PREDICTING LONGITUDINAL DECLINE IN INSTRUMENTAL ACTIVITIES OF DAILY LIVING IN PATIENTS WITH ALZHEIMER'S DISEASE

A Dissertation

Presented to

The Faculty of the Department

of Psychology

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

By

Jonathan M. Grabyan

December, 2014

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PREDICTING LONGITUDINAL DECLINE IN INSTRUMENTAL ACTIVITIES OF DAILY LIVING IN PATIENTS WITH ALZHEIMER'S DISEASE

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ABSTRACT

Appropriate planning for the future functional decline of patients with Alzheimer's disease (AD) is very important. An easy-to-utilize, reliable method for predicting progression of deficits in instrumental activities of daily living (IADL) would have great clinical utility. The literature predicting functional decline is sparse. This study sought to validate a "pre-progression" estimate of functional decline (rate of annual decline prior to AD diagnosis) for use in predicting future functional decline. Broader analyses of baseline correlates and future predictors of IADLs were also performed. Participants were 785 AD patients enrolled in the Alzheimer's Disease and Memory Disorders Center (ADMDC) at Baylor College of Medicine. Linear mixed-effects models were utilized to predict the decline over time in IADLs from baseline information. The IADL pre-progression estimate was found to significantly predict future rate of decline even after covariates of age, education, sex, and baseline dementia severity were taken into account. However, the direction of the effect, with lower pre-progression rates predictive of faster decline, was reverse of what was hypothesized. Older Age and more neuropsychiatric symptoms at baseline were significantly predictive of faster future decline (though with a negligible effect size), while MMSE scores and neuropsychological tests results were not. Multiple regressions were used to examine the baseline correlates of IADL performance. Age, MMSE, neuropsychological domains (except motor), and neuropsychiatric symptoms were significantly related to greater IADL impairment at baseline. In summary, there is a disparity between baseline relationships with IADL impairment and ability to predict future IADL decline. Due to the reversed direction of the expected effect, the pre-progression estimate of IADLs was not deemed a valid tool for predicting future decline in functional ability.

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Introduction

Presently in the United States, 11 percent of individuals 65 years or older have Alzheimer's disease (AD), while 32 percent of those 85 or older have the disease (Hebert, Weuve, Scherr, & Evans, 2013). In total, the current prevalence of AD among all age groups is approximately 5.2 million. Due to the aging baby boomer population, the number and proportion of individuals in the United States entering the age range at risk for developing AD is increasing. A concomitant increase in AD prevalence is a reasonable prediction; without more effective treatments or prevention, it is estimated that by 2050, between 13.8 and 16 million Americans 65 years of age or older will meet the current criteria for diagnosis of Alzheimer's (Hebert et al., 2013; Hebert et al., 2003). In 2014 the incidence of new cases of AD will be approximately 469,000 among those 65 years or older. Due to the aging population, by 2050 the number of annual new cases in America is expected to double (Hebert, Beckett, Scherr, & Evans, 2001).

The economic costs for caring for patients with AD and other dementias are high, and make them among the most costly chronic illnesses to society (Hurd, Martorell, Delavande, Mullen, & Lange, 2013). In total, the medical costs for Americans with AD and other dementias in 2014 will be approximately $214 billion. After partialling out Medicare, Medicaid, individual insurance coverage, and other forms of support, out of pocket expenses will be $36 billion (Alzheimer's Association, 2014). The financial cost to unpaid caregivers is substantial. The value (both in lost wages and time spent caregiving) of unpaid caregivers to loved ones is about equal to the actual amount spent on medical and long-term costs of dementia (Hurd et al., 2013).

The majority (up to 85 percent) of caregivers for AD patients are unpaid family members (Gitlin & Schulz, 2012). Providing care for a loved one is a large time commitment and when combined with other life responsibilities often results in significant burden on the caregiver. A majority (59 percent) of family caregivers report "high or very high emotional stress" and 38 percent report similar levels of physical stress (Alzheimer's Association, 2014). This emotional stress frequently manifests in mood difficulties, with 39 percent of caregivers of dementia patients suffering from depression (Pinquart & Sörensen, 2003).

The most common assistance given by caregivers is in the domain of activities of daily living, such as bathing and managing finances (Gaugler, Kane, & Kane, 2002), but as the disease progresses behavioral and/or personality changes frequently occur. These changes are reported as among the most stressful to caregivers (Ornstein & Gaugler, 2012). As the disease further progresses, caregiver burden worsens (Peacock, 2013) as the emotional, physical, temporal, and financial resources necessary to maintain adequate care grow (Schulz et al., 2004; Vitaliano, Zhang, & Scanlan, 2003; Alzheimer's Association, 2014).

Functional Abilities in AD Patients

Impairment in functional abilities in patients with dementia have been shown to decrease quality of life for both the patient and the caregiver (e.g., Vetter et al., 1999), increase caregiver burden (e.g., Razani et al., 2007; Schubert et al., 2008), and increase likelihood of utilization of higher levels of health-care services, including institutionalization (Hope, Keene, Gedling, Fairburn, & Jacoby, 1998; Severson, Smith, Tangalos, & Peterson, 1994).

In the context of dementia, functional abilities are often assessed by examining activities of daily living (ADLs). Basic ADLs consist of physical self-care tasks such as

feeding oneself, grooming, and bathing. Instrumental ADLs (IADLs) are more complex tasks with multiple steps, such as managing one's medications, transportation, and shopping. IADLs are more reliant on cognitive, than physical, ability, and therefore much more likely to be impacted early in the course of Alzheimer's dementia (Stern, Hesdroffer, Sano, & Mayeux, 1990). IADLs are therefore a more fruitful area of study for predicting future decline, as IADL impairment will be present for a much greater percentage of the disease course. Some (e.g., Kahle-Wrobleski et al., 2014) have very recently found evidence suggesting that ADLs be further subdivided into more distinct factors, but further research needs to be performed to precisely identify these factors.

Assessing ADLs. Measuring functional abilities (i.e., the ability to perform complex activities such as management of medications and of finances) is challenging. Some investigators (e.g. Karagiozis et al., 1998; McDougall et al., 2010; Schwartz, Segal, Veramonti, Ferraro, & Buxbaum, 2002) have made efforts to directly measure these abilities. These methods require a trained assessor to administer tests which purport to have ecological equivalence to real-world skills. The benefits of these types of tests include in-depth error analysis (e.g., commission v. omission), which have been hypothesized to be related to distinct neuropsychological processes (Giovannetti et al., 2008). However, the downside to this approach, as Cahn-Weiner and colleagues (2007) point out, is that it is time consuming (which reduces its use in large scale investigations) and may not be ecologically valid (e.g., since the assessor is present to prompt the patient).

While direct observation of a patient in a naturalistic environment would be ideal, it is often not practically possible. To that end, self-report and/or informant questionnaires have often been used. Lawton and Brody (1969) created an informant-report IADL measure

which, while not created specifically for dementia patients, is amongst the most widely used IADL measures in AD research (Sikkes et al., 2009). It measures degree of independence in the domains of telephone use, shopping, food preparation, housekeeping, laundry, transportation, responsibility for medications, and ability to handle finances. While not much research into the measure's validity and reliability has been undertaken (nor for most ADL measures in the context of dementia: Sikkes et al., 2009), it has been shown to be cross-culturally valid (Ng, Niti, Chiam, & Kua, 2006), with good interrater reliability (Hokoishi et al., 2001), sensitivity to change over time in mild and moderate AD (Green, Mohs, Schmeidler, & Aryan, 1993), and was comparably related to neuropsychological test results as a measure of direct ADL assessment (Farias, Harrel, Neumann, & Houtz, 2003). In contrast, it has not been shown to be able to independently diagnose dementia (Hancock & Larner, 2007), and in one study, ceiling effects among up to 20% of AD patients was observed (Green et al., 1993). As Sikkes and colleagues (2009) conclude, in the context of dementia, validation of ADL measures (and IADL measures in particular) remains a markedly under-investigated area.

Demographic variables and ADLs. The relationships between demographic variables and IADLs at baseline in the literature are decidedly mixed. Some studies (e.g., Ford, Haley, Thrower, West, & Harrell, 1996; Mok, Chu, Chung, Chan, & Hui, 2004) found that age and years of education were not related to IADLs at baseline, whereas Cahn-Weiner et al. (2007) reported that lower education was associated with lower IADL functioning at baseline (but age and gender were not). However, in a more recent study (Benke et al., 2013), old age and male gender were found to be independent predictors of reduced IADLs. In one large community study (Blazer, Fillenbaum, & Burchett, 2001), an interaction between

female gender and carrying the ApoE (ε4) allele was associated with decreased baseline functional ability; this study also found that ethnicity does not appear to be a factor.

In contrast to the relationship between cognitive decline and demographic variables in AD, the relationship between rate of functional decline and demographic variables in AD has been seldom studied, and results have been mixed. In some cases, age of onset has been shown to predict future functional decline. Jacobs et al. (1994) compared early onset (operationalized as symptom onset prior to age 65) to late-onset patients, and found that amongst the early onset group, earlier age of onset predicted faster functional decline (measured using the Blessed Dementia Rating Scale) at two year follow-up. In other studies, demographic variables, including age, were unrelated to functional decline (e.g., Mayeux, Stern, & Spanton, 1985). ApoE (ε4) status also does not appear to be related to decline in functional abilities in AD (Kleiman et al., 2006).

Dementia severity and ADLs. Previous research has demonstrated a significant, but imperfect, association between dementia severity (overall degree of cognitive impairment) and functional abilities. For example, Skurla, Rogers, and Sunderland (1988) found that among AD patients, directly assessed functional abilities were related to ratings on some, but not all, of the dementia severity scales examined, indicating that dementia severity is a distinct but related construct to functional ability. Patients with moderate to severe dementia, as a group, are significantly more functionally impaired than patients with mild dementia on ADLs (Aliberti et al., 2007), but there is significant variability in this relationship (e.g., some more severely demented patients showing relatively good functional abilities, and vice versa). Razani et al. (2009) observed a relationship between MMSE scores and directly

assessed daily functional tasks in AD patients. The MMSE orientation subscore was a particularly strong predictor of observed functional ability.

Dementia severity (overall cognitive impairment) measured at baseline has been shown to influence the rate of cognitive decline in AD patients, with lower baseline severity associated with slower cognitive decline (e.g., Atchison, Bradshaw, & Massman, 2004; Burns, Jacoby, & Levy, 1991; Drachman et al., 1990), but there is significantly less research investigating baseline severity's strength of association with functional decline. Schmeidler, Mohs, and Aryan (1998) divided a cohort of 151 AD patients into four severity groups and tracked their IADLs over one year. They found that patients in the moderate and severe groups, but not the mild or very severe groups, declined more quickly in IADLs. Atchison, Massman, & Doody (2007) found that baseline dementia severity modestly predicted faster decline on a measure of physical self-maintenance, despite equivalent baseline scores on this measure.

Neuropsychological test performance correlates of ADLs. Earlier studies examined overall global impairment and general measurements of functional ability, but found that a more nuanced approach would be warranted (e.g., Reed, Jagust, & Seab, 1989). In response, recent research has focused on investigating how individual domains of cognitive ability are associated with basic and/or instrumental activities of daily living.

A baseline relationship between functional ability and performance on neuropsychological tests has previously been demonstrated (e.g., Farias, Harrel, Neumann, & Houtz, 2003) with the most consistent and persuasive evidence in the domain of executive functioning. Razani et al. (2007) observed that deficits in verbal fluency and cognitive flexibility (i.e., Wisconsin Card Sorting Test performance) were associated with decreased

ADLs (both directly assessed and informant-reported) in dementia patients with relatively mild clinical presentations. Boyle et al. (2003) found a relationship between executive dysfunction on the Mattis Dementia Rating Scale (Initiation/Perseveration) and ADLs in mildly to moderately demented AD patients. Other research groups have found a significant relationship between executive dysfunction and IADL impairment across older adults in normal, mild cognitive impairment (MCI), and Alzheimer's disease groups (e.g., Marshall et al., 2011; Pereira, Yassuda, Oliveira, & Forlenza, 2008).

Relatively fewer studies have used neuropsychological measures to predict longitudinal rate of change of IADLs. One such study (Cahn-Weiner et al., 2007) of dementia patients found that while baseline measures of executive functioning, memory, and hippocampal and cortical volumes were associated with baseline IADLs, only executive dysfunction (assessed via a combination of Wechsler Memory Scale-R Digit Span backward, Visual Memory Span backward, Initation/Perseveration from the Mattis Dementia Rating Scale, and letter fluency) predicted future rate of functional decline. Boyle, Paul, Moser, and Cohen (2004) found that executive dysfunction predicted future functional decline one year later, but this was in the context of vascular dementia, and not AD.

Cognitive domains outside of executive functioning have also received some attention, although the results have been mixed. Nonverbal ability predicted faster decline in functional abilities (as opposed to cognitive decline) in a study by Mortimer and colleagues (1992). Visual-spatial deficits may differentially predict rapid functional (more so than cognitive) decline (Buccione et al., 2007). Atchison, Massman, and Doody (2007) also found visual spatial skills, in addition to processing speed and concept formation, were indicative of faster decline in physical self-maintenance. Interestingly, memory abilities have not been

found to be predictive of future functional decline in patients with dementia (Goldstein, McGue, Rogers, & Nussbaum, 1992), but have been observed in community dwelling samples (McCue, Rogers, & Goldstein, 1990; Farias et al., 2004). One possible explanation is that restricted variability and/or floor effects present in existing memory measures make finding significant associations with functional abilities difficult.

Neuropsychiatric symptoms and functional abilities. Neuropsychiatric symptoms have been associated with functional impairment. For example, Chen and colleagues (1998) reported that agitation and overall number/severity of neuropsychiatric symptoms were related with both functional impairment and executive dysfunction (the two of which have a strong relationship, as previously discussed). After controlling for executive dysfunction, apathy was found to be associated with IADL impairment (Boyle et al., 2003). In a large international study, baseline extrapyramidal symptoms (e.g., abnormal gait, bradykinesia, cogwheel rigidity, postural instability, and tremors) were significantly associated with greater impairment in both ADLs and IADLs in AD patients not taking neuroleptics (Choi et al., 2013).

Further, the presence of neuropsychiatric symptoms at or near baseline has been shown to be associated with hastened functional decline, and often in a different profile than predictions of cognitive decline. Behavioral disturbances such as hallucinations and paranoia in the first year, as well as extrapyramidal signs at baseline, predicted faster overall functional (compared to cognitive) decline (Mortimer et al., 1992). Lopez et al. (1997) also found extrapyramidal symptoms to be predictive of faster functional progression, with the specific symptom of tremors being most significant (though tremors are a rare symptom in mild AD). Stern and colleagues (1994) agreed that symptoms of psychosis are related to

functional decline, but found that extrapyramidal signs were related to more rapid cognitive decline.

In contrast, it has also been reported that other neuropsychiatric symptoms are more strongly related to faster functional decline than are psychotic symptoms. For example, Levy, Cummings, Fairbanks, and Bravi (1996) found that agitation was more highly associated with faster functional decline than was psychosis, which was associated with more rapid cognitive decline. A syndrome of affective symptoms (anxiety and depression) from the Neuropsychiatric Inventory was shown to differentially predict functional decline, while only manic symptoms were related to cognitive decline (Palmer et al., 2011). Similarly, several researchers have found that the presence of apathy predicted faster functional decline (Lechowski et al., 2009; Starkstein et al., 2006). In contrast, Drachman and colleagues (1990) did not find a relationship between functional decline and psychosis, anxiety, or depression.

However, the overall weight of the evidence indicates that the presence of neuropsychiatric symptoms at or near baseline is associated with a decline in functional status in a differential pattern than decline in cognitive abilities, though there is still some clarification needed to determine the specific profile of symptoms associated with each domain. Regardless of the specific profiles, what is known thus far is that clinical signs (such as neurological symptoms) occur much later in the disease process, after a long period of neurobiological changes.

Alzheimer's Disease Progression

The current prevailing model of the development of AD posits that cognitive and behavioral symptoms are the result of perhaps decades of pathological neurobiological changes. Viewing clinical symptoms as an end point of the process requires presymptomatic

investigations to shift to examining the biological signifiers of changes in the brain. These biomarkers signify changes to the brain typical of AD neuropathology. If the degenerative processes caused by the disease occur in predictable order, the presence of the biomarkers indicative of each such process should also be observed in a reliable temporal order. Jack and colleagues (2010) proposed an influential model of this order of neurological change, and revised it later in response to additional evidence (Jack et al., 2013).

The amyloid cascade hypothesis is a quite commonly held view in the literature that states that AD begins with atypical processing of amyloid precursor protein, which causes a disruption in the balance between production and clearance of amyloid β-peptide (Aβ) (Hardy & Selkoe, 2002). Excess extracellular deposits of Aβ in the brain begin a process of neurological degeneration involving hyperphosphorylated tau, dysfunction in the synapses, eventual cell death, and reduction in brain volume (Oddo et al., 2006). In their updated model, Jack et al. (2013) support the amyloid cascade hypothesis by stating that abnormally low levels of a specific type of beta amyloid in the cerebrospinal fluid (Aβ42) is the first biomarker to be observed in the process of AD development (see Figure 1). This is followed by observation of Aβ42 in PET imaging through use of Pittsburgh compound-B (e.g., Klunk et al., 2004). Of importance to Jack et al.'s model is that these signifiers of Aβ plaque development precede those of neuronal dysfunction, neuronal injury, and neurodegeneration (such as tau).

Increased concentration of CSF tau is the first biomarker to signal AD neurodegeneration in Jack et al.'s (2013) model. Increased CSF tau is not specific to AD, as it appears to signal general neuronal damage and is seen in both TBI and strokes (e.g., Hesse et al., 2001; Öst et al., 2006). However, there is an association between greater cognitive

impairment and higher concentrations of CSF tau among MCI/AD patients (Shaw et al., 2009). In the context of AD, hyperphosphorylated tau accrues inside neurons, which disrupts tau's normal role in axonal transport and in turn disturbs cellular function, eventually leading to ejection of tau into the intercellular space, the creation of neurofibrillary tangles, and neuronal loss (Blennow et al., 1995). This intercellular tau makes its way to the CSF, becoming the biomarker under discussion. Other, later biomarkers of neurodegeneration include imaging data indicative of gross neuronal loss. In this regard, Jack et al. point to overall decreased metabolism observed through decreased uptake of fluorodeoxyglucose on PET scans, and decreased brain volume observed through structural MRI.

Structural changes in the brain. Many structures are eventually damaged by AD, but the most prominently, and earliest, impacted region appears to be the medial temporal lobe (MTL), which includes structures related to memory such as the hippocampus and entorhinal cortex. These MTL structures are crucial to the formation of long-term memories, which is typically the earliest appearing and most pronounced cognitive deficit observed in AD patients (Weiner et al., 2013). This damage appears as diffuse atrophy in the implicated regions, and takes the form of shrunken cells, loss of neurons, and decreased synaptic density (Bobinski et al., 2000; Selkoe, 2002).

While the literature is sparse on brain structures damaged before cognitive symptom onset, current MRI evidence indicates that asymptomatic individuals who will later convert to AD have damage to the MTL, and specifically the hippocampus (den Heijer et al., 2006; Rusinek et al., 2003; Tondelli et al., 2012). Older adults with cognitively normal profiles but at higher genetic risk for developing AD (i.e., carriers of the apolipoprotein E (ApoE) ε4 allele) show lower hippocampal volume (Reiman et al., 1998) than non-carriers. Similarly,

those with maternal familial history of AD have been found to have reduced volume of MTL structures (hippocampus and parahippocampal gyrus) and the precuneus (Honea, Swerdlow, Vidoni, & Burns, 2011).

At the point when clinical symptoms are manifest, the picture of brain atrophy becomes clearer. Much research has been devoted to differentiating between patients with MCI do and do not later convert to AD. In comparison to normal controls and/or non-converting MCI patients, MCI patients who later develop AD have been shown to have more damage to the MTL, lateral temporal cortex, posterior parietal cortex (including precuneus), and posterior cingulate (Chételat et al., 2005; Hämäläinen et al., 2007; Karas et al., 2008; Risacher et al., 2009). As pointed out by Tondelli and colleagues (2012), there is some variation amongst studies regarding the degree of atrophy and laterality of these findings. However, the clear common thread in the literature remains the MTL, to the point that atrophy of MTL structures in MCI has been recommended by many to be a biomarker of future conversion to AD (e.g., Frisoni, Fox, Jack, Scheltens, & Thompson, 2010).

Once diagnostic criteria for AD have been met, more widespread cortical atrophy is observed in addition to the above-discussed regions. However, regionally specific atrophy is most pronounced in the MTL, specifically the hippocampus and entorhinal cortex (Busatto, Diniz, & Zanetti, 2008; Hua et al., 2010; Riscaher et al., 2010, Schuff et al., 2009), with expansion of the ventricles (Evans et al., 2010) and thinning of the neocortex (Desikan et al., 2010) also being prototypical.

Symptom appearance. In Jack et al.'s (2013) model, the last biomarkers to occur are imaging evidence of brain volume loss (discussed at length above). Of all the biomarkers, they propose imaging evidence should co-occur most closely with cognitive changes. Since

structures related to memory creation are most impacted by AD, it reasonable to expect that memory difficulties should be the earliest clinical sign of AD.

For example, in a longitudinal community study examining presymptomatic AD, Chen and colleagues (2001) examined the decline of cognitive abilities in elder adults. When comparing individuals who would develop AD 1.5 years later versus the non-demented, they found that cognitive decline during this presymptomatic stage was greatest in the domains of memory and executive functions. In support of this, others have found that before development of MCI in patients who will convert to AD, there was a slow, long stage of episodic memory decline which accelerates before development of MCI (Bäckman, Small, & Fratiglioni, 2001). During the MCI stage, verbal memory, semantic fluency, and visuospatial skills decline en route to development of full AD (Howieson et al., 2008). Unfortunately, as Sperling and colleagues (2011) discuss, presently there is no evidence that cognitive or self-report measure(s) can reliably predict the progression to AD in a given individual.

Profile of cognitive deficits in AD. The pattern of cognitive deficits observed once full AD diagnostic criteria are met has been extensively studied (see Weintraub, Wicklund, & Salmon, 2012 for a recent review). Episodic memory, tested in a variety of ways across multiple modalities, is greatly impaired (for an extensive review, see Salmon, 2000). The patterns of performance observed on these tests suggest that ineffective consolidation, not retrieval, is the source of memory deficits (Delis et al., 1991). Language deficits in object naming (Hodges, Salmon, & Butters, 1991), categorizing semantic information (Aronoff et al., 2006), and verbal fluency (Monsch, et al, 1992) are representative of a breakdown of semantic knowledge. In terms of verbal fluency, AD patients perform worse on tests of semantic fluency (which relies more heavily on semantic knowledge) than phonemic fluency,

which indicates a breakdown of semantic knowledge more so than a difficulty retrieving stored knowledge (Rorher, Wixted, Salmon, & Butters, 1995). Executive functions (itself an at-times nebulous concept) are variably impacted in AD. In mild AD, tests which require manipulation of information via sequencing or set-shifting (e.g., Trailmaking Test, Part B) are impacted first (Lafleche & Alpert, 1995), while problem solving is impacted later (Bondi, Monsch, Butters, Salmon, & Paulsen, 1993). Working memory is also impacted as AD progresses. In mild AD, deficits are seen in more complex working memory tasks involving divided attention and/or selective attention (Perry & Hodges, 1999). Only later in the illness are focusing ability and sustained attention impacted (e.g., Cherry, Buckwalter, & Henderson, 2002). Visuospatial abilities are commonly reduced in AD (Cronin-Golomb & Amick, 2001). Some have argued that the cause of these deficits are damage to the cortical connections between distinct information processing areas (Morrison, Hof, & Bouras, 1991), such that AD patients are significantly more impaired on visuoperception tasks requiring identification of multiple features (with each feature associated with a distinct brain region) than on equally difficult tasks with involving only single features (Foster, Behrman, & Stuss, 1999; Tales et al., 2002). Thus, while the profile of cognitive deficits in AD is well understood, Weintraub, Wicklund, and Salmon (2012) point out that the pattern is strongest earlier in the disease: The longer the neurodegenerative process continues, the more globally impaired the individual becomes, and the less distinct the boundaries between cognitive domains are.

Pre-progression Estimates

The prediction of future impairment utilizing easily assessed variables is an important goal. In studies performed at Baylor College of Medicine Alzheimer's Disease and Memory

Disorders Center (ADMDC), one variable associated with cognitive decline was "MMSE pre-progression." This variable is an estimate of the patient's rate of decline on the MMSE from the time when AD symptoms were first observed by informants (most often the patient's spouse) until the initial, baseline evaluation. It was calculated using the formula: (30 [perfect MMSE score] – MMSE score at the baseline evaluation) / physician's estimate of duration [in years] (Doody, Massman, & Dunn, 2001). A semi-structured interview was used by the physician to determine estimate of duration before baseline (Doody, Dunn, Huang, Azher, & Kataki, 2004). For example, a patient with a baseline MMSE of 21 with an estimated duration of three years would have a pre-progression rate of three points per year. Another patient with the same MMSE score but an estimated duration of one year would have a pre-progression rate of nine points per year.

As reviewed earlier, predicting rate of change of IADLs in AD is an under-researched area. Applying the above MMSE pre-progression paradigm to IADLs could prove beneficial to increasing our ability to determine future rate of change using information available at a patient's initial evaluation. It would be especially useful to patients and family members if information available from this evaluation could be used to predict subsequent rate of decline in complex functional abilities. Family members could be better able to plan for future care and expenses, such as how long the patient may be able to function independently and the timing of possibly moving into an assisted living facility. The present study utilized the large Baylor ADMDC longitudinal database to determine if a similarly derived "IADL pre-progression measure" had predictive validity and utility, i.e., was useful in predicting future rate of IADL decline.

Hypotheses

The goals of the present study were two-fold. The primary goal of the study was to examine the predictive utility of the IADL pre-progression (which is calculated at the baseline visit).

1. It was hypothesized that the baseline IADL pre-progression rate would significantly predict future rate of IADL decline in AD, with higher pre-progression rates indicating faster decline over time.
2. It was also hypothesized that these pre-progression estimates would significantly enhance prediction of IADL decline even when baseline dementia severity and baseline demographics were taken into account.

The secondary goal of the present study was to examine the baseline correlates of IADLs and the longitudinal predictors of IADL change over time. As detailed above, there is a reasonable amount of confusion in the literature. It was hoped that this large, well-characterized sample of probable AD patients would lend clarity to these topics.

3. It was hypothesized that the baseline demographic of age would be significantly correlated with baseline IADLs (with greater age associated with reduced IADL performance), and younger age at baseline would be predictive of faster IADL decline.
4. It was also hypothesized that greater baseline dementia severity (MMSE) would be associated with worse baseline IADLs and predict faster IADL decline.
5. Based on prior research, it was hypothesized that deficits in neuropsychological measures of executive functioning (specifically Controlled Oral Word Association and Verbal Series Attention Test), visuospatial/visuoconstructional skills (specifically

WAIS-R Block Design and Rey-Osterrieth Complex Figure Test – Copy), and motor ability (specifically Finger Tapping Test, dominant hand) would each be associated with decreased IADLs at baseline, and predictive of faster future decline. In contrast, it was hypothesized that neither memory (WMS-R Logical Memory 1 and Visual Reproduction 1) nor language (Boston Naming Test and Animal Naming) would be associated with decreased IADLs at baseline, and they would not be predictive of IADL change over time.

6. Lastly, presence of Parkinsonism and neuropsychiatric symptoms at baseline (Initial Examination interview) were hypothesized to be associated with higher baseline IADL impairment and faster IADL decline over time.

Methods

Participants

Participants were 785 patients (67% female) with age ranging from 44 to 93 years old (M = 74.1 years, SD = 8.4) at baseline. The sample was predominantly Caucasian (98%). Mean education attainment was 14.2 years (SD = 3.3). At the time of the initial baseline evaluation, the participants had a mean MMSE score of 21.6 (SD = 4.7) and a Lawton Brody IADL total score of 14.4 (SD = 6.2). The participants were selected from those enrolled in the Baylor College of Medicine Alzheimer's Disease and Memory Disorders Center (ADMDC) longitudinal database who met criteria for probable AD at initial and each annual follow-up evaluation using the NINCDS-ARDA diagnostic criteria (McKhann et al., 1984). Participants must have had undergone a full standard neuropsychological evaluation at their baseline visit, and at least one follow-up evaluation.

Procedures

Obtaining the archival data. The present study utilized archival data from the Baylor ADMDC longitudinal database. Started in 1989, the Baylor ADMDC's goal has been to translate laboratory findings into methods for augmenting AD prevention, diagnosis, and treatment. The ADMDC has participated in multiple major AD clinical trials, is an active clinical and research site in the Alzheimer's Disease Cooperative Study (ADCS), and a contributing site to the Alzheimer's Disease Neuroimaging Initiative (ADNI). The goal of the ongoing longitudinal database is to track the performance over time of individuals with probable AD in clinical and psychometric domains. Referral sources are diverse, coming from physicians, the Alzheimer's Association, self-referral, or family members (Doody et al., 2005). The patients' comprehensive evaluation includes interviews, neurological and physical work ups, blood work, genetic and other laboratory testing, neuroimaging, and a comprehensive neuropsychological assessment.

As part of their initial visit, the patient's AD symptom duration is calculated using a standardized method of chart review and semi-structured interview (Doody, Dunn, Huang, Azher, & Kataki, 2004). First, a questionnaire is given to the informant/caregiver which asks them to estimate the first occurrence of each of 34 symptoms. In concert with review of medical records, the neurologist makes an estimate of the earliest symptom onset. Next, during a semi-structured interview, the neurologist asks the patient and informant questions about what was occurring in their life around the time of the earliest symptom onset, including behavioral and cognitive functioning preceding, during, and subsequent to the event. Finally, with all of the above information in hand, the neurologist makes a determination of the duration of AD symptoms prior to the visit. Doody et al. (2004) found a

high interrater reliability (rho = 0.95, $p < 0.001$) between the neurologists participating in their study.

Comprehensive neuropsychological evaluations were conducted at the initial visit and annual follow ups. The battery consisted of standardized tests and/or questionnaires in major neuropsychological domains including language, learning and memory, executive function, attention, motor skills, mood, behavior, and functional ability.

The ADMDC utilizes a case consensus model for diagnosis of possible or probable AD with the NINCDS-ARDA diagnostic criteria (McKhann et al., 1984). After diagnosis, a feedback session with the patient and family is scheduled, where they are provided with information and psychoeducation about the diagnosis. They are then assessed for appropriateness of further services and/or treatment.

Informed consent is obtained from the patient or the individual with the appropriate power of attorney. Clinical, laboratory, and neuropsychological test results are then entered into the ADMDC longitudinal database. Germane approvals from the Baylor College of Medicine Institutional Review Board (and from the University of Houston Committee for the Protection of Human Subjects) were received for the present archival study.

Calculating pre-progression rates. The IADL pre-progression rate was calculated using a similar method to MMSE pre-progression described above. Lawton and Brody's (1969) IADL scale scores were obtained based on informant report (see Appendix 1). Estimations of illness duration prior to enrollment were made using standardized methods described above (Doody et al., 2004). A rate of pre-progression IADL decline was then calculated for each patient and used to predict their IADL change over time ((IADL at baseline – expected 'normal' IADL) / estimated duration). In order to adjust for "Not

Applicable" item scores (indicating that the patient never performed those tasks, such as laundry, prior to illness), those maximum item values were subtracted from 31 (the maximum total score) in order to derive an individualized maximum potential total score. For example, if a patient never performed laundry nor food preparation tasks, which are worth at most three points and five points respectively, then their individual maximum potential score would be 31 – 3 – 5 = 23. Then, their total score from the remaining items would be taken, subtracting one point for each remaining item (i.e., 'normal' functioning), and divided by the above potential IADL total score to arrive at an IADL ratio. In our example, assume the patient's score on the IADL instrument is 12. As there are eight maximum items on the instrument and two are excluded for this patient, the IADL ratio would be 12 - (8 – 2), divided by the above 23, to equal 0.261. Finally, dividing this ratio by estimated disease duration prior to enrollment would result in an estimate of IADL pre-progression. The full equation:

$$\frac{\left(\frac{Baseline\ IADL\ total - Number\ of\ items\ included}{31 - excluded\ items'\ maximum\ value}\right)}{Estimated\ duration\ prior\ to\ enrollment}$$

Continuing with the above example, if a patient had a baseline IADL score of 12, with an N.A. on Laundry and Food Preparation, and an estimated prior duration of 3 years, the equation for her estimated annual IADL decline would be:

$$\frac{\left(\frac{12-6}{31-8}\right)}{3} = 0.087$$

Multiplying this ratio by 100 would result in a percentage estimate of this patient's annual linear decline in IADL functioning prior to the initial visit. In this example, the patient's IADL pre-progression is 8.7% decline annually.

Measures

IADLs

Lawton Brody Instrumental Activities of Daily Living (Lawton IADL). The Lawton IADL is an informant-report rating scale consisting of eight domains measuring the informant's view of the patient's degree of independence in each domain of IADLs (Lawton & Brody, 1969). A maximum score of 31 points is possible, with each domain weighting between three to five points and a higher score indicating greater impairment. For domains where the patient had not historically participated (e.g., laundry), that domain was removed from the patient's potential total score and a ratio score was calculated. This ratio score for each patient was used in the present study.

Dementia severity

Mini-Mental Status Examination (MMSE). The MMSE is a widely-used brief measure used to screen for dementia and/or cognitive impairment (Folstein, Folstein, & McHugh, 1975). It consists of 11 short, simple items assessing domains of orientation, memory, attention, working memory, language, and visuoconstruction (copying a geometric figure). A total of 30 points are possible.

Language

The Boston Naming Test (BNT). The BNT is a word retrieval confrontation naming test consisting of 60 line drawings of everyday objects (e.g., "bench", "beaver", "funnel," "latch") (Kaplan, Goodglass, & Weintraub, 1983). The drawings were serially presented (in order of increasing difficulty) and the participant was tasked with naming each object. A semantic cue was provided if the participant initially misperceived the picture, and a phonemic cue of the first sound of the word was presented if the participant did not provide

the correct name but did not misperceive the picture. Participants began on item 30, with a reversal rule of eight consecutive correct answers to establish basal level. The total score, out of 60, consisted of the sum of basal items, uncued correct answers, and correct answers following semantic (but not phonemic) cues.

Animal Naming. Animal Naming is a timed task of verbal category (sometimes called semantic) fluency. Participants were asked to name as many animals as they can in 60 seconds without duplication. While other category groups have been used in the past (e.g., items found in a supermarket or fruits and vegetables; Randolph, Braun, Goldberg, & Chase, 1993), Animals was selected as it is the most widely used and well-researched. Total score is the patient's correct answers.

Visuospatial functioning

WAIS-R Block Design (BD). BD is a timed test of visuospatial perception and visuoconstructional ability from the Wechsler Adult Intelligence Scale – Revised (Wechsler, 1981). Participants used cubes (with two red sides, two white sides, and 2 red/white sides) to duplicate a two dimensional red and white image in the time allotted. Adult starting points involved items with four blocks, increasing in difficulty and eventually involving nine blocks. Bonus points were allotted for quickly completing later items, with a total possible score of 51. As the Baylor ADMC longitudinal database is a decades-spanning project, the measures included have undergone periodic revision and update. For example, newer patients have been given a more modern version of BD (WAIS-III Block Design; Wechsler, 1997). In order to maintain consistency for the analyses, only the WAIS-R version was used in the present study.

Rey Complex Figure Test (RCFT), Copy. In the RCFT, copy administration, the participant was presented with a complex geometric figure and tasked with copying it as exactly as possible without rotating the stimulus or their own sheet of paper. There were 18 specific, discrete elements identified in the scoring system, and the participant was measured on their ability to reproduce both the placement and form of each element (Osterrieth, 1944), yielding a maximum score of 36 points.

Attention/executive functioning

Controlled Oral Word Association Test (COWA). The COWA is a test of verbal phonemic fluency, where the participant was asked to say as many words as they can think of in 60 seconds that started with a given letter (excluding proper nouns, numbers, and words with the same ending such as "takes," "taken," "taking") (Strauss, Sherman, & Spreen, 2006). This task was repeated for a total of three letters. While norms exist for several three letter sets, the present study utilized the most commonly used set: F-A-S. The total score was the sum of correct responses across the three trials ignoring repeated answers.

Verbal Series Attention Test (VSAT). The VSAT is a measure designed to test working memory and attention (Mahurin & Cooke, 1996). The participant was given nine tasks, including reciting the alphabet, counting backwards from 20 and backwards from 100 by threes, reciting the days of the week and months of the year both forward and backward, reciting alternating numbers and letters in numeric and alphabetical order (i.e., "1-A, 2-B… 10-J"), and indicating when they heard a target letter from a list of letters examiners read aloud. The time elapsed and errors were recorded for each task individually (except the vigilance task, which was not timed) and totaled overall. The participant was allowed a maximum of 60 seconds or 5 errors for each task. For the present study, the total timed score

and the individual timed scores for the items with the greatest working memory/executive functioning demands (100 by threes, days of the week and months of year backwards, and alternating numbers and letters) were used.

Memory

Logical Memory I (LM). LM I and II are subtests of the Wechsler Memory Scale – Revised (WMS-R; Wechsler, 1987). In LM I, the participant was read a total of two short stories and tasked with repeating each back to the examiner verbatim after they were presented. LM II began after 20-30 minute delay, and the participant was asked to repeat the stories again with little to minimal prompting. Scoring criteria were identical for each subtest: The participant was scored on their ability to recall discrete story elements, with each story worth 25 points, for a maximum of 50 points possible in each of LM I and LM II. However, due to the common observation of floor effects in AD populations for LM II, only LM I was used in the present study.

Visual Reproduction I (VR). VR I and II are also subtests of the WMS-R (Wechsler, 1987). In VR I, the participant was presented with four cards with drawings of increasingly complex geometric figures. The first three cards contained one figure, and the final contained two. After a ten second presentation and subsequent removal of each card, the participant was tasked with drawing the figure from memory as accurately as possible. VR II began after a 20-30 minute delay, and the participant was asked to draw the figures as best they could from memory. Scoring was identical for both subtests. Individual elements of each figure were scored for accuracy/proportionality. Later cards in the series were worth more points in accordance with their increasing complexity (7, 7, 9, and 18 points respectively) for a total of

41 points for each of VR I and VR II. As with LM I above, floor effects are commonly seen in AD patients for VR II. As such, only VR I was used in the present study.

Motor functioning

Finger Tapping Test (FTT). The FTT is a manual dexterity instrument which utilizes a small lever attached to a counting mechanism (Reitan & Wolfson, 1993). The participant was tasked with tapping as rapidly as possible with their index finger for 10 seconds (the dominant and non-dominant hands were tested on alternating trials to reduce fatigue). A series of three trials were performed, with short breaks between repetitions. The total scores for each hand are the average of these three trials. Only the dominant hand was used in the present study.

Neuropsychiatric and extrapyramidal symptoms

The presence of neuropsychiatric and extrapyramidal symptoms experienced were collected via structured interview during the patients' initial examination. Assessed domains were mood disturbance, anxiety, antisocial behaviors, paranoia, hallucinations (auditory, visual, olfactory), and Parkinsonisms. The total count of the reported symptoms was used, yielding a maximum score of 8.

Analyses

The primary goal of the present study was to examine the utility of the IADL pre-progression estimate. Longitudinal data can be examined with linear mixed models (LMM), which have been referred to in various contexts as mixed-effects models, hierarchical linear models, multilevel models, and independent growth curve models. LMM has many advantages over other repeated measures analyses: 1) They have frequently been used to examine unbalanced longitudinal data sets where participants have varying numbers of data

points and these data points are not collected at fixed time intervals (Armitage & Colton, 2005); 2) Missing data can be accommodated for by LMM (which is frequently the case in large datasets such as this), but a single missing data point can result in a listwise deletion of an entire participant in other analyses such as repeated measures ANOVA; 3) Subject-level predictor variables (such as ethnicity or education level) can be added as a random effect in LMM and used to determine how much of the random between-subjects variance in growth curves can be attributed to it after taking the fixed effects into account; and 4) Alternate covariance structures can be selected in LMM and compared using likelihood ratio test and information criteria, allowing selection of a covariance type that best fits one's data (West, 2009). Given the goals of the present study and the make-up of the extant database (including occasional missing data points and varied time lengths between visits), LMM was the most appropriate analysis type to utilize.

Independent growth curves utilizing LMM procedures were used to examine the basic validity of the IADL pre-progression estimate by examining the relationship between it and the actual rate of change over time in IADLs (Hypothesis 1). The first preliminary step of LMM analysis involves examining the outcome variable (IADL ratio). This unconditional mean model analysis is a one-way ANOVA with a random effect and no predictors. This analysis allows examination of the mean IADL ratio over time and how much variation is attributable to intra- and inter-individual levels. The proportion of outcome variability attributable to differences between participants is the intraclass correlation coefficient (ICC). In general, ICC below .25 indicates LMM analysis of independent growth curves may not be necessary and an ANOVA approach may be adequate (de Leeuw & Kreft, 1995). The formula for ICC is residual estimate / (residual estimate + intercept estimate).

The next preliminary step was an unconditional linear growth curve model that, in addition to examining IADL ratio change across participants, also assessed individual changes over time (Singer & Willett, 2003). If the Time variable was not significant, then individuals did not have different rates of change over time from the overall average rate of change, and the LMM analysis would have been discontinued. Provided the linear Time variable was significant, the final preliminary model was an extension of the above. Due to the fact that individual growth rates are often not strictly linear over time, a quadratic parameter was added to the prior model to investigate this. This model was the base model to which other, more elaborate models were compared.

For Hypothesis 1, IADL pre-progression and its interaction with time were added to the base model. If this time and IADL pre-progression interaction was significant, it would lend support to Hypothesis 1, that IADL pre-progression estimate is a valid predictor of future IADL ratio change.

To test whether the relevant predictor significantly predicts IADL ratio rate of change when accounting for covariates (as in Hypothesis 2 and the longitudinal portions of Hypotheses 3-6), the first step was to run the base LMM model previously described with the addition of relevant covariates as main effects. Covariates were selected amongst age at baseline, sex, education, and dementia severity at baseline (MMSE score). A covariate was initially excluded only when theoretically appropriate (e.g., excluding age as a covariate when examining whether age predicts IADL ratio decline). Significant covariates were then retained and their interaction with Time added to the next model. Finally, from that model, the remaining significant covariates and significant covariate*time interactions were retained and the predictor and its interaction with IADL pre-progression and its interaction with time

were added. If the predictor*time interaction was significant, it would lend support to the hypothesis that it is a valid predictor of IADL ratio change over time. Then the residuals from the base model and the new model were compared (using a measure of effect size common to these types of analyses, the "pseudo-R_1^2"; Singer & Willett, 2003), to see how much of the IADL ratio variance is explained by the predictor, above and beyond the influence of time and the covariates. Two models (visuospatial/visuoconstructional skills from Hypothesis 5, and neuropsychiatric symptoms from Hypothesis 6) necessitated a new base model to be created for comparison, as they had a markedly lower N's than the other models.

Regarding Hypothesis 5 (which involves neuropsychological measures as predictors): Instead of analyzing each measure individually, or all together as a single large group, a series of these analyses were performed with the measures grouped into neuropsychological domains (language, memory, visuospatial/visuoconstructional, executive functioning/attention, and motor). Raw scores were used because covariates such as age and education were already included in the model, and using normed scores such as scaled or Z scores would have essentially corrected the data for those factors twice. Further, as the tests' standardized scores were derived from different normative sources, this double correction could have influenced different tests to varying degrees depending on the quality and character of their original normative sample.

Selection of covariance type for the model is an important step in drawing accurate conclusions. The covariance type was selected by analyzing the final model with different common covariance types and comparing -2 log likelihood (-2LL), Akaike's Information Criterion (AIC), and Schwarz' Bayesian Criterion (BIC) following a procedure outlined by

Shek and Ma (2011). Lower numbers indicate better model fit, and were statistically evaluated for significant differences with chi-square tests. Covariance structures examined were unstructured (UN), compound symmetry (CS), compound symmetry: heterogeneous (CSH), and first order autoregressive (AR1), common selections for this type of data (Shek & Ma, 2009; West 2011). These information criteria and likelihood ratio were also reviewed at each step of the model building processes detailed above to ensure each successive elaboration on the base model improved fit.

In addition to hypothesizing the role that baseline information has in predicting the future decline in IADL ratio, Hypotheses 3-6 also involved the nature of the relationships between baseline variables and IADL ratios solely at the baseline time point. To test whether baseline IADL ability was associated with each of these respective baseline variables above and beyond the role of covariates, multiple regression analyses were performed for each hypothesis with the relevant covariates added as the first model of dependent variables, and the second model dependent variables were taken from each respective hypothesis (age, dementia severity, neuropsychological performance, and neuropsychiatric symptoms for Hypothesis 3-6, respectively). Lawton IADL ratio score was the predictor variable.

Results

The descriptive statistics of the non-categorical variables used are found in Table 1, and correlations between IADL pre-progression and baseline variables are found in Table 2. The normality of the distributions was examined, and when appropriate, outliers were discarded (which occurred once, for Animal Naming). Covariates were centered to aid in intercept interpretation. In order to be included in the analyses, a participant had to have a baseline score and at least one follow-up score on the appropriate measure(s). Due to floor

effects in multiple variables, time points of interest were restricted to baseline visit and six follow-ups, a common cut-off point with this data set (Doody et al., 2010; Pavlik, Doody, Massman, & Chan, 2006). The number of participants with adequate data at each visit and their respective average times since the baseline visit can be seen in Table 3.

Preliminary Analyses

To examine if LMM is an appropriate analysis type for the IADL ratio, an unconditional mean model (a one-way ANOVA with random effect and no parameters) was performed. The ICC of this model was .021486/(.021486 + .034695) = .39. This implied that approximately 39% of the total variation in IADL ratio scores was due to interindividual differences, and that LMM is appropriate.

To examine if individuals do have different rates of change over time from the overall average rate of change, an unconditional linear growth curve model (Model 1) was performed. See Table 4 for a summary of this model building process. The intercept and linear slope (time) parameters were significant, indicating that baseline IADL ratio and rate of its change over time were not static between participants in the sample: The average baseline IADL ratio was .48 ($\beta = .482$, SE = .007, $p < .001$) and annual average increase of IADL ratio score was .08 ($\beta = .083$, SE = .001, $p < .001$). This analysis also indicates that between-individual predictors can explain variability in the intercept and linear time effect as evidenced by the significance of their random errors ($p < .001$).

In order to examine if there is also a quadratic component of the growth curves, a Time*Time variable was added to the prior model (Model 2 in Table 4). Both linear and quadratic growth parameters were significant. The linear effect was positive ($\beta = .098$, SE = .003, $p < .001$), indicating that linear growth increased over time. The quadratic effect was

negative (β = - .004, SE = .0001, $p < .001$), indicating the slope of the curve decelerated over time. However, the linear change rate (.098) is markedly larger than the quadratic rate (.004). The quadratic term will be retained for future models, however, given that the model fit is significantly greater with its presence ($\chi 2$ (1) = -2572.73 - -2602.09 = 29.36, $p < .001$ for Δ -2LL; -2560.73 - -2588.05 = 27.36, $p < .001$ for Δ AIC; -2524.98 - -2546.38 = 21.40, $p < .001$ for Δ BIC). A model adding a cubic parameter was run, but was not significant. The above base model (Model 2 from Table 4) will serve as the starting point for the later longitudinal analyses.

Hypothesis 1

To test if IADL pre-progression predicts future IADL ratio decline, IADL pre-progression and its interaction with time were added to the above base model to create Model 3 in Table 4. The IADL pre-progression estimate significantly predicted rate of change over time in IADL ratio (β = - 0.11, SE = .018, $p < .001$), although importantly, the direction of the effect is the opposite of what was predicted. IADL pre-progression also significantly predicted IADL ratio scores collapsed across time (β = .597, SE = .062, $p < .001$). Comparing residuals of this model and the base model, IADL pre-progression estimates explain 3.9% of the overall within-individuals variation of IADL ratio [(.010022 - .009983)/.010022 = .0389].

In light of the above results, and in order to see if IADL pre-progression's prediction of future IADL ratio decline was more effective closer to baseline, the analysis was replicated with a restriction of time points up to three visits (baseline and one or two follow ups) as opposed to up to seven. In this restricted sample, the IADL pre-progression estimate significantly predicted rate of change over time in IADL ratio (β = - 0.13, SE = .026, $p <$

.001) (with the direction of effect similar to above, and opposite of what was predicted) and IADL ratio scores collapsed across time (β = .612, SE = .061, $p < .001$). Comparing residuals between this model and a newly created base model with this restricted range, IADL pre-progression estimates explain 9.5% of the overall within-individuals variance of the IADL ratio.

Hypothesis 2

To test whether IADL pre-progression still significantly predicts IADL ratio rate of change when including covariates, education, age at baseline, sex, and MMSE score at baseline were added (Model 2) to the base model (Model 1). Refer to Table 5 for a summary of the model building process and the final results. Education was discarded during model building, and covariate*time interactions retained for the final model were age*time and sex*time. The final model (Model 4) added IADL ratio and its interaction with time.

IADL pre-progression was a significant predictor of the linear change over time in IADL ratio ($p < 0.001$) and was significantly associated with initial IADL ratio across time points (β = 0.43, SE = 0.05, $p < 0.001$). The linear change over time was faster for individuals with lower pre-progression estimates (β = -0.10, SE = 0.18, $p < 0.001$). But again, the direct of this effect is opposite of what was predicted. IADL pre-progression (the predictor) accounted for 3.5% of the within-individuals variation in IADL ratio [(.010022-.009987)/.010022) = .03492) when taking covariates into account.

As with Hypothesis 1, this model building process was replicated with a restricted range of time points (baseline plus up to two follow ups) in order to see if IADL pre-progression's ability to predict future IADL rate decline closer to baseline when including covariates differed from the previous analysis including up to seven time points. IADL pre-

progression was a significant predictor of linear change over time in IADL ratio ($p < 0.001$) and was significantly associated with change across time points ($\beta = 0.45$, SE = 0.05, $p < 0.001$). The linear change over time was faster for individuals with lower pre-progression estimates ($\beta = -0.13$, SE = 0.03, $p < 0.001$). With this restricted time point sample, IADL pre-progression accounted for 3.8% of the within-individual variation in IADL ratio when covariates were taken into account.

Selection of covariance type for the model was performed by analyzing the model with different covariance types and comparing -2LL, AIC, and BIC, with lower numbers indicative of better model fit. Covariance structures examined were unstructured (UN), compound symmetry (CS), compound symmetry: heterogeneous (CSH), and first order autoregressive (AR1).

As presented in Table 6, the CSH and UN covariance structures yielded identical values, and were significantly lower than AR1 and CS (which were also identical) ($\chi 2$ (1) = -2662.79 - -3120.92 = 458.13, $p < .001$ for Δ -2LL; -2636.79 - -3092.92 = 484.13, $p < .001$ for Δ AIC; -2559.33 - -3009.50 = 450.17, $p < .001$ for Δ BIC). CSH was selected over UN for use in the present study because some participants' visits were not evenly spaced in time (e.g., two years between some visits instead of the normal one), and one of the assumptions of UN is that there is approximately equal time intervals between measurements.

Hypothesis 3: Age

Baseline. In order to assess the relationship between age and IADL ratio score at baseline, a multiple regression analysis was conducted with baseline age as a predictor; education, sex, and baseline MMSE score as covariates; and baseline IADL as the dependent variable. The covariates were first inserted into the model before the predictor in order to

examine its individual contribution above and beyond the covariates. The covariates were found to account for a significant amount of the IADL variability $R^2 = .34$, $F(3,781) = 134.85$, $p < .001$, and lower education, lower MMSE score, and female gender were related to higher values (and thus worse performance) on IADL ratings. In the second step of the model, age was found to account for a significant amount of the IADL variability above and beyond the covariates, R^2 change = .038, $F(1, 780) = 47.38$, $p < .001$. These results suggest that Alzheimer's patients with similar education, MMSE performance, and sex are likely to have worse IADL performance if they are older.

Longitudinal. To test whether age at baseline predicts IADL ratio rate of change when including covariates, education, sex, and MMSE score at baseline were added to the base model to create Model 2 in Table 7. Education was discarded during model building, and the only covariate*time interaction retained for the final model (Model 4) was Sex*Time.

Age at baseline was significantly associated with initial IADL ratio across time ($\beta = -0.005$, SE = 0.001, $p < 0.001$), and was a significant predictor of the linear change over time in IADL ratio ($p < 0.001$). The linear change over time was faster for individuals with age less than the mean ($\beta = -0.001$, SE = 0.0002, $p < 0.001$). However, age at baseline (the predictor) accounted for none of the within-individuals variation in IADL ratio [(.010022-.0010022)/.010022) = .00) when taking covariates and time into account. Thus, while the effects observed are significant, they are not necessarily noteworthy.

Hypothesis 4: MMSE

Baseline. In order to assess the relationship between dementia severity and IADL ratio score at baseline, a multiple regression analysis was conducted with baseline MMSE as

predictor; education, sex, and baseline age as covariates; and baseline IADL as the dependent variable. The covariates were first inserted into the model before the predictor in order to examine its individual contribution above and beyond the covariates. The covariates were found to account for a significant amount of the IADL variability, $R^2 = .114$, $F(3,781) = 33.47$, $p < .001$, and lower education, older age, and female gender were related to higher scores (and thus worse performance) on IADL ratings. In the second step of the model, MMSE was found to account for a significant amount of the IADL variability above and beyond the covariates, R^2 change = .27, $F(1, 780) = 332.89$, $p < .001$. These results suggest that Alzheimer's patients with similar education, age, and sex are likely to have worse IADL performance if they perform more poorly on the MMSE.

Longitudinal. To test whether MMSE at baseline predicts IADL ratio rate of change when including covariates, education, sex, and age at baseline were added to the base model to create Model 2 in Table 8. No covariates were discarded during model building, and the covariate*time interactions retained for the final model (Model 4) were Age*Time and Education*Time.

MMSE at baseline was significantly associated with initial IADL ratio collapsed across time ($\beta = -0.02$, SE = 0.001, $p < 0.001$). However, it was not a significant predictor of the linear change over time in IADL ratio ($p = 0.38$).

Hypothesis 5: Neuropsychological Tests

Baseline. In order to assess the relationship between neuropsychological test scores and IADL ratio score at baseline, a series of five multiple regression analyses were conducted in five domains (executive functioning, memory, language, motor, and visuospatial/visuoconstructional skills) with baseline scores as a predictors; education, sex,

baseline age, and baseline MMSE score as covariates; and baseline IADL as the dependent variable. The covariates were first inserted into the model before the predictor in order to examine its individual contribution above and beyond the covariates. The findings are presented in Table 9.

The covariates were found to account for a significant amount of the IADL variability R^2 in all models ($p < .001$), indicating that lower MMSE score, older age, and female gender were related to higher values (and thus worse performance) on baseline IADL ratings (education was not significant).

Above and beyond the covariates, motor skills (Finger Tapping-Dominant), and visuospatial/visuoconstructional skills (Block Design, Rey Copy) were not significantly predictive of IADL ratio scores. Executive functioning tasks (VSAT time and COWA) were significantly predictive of the IADL ratio after the covariates were taken into account, ($p < .006$), but only VSAT significantly contributed individually ($\beta = .078$, $p = .024$). Memory tasks (LM1, VR1) were significant ($p < .001$), with both LM1 ($\beta = -.096$, $p = .024$) and VR1 ($\beta = -.081$, $p = .007$) contributing individually. Language tasks (BNT, Animal Naming) significantly predicted IADL ratio above and beyond the covariates, but only Animal Naming contributed individually ($\beta = -.078$, $p = .028$). Of the significant relationships, all indicated that worse performances on neuropsychological tests were modestly related to worse IADL ratio scores at baseline.

Longitudinal. In order to examine the ability of baseline neuropsychological functioning to predict rate of change in IADL ratio over time, a series of five analyses in standard neuropsychological domains (executive functioning, memory, language, motor, and visuospatial/visuoconstructional skills) following the above procedures were performed

(Visuospatial/visuoconstructional skills necessitated a new base model due to a much smaller N). The results are presented in Table 10. There were no significant time*neuropsychological test interactions, though some tests were significantly associated with IADL ratio collapsed across time (VSAT, $p = .004$; Logical Memory 1, $p = .002$; Visual Reproduction 1, $p = .001$; Animal Naming, $p = .002$).

Hypothesis 6: Neuropsychiatric Symptoms

Baseline. In order to assess the relationship between neuropsychiatric symptoms and IADL ratio score at baseline, a multiple regression analysis was conducted with total neuropsychiatric symptoms at baseline as a predictor; education, sex, baseline age, and baseline MMSE as covariates; and baseline IADL as the dependent variable. The covariates were first inserted into the model before the predictor in order to examine its individual contribution above and beyond the covariates. The covariates were found to account for a significant amount of the IADL variability $R^2 = .40$, $F(4,553) = 90.22$, $p < .001$, indicating that lower education, older age, female gender, and lower MMSE scores were related to higher scores (and thus worse performance) on IADL ratings. In the second step of the model, neuropsychiatric symptom total was found to account for a significant amount of the IADL variability above and beyond the covariates, R^2 change = .032, $F(1, 552) = 30.58$, $p < .001$. These results suggest that Alzheimer's patients with similar education, age, gender, and MMSE scores are likely to have worse IADL performance if they have a greater number of neuropsychiatric symptoms.

Longitudinal. To test whether neuropsychiatric symptoms at baseline predict IADL ratio rate of change when including covariates, a new base model (Model 1) was created, as the participants with neuropsychiatric data are a smaller subset of the total sample (n = 558 as

opposed to N = 785). Refer to Table 11 for a summary of this model building process. The results of this new base model are very similar to the base model in Hypothesis 1 (see above for description).

Covariates added were education, sex, and age at baseline and MMSE score at baseline (Model 2). Education was discarded during model building, and the covariate*time interactions retained for the final model (Model 4) were and Age*Time and Sex*Time.

Neuropsychiatric symptoms at baseline were significantly associated with IADL ratio collapsed across time ($\beta = -0.02$, SE = 0.004, $p < 0.001$), and were a significant predictor of the linear change over time in IADL ratio ($p = 0.041$). The linear change over time was faster for individuals with more symptoms ($\beta = 0.002$, SE = 0.001, $p = 0.041$).

Discussion

Prior research has shown functional and cognitive decline in AD to be related, but distinct, domains (Buccione et al., 2007). While there is a large body of research examining the pattern of decline of cognitive abilities in AD (see Weintraub, Wicklund, & Salmon, 2012 for a review), functional decline is under-researched. Specifically, there would be great utility if data collected at the time of diagnosis could be used to predict future functional decline. The primary goal of the present study was to apply the pre-progression methodology (e.g., Doody, Massman, & Dunn, 2001) to IADLs, with the intention of validating it as a useful tool for predicting the future rate of decline in IADLs in AD patients (first and second hypotheses). The secondary goal was to more broadly examine the relationships between information commonly available at baseline and baseline IADLs, as well as this information's ability to predict future IADL decline (third through sixth hypotheses).

The first hypothesis was an attempt to validate the basic concept that IADL pre-progression can predict future rate of IADL decline, with higher pre-progression rates (and thus quicker decline prior to first visit) predictive of faster decline over time. This hypothesis was only partially supported. The IADL pre-progression estimate was significantly related to the linear change over time of the IADL ratio. However, lower pre-progression rates were predictive of faster decline over time, which is opposite of what was predicted. This could potentially be explained by imagining a ceiling effect on IADL ratio, with patients exhibiting higher pre-progression rates by necessity having less mathematical room in their IADL ratio score to lose in the future, thus causing annual change over time to be slower as they approach maximum impairment. An investigation of the possibility of ceiling effects was undertaken by examining the correlation between baseline IADL ratio and IADL pre-progression, $r(783) = .35$, $p < .001$, which was expected to be significant (due to baseline IADL ratio being a component of the IADL pre-progression equation) but was not large enough to warrant direct concerns about ceiling effects.

Also regarding the outcome of the first hypothesis' analyses, it should be noted that the amount of residual variance explained by the pre-progression estimate was small (3.9%). (A replication predicting rate of decline at two years after baseline yielded a larger effect size of 9.5%, but this difference disappeared when taking covariates into account.) This can partially be explained by the strength of the linear effect of time; there was not a great deal of variance in the curve of IADL change over time to be accounted for by differences between participants (ICC = 0.39). But it should be noted that in some situations, this commonly used measure of effect size, pseudo-R_1^2 (Singer & Willett, 2003), can be an underestimate: An important part of the equation is the residual variance estimate from the unconditional model,

but this value can be an underestimate (while also ascribing too much variance to the level-two variance component, time). With an underestimated initial residual, the residuals from the new models have less numeric room to indicate a difference in effect (Hox, 2002). This issue will become even more salient in interpreting the results of later hypotheses. In contrast, adding IADL pre-progression to the model also resulted in a greatly improved model fit. So while the IADL pre-progression effect size may be small, it appears to be robust.

The second hypothesis added baseline covariates to the above model, and stated that the effect would maintain even after taking these covariates into account. This hypothesis was also only partially supported. Even after taking demographics (age, education, sex) and baseline dementia severity into account, IADL pre-progression was significantly predictive of IADL ratio's linear change over time. As with the first hypothesis, however, lower pre-progression rates were predictive of faster decline over time, which was in the opposite direction than predicted. The small effect size was very slightly diminished from Hypothesis 1, but model fit was greater, indicating that the covariates in the final model were useful additions towards the goal of maximizing prediction of IADL decline. A replication of this model with restricted time points yielded very similar results, indicating that IADL pre-progression's ability to predict IADL ratio score did not vary between two and six years after baseline when taking covariates into account. In the third hypothesis, age at baseline, in the presence of the other above-mentioned covariates, was predicted to be significantly correlated with baseline IADLs, with older age related to worse IADL performance. Younger age at baseline was also predicted to be related to faster future rate of IADL decline when covariates were taken into account. The first part of the hypothesis was supported: older age

was significantly related to worse IADL performance at the baseline visit. The increase in predictive power beyond the influence of the covariates was small, however. The second part of the hypothesis was also supported, with a caveat: The significant relationship between baseline age and future IADL decline, with younger age related to faster decline, had a mathematically undetectable effect size. However, the significant findings and the improved model fit with Age's inclusion suggest that the pseudo-R^2 measure of effect size in this situation is potentially problematic, as mentioned by Hox's work (2002) above.

The fourth hypothesis predicted that greater dementia severity (measured by MMSE) at baseline (after accounting for covariates) would be related to worse baseline IADL performance, and would be predictive of faster IADL decline over time. The former was supported, with a significant positive relationship between MMSE performance and baseline IADL performance. Further, MMSE accounted for twice as much variance as the other covariates combined, even with said covariates being entered into the model first. The second part of this hypothesis was not supported: MMSE at baseline was not significantly related to the linear change over time in IADLs. This supports the contention that the functional and cognitive abilities of AD patients are at least somewhat distinct entities; while MMSE and IADLs have a robust baseline relationship, MMSE at baseline is not a useful tool for predicting IADL's change over time.

The fifth hypothesis was related to baseline neuropsychological function. It predicted that above and beyond the influence of covariates, baseline deficits in measures of executive functioning, visuospatial/visuoconstructional skills, and motor ability would each be related to worse baseline IADL performance, and predictive of faster IADL decline. It also predicted that neither memory nor language measures would be related to the baseline performance or

the future change in IADLs. Overall, this hypothesis was only modestly supported. The hypothesized baseline relationships between motor skills with IADLs were not significant. Worse performance on executive functioning and visuospatial/visuoconstructional measures were each significantly related to worse IADLs at baseline, but to a very small degree after taking covariates into account. In contrast, while both memory and language were hypothesized to not have a baseline relationship with IADLs, both domains had significant, albeit small, relationships, with worse performance related to worse IADLs. There was no support regarding the ability of the neuropsychological domains to predict future IADL decline. No measure was significantly related to the linear change in IADL ratio over time. This is a somewhat surprising result given the extant literature. Executive functioning has most consistently been shown to have a relationship with IADLs both at baseline (e.g., Marshall et al., 2011, Razani et al., 2007) and in predicting future functional decline (Cahn-Weiner et al., 2007). While the baseline relationship was supported by the present study, the longitudinal relationship was not. One possible explanation is that while the two executive functioning measures used (COWA and VSAT) do make demands on working memory/executive functioning, they are both speeded tasks with strong verbal requirements. Other skills under the executive functioning umbrella (e.g., problem solving, response monitoring, and inhibition) are tapped either indirectly or not at all by these measures. Thus, the relationship between these skills on longitudinal change in functional abilities is not well-answered by the present study. Another possibility is that using domain specific breakdowns (e.g., executive function, memory, visuospatial, etc.) of cognitive abilities to predict future decline is an under-utilized technique, and the current results are a worthwhile contribution to

the literature. The literature is decidedly mixed in other domains, so the lack of longitudinal findings in the present study is a plausible outcome.

The sixth and final hypothesis predicted a baseline relationship between neuropsychiatric and Parkinsonism symptoms and IADLs, with higher symptom count related to worse IADL performance at baseline and faster future IADL decline. The baseline relationship was supported. After taking covariates into account, higher symptom count was significantly related to IADL performance to a small degree. There was also support for the longitudinal portion of the hypothesis, with a significant relationship between higher baseline neuropsychiatric and Parkinsonism symptom count and faster IADL decline. However, while the final model resulted in a better model fit than the unconditional base model or the model with covariates, the residual variance of this final model was surprisingly greater than the unconditional model. This is an extreme example of the above mentioned limitation of the widely-used pseudo-R^2 method for measuring effect size in growth curve models. That having been said, it is unlikely that a correction for this would result in a meaningful effect size, so as with the third hypothesis, while this longitudinal relationship is significant in this sample, it is unlikely to be meaningful.

Limitations

One limitation of this study is that the basis of every analysis was prediction of IADL ratio, which was based on an informant report measure. Such a measure can introduce biases of the person completing it, and be less objective than a direct assessment of functional ability.

While LMM analyses can easily account for participants with varying numbers of longitudinal time points, 28% of the participants in this sample had only two time points.

This could lead to a reduction in granularity of the shape of the change in IADL ratio over time, and in turn lead to a reduction in the ability of baseline measures (including IADL pre-progression) to accurately predict it. Conversely, it is possible that some effects which were significant, but with very small effect sizes, were only found to be significant due to the large sample size.

Specifically regarding neuropsychological measures, there were many more measures in the dataset than were included in the present study. These were excluded for various reasons, including inconsistent measurement over the long timespan of this longitudinal dataset, changes in the version of a test given over this long duration, or inclusion (and in some cases later removal) of measures at different times as the study aged. This inconsistent presence of neuropsychological tests over time lead to a rapidly dwindling sample size when attempting to create a sample with many measures in common. In many cases, this resulted in measures being excluded from the study. Therefore, it is possible that the tests used in the present study are not good exemplars of their respective neuropsychological domains (executive functioning in particular, as noted above) in this IADL context. A blanket conclusion that a given domain is not predictive of IADL decline may be premature.

Finally, a possible limitation is that the sample in this study may not accurately represent the population of AD patients as a whole. It was homogenously Caucasian, and on average highly educated.

Implications

These results indicate that the IADL pre-progression estimate is not a valid tool for predicting the future decline in the IADLs of AD patients over time. While the significant relationship is a promising outcome, the direction of the effect (with slower pre-progression

predicting faster future decline) was in the opposite direction of what was expected by a theory-driven hypothesis. Additionally, the (possibly problematic) measure of effect size is small. Therefore, though IADL pre-progress does predict future IADL change, the model needs to be reconceptualized and refined before it can be recommended for use as an aspect of planning for an individual patient's future.

Fittingly, future studies will attempt to enhance and refine the current model of pre-progression estimates on IADL decline. For example, MMSE at baseline was the most impactful of the significant covariates, especially in the baseline portions of the present study. Therefore, MMSE pre-progression may be a fruitful addition to the model in order to control for dementia severity not only as a measure at baseline, but as an estimate of the future rate of change in dementia severity. Other possible predictors of future decline did not show promising results.

While there were baseline relationships between performance on these measures (such as neuropsychological tests and neuropsychiatric/Parkinsonism symptoms) and IADLs, these relationships drastically deteriorated when attempting to predict future change in IADLs. This implies that the trajectories of IADLs and these measures in AD may diverge. Alternatively, without a pre-progression estimate of their rate of change, baseline measures of factors that are expected to change in AD (in comparison to static information, such as demographics) may inherently be poor estimates of future change in IADLs. One future direction for this would be to compare the structures of change in IADLs (and other functional abilities) and neuropsychological information at multiple time points to examine how, if at all, these rates of change diverge (e.g., following the methodology of Tucker-Drob, 2011).

References

Aliberti, M., Kikuchi, E., Magaldi, R., Paschoal, S. M. P., & Filho, W. J. (2007). Comprehensive Geriatric Assessment in elderly outpatients with dementia. *Dementia & Neuropsychologia*, *3*, 303-310.

Alzheimer's Association (2014). Alzheimer's Disease Facts and Figures, *Alzheimer's & Dementia*, *10*(2), e47-e92. doi:10.1016/j.jalz.2014.02.001

Armitage, P., & Colton, T. (Eds.). (2005). *Encyclopedia of Biostatics.* (Vol. 4). West Sussex, England: Wiley.

Aronoff, J. M., Gonnerman, L. M., Almor, A., Arunachalam, S., Kempler, D., & Andersen, E. S. (2006). Information content versus relational knowledge: Semantic deficits in patients with Alzheimer's disease. *Neuropsychologia*, *44*(1), 21-35.

Atchison, T. B., Bradshaw, M., & Massman, P. J. (2004). Investigation of profile difference between Alzheimer's disease patients declining at different rates: examination of baseline neuropsychological data. *Archives of Clinical Neuropsychology*, *19*(8), 1007-1015. doi:10.1016/j.acn.2003.12.011

Atchison, T. B., Massman, P. J., & Doody, R. S. (2007). Baseline cognitive function predicts rate of decline in basic-care abilities of individuals with dementia of the Alzheimer's type. *Archives of Clinical Neuropsychology*, *22*(1), 99-107. doi:10.1016/j.acn.2006.11.006

Bäckman, L., Small, B. J., & Fratiglioni, L. (2001). Stability of the preclinical episodic memory deficit in Alzheimer's disease. *Brain*, *124*(1), 96-102.

Benke, T., Delazer, M., Sanin, G., Schmidt, H., Seiler, S., Ransmayr, G., & ... Schmidt, R. (2013). Cognition, gender, and functional abilities in Alzheimer's disease: How are

they related? *Journal of Alzheimer's Disease, 35*(2), 247-252. doi:10.3233/JAD-122383.

Blazer, D. G., Fillenbaum, G., & Burchett, B. (2001). The APOE-E4 allele and the risk of functional decline in a community sample of African American and White older adults. *The Journals of Gerontology: Series A: Biological Sciences and Medical Sciences, 56A*(12), M785-M789. doi:10.1093/gerona/56.12.M785

Blennow, K., Wallin, A., Ågren, H., Spenger, C., Siegfried, J., & Vanmechelen, E. (1995). Tau protein in cerebrospinal fluid: A biochemical marker for axonal degeneration in Alzheimer's disease? *Molecular and Chemical Neuropathology, 26*(3), 231-245.

Bobinski, M., de Leon, M. J., Wegiel, J., Desanti, S., Convit, A., Saint Louis, L. A., Rusinek, H., & Wisniewski, H. M. (2000). The histological validation of post mortem magnetic resonance imaging-determined hippocampal volume in Alzheimer's disease. *Neuroscience, 95*(3), 721–725.

Bondi, M. W., Monsch, A. U., Butters, N., Salmon, D. P., & Paulsen, J. S. (1993). Utility of a modified version of the Wisconsin Card Sorting Test in the detection of dementia of the Alzheimer type. *The Clinical Neuropsychologist, 7*(2), 161-170.

Boyle, P. A., Malloy, P. F., Salloway, S., Cahn-Weiner, D. A., Cohen, R., & Cummings, J. L. (2003). Executive dysfunction and apathy predict functional impairment in Alzheimer disease. *The American Journal of Geriatric Psychiatry, 11*(2), 214-221. doi:10.1176/appi.ajgp.11.2.214

Boyle, P. A., Paul, R. H., Moser, D. J., & Cohen, R. A. (2004). Executive impairments predict functional declines in vascular dementia. *The Clinical Neuropsychologist, 18*(1), 75-82. doi:10.1080/13854040490507172

Buccione, I., Perri, R. R., Carlesimo, G. A., Fadda, L. L., Serra, L. L., Scalmana, S. S., & Caltagirone, C. C. (2007). Cognitive and behavioural predictors of progression rates in Alzheimer's disease. *European Journal of Neurology*, *14*(4), 440-446. doi:10.1111/j.1468-1331.2007.01693.x

Burns, A., Jacoby, R., & Levy, R. (1991). Progression of cognitive impairment in Alzheimer's disease. *Journal of the American Geriatrics Society*, *39*(1), 39-45.

Busatto, G. F., Diniz, B. S., & Zanetti, M. V. (2008). Voxel-based morphometry in Alzheimer's disease. *Expert Reviews of Neurotherapeutics*, *8*(11), 1691-1702. doi:10.1586/14737175.8.11.1691

Cahn-Weiner, D. A., Farias, S., Julian, L., Harvey, D. J., Kramer, J. H., Reed, B. R., & ... Chui, H. (2007). Cognitive and neuroimaging predictors of instrumental activities of daily living. *Journal of the International Neuropsychological Society*, *13*(5), 747-757. doi:10.1017/S1355617707070853

Chen, P., Ratcliff, G., Belle, S. H., Cauley, J. A., DeKosky, S. T., & Ganguli, M. (2001). Patterns of cognitive decline in presymptomatic Alzheimer disease. *Archives of General Psychiatry*, *58*(9), 853-858. doi:10.1001/archpsyc.58.9.853

Chen, S. T., Sultzer, D. L., Hinkin, C. H., Mahler, M. E., & Cummings, J. L. (1998). Executive dysfunction in Alzheimer's disease: Association with neuropsychiatric symptoms and functional impairment. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *10*(4), 426-432.

Cherry, B. J., Buckwalter, J. G., & Henderson, V. W. (2002). Better preservation of memory span relative to supraspan immediate recall in Alzheimer's disease. *Neuropsychologia*, *40*(7), 846-852.

Chételat, G., Landeau, B., Eustache, F., Mezenge, F., Viader, F., de La Sayette, V., ... & Baron, J. C. (2005). Using voxel-based morphometry to map the structural changes associated with rapid conversion in MCI: a longitudinal MRI study. *Neuroimage*, *27*(4), 934-946.

Choi, J., Myung, W., Chung, J., Kang, H., Na, D. L., Kim, S., & ... Kim, D. (2013). Association between functional impairment, depression, and extrapyramidal signs in neuroleptic-free patients with Alzheimer disease. *Journal of Geriatric Psychiatry and Neurology*, *26*(3), 144-150. doi:10.1177/0891988713490993

Cronin-Golomb, A., & Amick, M. (2001). Spatial abilities in aging, Alzheimer's disease, and Parkinson's disease. In F. Boller & S. Cappa (Eds.) *Handbook of neuropsychology, vol. 6: Aging and dementia,* (2nd ed.) (pp. 119–143). Amsterdam, Netherlands: Elsevier.

Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., & Gornbein, J. (1994). The Neuropsychiatric Inventory comprehensive assessment of psychopathology in dementia. *Neurology*, *44*(12), 2308-2308.

Delis, D. C., Massman, P. J., Butters, N., Salmon, D. P., Cermak, L. S., & Kramer, J. H. (1991). Profiles of demented and amnesic patients on the California Verbal Learning Test: Implications for the assessment of memory disorders. *Psychological Assessment: A Journal of Consulting and Clinical Psychology*, *3*(1), 19.

Desikan, R. S., Cabral, H. J., Settecase, F., Hess, C. P., Dillon, W. P., Glastonbury, C. M., ... & Fischl, B. (2010). Automated MRI measures predict progression to Alzheimer's disease. *Neurobiology of Aging*, *31*(8), 1364-1374. doi:10.1016/j.neurobiolaging.2010.04.023.

Doody, R. S., Dunn, J. K., Huang, E., Azher, S., & Kataki, M. (2004). A method for estimating duration of illness in Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders, 17*(1-2), 1-4. doi:10.1159/000074078

Doody, R. S., Massman, P. J., & Dunn, K. (2001). A method for estimating progression rates in Alzheimer disease. *Archives of Neurology, 58*(3), 449-454. doi:10.1001/archneur.58.3.449

Doody, R., Pavlik, V., Massman, P., Kenan, M., Yeh, S., Powell, S., ... & Chan, W. (2005). Changing patient characteristics and survival experience in an Alzheimer's center patient cohort. *Dementia and Geriatric Cognitive Disorders*, *20*(2-3), 198-208. doi:10.1159/000087300

Doody, R. S., Pavlik, V., Massman, P., Rountree, S., Darby, E., & Chan, W. (2010). Predicting progression of Alzheimer's disease. *Alzheimer's Research and Therapy*, *2*, 2-10.

Drachman, D. A., O'Donnell, B. F., Lew, R. A., & Swearer, J. M. (1990). The prognosis in Alzheimer's disease. 'How far' rather than 'how fast' best predicts the course. *Archives of Neurology, 47*(8), 851-856.

Evans, M. C., Barnes, J., Nielsen, C., Kim, L. G., Clegg, S. L., Blair, M., ... & Fox, N. C. (2010). Volume changes in Alzheimer's disease and mild cognitive impairment: cognitive associations. *European Radiology*, *20*(3), 674-682. doi:10.1007/s00330-009-1581-5.

Farias, S., Harrell, E., Neumann, C., & Houtz, A. (2003). The relationship between neuropsychological performance and daily functioning in individuals with

Alzheimer's disease: Ecological validity of neuropsychological tests. *Archives of Clinical Neuropsychology*, *18*(6), 655-672. doi:10.1016/S0887-6177(02)00159-2

Farias, S., Mungas, D., Reed, B., Haan, M. N., & Jagust, W. J. (2004). Everyday functioning in relation to cognitive functioning and neuroimaging in community-dwelling Hispanic and Non-Hispanic older adults. *Journal of the International Neuropsychological Society*, *10*(3), 342-354. doi:10.1017/S1355617704103020

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189-198.

Ford, G. R., Haley, W. E., Thrower, S. L., West, C. C., & Harrell, L. E. (1996). Utility of Mini-Mental State Exam scores in predicting functional impairment among White and African American dementia patients. *The Journals of Gerontology: Series A: Biological Sciences and Medical Sciences*, *51A*(4), M185-M188. doi:10.1093/gerona/51A.4.M185

Foster, J. K., Behrmann, M., & Stuss, D. T. (1999). Visual attention deficits in Alzheimer's disease: simple versus conjoined feature search. *Neuropsychology*, *13*(2), 223.

Frisoni, G. B., Fox, N. C., Jack, C. R., Scheltens, P., & Thompson, P. M. (2010). The clinical use of structural MRI in Alzheimer disease. *Nature Reviews Neurology*, *6*(2), 67-77. doi:10.1038/nrneurol.2009.215.

Gaugler, J. E., Kane, R. L., & Kane, R. A. (2002). Family care for older adults with disabilities: Toward more targeted and interpretable research. *The International Journal of Aging & Human Development*, *54*(3), 205-231. doi:10.2190/FACK-QE61-Y2J8-5L68

Giovannetti, T., Bettcher, B., Brennan, L., Libron, D. J., Kessler, R. K., & Duey, K. (2008). Coffee with jelly or unbuttered toast: Commissions and omissions are dissociable aspects of everyday action impairment in Alzheimer's disease. *Neuropsychology, 22*(2), 235-245. doi:10.1037/0894-4105.22.2.235

Gitlin, L. N. & Schulz, R. (2012). Family caregiving of older adults. In: R. T. Prohaska, L. A. Anderson, & R. H. Binstock (Eds.), *Public health for an aging society* (pp. 181-204). Baltimore, MD.: The Johns Hopkins University Press.

Golden, C. J. (1978). *Stroop Color and Word Test.* Chicago: Stoelting.

Goldstein, G., McCue, M., Rogers, J., & Nussbaum, P. D. (1992). Diagnostic differences in memory test based predictions of functional capacity in the elderly. *Neuropsychological Rehabilitation*, *2*(4), 307-317. doi:10.1080/09602019208401416

Goodglass, H. & Kaplan, E. F. (1983). *The assessment of aphasia and related disorders.* (2nd ed.) Philadelphia, PA: Lea & Febiger.

Green, C. R., Mohs, R. C., Schmeidler, J., & Aryan, M. (1993). Functional decline in Alzheimer's disease: A longitudinal study. *Journal of the American Geriatrics Society*, *41*(6), 654-661.

Hämäläinen, A., Tervo, S., Grau-Olivares, M., Niskanen, E., Pennanen, C., Huuskonen, J., ... & Soininen, H. (2007). Voxel-based morphometry to detect brain atrophy in progressive mild cognitive impairment. *Neuroimage*, *37*(4), 1122-1131.

Hancock, P. P., & Larner, A. J. (2007). The diagnosis of dementia: Diagnostic accuracy of an instrument measuring activities of daily living in a clinic-based population. *Dementia and Geriatric Cognitive Disorders*, *23*(3), 133-139. doi:10.1159/000097994

Hardy, J., & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science, 297*(5580), 353-356.

Hebert, L. E. Beckett, L. A., Scherr, P. A., & Evans, D. A. (2001). Annual incidence of Alzheimer disease in the United States projected to the years 2000 through 2050. *Alzheimer's Disease and Associated Disorders, 15*(4), 169–73.

Hebert, L. E., Scherr, P. A., Bienias, J. L., Bennett, D. A., & Evans, D. A. (2003). Alzheimer Disease in the US Population. *Archives of Neurology, 60*(8), 1119-1122. doi:10.1001/archneur.60.8.1119

Hebert, L. E., Weuve, J., Scherr, P. A., & Evans, D. A. (2013). Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology, 80*(19), 1778-1783. doi:10.1212/WNL.0b013e31828726f5

den Heijer, T., Geerlings, M. I., Hoebeek, F. E., Hofman, A., Koudstaal, P. J., & Breteler, M. M. (2006). Use of hippocampal and amygdalar volumes on magnetic resonance imaging to predict dementia in cognitively intact elderly people. *Archives of General Psychiatry, 63*(1), 57-62.

Hesse, C., Rosengren, L., Andreasen, N., Davidsson, P., Vanderstichele, H., Vanmechelen, E., & Blennow, K. (2001). Transient increase in total tau but not phospho-tau in human cerebrospinal fluid after acute stroke. *Neuroscience Letters, 297*(3), 187-190.

Hodges, J. R., Salmon, P., & Butters, N. (1991). The nature of the naming deficit in Alzheimer's and Huntington's disease. *Brain, 114*(4), 1547-1558

Hokoishi, K., Ikeda, M., Maki, N., Nomura, M., Torikawa, S., Fujimoto, N., & ... Tanabe, H. (2001). Interrater reliability of the Physical Self-Maintenance Scale and the Instrumental Activities of Daily Living Scale in a variety of health professional

representatives. *Aging & Mental Health*, *5*(1), 38-40. doi:10.1080/13607860020020627

Honea, R. A., Swerdlow, R. H., Vidoni, E. D., & Burns, J. M. (2011). Progressive regional atrophy in normal adults with a maternal history of Alzheimer disease. *Neurology*, *76*(9), 822-829. doi:10.1212/WNL.0b013e31820e7b74.

Hope, T., Keene, J., Gedling, K., Fairburn, C. G., & Jacoby, R. (1998). Predictors of institutionalization for people with dementia living at home with a carer. *International Journal of Geriatric Psychiatry*, *13*(10), 682-690. doi:10.1002/(SICI)1099-1166(1998100)13:10<682::AID-GPS847>3.0.CO;2-Y

Howieson, D. B., Carlson, N. E., Moore, M. M., Wasserman, D., Abendroth, C. D., Payne-Murphy, J., & Kaye, J. A. (2008). Trajectory of mild cognitive impairment onset. *Journal of the International Neuropsychological Society*, *14*(02), 192-198. doi:10.1017/S1355617708080375.

Hox, J. J. (2010). *Multilevel analysis: Techniques and applications.* (2nd ed.) Routledge, New York.

Hua, X., Hibar, D. P., Lee, S., Toga, A. W., Jack Jr, C. R., Weiner, M. W., & Thompson, P. M. (2010). Sex and age differences in atrophic rates: an ADNI study with n=1368 MRI scans. *Neurobiology of Aging*, *31*(8), 1463-1480. doi:10.1016/j.neurobiolaging.2010.04.033.

Hughes, C. P., Berg, L., Danziger, W. L., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for the staging of dementia. *The British Journal of Psychiatry*, *140*(6), 566-572.

Hurd, M. D., Martorell, P., Delavande, A., Mullen, K. J., & Langa, K. M. (2013). Monetary costs of dementia in the United States. *The New England Journal of Medicine, 368*(14), 1326-1334. doi:10.1056/NEJMsa1204629.

Jack Jr, C. R., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., ... & Trojanowski, J. Q. (2013). Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *The Lancet Neurology, 12*(2), 207-216. doi:10.1016/S1474-4422(12)70291-0.

Jack Jr, C. R., Knopman, D. S., Jagust, W. J., Shaw, L. M., Aisen, P. S., Weiner, M. W., ... & Trojanowski, J. Q. (2010). Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *The Lancet Neurology, 9*(1), 119-128. doi:10.1016/S1474-4422(09)70299-6.

Jacobs, D., Sano, M., Marder, K., Bell, K., Bylsma, F., Lafleche, G., ... & Stern, Y. (1994). Age at onset of Alzheimer's disease: relation to pattern of cognitive dysfunction and rate of decline. *Neurology, 44*(7), 1215-1220.

Kahle-Wrobleski, K., Coley, N., Lepage, B., Cantet, C., Vellas, B., & Andrieu, S. (2014). Understanding the complexities of functional ability in Alzheimer's disease: More than just basic and instrumental factors. *Current Alzheimer Research, 11*(4), 357-366.

Kaplan, E. F., Goodglass, H., & Weintraub, S. (1983). *The Boston Naming Test* (2nd ed.). Philadelphia, PA: Lea & Febiger.

Karagiozis, H., Gray, S., Sacco, J., Shapiro, M., & Kawas, C. (1998). The Direct Assessment of Functional Abilities (DAFA): A comparison to an indirect measure of instrumental activities of daily living. *The Gerontologist, 38*(1), 113-121. doi:10.1093/geront/38.1.113

Karas, G., Sluimer, J., Goekoop, R., Van Der Flier, W., Rombouts, S. A. R. B., Vrenken, H., ... & Barkhof, F. (2008). Amnestic mild cognitive impairment: structural MR imaging findings predictive of conversion to Alzheimer disease. *American Journal of Neuroradiology*, *29*(5), 944-949. doi:10.3174/ajnr.A0949.

Kaufer, D. I., Cummings, J. L., Ketchel, P., Smith, V., MacMillan, A., Shelley, T., ... & DeKosky, S. T. (2000). Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *12*(2), 233-239.

Kleiman, T., Zdanys, K., Black, B., Rightmer, T., Grey, M., Garman, K., & ... van Dyck, C. (2006). Apolipoprotein E ε4 Allele Is Unrelated to Cognitive or Functional Decline in Alzheimer's Disease: Retrospective and Prospective Analysis. *Dementia and Geriatric Cognitive Disorders*, *22*(1), 73-82. doi:10.1159/000093316

Klunk, W. E., Engler, H., Nordberg, A., Wang, Y., Blomqvist, G., Holt, D. P., ... & Långström, B. (2004). Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Annals of Neurology*, *55*(3), 306-319.

Lafleche, G., & Albert, M. S. (1995). Executive function deficits in mild Alzheimer's disease. *Neuropsychology*, *9*(3), 313.

Lawton, M., & Brody, E. M. (1969). Assessment of older people: Self-maintaining and instrumental activities of daily living. *The Gerontologist*, *9*(3, Pt 1), 179-186. doi:10.1093/geront/9.3_Part_1.179

Lechowski, L. L., Benoit, M. M., Chassagne, P. P., Vedel, I. I., Tortrat, D. D., Teillet, L. L., & Vellas, B. B. (2009). Persistent apathy in Alzheimer's disease as an independent

factor of rapid functional decline: The REAL longitudinal cohort study. *International Journal of Geriatric Psychiatry*, *24*(4), 341-346. doi:10.1002/gps.2125

de Leeuw, J., & Kreft, I. G. (1995). Questioning multilevel models. *Journal of Educational and Behavioral Statistics*, *20*(2), 171-189. doi:10.2307/1165355

Levy, M. L., Cummings, J. L., Fairbanks, L. A., & Bravi, D. (1996). Longitudinal assessment of symptoms of depression, agitation, and psychosis in 181 patients with Alzheimer's disease. *The American Journal of Psychiatry*, *153*(11), 1438-1443.

Lopez, O. L., Wisnieski, S. R., Becker, J. T., Boller, F., & DeKosky, S. T. (1997). Extrapyramidal signs in patients with probable Alzheimer disease. *Archives of Neurology, 54*(8), 969-975. doi:10.1001/archneur.1997.00550200033007

Mahurin, R. K. & Cooke, N. (2007). Verbal series attention test: Clinical utility in the assessment of dementia. *The Clinical Neuropsychologist, 10*(1), 43-53. doi:10.1080/13854049608406662

Marshall, G. A., Rentz, D. M., Frey, M. T., Locascio, J. J., Johnson, K. A., & Sperling, R. A. (2011). Executive function and instrumental activities of daily living in mild cognitive impairment and Alzheimer's disease. *Alzheimer's & Dementia*, *7*(3), 300-308. doi:10.1016/j.jalz.2010.04.005

Mayeux, R., Stern, Y., & Spanton, S. (1985). Heterogeneity in dementia of the Alzheimer type: evidence of subgroups. *Neurology, 35*(4), 453-461.

McCue, M., Rogers, J. C., & Goldstein, G. (1990). Relationships between neuropsychological and functional assessment in elderly neuropsychiatric patients. *Rehabilitation Psychology*, *35*(2), 91-99. doi:10.1037/h0079052

McDougall, G. J., Becker, H., Vaughan, P. W., Acee, T. W., & Delville, C. L. (2010). The Revised Direct Assessment of Functional Status for independent older adults. *The Gerontologist*, *50*(3), 363-370. doi:10.1093/geront/gnp139

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, *34*(7), 939-939. doi:10.1212/WNL.34.7.939

Mok, W. W., Chu, L. W., Chung, C. P., Chan, N. Y., & Hui, S. L. (2004). The relationship between non-cognitive symptoms and functional impairment in Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *19*(11), 1040-1046. doi:10.1002/gps.1207

Monsch, A. U., Bondi, M. W., Butters, N., Salmon, D. P., Katzman, R., & Thal, L. J. (1992). Comparisons of verbal fluency tasks in the detection of dementia of the Alzheimer type. *Archives of Neurology*, *49*(12), 1253-1258. doi:10.1001/archneur.1992.005303600510173

Morrison, J. H., Hof, P. R., & Bouras, C. (1991). An anatomic substrate for visual disconnection in Alzheimer's disease. In J. Growdon, S. Corkin, E. Ritter-Walker, & R. J. Wurtman (Eds.). *Aging and Alzheimer's disease: Sensory systems, neuronal growth, and neuronal metabolism* (pp. 36-43). New York, NY: New York Academy of Sciences.

Mortimer, J. A., Ebbitt, B., Jun, S., & Finch, M. D. (1992). Predictors of cognitive and functional progression in patients with probable Alzheimer's disease. *Neurology*, *42*(9), 1689-1696.

Ng, T., Niti, M., Chiam, P., & Kua, E. (2006). Physical and Cognitive Domains of the Instrumental Activities of Daily Living: Validation in a Multiethnic Population of Asian Older Adults. *The Journals of Gerontology: Series A: Biological Sciences and Medical Sciences*, *61A*(7), 726-735. doi:10.1093/gerona/61.7.726

Oddo, S., Caccamo, A., Tran, L., Lambert, M. P., Glabe, C. G., Klein, W. L., & LaFerla, F. M. (2006). Temporal profile of amyloid-β (Aβ) oligomerization in an in vivo model of Alzheimer disease A link between Aβ and tau pathology. *Journal of Biological Chemistry*, *281*(3), 1599-1604.

Ornstein, K., & Gaugler, J. E. (2012). The problem with 'problem behaviors': A systematic review of the association between individual patient behavioral and psychological symptoms and caregiver depression and burden within the dementia patient–caregiver dyad. *International Psychogeriatrics*, *24*(10), 1536-1552. doi:10.1017/S1041610212000737

Öst, M., Nylén, K., Csajbok, L., Öhrfelt, A. O., Tullberg, M., Wikkelsö, C., ... & Nellgård, B. (2006). Initial CSF total tau correlates with 1-year outcome in patients with traumatic brain injury. *Neurology*, *67*(9), 1600-1604.

Osterrieth, P. A. (1944). Le test de copie d'une figure complexe. *Archives de Psychologie*, *30*, 206-356.

Palmer, K., Lupo, F., Perri, R., Salamone, G., Fadda, L., Caltagirone, C., ... & Cravello, L. (2011). Predicting disease progression in Alzheimer's disease: The role of neuropsychiatric syndromes on functional and cognitive decline. *Journal of Alzheimer's Disease, 24,* 35-45. doi:10.3233/JAD-2010-101836.

Pavlik, V. N., Doody, R. S., Massman, P. J., & Chan, W. (2006). Influence of premorbid IQ and education on progression of Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *22*, 367-377. doi:10.1159/000095640

Peacock, S. C. (2013). The experience of providing end-of-life care to a relative with advanced dementia: An integrative literature review. *Palliative Support Care, 11*(2), 155-68. doi:10.1017/S1478951512000831.

Pereira, F. S., Yassuda, M. S., Oliveira, A. M., & Forlenza, O. V. (2008). Executive dysfunction correlates with impaired functional status in older adults with varying degrees of cognitive impairment. *International Psychogeriatrics*, *20*(6), 1104-1115. doi:10.1017/S1041610208007631

Perry, R. J., & Hodges, J. R. (1999). Attention and executive deficits in Alzheimer's disease: A critical review. *Brain*, *122*(3), 383-404.

Pinquart, M., & Sörensen, S. (2003). Associations of stressors and uplifts of caregiving with caregiver burden and depressive mood: A meta-analysis. *The Journals of Gerontology: Series B: Psychological Sciences and Social Sciences*, *58B*(2), 112-128. doi:10.1093/geronb/58.2.P112

Randolph, C., Braun, A. R., Goldberg, T. E., & Chase, T. N. (1993). Semantic fluency in Alzheimer's, Parkinson's, and Huntington's disease: Dissociation of storage and retrieval failures. *Neuropsychology*, *7*(1), 82. doi:10.1037/0894-4105.7.1.82

Razani, J., Casas, R., Wong, J. T., Lu, P., Alessi, C., & Josephson, K. (2007). Relationship between executive functioning and activities of daily living in patients with relatively mild dementia. *Applied Neuropsychology*, *14*(3), 208-214. doi:10.1080/09084280701509125

Razani, J., Kakos, B., Orieta-Barbalace, C., Wong, J. T., Casas, R., Lu, P., & ... Josephson, K. (2007). Predicting caregiver burden from daily functional abilities of patients with mild dementia. *Journal of the American Geriatrics Society*, *55*(9), 1415-1420. doi:10.1111/j.1532-5415.2007.01307.x

Razani, J., Wong, J. T., Dafaeeboini, N., Edwards-Lee, T., Lu, P., Alessi, C., & Josephson, K. (2009). Predicting everyday functional abilities of dementia patients with the Mini-Mental State Examination. *Journal of Geriatric Psychiatry and Neurology*, *22*(1), 62-70. doi:10.1177/0891988708328217

Reed, B. R., Jagust, W. J., & Seab, J. (1989). Mental status as a predictor of daily function in progressive dementia. *The Gerontologist*, *29*(6), 804-807. doi:10.1093/geront/29.6.804

Reiman, E. M., Uecker, A., Caselli, R. J., Lewis, S., Bandy, D., De Leon, M. J., ... & Thibodeau, S. N. (1998). Hippocampal volumes in cognitively normal persons at genetic risk for Alzheimer's disease. *Annals of Neurology*, *44*(2), 288-291.

Reitan, R. M. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills*, *8*(3), 271-276.

Reitan, R. M. & Wolfson, D. (1993). *The Halstead-Reitan Neuropsychological Test Battery: Theory and clinical applications* (2nd ed.). Tucson, AZ: Neuropsychology Press.

Risacher, S. L., Saykin, A. J., Wes, J. D., Shen, L., Firpi, H. A., & McDonald, B. C. (2009). Baseline MRI predictors of conversion from MCI to probable AD in the ADNI cohort. *Current Alzheimer Research*, *6*(4), 347-361.

Risacher, S. L., Shen, L., West, J. D., Kim, S., McDonald, B. C., Beckett, L. A., ... & Saykin, A. J. (2010). Longitudinal MRI atrophy biomarkers: relationship to conversion in the

ADNI cohort. *Neurobiology of Aging, 31*(8), 1401-1418. doi:10.1016/j.neurobiolaging.2010.04.029.

Rohrer, D., Wixted, J. T., Salmon, D. P., & Butters, N. (1995). Retrieval from semantic memory and its implications for Alzheimer's disease. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 21*(5), 1127- 1139. doi:10.1037/0278-7393.21.5.1127

Rusinek, H., De Santi, S., Frid, D., Tsui, W. H., Tarshish, C. Y., Convit, A., & de Leon, M. J. (2003). Regional brain atrophy rate predicts future cognitive decline: 6-year longitudinal MR imaging study of normal aging. *Radiology, 229*(3), 691-696.

Salmon, D. P. (2000). Disorders of memory in Alzheimer's disease. In L. S. Cermak (Ed.). *Handbook of neuropsychology: Vol 2: Memory and its disorders* (2nd ed.). (pp. 155-195). Amsterdam, Netherlands: Elsevier Science Publishers B.V.

Schmeidler, J., Mohs, R. C., & Aryan, M. (1998). Relationship of disease severity to decline on specific cognitive and functional measures in Alzheimer disease. *Alzheimer Disease and Associated Disorders, 12*(3), 146-151. doi:10.1097/00002093-199809000-00005

Schubert, C. C., Boustani, M., Callahan, C. M., Perkins, A. J., Hui, S., & Hendrie, H. C. (2008). Acute care utilization by dementia caregivers within urban primary care practices. *Journal of General Internal Medicine, 23*(11), 1736-1740. doi:10.1007/s11606-008-0711-0

Schuff, N., Woerner, N., Boreta, L., Kornfield, T., Shaw, L. M., Trojanowski, J. Q., ... & Weiner, M. W. (2009). MRI of hippocampal volume loss in early Alzheimer's disease

in relation to ApoE genotype and biomarkers. *Brain, 132*(4), 1067-1077. doi:10.1093/brain/awp007.

Schulz, R., Belle, S. H., Czaja, S. J., McGinnis, K. A., Stevens, A., & Zhang, S. (2004). Long-term care placement of dementia patients and caregiver health and well-being. *Journal of the American Medical Association, 292*(8), 961-967.

Schwartz, M. F., Segal, M., Veramonti, T., Ferraro, M., & Buxbaum, L. J. (2002). The Naturalistic Action Test: A standardised assessment for everyday action impairment. *Neuropsychological Rehabilitation, 12*(4), 311-339. doi:10.1080/09602010244000084

Selkoe, D. J. (2002). Alzheimer's disease is a synaptic failure. *Science, 298*(5594), 789-791. doi:10.1126/science.1074069

Severson, M. A., Smith, G. E., Tangalos, E. G., & Petersen, R. C. (1994). Patterns and predictors of institutionalization in community-based dementia patients. *Journal of the American Geriatrics Society, 42*(2), 181-185.

Shaw, L. M., Vanderstichele, H., Knapik-Czajka, M., Clark, C. M., Aisen, P. S., Petersen, R. C., ... & Trojanowski, J. Q. (2009). Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Annals of Neurology, 65*(4), 403-413. doi:10.1002/ana.21610.

Shek, D. T.,& Ma, C. M. (2011). Longitudinal data analyses using linear mixed models in SPSS: Concepts, procedures and illustrations. *The Scientific World Journal*, *11*, 42-76. doi:10.1100/tsw.2011.2

Sikkes, S. M., de Lange-de Klerk, E. M., Pijnenburg, Y. L., Scheltens, P. P., & Uitdehaag, B. J. (2009). A systematic review of Instrumental Activities of Daily Living scales in

dementia: Room for improvement. *Journal of Neurology, Neurosurgery & Psychiatry*, *80*(1), 7-12. doi:10.1136/jnnp.2008.155838

Singer, J.D. and Willett, J.B. (2003). *Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence.* Oxford Press, New York.

Skurla, E., Rogers, J. C., & Sunderland, T. (1988). Direct assessment of activities of daily living in Alzheimer's disease: A controlled study. *Journal of the American Geriatrics Society, 36*(2), 97-103.

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., ... & Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, *7*(3), 280-292. doi:10.1016/j.jalz.2011.03.003.

Starkstein, S. E., Jorge, R. R., Mizrahi, R. R., & Robinson, R. G. (2006). A prospective longitudinal study of apathy in Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 77*(1), 8-11. doi:10.1136/jnnp.2005.069575

Stern, Y., Albert, M. M., Brandt, J. J., Jacobs, D. M., Tang, M. X., Marder, K. K., & ... Bylsma, F. F. (1994). Utility of extrapyramidal signs and psychosis as predictors of cognitive and functional decline, nursing home admission, and death in Alzheimer's disease: Prospective analyses from the Predictors Study. *Neurology, 44*(12), 2300-2307. doi:10.1212/WNL.44.12.2300

Stern, Y., Hesdorffer, D., Sano, M., & Mayeux, R. (1990). Measurement and prediction of functional capacity in Alzheimer's disease. *Neurology, 40*(1), 8-14. doi:10.1159/000138633

Strauss, E., Sherman, E. S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary* (3rd ed.). New York, NY: Oxford University Press.

Tales, A., Butler, S. R., Fossey, J., Gilchrist, I. D., Jones, R. W., & Troscianko, T. (2002). Visual search in Alzheimer's disease: a deficiency in processing conjunctions of features. *Neuropsychologia*, *40*(12), 1849-1857.

Tondelli, M., Wilcock, G. K., Nichelli, P., De Jager, C. A., Jenkinson, M., & Zamboni, G. (2012). Structural MRI changes detectable up to ten years before clinical Alzheimer's disease. *Neurobiology of Aging*, *33*(4), 825-36. doi:10.1016/j.neurobiolaging.2011.05.018

Tucker-Drob, E. M. (2011). Neurocognitive functions and everyday functions change together in old age. *Neuropsychology*, *25*(3), 368. doi:10.1037/a0022348

Vetter, P. H., Krauss, S., Steiner, O., Kropp, P., Möller, W. D., Moises, H. W., & Köller, O. (1999). Vascular dementia versus dementia of Alzheimer's type: Do they have differential effects on caregiver's burden?. *The Journals of Gerontology: Series B: Psychological Sciences and Social Sciences*, *54B*(2), S93-S98. doi:10.1093/geronb/54B.2.S93

Vitaliano, P. P., Zhang, J., & Scanlan, J. M. (2003). Is Caregiving Hazardous to One's Physical Health? A Meta-Analysis. *Psychological Bulletin*, *129*(6), 946-972. doi:10.1037/0033-2909.129.6.946

Weiner, M. W., Veitch, D. P., Aisen, P. S., Beckett, L. A., Cairns, N. J., Green, R. C., ... & Trojanowski, J. Q. (2013). The Alzheimer's Disease Neuroimaging Initiative: A

review of papers published since its inception. *Alzheimer's & Dementia, 9*(5), e111-e194. doi:10.1016/j.jalz.2013.05.1769.

Weintraub, S., Wicklund, A. H., & Salmon, D. P. (2012). The neuropsychological profile of Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine*, *2*(4). 1-18. doi:10.1101/cshperspect.a006171

Wechsler, D. (1981). *The WAIS-R manual.* New York, NY: The Psychological Corporation.

Wechsler, D. (1987). *Wechsler Memory Scale-Revised manual.* San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1997). *The Wechsler Adult Intelligence Scale -- III.* San Antonio, TX: The Psychological Corporation.

West, B. T. (2009). Analyzing longitudinal data with the linear mixed models procedure in SPSS. *Evaluation & the Health Professions*, *32*(3), 207-228. doi:10.1177/0163278709338554

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1983). Development and validation of a geriatric depression screening scale: a preliminary report. *Journal of Psychiatric Research*, *17*(1), 37-49.

Table 1

Descriptive Statistics of Baseline Variables

	N	Mean	SD	Minimum	Maximum
IADL ratio	785	0.47	0.21	0.06	0.97
IADL pre-progression	785	0.16	0.11	0.02	0.77
MMSE	785	21.59	4.74	10	30
Age	785	74.10	8.39	44	93
Education	783	14.21	3.30	0	29
Controlled Oral Word Association	751	23.85	11.90	0	65
Verbal Series Attention Test-Time (Sec)	783	139.60	72.90	0	280
Logical Memory I	777	7.25	5.29	0	28
Visual Reproduction I	769	14.90	8.08	0	37
Boston Naming Test	774	39.61	13.80	4	60
Animal Naming	777	8.86	4.46	0	27
Finger Tapping (dominant hand)	757	38.59	12.20	0	69
Block Design (WAIS-R)	237	12.70	8.10	0	32
Rey Complex Figure Test - Copy	237	25.29	8.61	0	36
Neuropsychiatric and Parkinsonism symptom total	558	6.13	1.59	1	8

Table 2

Correlations Between IADL Pre-progression and Baseline Variables

	N	R	P value
IADL ratio	785	0.347	$p < .001$
MMSE	785	-0.114	$p = .001$
Age	785	0.084	$p = .019$
Education	783	-0.100	$p = .005$
Sex	785	0.129	$p < .001$
Controlled Oral Word Association	751	-0.096	$p = .009$
Verbal Series Attention Test	783	0.127	$p < .001$
Logical Memory I	777	-0.064	$p = .074$
Visual Reproduction I	769	-0.148	$p < .001$
Boston Naming Test	774	-0.004	$p = .955$
Animals	777	-0.117	$p = .001$
Finger Tapping (dominant hand)	757	-0.153	$p < .001$
Block Design (WAIS-R)	237	-0.052	$p = .305$
Rey Complex Figure Test - Copy	237	-0.018	$p = .784$
Neuropsychiatric and Parkinsonism symptom total	558	-0.085	$p = .044$

Table 3

Number of Participants at Each Visit and Average Time Since Baseline (Visit 1)

Visit	N	M (SD)
1	785	
2	785	1.21 (0.50)
3	562	2.35 (0.64)
4	392	3.39 (0.72)
5	249	4.37 (0.62)
6	152	5.39 (0.62)
7	88	6.52 (0.79)

Table 4

Fixed Effects Estimates (Top), Estimates of Covariance Parameters (Middle), and Information Criteria (Bottom) for Models Predicting IADL Ratio Decline with IADL Pre-progression Estimates (Hypothesis 1)

Parameter	Model 1	Model 2	Model 3
Intercept	0.48 (0.01)***	0.474 (0.008)***	0.38 (0.01)***
Time	0.08 (0.002)***	0.098 (0.004)***	0.12 (0.004)***
Time_sq		-0.004 (0.001)***	-0.004 (0.001)***
IADL Pre-progression			0.60 (0.06)***
Time*IADL Pre-progression			-0.11 (0.02)***
Residual	0.009950 (0.0004)***	0.010022 (0.004)***	0.009983 (.0004)***
Intercept+Time			
Var: Intercept	0.04 (0.002)***	0.04 (0.002)***	0.03 (0.002)***
Var: Time	0.001 (0.0001)***	0.001 (0.0001)***	0.001(0.0001)***
CSH rho	-0.31 (0.06)***	-0.36 (0.06)***	-0.26 (0.06)***
-2LL	-2572.73	-2602.09	-2696.44
AIC	-2560.73	-2588.09	-2678.44
BIC	-2524.98	-2546.38	-2624.82

Note. Standard errors are in parentheses. -2LL =-2*log likelihood; AIC = Akaike's information criterion; BIC = Schwarz's Bayesian criterion.

*p < .05. **p < .01. ***p < .001.

Table 5

Fixed Effects Estimates (Top), Estimates of Covariance Parameters (Middle), and Information Criteria (Bottom) for Models Predicting IADL Ratio Decline with IADL Pre-progression Estimates and Covariates (Hypothesis 2)

Parameter	Model 1	Model 2	Model 3	Model 4
Intercept	0.474 (0.008)***	1.00 (0.03)***	1.01 (0.03)	0.91 (0.03)***
Time	0.098 (0.004)***	0.98 (0.004)***	0.09 (0.01)***	0.11 (0.005)***
Time_sq	-0.004 (0.001)***	-0.003 (0.001)***	-0.004 (0.001)***	-0.004 (0.001)***
Age		0.004 (0.001)***	0.005 (0.001)***	0.01 (0.001)***
Education		0.002 (0.002)		
Sex		-0.05 (0.01)***	-0.06 (0.01)***	-0.05 (0.01)***
MMSE		-0.02 (0.001)***	-0.02 (0.001)***	-0.02 (0.001)***
Age*time			-0.001 (0.0002)***	-0.001 (0.0002)***
Sex*time			0.01 (0.004)*	0.01 (0.004)
MMSE*time			0.0005 (0.0005)	
IADL Preprog				0.43 (0.05)***
Time*IADL Preprog				-0.10 (0.02)***
Residual	0.010022 (0.004)***	0.009992 (0.0001)***	0.010028 (0.0004)***	0.009987 (0.0004)***
Intercept+Time				
Var: Intercept	0.04 (0.002)***	0.02 (0.001)***	0.02 (0.001)***	0.02 (0.001)***
Var: Time	0.001 (0.0001)***	0.001 (0.0002)***	0.001 (0.0.0001)***	0.001 (0.0001)***
CSH rho	-0.36 (0.06)***	-0.30 (0.06)***	-0.28 (0.06)***	-0.18 (0.07)**
-2LL	-2602.09	-3009.44	-3044.44	-3120.92
AIC	-2588.09	-2987.44	-3018.44	-3092.92
BIC	-2546.38	-2921.90	-2940.98	-3009.50

Note. Standard errors are in parentheses. IADL Preprog = IADL pre-progression; -2LL =-2*log likelihood; AIC = Akaike's information criterion; BIC = Schwarz's Bayesian criterion. *p < .05. **p < .01. ***p < .001.

Table 6

Comparison of Covariance Types

Covariance Type	-2LL	AIC	BIC
Unstructured	-3120.92	-3092.92	-3009.50
First-order autoregressive	-2662.79	-2636.79	-2559.33
Compound symmetry	-2662.79	-2636.79	-2559.33
Compound symmetry: heterogeneous	-3120.92	-3092.92	-3009.50

Table 7

Fixed Effects Estimates (Top), Estimates of Covariance Parameters (Middle), and Information Criteria (Bottom) for Models Predicting IADL Ratio Decline with Age and Covariates (Hypothesis 3)

Parameter	Model 1	Model 2[a]	Model 3	Model 4
Intercept	0.474 (0.008)***	1.02 (0.03)***	1.04 (0.03)***	1.00 (0.03)***
Time	0.098 (0.004)***	0.10 (0.004)***	0.08 (0.01)***	0.10 (0..004)***
Time_sq	-0.004 (0.001)***	-0.003 (0.001)***	-0.004 (0.001)***	-0.004 (0.0006)***
Education		0.002 (0.002)		
Sex		-0.06 (0.01)***	-0.07 (0.01)***	-0.06 (0.01)***
MMSE		-0.02 (0.001)***	-0.03 (0.001)***	-0.02 (0.001)***
Sex*time			0.01 (0.004)*	0.01 (0.004)*
MMSE*time			0.001 (0.0001)	
Age				0.01 (0.001)***
Age*time				-0.001 (0.0002)***
Residual	0.010022 (0.004)***	0.01 (0.001)***	0.010047 (0.0003)***	0.010022 (0.0004)***
Intercept+Time				
Var: Intercept	0.04 (0.002)***		0.02 (0.001)***	0.02 (0.001)***
Var:Time	0.001 (0.0001)***		0.001 (0.0002)***	0.001 (0.0001)***
CSH rho	-0.36 (0.06)***		-0.34 (0.06)***	-0.28 (0.06)***
-2LL	-2602.09	-2974.22	-2982.7	-3043.33
AIC	-2588.09	-2954.22	-2960.7	-3019.33
BIC	-2546.38	-2894.64	-2895.16	-2947.83

Note. Standard errors are in parentheses. -2LL =-2*log likelihood; AIC = Akaike's information criterion; BIC = Schwarz's Bayesian criterion.

[a]Compound Symmetry: Heterogeneous was not appropriate for this model. The Unstructured covariance type was used for just this model, and therefore direct comparisons with other models are not appropriate.

*p < .05. **p < .01. ***p < .001.

Table 8

Fixed Effects Estimates (Top), Estimates of Covariance Parameters (Middle), and Information Criteria (Bottom) for Models Predicting IADL Ratio Decline with MMSE and Covariates (Hypothesis 4)

Parameter	Model 1	Model 2	Model 3	Model 4
Intercept	0.474 (0.008)***	0.50 (0.01)***	0.5 (0.01)***	1.01 (0.03)***
Time	0.098 (0.004)***	0.10 (0.004)***	0.10 (0.004)***	0.09 (0.01)***
Time_sq	-0.004 (0.001)***	-0.003 (0.001)***	-0.004 (0.001)***	-0.003 (0.001)***
Age		0.01 (0.001)***	0.01 (0.001)***	0.01 (0.001)***
Education		-0.004 (0.002)*	-0.01 (0.002)**	0.00003 (0.002)
Sex		-0.07 (0.1)***	-0.08 (0.02)***	-0.05 (0.01)***
Age*time			-0.001 (0.0002)***	-0.001 (0.0002)***
Education* time			0.001 (0.001)*	0.001 (0.001)*
Sex*time			0.01 (0.004)	
MMSE				-0.02 (0.001)***
MMSE*time				0.0004 (0.0004)
Residual	0.010022 (0.004)***	0.009972 (0.0004)***	0.009996 (0.0004)***	0.010009 (0.0004)***
Intercept+Time				
Var: Intercept	0.04 (0.002)***	0.03 (0.002)***	0.03 (0.002)***	0.02 (0.001)***
Var: Time	0.001 (0.0001)***	0.001 (0.0002)***	0.001 (0.0001)***	0.001 (0.0001)***
CSH rho	-0.36 (0.06)***	-0.26 (0.06)***	-0.25 (0.06)***	-0.29 (0.06)***
-2LL	-2602.09	-2681.15	-2721.55	-3046.48
AIC	-2588.09	-2661.15	-2695.55	-3018.48
BIC	-2546.38	-2601.57	-2618.09	-2935.06

Note. Standard errors are in parentheses. -2LL =-2*log likelihood; AIC = Akaike's information criterion; BIC = Schwarz's Bayesian criterion.

*p < .05. **p < .01. ***p < .001.

Table 9

Multiple Regression Model Comparisons (Hypothesis 5)

Domain	Model	Variables	β	P value	R^2	R^2 Δ	F Δ	Sig. F Δ
Executive Functions	1	Covariates			0.341	0.341	96.15	$p < .001$
	2	VSAT	0.078	$p = .024$	0.350	0.009	5.19	$p = .006$
		COWA	-0.057	$p = .103$				
Motor	1	Covariates			0.371	0.371	110.75	$p < .001$
	2	Finger Tap	-0.04	$p = .222$	0.372	0.001	1.50	$p = .222$
Memory	1	Covariates			0.369	0.369	111.19	$p < .001$
	2	LM1	-0.096	$p = .024$	0.381	0.012	7.34	$p = .001$
		VR1	-0.081	$p = .007$				
Language	1	Covariates			0.368	0.368	111.44	$p < .001$
	2	BNT	-0.024	$p = .525$	0.373	0.006	3.44	$p = .032$
		Animals	-0.078	$p = .028$				
Visuospatial/ Visuocon-structional	1	Covariates			0.278	0.278	22.36	$p < .001$
	2	Blocks	-0.112	$p = .070$	0.305	0.027	4.51	$p = .012$
		Rey Copy	-0.095	$p = .153$				

Note: BNT = Boston Naming Test; Blocks = Block Design.

Table 10

Summary of Final Models for Neuropsychological Tests Predicting IADL Ratio Decline

Domain	Parameter	Estimate (β)	Std. Error	Sig. (*p*)
Executive Functions	VSAT	0.0003	0.00009	*p* = .004
	VSAT*time	0.00004	0.00003	*p* = .237
	COWA	-0.001	0.0006	*p* = .210
	COWA*time	0.0001	0.0002	*p* = .634
Memory	Logical Memory I	-0.004	0.001	*p* = .002
	Logical Memory I*time	-0.0003	0.0004	*p* = .410
	Visual Reproduction I	-0.003	0.0009	*p* = .001
	Visual Reproduction I*time	-0.0004	0.0003	*p* = .163
Language	Boston Naming	-0.0005	0.0006	*p* = .415
	Boston Naming*time	-0.0001	0.0002	*p* = .713
	Animals	-0.01	0.002	*p* = .002
	Animals*time	-0.001	0.0005	*p* = .258
Motor	Finger Tapping	-0.001	0.0006	*p* = .087
	Finger Tapping*time	-0.0001	0.0002	*p* = .640
Visuo-spatial/ constructional	Block Design	-0.003	0.002	*p* = .036
	Block Design*time	-0.001	0.0005	*p* = .284
	RCFT Copy	-0.001	0.001	*p* = .495
	RCFT Copy*time	-0.0001	0.0005	*p* = .807

Note: VSAT = Verbal Series Attention Test; COWA = Controlled Oral Word Association test; RCFT Copy = Rey Complex Figure Test, Copy task.

Table 11

Fixed Effects Estimates (Top), Estimates of Covariance Parameters (Middle), and Information Criteria (Bottom) for Models Predicting IADL Ratio Decline with Neuropsychiatric/Parkinsonism symptoms and Covariates (Hypothesis 6)

Parameter	Model 1	Model 2	Model 3	Model 4
Intercept	0.45 (0.01)***	1.00 (0.03)***	0.98 (0.03)***	1.08 (0.04)***
Time	0.10 (0.004)***	0.10 (0.004)***	0.08 (0.01)***	0.07 (0.01)***
Time_sq	-0.002 (0.001)***	-0.002 (0.001)**	-0.003 (0.001)***	-0.003 (0.001)***
Age		0.004 (0.001)***	0.001 (0.001)***	0.01 (0.001)***
Education		0.003 (0.002)		
Sex		-0.07 (0.01)***	-0.08 (0.01)***	-0.08 (0.01)***
MMSE		-0.02 (0.001)***	-0.02 (0.01)***	-0.02 (0.001)***
Age*time			-0.001 (0.0003)***	-001 (0.0002)***
Sex*time			0.01 (0.004)*	0.01 (0.005)*
MMSE*time			0.0003 (0.001)	
NeuropsyP				-0.02 (0.004)***
NeuropsyP*time				0.003 (0.001)*
Residual	0.009461 (0.0004)***	0.009452 (0.0004)***	0.009473 (0.0004)***	0.009476 (0.0004)***
Intercept+Time				
Var: Intercept	0.04 (0.003)***	0.02 (0.002)***	0.02 (0.002)***	0.02 (0.002)***
Var: Time	0.001 (0.0002)***	0.001 (0.0002)***	0.001 (0.0001)***	0.001 (0.0002)***
CSH rho	-0.29 (0.07)***	-0.21 (0.07)**	-0.19 (0.08)*	-0.16 (0.08)*
-2LL	-2028.71	-2314.38	-2342.42	-2371.11
AIC	-2014.71	-2292.38	-2316.42	-2343.11
BIC	-1975.07	-2230.1	-2242.81	-2263.84

Note. Standard errors are in parentheses. NeuropsyP = Neuropsychiatric and Parkinsonism symptoms; -2LL =-2*log likelihood; AIC = Akaike's information criterion; BIC = Schwarz's Bayesian criterion.

*p < .05. **p < .01. ***p < 001.

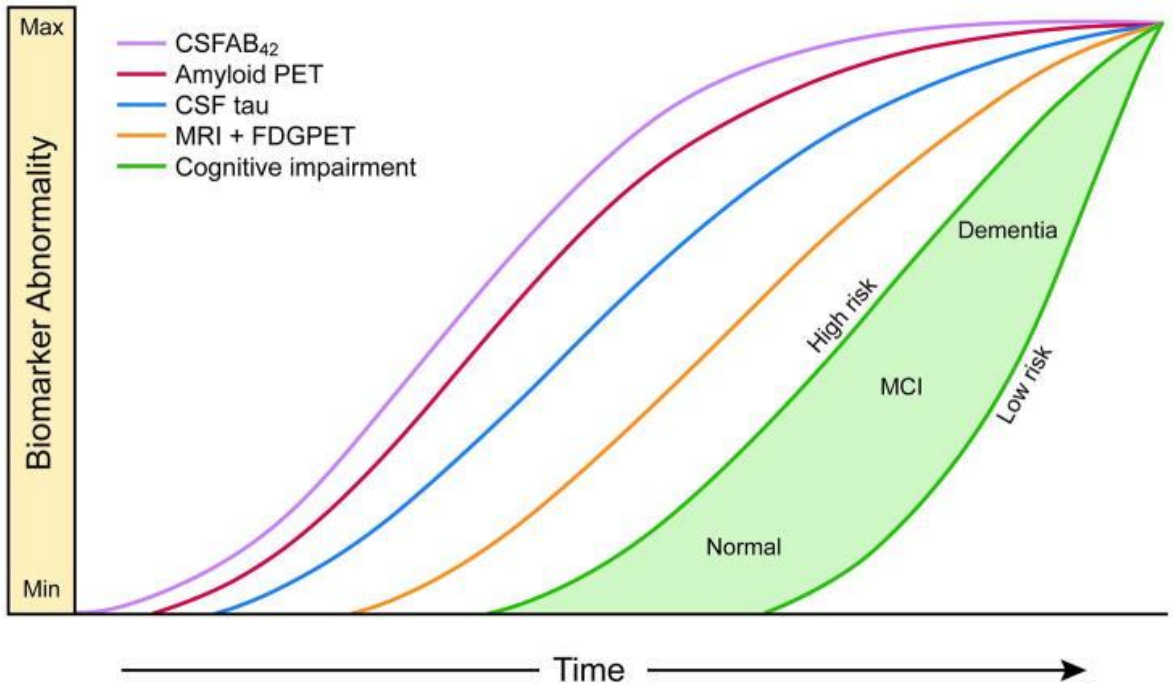

Figure 1. Jack et al.'s (2013) updated model of the order of abnormal biomarker occurrence in Alzheimer's disease.

Appendix 1

Instrumental Activities of Daily Living Scale (IADL)

1. ABILITY TO USE TELEPHONE

1 □ Operates telephone on own initiative, looks up and dials numbers, etc.
2 □ Dials a few well-known numbers.
3 □ Answers telephone, but does not dial.
4 □ Does not use telephone at all under own initiative, but may talk if put on line.
5 □ Incapable of using phone

2. SHOPPING

1 □ Takes care of all shopping needs independently.
2 □ Shops independently for a limited number of purchases (3 or less).
3 □ Needs to be accompanied on any shopping trip.
4 □ Completely unable to shop.

3. FOOD PREPARATION

0 □ Not applicable: Never did prepare meals
1 □ Plans, prepares, and serves adequate meals independently.
2 □ Prepares adequate meals if supplied with ingredients, or given supervision or reminding.
3 □ Heats & serves prepared meals, or prepares meals but does not maintain adequate diet.
4 □ Needs to have meals prepared and served.

4. HOUSEKEEPING

0 □ Not applicable: Never did housekeeping.
1 □ Maintains house alone or with occasional assistance.
2 □ Performs light daily tasks such as dish-washing & bed-making.
3 □ Performs light daily tasks but cannot maintain acceptable level of cleanliness.
4 □ Needs help with all home maintenance tasks.
5 □ Is unable to participate in any housekeeping tasks.

5. LAUNDRY

0 □ Not Applicable: Never did laundry.
1 □ Does personal laundry completely
2 □ Launders small items, rinses socks, may fold some items, etc.
3 □ All laundry must be done by others.

6. MODE OF TRANSPORTATION

1 □ Travels independently on public transportation or drives own car.
2 □ Arranges own travel via taxi/bus, but does not drive own car.
3 □ Travels on public transportation when accompanied by another.
4 □ Travel limited to taxi or automobile with assistance of another.

7. ABILITY TO HANDLE FINANCES

0 □ Not Applicable: Never handled finances
1 □ Manages financial matters independently (budgets, write checks, pays rent/bills, goes to bank, balances checkbook), collects and keep tracks of income.
2 □ Manages day-to-day purchases, but needs help with banking, major purchases, etc.
3 □ Incapable of handling money.

8. RESPONSIBILITY FOR OWN MEDICATION

0 □ Not applicable: Not taking any medications.
1 □ Is responsible for taking medications in correct dosages at correct time.
2 □ Takes responsibility if medication is prepared in advance in separate dosages, or if reminded.
3 □ Is not capable of dispensing own medication.