive function ability, as measured by the Ecog (self), over and above other indicators of AD. At baseline, the following individual neuropsychiatric symptoms were significant predictors within the collective set of predictors: Delusions ($\beta = 0.125$; $p < 0.05$) and Depression/Dysphoria ($\beta = 0.121$; $p < 0.05$).

Entering baseline neuropsychiatric symptoms as a predictor did not significantly improve the model when residualized Ecog (self) scores from 12 or 24 months follow-up were used as the outcome variables ($p > 0.05$). Results of these regression analyses are presented in Tables 10a through 10c.

Entering baseline neuropsychiatric symptoms as a predictor significantly improved the model when baseline Ecog (informant) score was used as the outcome variable ($p < 0.01$). This suggests that variance in baseline neuropsychiatric symptoms

accounts for unique variance in baseline adaptive function ability, as measured by the Ecog (informant), over and above other indicators of AD. At baseline, the following individual neuropsychiatric symptoms were significant predictors within the collective set of predictors: Hallucinations ($\beta = 0.157$; $p < 0.01$), Agitation/Aggression ($\beta = 0.153$; $p < 0.01$), Apathy/Indifference ($\beta = 0.122$; $p < 0.01$), Disinhibition ($\beta = 0.087$; $p < 0.05$), and Disordered Appetite/Eating ($\beta = 0.101$; $p < 0.05$).

Furthermore, entering baseline neuropsychiatric symptoms as a predictor significantly improved the model when residualized Ecog (informant) score from 12 months follow-up was used as the outcome variable ($p < 0.05$). This suggests that variance in baseline neuropsychiatric symptoms accounts for unique variance in adaptive function ability at 12 months follow-up, as measured by the Ecog (informant), even after controlling for adaptive function ability at baseline. At 12 months follow-up, the following individual neuropsychiatric symptoms were significant predictors within the collective set of predictors: Elation/Euphoria ($\beta = -0.140$; $p < 0.05$) and Irritability/Lability ($\beta = 0.185$; $p < 0.01$).

Entering baseline neuropsychiatric symptoms as a predictor also improved the model when residualized Ecog (informant) score from 24 months follow-up was used as the outcome variable ($p < 0.01$). This suggests that variance in baseline neuropsychiatric symptoms accounts for unique variance in adaptive function ability at 24 months follow-up, as measured by the Ecog (informant), even after controlling for adaptive function ability at baseline and 12 months follow-up. At 24 months follow-up, the following individual neuropsychiatric symptoms were significant predictors within the collective

set of predictors: Elation/Euphoria ($\beta = 0.244$; $p < 0.01$), Apathy/Indifference ($\beta = 0.130$; $p < 0.05$), and Disinhibition ($\beta = -0.122$; $p < 0.05$). Results of these regression analyses are presented in Tables 11a through 11c.

CHAPTER IV

DISCUSSION

The purpose of this study was to take the first steps towards understanding the relationships between cognitive function, neuropsychiatric symptoms, and adaptive function in Alzheimer's disease. Specifically, we sought to determine the extent to which performance on measures of cognitive function, as well as neuropsychiatric symptoms, accounted for unique variance in adaptive function ability. We also examined if caregiver distress correlated to patient adaptive function.

Results indicated that entering baseline neuropsychological test performance as a predictor significantly improved the model when baseline FAQ and baseline Ecog (informant) scores were used as the outcome variable, suggesting that variance in baseline neuropsychological test performance accounts for unique variance in baseline adaptive function ability, as measured by informant report measures, over and above other indicators. Entering baseline neuropsychological test performance as a predictor did not significantly improve the model when baseline Ecog (self) score was used as the outcome variable.

Regarding follow-up, entering baseline neuropsychological test performance as a predictor significantly improved the model when residualized FAQ scores from both 12 and 24 months follow-up were used as the outcome variable. This suggests that not only does this effect holds over time, but that it does even after controlling for adaptive function ability at both baseline and 12 months follow-up. Furthermore, this effect was replicated when residualized Ecog (informant) score from 24 months follow-up was used

as the outcome variable. Entering baseline neuropsychological test performance as a predictor did not significantly improve the model when residualized Ecog (self) scores from 12 or 24 months follow-up were used as the outcome variable.

In addition to examining the omnibus effect of neuropsychological test performance as a whole, we looked at individual metrics within the collective set of predictors. The ADAS-cog, Boston Naming Test, Rey Auditory Verbal Learning Test, and Clock Drawing Test were most often found to be statistically significant predictors of adaptive function ability, across outcome measures and time-points. Interestingly, these measures span across the four cognitive domains represented in this study (memory, language, visuospatial reasoning, and executive functioning/processing speed), suggesting that all four domains are relevant when considering adaptive function ability.

A similar pattern of results was observed when baseline neuropsychiatric symptoms were examined as the predictor of interest. Specifically, entering baseline neuropsychiatric symptoms as a predictor significantly improved the model when baseline FAQ and Ecog (self and informant) scores were used as the outcome variable, suggesting that variance in baseline neuropsychiatric symptoms accounts for unique variance in baseline adaptive function ability across measures.

Regarding follow up, entering baseline neuropsychiatric symptoms as a predictor significantly improved the model when residualized FAQ score from both 12 and 24 months follow-up was used as the outcome variable. Furthermore, this effect was replicated when residualized Ecog (informant) score from 12 and 24 months follow-up

was used as the outcome variable. Entering baseline neuropsychiatric symptoms as a predictor did not significantly improve the model when residualized Ecog (self) scores from 12 or 24 months follow-up were used as the outcome variable.

In addition to examining the omnibus effect of neuropsychiatric symptoms as a whole, we looked at individual symptoms within the collective set of predictors. Hallucinations, agitation/aggression, depression/dysphoria, elation/euphoria, apathy/indifference, and disordered appetite/eating were most often found to be statistically significant predictors of adaptive function ability, across outcome measures and time-points. Interestingly, these symptoms span across subsets of neuropsychiatric symptoms (psychotic, affective, behavioral), suggesting that all subsets of symptoms are relevant when considering adaptive function ability.

The association between caregiver distress and adaptive function was also examined. Specifically, baseline caregiver distress in response to neuropsychiatric symptoms was significantly correlated with FAQ and Ecog (self and informant) scores at baseline. Furthermore, baseline caregiver distress was significantly correlated with FAQ and Ecog (self and informant) scores at 12 and 24 months follow-up, suggesting that this association holds over time. This finding is interesting as it suggests that caregiver distress may reasonably be used as a proxy for neuropsychiatric symptoms in assessing the impacts on adaptive function ability, regardless of the outcome measure used or time point of assessment.

In summary, cognitive and neuropsychiatric indicators of AD appear to be associated with adaptive function indicators at baseline and through 12 and 24 months

follow-up. The pattern of results obtained from this study supports the hypotheses that cognitive and neuropsychiatric indicators of AD may be used to foreshadow potential changes in patient adaptive function ability over time. The direct mechanism through which these associations manifest is unclear. However, many of the adaptive function abilities assessed by the FAQ and Ecog are predicated on cognitive processes assessed by neuropsychological testing, as discussed previously. Thus, the notion that performance on neuropsychological testing would be somewhat indicative of adaptive function ability is reasonable. Furthermore, given the demonstrated association between cognitive ability and neuropsychiatric symptoms, as well as neuropsychiatric symptoms and caregiver distress, it follows that the latter two indicators would also be tied to measures of adaptive function ability.

It is worth considering the pattern of results observed regarding the adaptive function measures used. The FAQ is scored on a 30-point scale, whereas the Ecog is scored on a 4-point scale. Consequently, the FAQ is able to capture more variance as a quantified measure of adaptive function than can the Ecog. This may explain why regression models featuring the FAQ as the outcome variable were more often statistically significant than those models that utilized the Ecog as the outcome variable. Nonetheless, some models using the Ecog as the outcome variable were statistically significant, suggesting that there may be at least some reliability of this effect across measures.

Additionally, the FAQ and Ecog (informant) are both informant report measures of adaptive function ability; results from the regression analyses wherein these measures

were used as the outcome variable were generally more consistent with each other, compared to when the Ecog (self) score was used as the outcome variable. Given the extensive literature on differences in self versus informant report, it may be that patients are able to accurately report on their own functioning up to a certain point along the continuum of AD severity, after which this ability to accurately self-assess starts to become compromised. This is also consistent with the pattern of insight or self-awareness into one's own condition that is typical of the progression of AD. Perhaps the most important conclusion that can be drawn here is the utility of informant report in assessing patient function, particularly over time.

Collectively, the findings from this study add support to the idea that declines in adaptive function ability, which can be particularly costly and distressing for families to accommodate, may be reliably anticipated earlier in the disease course, before such declines actually begin to manifest. This has important clinical implications, mostly for families as they begin to accommodate functional and lifestyle changes that accompany a diagnosis of AD. For example, families who are able to anticipate declines in adaptive function earlier may have more time to budget for expenses related to caregiving or making safety accommodations around the home. This may also allow families more time to research and plan for major changes, such as hospice care of institutionalization, and make better-informed decisions regarding long-term patient care.

While these preliminary findings are intriguing, limitations of this study (largely based in data availability and design) likely influenced the results. First, a larger sample size would have increased our power in detecting more statistically significant effects.

Our sample size ($N = 332$) was derived after eliminating participants for whom there was missing or incomplete key data across the three time points (baseline, 12, 24 months follow-up). Additionally, the probability of detecting an effect may have increased had we included data from additional time points, such as 36 or 48 months follow-up. However, given the population, participants were at increased risk of mortality as time went on; as such, in order to maximize our sample size, we did not extend our data mining beyond 24 months follow-up. Regarding study design, our list of indicators to operationalize disease severity was not exhaustive, nor were they perfect. However, we extrapolated based on the research and included indicators that are strongly linked to AD pathology.

In spite of methodological limitations, this study yielded promising preliminary results that supported our hypotheses. Future research should address all of these limitations by utilizing a larger, more demographically diverse sample with more extensive longitudinal follow-up and operationalization of AD severity across multiple measurable indicators. Additionally, examining which indicators of AD severity are predictive of rate-of-change in adaptive function may be clinically useful for anticipating subsets of patients who are at greater risk of more precipitous decline over time.

CHAPTER V

SUMMARY AND CONCLUSIONS

Understanding and characterizing the potential relationships between cognitive function, neuropsychiatric symptoms, and adaptive function may shed light on the nature of adaptive function impairment in AD, which in turn may inform and improve treatment planning procedures. This can provide clinicians with insight for potential targets of intervention to reduce symptoms and/or improve function, which in turn may contribute to increased patient quality-of-life, reduced caregiver distress, and less economic burden on the family and societal scales.

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APPENDIX

TABLES

Table 1

Neuropsychological battery

Memory	Language	Visuospatial Reasoning	Executive Function/Processing Speed
RAVLT Learning	VFT Animals	CDT	TMT A
RAVLT Short Delay Recall	BNT	CDT Copy	TMT B
RAVLT Long Delay Recall	ADAS-cog Naming	ADAS-cog Construction	ADAS-cog Number Cancellation
RAVLT Recognition			
ADAS-cog Word Recall			
ADAS-cog Recognition			

Note: RAVLT: Rey Auditory Verbal Learning Test; ADAS-cog: Alzheimer's Disease Assessment Scale; VFT: Verbal Fluency Test; BNT: Boston Naming Test; CDT: Clock Drawing Test; TMT: Trailmaking Test.

Table 2

Baseline neuropsychological test performance

Measure	*M* (*SD*)	Max
RAVLT Learning	5.02 (2.66)	15
RAVLT Short Delay	6.93 (4.17)	15
RAVLT Long Delay	5.56 (4.45)	15
RAVLT Recognition	11.61 (3.18)	15
ADAS-cog Short Delay	3.83 (1.54)	10
ADAS-cog Long Delay	4.46 (2.68)	10
ADAS-cog Recognition	2.98 (2.40)	12
VFT Animals	19.46 (5.22)	---
BNT	27.05 (2.96)	30
ADAS-cog Naming	0.12 (0.35)	17
CDT	4.5 (0.81)	15
CDT Copy	4.78 (0.55)	15
ADAS-cog Construction	0.46 (0.56)	4
TMT A	36.24 (16.22)	---
TMT B	95.70 (55.03)	---
ADAS-cog Number Cancellation	0.48 (0.77)	---

Table 3a

Categorical patient variables and baseline adaptive function (FAQ)

Variable	SS	df	MS	F	p
Gender	20.258	1	20.258	1.282	0.258
Error	5214.983	330	15.803		
Race	40.671	3	20.335	1.275	0.281
Error	5182.634	328	15.947		
Marital status	89.594	3	29.865	1.904	0.129
Error	5145.647	328	15.688		
Baseline diagnosis	1594.783	2	797.391	72.063	0.000**
Error	3640.458	329	11.065		

**$p < 0.01$

Table 3b

Categorical patient variables and baseline adaptive function (Ecog self)

Variable	SS	df	MS	F	p
Gender	0.000	1	0.000	0.001	0.975
Error	85.183	330	0.258		
Race	0.512	3	0.256	0.987	0.374
Error	84.263	328	0.259		
Marital status	0.142	3	0.047	0.182	0.908
Error	85.041	328	0.259		
Baseline diagnosis	17.033	2	8.517	41.115	0.000**
Error	68.150	329	0.207		

$**p < 0.01$

Table 3c

Categorical patient variables and baseline adaptive function (Ecog informant)

Variable	SS	df	MS	F	p
Gender	0.945	1	0.945	2.313	0.129
Error	134.766	330	0.408		
Race	0.279	3	0.139	0.336	0.715
Error	134.876	328	0.415		
Marital status	1.515	3	0.505	1.234	0.297
Error	134.196	328	0.409		
Baseline diagnosis	47.863	2	23.931	89.624	0.000**
Error	87.848	329	0.267		

$**p < 0.01$

Table 4

Continuous patient variables and baseline adaptive function

	FAQ	Ecog (self)	Ecog (informant)
Age	0.011	-0.124*	-0.052
Education	-0.142**	-0.013	-0.136*
Whole brain	-0.125*	-0.098	-0.109*
Entorhinal cortex	-0.316**	-0.180**	-0.272**
Hippocampus	-0.328**	-0.238**	-0.328**
Middle temporal gyrus	-0.166**	-0.120*	-0.177**
Fusiform gyrus	-0.178**	-0.133*	-0.188**
FDG-PET	-0.392**	-0.219**	-0.399**
ADAS-cog	0.506**	0.319**	0.519**

$*p < 0.05, **p < 0.01$

Table 5a

Baseline caregiver distress and adaptive function (baseline)

	1	2	3	4
1. Caregiver distress	---			
2. FAQ	0.459**	----		
3. Ecog (self)	0.229**	0.322**	---	
4. Ecog (informant)	0.522**	0.760**	0.445**	---

$**p < 0.01$

Table 5b

Baseline caregiver distress and adaptive function (12 months follow-up)

	1	2	3	4
1. Caregiver distress	---			
2. FAQ	0.392**	----		
3. Ecog (self)	0.198**	0.261**	---	
4. Ecog (informant)	0.449**	0.815**	0.361**	---

**$p < 0.01$

Table 5c

Baseline caregiver distress and adaptive function (24 months follow-up)

	1	2	3	4
1. Caregiver distress	---			
2. FAQ	0.378**	----		
3. Ecog (self)	0.183**	0.282**	---	
4. Ecog (informant)	0.468**	0.859**	0.336**	---

**$p < 0.01$

Table 6a

Effects of baseline neuropsychological test performance on adaptive function (FAQ; baseline)

Model	β	R^2	ΔR^2	F	p
1. Demographics		0.029	0.029	3.274	0.021
2. Baseline diagnosis		0.321	0.292	70.139	0.000
3. MRI volumes		0.354	0.033	3.302	0.006
4. FDG-PET		0.386	0.032	16.478	0.000
5. NPI		0.559	0.173	124.993	0.000
6. RAVLT Learning	-0.100				
RAVLT Short Delay	0.170*				
RAVLT Long Delay	-0.119				
RAVLT Recognition	-0.123*				
ADAS-cog Short Delay	0.034				
ADAS-cog Long Delay	-0.001				
ADAS-cog Recognition	0.007				
VFT Animals	-0.007				
BNT	0.083				
ADAS-cog Naming	-0.001				
CDT	-0.102*				
CDT Copy	-0.003				
ADAS-cog Construction	-0.043				
TMT A	-0.099				
TMT B	0.026				
ADAS-cog Cancellation	0.152**	0.670	0.054	2.973	0.000**

$*p < 0.05, **p < 0.01$

Table 6b

Effects of baseline neuropsychological test performance on adaptive function (FAQ; 12 months follow-up)

Model	β	R^2	ΔR^2	F	p
1. Demographics		0.001	0.001	0.070	0.976
2. Baseline diagnosis		0.020	0.019	3.137	0.045
3. MRI volumes		0.079	0.059	4.117	0.001
4. FDG-PET		0.102	0.024	8.512	0.004
5. NPI		0.110	0.007	2.523	0.113
6. RAVLT Learning	0.002				
RAVLT Short Delay	-0.093				
RAVLT Long Delay	0.035				
RAVLT Recognition	0.074				
ADAS-cog Short Delay	0.007				
ADAS-cog Long Delay	0.194				
ADAS-cog Recognition	0.012				
VFT Animals	-0.046				
BNT	0.175**				
ADAS-cog Naming	0.198**				
CDT	0.049				
CDT Copy	-0.143*				
ADAS-cog Construction	-0.034				
TMT A	0.060				
TMT B	0.026				
ADAS-cog Cancellation	-0.172*	0.209	0.099	2.376	0.002**

*$p < 0.05$, **$p < 0.01$

Table 6c

Effects of baseline neuropsychological test performance on adaptive function (FAQ; 24 months follow-up)

Model	β	R^2	ΔR^2	F	p
1. Demographics		0.020	0.020	2.208	0.087
2. Baseline diagnosis		0.034	0.014	2.416	0.091
3. MRI volumes		0.072	0.038	2.598	0.025
4. FDG-PET		0.093	0.021	7.530	0.006
5. NPI		0.094	0.001	0.259	0.611
6. RAVLT Learning	0.067				
RAVLT Short Delay	-0.095				
RAVLT Long Delay	0.174				
RAVLT Recognition	0.021				
ADAS-cog Short Delay	0.115				
ADAS-cog Long Delay	0.248**				
ADAS-cog Recognition	-0.059				
VFT Animals	-0.085				
BNT	-0.275**				
ADAS-cog Naming	-0.017				
CDT	0.089				
CDT Copy	0.076				
ADAS-cog Construction	0.041				
TMT A	-0.152*				
TMT B	0.092				
ADAS-cog Cancellation	0.098	0.247	0.154	3.867	0.000**

*$p < 0.05$, **$p < 0.01$

Table 7a

Effects of baseline neuropsychological test performance on adaptive function (Ecog self; baseline)

Model	R^2	ΔR^2	F	p
1. Demographics	0.016	0.016	1.803	0.146
2. Baseline diagnosis	0.205	0.188	38.578	0.000
3. MRI volumes	0.225	0.021	1.713	0.131
4. FDG-PET	0.228	0.003	1.336	0.249
5. NPI	0.237	0.009	3.799	0.052
6. Neuropsychological testing	0.289	0.051	1.361	0.160

Table 7b

Effects of baseline neuropsychological test performance on adaptive function (Ecog self;

12 months follow-up)

Model	R^2	ΔR^2	F	p
1. Demographics	0.020	0.020	2.220	0.086
2. Baseline diagnosis	0.024	0.005	0.757	0.470
3. MRI volumes	0.039	0.015	1.004	0.415
4. FDG-PET	0.042	0.003	0.996	0.319
5. NPI	0.045	0.003	0.890	0.346
6. Neuropsychological testing	0.108	0.063	1.336	0.174

Table 7c

Effects of baseline neuropsychological test performance on adaptive function (Ecog self; 24 months follow-up)

Model	R^2	ΔR^2	F	p
1. Demographics	0.005	0.005	0.600	0.615
2. Baseline diagnosis	0.016	0.011	1.746	0.176
3. MRI volumes	0.025	0.009	0.563	0.728
4. FDG-PET	0.025	0.000	0.059	0.808
5. NPI	0.025	0.000	0.067	0.796
6. Neuropsychological testing	0.065	0.040	0.808	0.677

Table 8a

Effects of baseline neuropsychological test performance on adaptive function (Ecog informant; baseline)

Model	β	R^2	ΔR^2	F	p
1. Demographics		0.038	0.038	4.276	0.006
2. Baseline diagnosis		0.371	0.333	86.436	0.000
3. MRI volumes		0.399	0.028	3.013	0.011
4. FDG-PET		0.425	0.026	14.404	0.000
5. NPI		0.526	0.101	68.093	0.000
6. RAVLT Learning	-0.056				
RAVLT Short Delay	0.182*				
RAVLT Long Delay	-0.220*				
RAVLT Recognition	-0.065				
ADAS-cog Short Delay	-0.137*				
ADAS-cog Long Delay	0.200**				
ADAS-cog Recognition	0.031				
VFT Animals	-0.048				
BNT	0.091*				
ADAS-cog Naming	-0.008				
CDT	0.072				
CDT Copy	-0.114**				
ADAS-cog Construction	-0.005				
TMT A	-0.042				
TMT B	0.039				
ADAS-cog Cancellation	0.024	0.594	0.068	3.149	0.000**

*$p < 0.05$, **$p < 0.01$

Table 8b

Effects of baseline neuropsychological test performance on adaptive function (Ecog informant; 12 months follow-up)

Model	R^2	ΔR^2	F	p
1. Demographics	0.005	0.005	0.536	0.658
2. Baseline diagnosis	0.028	0.023	3.805	0.023
3. MRI volumes	0.094	0.066	4.707	0.000
4. FDG-PET	0.132	0.038	13.836	0.000
5. NPI	0.133	0.001	0.357	0.550
6. Neuropsychological testing	0.191	0.059	1.373	0.153

Table 8c

Effects of baseline neuropsychological test performance on adaptive function (Ecog informant; 24 months follow-up)

Model	β	R^2	ΔR^2	F	p
1. Demographics		0.004	0.004	0.439	0.725
2. Baseline diagnosis		0.013	0.009	1.487	0.228
3. MRI volumes		0.034	0.021	1.397	0.225
4. FDG-PET		0.062	0.028	9.593	0.002
5. NPI		0.069	0.007	2.508	0.114
6. RAVLT Learning	0.132				
RAVLT Short Delay	-0.153				
RAVLT Long Delay	0.022				
RAVLT Recognition	-0.110				
ADAS-cog Short Delay	0.176*				
ADAS-cog Long Delay	-0.123				
ADAS-cog Recognition	-0.143				
VFT Animals	-0.051				
BNT	-0.160*				
ADAS-cog Naming	-0.024				
CDT	0.076				
CDT Copy	0.106				
ADAS-cog Construction	0.023				
TMT A	-0.100				
TMT B	0.009				
ADAS-cog Cancellation	0.141*	0.159	0.090	2.029	0.011*

*$p < 0.05$, **$p < 0.01$

Table 9a

Effects of baseline neuropsychiatric symptoms on adaptive function (FAQ; baseline)

Model	β	R^2	ΔR^2	F	p
1. Demographics		0.029	0.029	3.274	0.021
2. Baseline diagnosis		0.321	0.292	70.139	0.000
3. MRI volumes		0.354	0.033	3.302	0.006
4. FDG-PET		0.386	0.032	16.478	0.000
5. Neuropsychological test performance		0.469	0.083	2.965	0.000
6. Delusions	0.094*				
Hallucinations	0.088*				
Agitation/aggression	0.179**				
Depression/dysphoria	0.131**				
Anxiety	-0.012				
Elation/euphoria	0.145**				
Apathy/indifference	0.222**				
Disinhibition	-0.009				
Irritability/lability	0.008				
Aberrant motor behavior	0.060				
Sleep disturbances	0.046				
Disordered appetite/eating	0.099*	0.670	0.201	14.862	0.000**

*$p < 0.05$, **$p < 0.01$

Table 9b

Effects of baseline neuropsychiatric symptoms on adaptive function (FAQ; 12 months

follow-up)

Model	β	R^2	ΔR^2	F	p
1. Demographics		0.001	0.001	0.070	0.976
2. Baseline diagnosis		0.020	0.019	3.137	0.045
3. MRI volumes		0.079	0.059	4.117	0.001
4. FDG-PET		0.102	0.024	8.512	0.004
5. Neuropsychological test performance		0.197	0.095	2.241	0.004
6. Delusions	0.031				
Hallucinations	0.153**				
Agitation/aggression	-0.121*				
Depression/dysphoria	-0.124*				
Anxiety	-0.025				
Elation/euphoria	-0.241**				
Apathy/indifference	-0.107				
Disinhibition	0.082				
Irritability/lability	0.138*				
Aberrant motor behavior	-0.105				
Sleep disturbances	-0.030				
Disordered appetite/eating	0.117*	0.329	0.132	4.778	0.000**

*$p < 0.05$, **$p < 0.01$

Table 9c

Effects of baseline neuropsychiatric symptoms on adaptive function (FAQ; 24 months

follow-up)

Model	β	R^2	ΔR^2	F	p
1. Demographics		0.020	0.020	2.208	0.087
2. Baseline diagnosis		0.034	0.014	2.416	0.091
3. MRI volumes		0.072	0.038	2.598	0.025
4. FDG-PET		0.093	0.021	7.530	0.006
5. Neuropsychological test performance		0.247	0.154	3.895	0.000
6. Delusions	-0.053				
Hallucinations	-0.006				
Agitation/aggression	0.004				
Depression/dysphoria	0.028				
Anxiety	0.102				
Elation/euphoria	0.237**				
Apathy/indifference	0.005				
Disinhibition	0.015				
Irritability/lability	-0.089				
Aberrant motor behavior	-0.145**				
Sleep disturbances	-0.039				
Disordered appetite/eating	-0.025	0.325	0.077	2.780	0.001**

*$p < 0.05$, **$p < 0.01$

Table 10a

Effects of baseline neuropsychiatric symptoms on adaptive function (Ecog self; baseline)

Model	β	R^2	ΔR^2	F	p
1. Demographics		0.016	0.016	1.803	0.146
2. Baseline diagnosis		0.205	0.188	38.578	0.000
3. MRI volumes		0.225	0.021	1.713	0.131
4. FDG-PET		0.228	0.003	1.336	0.249
5. Neuropsychological test performance		0.277	0.048	1.268	0.216
6. Delusions	0.125*				
Hallucinations	-0.001				
Agitation/aggression	0.110				
Depression/dysphoria	0.121*				
Anxiety	-0.041				
Elation/euphoria	0.098				
Apathy/indifference	0.063				
Disinhibition	-0.101				
Irritability/lability	-0.040				
Aberrant motor behavior	-0.086				
Sleep disturbances	-0.039				
Disordered appetite/eating	0.038	0.340	0.063	2.325	0.007**

*$p < 0.05$, **$p < 0.01$

Table 10b

Effects of baseline neuropsychiatric symptoms on adaptive function (Ecog self; 12 months follow-up)

Model	R^2	ΔR^2	F	p
1. Demographics	0.020	0.020	2.220	0.086
2. Baseline diagnosis	0.024	0.005	0.757	0.470
3. MRI volumes	0.039	0.015	1.004	0.415
4. FDG-PET	0.042	0.003	0.996	0.319
5. Neuropsychological test performance	0.106	0.063	1.341	0.171
6. NPI	0.126	0.020	0.567	0.868

Table 10c

Effects of baseline neuropsychiatric symptoms on adaptive function (Ecog self; 24 months follow-up)

Model	R^2	$\varDelta R^2$	F	p
1. Demographics	0.005	0.005	0.600	0.615
2. Baseline diagnosis	0.016	0.011	1.746	0.176
3. MRI volumes	0.025	0.009	0.563	0.728
4. FDG-PET	0.025	0.000	0.059	0.808
5. Neuropsychological test performance	0.064	0.039	0.800	0.686
6. NPI	0.089	0.025	0.663	0.787

Table 11a

Effects of baseline neuropsychiatric symptoms on adaptive function (Ecog informant; baseline)

Model	β	R^2	ΔR^2	F	p
1. Demographics		0.038	0.038	4.276	0.006
2. Baseline diagnosis		0.371	0.333	86.436	0.000
3. MRI volumes		0.399	0.028	3.013	0.011
4. FDG-PET		0.425	0.026	14.404	0.000
5. Neuropsychological test performance		0.522	0.097	3.837	0.000
6. Delusions	0.058				
Hallucinations	0.157**				
Agitation/aggression	0.153**				
Depression/dysphoria	0.075				
Anxiety	0.074				
Elation/euphoria	0.054				
Apathy/indifference	0.122**				
Disinhibition	0.087*				
Irritability/lability	0.006				
Aberrant motor behavior	-0.059				
Sleep disturbances	-0.021				
Disordered appetite/eating	0.101*	0.649	0.127	8.839	0.000**

$*p < 0.05$, $**p < 0.01$

Table 11b

Effects of baseline neuropsychiatric symptoms on adaptive function (Ecog informant; 12 months follow-up)

Model	β	R^2	ΔR^2	F	p
1. Demographics		0.005	0.005	0.536	0.658
2. Baseline diagnosis		0.028	0.023	3.805	0.023
3. MRI volumes		0.094	0.066	4.707	0.000
4. FDG-PET		0.132	0.038	13.836	0.000
5. Neuropsychological test performance		0.190	0.058	1.359	0.161
6. Delusions	-0.075				
Hallucinations	0.021				
Agitation/aggression	-0.057				
Depression/dysphoria	0.002				
Anxiety	-0.023				
Elation/euphoria	-0.140*				
Apathy/indifference	0.051				
Disinhibition	-0.085				
Irritability/lability	0.185**				
Aberrant motor behavior	-0.058				
Sleep disturbances	-0.078				
Disordered appetite/eating	0.044	0.250	0.061	1.978	0.026*

*$p < 0.05$, **$p < 0.01$

Table 11c

Effects of baseline neuropsychiatric symptoms on adaptive function (Ecog informant; 24 months follow-up)

Model	β	R^2	ΔR^2	F	p
1. Demographics		0.004	0.004	0.439	0.725
2. Baseline diagnosis		0.013	0.009	1.487	0.228
3. MRI volumes		0.034	0.021	1.397	0.225
4. FDG-PET		0.062	0.028	9.593	0.002
5. Neuropsychological test performance		0.151	0.089	1.996	0.013
6. Delusions	-0.081				
Hallucinations	-0.076				
Agitation/aggression	-0.014				
Depression/dysphoria	-0.033				
Anxiety	0.098				
Elation/euphoria	0.244**				
Apathy/indifference	0.130*				
Disinhibition	-0.122*				
Irritability/lability	-0.024				
Aberrant motor behavior	-0.024				
Sleep disturbances	0.068				
Disordered appetite/eating	-0.022	0.231	0.080	2.529	0.003**

*$p < 0.05$, **$p < 0.01$