PREDICTORS OF RATE OF COGNITIVE AND FUNCTIONAL DECLINE IN PATIENTS WITH AMNESTIC MILD COGNITIVE IMPAIRMENT

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

Brittany Cerbone

June 2019

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ABSTRACT

Amnestic Mild Cognitive Impairment (MCI) is a known risk factor for conversion to Alzheimer's disease (AD). Although substantial research has been conducted on the general profile of amnestic MCI subjects and predictors of conversion to AD, the research on predictors of rate of decline has been less comprehensive and studied. The present study sought to fill the gaps in this portion of research by systematically and comprehensively examining predictors of rate of decline in a longitudinal sample of individuals with MCI. Specifically, this study identified predictors of rate of cognitive and functional decline, including age, genetic vulnerability, baseline cognitive performance, baseline functional ability, and baseline neuropsychiatric severity. Participants with single or multi-domain aMCI (N = 151) were assessed at baseline and for a mean of 1.32 follow-up visits (mean interval from baseline to last follow-up = 1.61 years). Results showed that carriers of the ApoE ε4 allele declined more quickly on all three dementia severity measures, but not on instrumental activities of daily living (iADL) functioning, compared to non-carriers. Older individuals declined more rapidly on iADL functioning (but not in dementia severity). Participants with average baseline iADL ratio scores declined more quickly compared to participants with above or below average baseline iADL ratio scores. Participants with lower Executive Functions composite scores at baseline declined more quickly on dementia severity measures but more slowly on iADL functioning. In addition, lower Memory composite scores at baseline predicted faster decline on iADL functioning only. Greater memory impairment severity (operationalized as the number of memory scores in the impaired range) at baseline predicted faster decline on the MMSE in particular. Contrary to hypotheses, those with lower levels of depression at baseline declined more rapidly on

dementia severity measures compared to those with higher levels of depression. Identifying potential predictors of rate of decline from amnestic MCI to AD could be clinically meaningful for prognostic purposes, understanding risk and protective factors, as well as guiding future treatments and clinical trials that could aim to target and delay progression among those patients who are particularly vulnerable to more quickly convert to AD.

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Introduction

Over the past 25 years, researchers have been studying a transitional phase between being cognitively normal and meeting criteria for dementia due to Alzheimer's disease (AD). This transitional phase, termed "mild cognitive impairment (MCI) due to AD" or "amnestic MCI" (aMCI) is a critical period in which early identification and diagnosis can allow clinicians the opportunity to intervene and provide recommendations for treatment of symptoms as early as possible (Petersen et al., 1999).

The focus of this study will be to identify neuropsychological, functional, sociodemographic, genetic, and neuropsychiatric predictors of rate of cognitive and functional decline among MCI patients. In order to develop well-reasoned hypotheses regarding possible predictors of rate of decline, it is important to review the existing literature regarding the definition of amnestic MCI, statistics on prevalence rates and variability of progression to AD, the neuropsychological profile of amnestic MCI, and demographic, cognitive, functional, neuropsychiatric, neuroanatomical, and genetic predictors of progression/conversion to an AD diagnosis. As it will be illuminated in this proposal, although there has been substantial research on the general profile of amnestic MCI subjects and predictors of conversion to AD, the research on predictors of rate of decline has been less comprehensive and studied. Therefore, this present study will seek to fill the gaps in this portion of research by examining predictors of rate of decline in MCI in a systematic and comprehensive way that has not been performed to date. Identifying potential predictors of rate of decline from amnestic MCI to AD could be clinically meaningful for prognostic purposes, understanding risk and protective factors, and guiding future treatments and

clinical trials that could aim to target and delay progression among those patients who are particularly vulnerable to more quickly convert to AD.

Diagnostic Criteria and Prevalence of MCI

Mild cognitive impairment can be separated into amnestic and non-amnestic sub-categories based on clinical presentation (Petersen et al., 2009). Research has generally found that amnestic MCI subjects are at much greater likelihood of converting to AD compared to non-amnestic MCI subjects (Ferman et al., 2013), and therefore individuals with amnestic MCI have become of particular interest when understanding susceptibility to AD. According to MCI diagnostic criteria developed by the National Institute on Aging and the Alzheimer's Association (NIA-AA; Albert et al., 2011), those with amnestic MCI are characterized by having subjective cognitive decline and objective cognitive impairment without meeting criteria for dementia. Concerns or suspicions about cognitive decline can originate from the patient, an informant, or clinician. Objective impairment, as assessed by neuropsychological measures, must be observed in one or more cognitive domains (e.g. single versus multi-domain impairment), most commonly in episodic memory, and must be mild enough in severity so as to not meet criteria for dementia. "Mild impairment" is typically considered to be 1 to 1.5 standard deviations below the mean for those of similar age and education, however neuropsychological results are guidelines to be taken into consideration in the context of other historical and functional information. The emphasis should be on intraindividual change, and when available, multiple assessments should be performed over time to determine progressive cognitive decline.

Mild cognitive impairment does not cause impairments in basic activities of daily living (ADL's), such as bathing, grooming, toileting, etc. There may be mild difficulties in

instrumental activities of daily living (iADLs), in which completing more complex tasks, such as handling finances, cooking, or managing medications, may be more difficult, may require the use of compensatory techniques (e.g. calendars, pill boxes), and may result in more errors or inefficiencies (Winblad et al., 2004). However, an important aspect of iADL performance in those with MCI due to AD is that they are able to maintain functional independence without aid from another person. In addition, there should not be evidence of occupational or social impairment. In-depth neuropsychological testing and historical documentation are commonly supplemented with evaluation of various biomarkers, including evidence of neuronal atrophy through magnetic resonance imaging (MRI), AD biomarker levels in plasma and cerebrospinal fluid, and amyloid protein build-up in the brain through Positron Emission Tomography (PET). Determining increased genetic risk based on APOE e4 allele status can also provide supportive evidence of MCI due to AD pathology.

Prevalence estimates of MCI vary considerably in the literature due to factors such as operationalization and etiology of MCI and subject sampling (population or clinic-based). A recent review by Petersen and colleagues (2017) found that MCI prevalence increased with age, and ranged from 6.7% for ages 60-64 years old to 25.2% for ages 80-84 years old. Prevalence of the amnestic MCI subtype specifically has been estimated to be between 3-6% (Lopez et al., 2003; Manly et al., 2005; Mariani et al., 2007). These findings highlight the variability and complexity of MCI as a construct, and thus it is integral to have a rigorous, standardized set of diagnostic criteria for MCI due to AD to help differentiate it from other possible etiologies of MCI.

The relative risk of dementia, including AD, in the MCI population is three times greater compared to the general elderly population (Petersen et al., 2017). A meta-analysis

found that the cumulative proportion of individuals who converted from amnestic MCI to AD over 10 years was 33.6% in clinic settings and 28.9% in population studies, with an annual conversion rate (ACR) of 11.7% (Mitchell & Shiri-Feshki, 2009). A review by Gainotti et al. (2014) found that among thirty-five longitudinal studies on MCI progression to AD, annual conversion rate varied between 6% and 33%. Comparatively, cognitively normal elderly tended to convert to cognitive impairment at a rate of 1-2% a year (Petersen et al., 1999). In addition, although having MCI as a risk factor for developing dementia, only a proportion of those with the diagnosis will progress to AD. In fact, studies have found that up to 44% of individuals with MCI (presumably not due to AD) revert to normal (Ganguli, Dodge, Shen, & DeKosky, 2004; Roberts & Knopman, 2013; Petersen et al., 2017). Despite this variability of progression rates and prognosis across studies, it is apparent that those with amnestic MCI are at a heightened risk for progressing to meet criteria for dementia due to AD, although the rate at which individuals convert varies greatly.

Neuropsychological Profile in Amnestic MCI and Predictors of Decline

Amnestic MCI patients perform more poorly on various measures of immediate and delayed episodic memory, including word lists, stories, and nonverbal material, compared to cognitively normal individuals (Griffith et al., 2006; Kramer et al., 2006; Petersen et al., 1999). Some research has suggested that impaired learning and free recall, poor retention, intrusion errors, and limited benefit from cueing are indicative of MCI due to AD (Dubois & Albert, 2004; Greenaway et al., 2006; Sarazin et al., 2007; Tounsi et al., 1999). Impaired recognition discrimination has also been shown to be more frequent in amnestic MCI individuals compared to normal controls (Clark et al., 2012; Greenaway et al., 2006; Libon et al., 2011) and those with non-amnestic MCI (Hildebrandt, Haldenwanger, & Eling, 2009).

Compromised semantic clustering performance during list learning for amnestic MCI individuals relative to healthy older adults suggests reduced ability to engage in effective memory encoding strategies, and may suggest executive dysfunction and disruption to semantic networks (McLaughlin et al., 2014; Price et al., 2010). There has also been some research suggesting non-episodic memory impairments in amnestic MCI, particularly in time-based prospective memory. Research has shown that time-based prospective memory is more impaired in amnestic MCI subjects compared to normal controls, reflecting involvement of the frontal system (Karantzoulis, Troyer, & Rich, 2009; Troyer & Murphy, 2007). While explicit memory is particularly impacted, implicit memory (Gobel et al., 2013; Perri et al., 2007) generally remains intact, highlighting the distinctiveness of these memory systems.

In addition to impaired memory function, other cognitive domains can be impaired in those with multi-domain amnestic MCI. Scores on measures of language functioning, such as confrontation naming, letter fluency (Petersen et al., 1995; 1999), and semantic fluency (Murphy, Rich, & Troyer, 2006; Kramer et al., 2006) have been found to be significantly lower compared to cognitively normal controls. Semantic fluency performance has been shown to be predictive of semantic clustering ability in amnestic MCI subjects (Price et al., 2010). Executive functions, such as cognitive flexibility, working memory, divided attention, inhibitory control, and planning, have been found to be more impaired (> 1.0 *SD* below mean) in amnestic MCI individuals compared to normal elderly controls (Belleville, Chertkow, & Gauthier, 2007; Johns et al., 2012; Kramer et al., 2006). Kramer et al. also found that over half of the MCI subjects had mild impairment on four or more non-memory cognitive tasks. Research has had mixed findings on visuospatial functioning in MCI, with

one study showing deficits (Johnson et al., 2012) and others not (Hodges et al., 2006; Kramer et al., 2006) compared to controls. Other research has shown that general intellectual ability remains relatively intact and that measures of global cognition, such as the MMSE and MOCA, are often in the normal/borderline impaired range (Petersen et al., 1995; 1999). Rate of decline in these global measures is relatively greater than normal controls but not as great as those with AD, although sensitivity of these global cognition measures may not be uniform throughout the disease process.

Among neuropsychological measures, those with MCI who progress to AD ("converters") perform relatively worse on baseline global cognition and dementia severity measures than those who are stable (Jack et al. 2008; Tierney et al. 1996). In addition, converters have been shown to have lower immediate, delayed, and cued recall and recognition scores and retention rates on episodic memory tests at baseline compared to individuals who did not convert to AD (Fleisher et al., 2007; Perri et al., 2007; Petersen et al., 1995). Word-list performance in particular has been found to be predictive of progression to AD (Silva et al., 2012; Tierney et al., 1996). Griffith and colleagues (2006) found that percent retention scores of nonverbal material assisted in correctly classifying a sample of amnestic MCI subjects who converted to AD over a two-year period with high sensitivity and specificity.

Research has also shown predictive power of executive functions measures at baseline (Albert et al., 2007; Dickerson et al., 2007, Rozzini et al., 2007). Poorer performance in semantic fluency is also predictive of conversion to AD (Gainotti et al., 2014; Griffith et al., 2006). In contrast, research has suggested that visuospatial functioning is not predictive of conversion to AD (Gainotti et al., 2014).

Neuroanatomical and Functional Correlates of Amnestic MCI

Research findings have highlighted atrophy in the medial temporal lobes (MTLs), particularly in the entorhinal cortex, in the early stages of AD (Juottonen et al., 1998; Killiany et al., 2002). Therefore, much of the research on neuroanatomical correlates in amnestic MCI has also focused on the MTLs. The neuroanatomical profile of amnestic MCI individuals has been found to closely parallel those with AD and appears to lie on a continuum between normal controls and AD. Particularly, entorhinal cortex atrophy has been shown to precede hippocampal volume loss in MCI (Pennanen et al., 2004) and to distinguish MCI from AD (Du et al., 2001). Two meta-analytic studies found gray matter reductions in MCI subjects compared to healthy controls in the MTL (including the entorhinal cortex, hippocampus, parahippocampus, amygdala, and uncus), left superior and middle temporal gyri, thalamus, bilateral precuneus, and anterior cingulate cortex (Nickl-Jockschat et al., 2012; Yang et al., 2012). Furthermore, Nickl-Jockschat et al. found a correlation between gray matter atrophy (in the right hippocampus and amygdala and left thalamus) and cognitive decline.

The use of imaging techniques such as fluorodeoxyglucose positron emission tomography (FDG-PET), amyloid PET, and functional magnetic resonance imaging (fMRI) have helped elucidate the functional deficits, and perhaps affected networks, in the brains of those with amnestic MCI. Hypometabolism has been observed in amnestic MCI and AD patients compared to normal controls in the limbic system network, including the hippocampal complex, medial thalamus, mammillary bodies, and posterior cingulate, as well as the precuneus and superior parietal lobe (Jauhiainen et al., 2008; Morbelli et al., 2010; Nestor, Fryer, Smielewski, & Hodges, 2003). A study by Wolk et al., 2009 found that

amnestic MCI patients with greater than typical levels of amyloid deposition in the brain ("amyloid-positive"), as measured by an amyloid PET scan, had poorer episodic memory and greater MTL atrophy compared to those who were amyloid negative. While amyloid PET has been better associated with cerebrospinal fluid (CSF) biomarker levels of amyloid and tau, FDG-PET may be better associated with global cognition, suggesting complementary contributions of each towards identification of disease (Jagust et al., 2009).

Functional MRI studies have identified a "default mode network" (DMN), which is a set of brain regions that are metabolically active at rest and deactivated during successful memory formation (Buckner et al., 2008; Daselaar et al., 2004; Raichle et al., 2001). These brain regions include medial prefrontal and temporo-parietal areas, including the posterior cingulate, precuneus, and lateral parietal, and medial prefrontal regions (Ruan et al., 2016; Sperling et al., 2010). Functional MRI studies on memory functioning in amnestic MCI patients have shown reduced functional connectivity at rest and impaired deactivation during memory tasks in DMN brain regions (Jin, Pelak, & Cordes, 2012; De Vogelaere, Santens, Achten, Boon, & Vingerhoets, 2012; Wang et al., 2013). Jin et al., 2012 found that, compared to normal controls, MCI patients had increased resting-state activity in the middle cingulate, medial prefrontal, and left inferior parietal cortices, and decreased activity in the lateral prefrontal cortex, left MTL, left medial temporal gyrus, posterior cingulate cortex, precuneus, and right angular gyrus. In addition, these functional differences were apparent in the absence of significant MTL volume differences, suggesting that functional changes may be apparent before structural changes occur. Increases in brain activity in certain regions are a consistent finding and may suggest compensatory mechanisms to maintain memory performance or alternatively, excitotoxicity (Sperling et al., 2010). Petrella et al. (2011)

found that their baseline DMN connectivity map goodness of fit indices significantly predicted progression to AD. Zhu, Majumdar, Korolev, Berger, & Bozoki (2013) assessed weakened connections in MCI patients using a multi-modal neuroimaging approach, and found that resting-state fMRI dysfunction was consistent with regional hypometabolism and atrophy within the DMN, as measured by FDG-PET and structural MRI.

Instrumental Activities of Daily Living in Amnestic MCI and Predictors of Decline

Although diagnostic criteria for amnestic MCI require minimal or no impairments in ADLs, subtle but important differences have been identified and described in the MCI population regarding instrumental ADLs. Particularly, deficits have been shown both globally on iADLs and in the sub-domains that rely on memory and complex reasoning, including finances, shopping, appointment keeping, medication adherence, and driving compared to normal controls (see review, Jekel et al., 2015; Perneczky et al., 2006). These MCI patients also performed everyday tasks slower and less accurately, and were more likely to convert to AD. A study by Teng, Becker, Woo, Cummings, & Lu (2010) found that deficits in iADLs were greater in amnestic compared to non-amnestic MCI patients, however single versus multiple domain impairment within each subgroup did not differ in iADL functioning. Cognitive correlates of functional ability in those with amnestic MCI include memory, processing speed, and executive functions, as well as global cognition (Jefferson et al., 2008; Marshall et al., 2011; Perneczky et al., 2006; Teng et al., 2010). Baseline executive dysfunction has been associated with more rapid iADL decline in amnestic MCI patients (Cahn-Weiner et al., 2007). Longitudinal changes in memory and executive functions have been associated with iADL change in cognitively normal older adults, suggesting that memory, in addition to executive functions, may also be an important for functional decline

(Tomaszewski et al., 2009). Greater dementia severity at baseline has been shown to be predictive of faster iADL decline among AD patients (Schmeidler et al., 1998), although this rate of functional decline has not been examined in MCI. Rozzini et al. (2007) found that iADLs were more compromised in MCI converters to AD at baseline and a year later compared to nonconverters and significantly predicted conversion to AD. Other studies have also found that functional deficits predict later conversion to AD (Reppurmund et al., 2013; Tabert et al., 2002). Regarding neuroanatomical correlates, hippocampal and cortical gray matter volumes have been shown to be significantly related to iADL scores, and hippocampal volume loss has been associated with iADL decline over time (Cahn-Weiner et al., 2007). MCI subjects with greater amyloid burden on PET also had greater functional impairments (Marshall et al., 2011). In summary, based on the subtle deficits in iADLs seen among amnestic MCI patients, and the dearth of research assessing predictors of rate of functional decline, identifying predictors of rate of functional decline can be useful and informative in understanding who may be at particular risk of converting more quickly to AD.

Neuropsychiatric Profile in Amnestic MCI and Predictors of Decline

Neuropsychiatric symptoms consist of behavioral and mood changes that are commonly observed in patients with dementia, including Alzheimer's disease, and can be important in understanding patient decline, treatment response, and caregiver burden (Finkel et al., 1997; Rabins et al., 2007). Research has shown that neuropsychiatric symptoms are common in MCI patients, with overall prevalence rates ranging from 35-75% (for review, see Apostolova & Cummings, 2007). The most commonly reported changes in MCI patients include depression, apathy, anxiety, and irritability (Feldman et al., 2004; Hwang et al., 2004; Lyketsos et al., 2002; Peters et al., 2012). These common symptoms have been reported to be

present in 15-20% of MCI patients in a population-based study (Lyketsos et al., 2002), however frequencies can be substantially higher in the referral clinic setting (Lopez, Becker, & Sweet 2005). The MCI neuropsychiatric symptom profile is similar to what is reported in the AD population, however the frequency and severity of symptoms are reduced (Lyketsos et al., 2002; Peters et al., 2012). In addition, there have been no reported differences in symptom profile among MCI subgroups (Lopez et al., 2005; Peters et al., 2012). Presence of neuropsychiatric symptoms in MCI has been associated with lower levels of global cognition and iADL functioning compared to MCI patients without symptoms (Feldmen et al., 2004). MCI patients with apathy in particular have been shown to perform poorer on list-learning memory (Robert et al., 2006a) and executive functions tasks that require initiation (Drijgers et al., 2011), and have more rapid functional decline over time (Copeland et al., 2003) compared to MCI patients without apathy. Several longitudinal studies have shown that baseline neuropsychiatric symptoms, such as apathy and depression, are more common in MCI individuals who later convert to AD (Copeland et al., 2003, Modrego & Ferrandez, 2004; Palmer et al., 2010; Robert et al., 2006b; Teng, Lu, & Cummings, 2007) and are associated with faster rate of progression to dementia (Somme, Fernandez-Martinez, Molano, & Zarranz, 2013).

Other Clinical Predictors of Decline and Conversion to AD

Demographics (Sex, age, premorbid IQ/education).

A number of studies have found that older age at baseline is a significant predictor of conversion (Amieva et al., 2004; Ganguli et al., 2004; Kryscio et al., 2006; Perri et al., 2007), however one study found no influence of age on progression to AD (Fleisher et al., 2007). Generally, findings have been consistent with concluding that sex is not associated with risk

of conversion to AD (Fleisher et al., 2007; Ganguli et al., 2004; Kryscio et al., 2006) and that there are no sex differences in incidence or prevalence of amnestic MCI (Au, Dale-McGrath, & Tierney, 2017), although women have greater incidence of AD compared to men (Gao, Hendrie, Hall, & Hue, 1998).

Educational level is believed to influence the clinical phenotype and progression of AD (Stern, Albert, Tang, & Tsai, 1999), and enhance resilience to the pathophysiological effects of the disease (Stern, 2009). Garibotto et al. (2008) found that among amnestic MCI individuals, despite having similar cognitive impairment severity, there was a significant relationship between higher education/occupation and lower brain glucose metabolism in temporal-parietal areas in converters. This study concluded that education and occupation might be protective against the effects of neurodegeneration among those who convert to AD, since despite evidence of pathophysiological effects of the disease, those with higher education performed on par cognitively compared to those without these pathophysiological effects. Two studies found reduced risk of conversion from MCI to AD among those with higher education and socioeconomic status (Artero et al., 2008; Sattler et al., 2012), further supporting the cognitive reserve hypothesis. However, Tifratene et al. (2015) reported contradictory findings compared to the studies above, concluding that higher education was associated with increased risk of conversion to AD. A possible reason for these discrepant findings on education may be related to variability in MCI severity, since Ye et al. (2012) found that amnestic MCI participants with higher education had a higher risk of conversion to AD in late-stage (defined as -1.5 SD below mean performance) but not early-stage MCI (defined as -1.0 to -1.5 SD below mean performance). In addition, Ye and colleagues found that higher education in late-stage MCI was associated with more rapid cognitive decline,

while higher education in early-stage MCI was associated with slower cognitive decline, potentially showing the protective effects of cognitive reserve early in the disease process. Although research has suggested that estimates of premorbid intellectual functioning is a better predictor than education of baseline cognitive performance and rate of cognitive decline in AD (Pavlik, Doody, Massman, & Chan, 2006), there is lack of research on whether premorbid intellectual functioning is also a predictor in amnestic MCI. Regarding education and functional decline, Cahn-Weiner et al., (2007) found that lower education in MCI and AD subjects was associated with worse iADL performance. Other studies on sociodemographic predictors of iADL performance in MCI are particularly lacking, although one could suspect that the existing literature on sociodemographic predictors of conversion to AD could also reflect decline in function (as per its definition).

Regarding sociodemographic predictors of rate of cognitive decline, in contrast to conversion to AD literature, one study found that age and education, in addition to sex, were found not be predictive of faster decline on a global composite of 17 measures of cognition (Boyle et al., 2006), while Holland, Desikan, Dale, & McEvoy (2013) found that women progressed more rapidly on dementia severity measures compared to men.

In summary, the literature on sociodemographic predictors of conversion to AD and rate of cognitive and functional decline are either lacking or largely inconsistent, the latter of which is likely attributed to differing methodology among studies.

Apoliproprotein E Genotype.

One particular gene of interest in Alzheimer's disease is the apolipoprotein E (ApoE) gene on chromosome 19. The ε4 allele variant has been associated with higher risk of developing Alzheimer's disease (Corder et al., 1993; Strittmatter et al., 1993). In

neuropsychological studies, this genotype has been studied in those with AD to see how this risk factor may affect cognition (e.g., Lehtovirta et al., 1996; McGuinness, Carson, Barrett, Craig, & Passmore, 2010). Researchers have also been interested in determining whether this susceptibility gene affects cognition and progression to AD among those with amnestic MCI. A study by Farlow, Tekin, Lane, & Charles (2004) compared ε4 carriers and non-carriers with MCI cross-sectionally and found that the carrier group performed significantly worse on dementia severity measures and memory performance tasks, were more impaired in activities of daily living, and had greater hippocampal atrophy. MCI ε4 carriers have also been shown to have reduced memory and executive function performance at baseline and to attain lower levels of cognitive performance (and probably AD diagnosis) at an earlier age than non-carriers (Albert et al., 2007).

Two studies examined APOE ε4 allele status among MCI converters and non-converters and found that being an ε4 carrier was a strong predictor of conversion to AD (Jack et al., 2008; Petersen et al., 1995). In addition, Petersen et al. (1995) performed a Kaplan-Meier survival analysis of conversion status across 6 years for carriers versus non-carriers and found differing trajectories between the groups. Non-carriers had a linear pattern of conversion to AD over the first 3 years of assessment after baseline, with approximately 30% of MCI non-carriers ultimately converting to AD, but the trajectory became stagnant after the third time point. Carriers had a linear pattern of conversion to AD across all 6 years of assessment after baseline, with over 90% of MCI carriers ultimately converting to AD. In contrast, Fleisher et al. (2007) found that although the best fitting regression model of conversion included ApoE genotype, its inclusion did not significantly improve prediction of progression compared to a model that solely used neuropsychological measures as predictors.

Tierney et al. (1996) found that APOE status was only a useful predictor of conversion if it was combined with memory scores.

A longitudinal study conducted by Xu and colleagues (2013) found that amnestic MCI individuals who were heterozygous or homozygous carriers of the ε4 allele were more than twice as likely to progress to AD compared to non-carriers, and being a homozygous carrier accelerated progression to dementia by more than 3 years. Another study found that clinical biomarkers, such as CSF t-tau and p-tau, in addition to homozygote ε4 allele status, were associated with more rapid progression from MCI to AD (Blom et al., 2009). Holland, Desikan, Dale, & McEvoy (2013) found that ε4 allele status was associated with faster decline on dementia severity measures, such as MMSE, ADAS-Cog, and CDR-SB. Other research studies have suggested that more rapid decline occurs in carriers of the ApoE ε4 allele (Aggarwal et al., 2005; Petersen et al., 1995). However, Albert et al.'s (2007) longitudinal study suggested that although ε4 carrier status is hypothesized to lower the age of onset of AD in those with MCI, their study did not show acceleration in slope of any cognitive measures among carriers. A study by Jack et al. (2008) found that ε4 carriers who had amnestic MCI had greater rates of brain atrophy on an MRI scan compared to noncarriers, although the study did not compare carrier status and progression to AD or performance on neuropsychological measures. Overall, ApoE ε4 status appears to be a meaningful predictor of conversion to AD, but it should not be considered in isolation from other predictors.

Lastly, a few studies have specifically examined the relationship between ApoE status and functional decline in MCI. Okonkwo et al., (2010) found that amnestic MCI subjects who were carriers of the ε4 allele had faster rates of decline on a functional measure across

three years. Bonner-Jackson et al., (2012) studied functional decline in normal controls, amnestic MCI, and AD subjects among those who were carriers of the ε2 allele (which is believed to be a protective factor against the development of AD), and found that, across all diagnostic groups, ε2 allele status was associated with less functional decline over time. Significant interactions remained among time, diagnostic group, and ApoE status; however, when diagnostic groups were assessed individually, relationships were no longer statistically significant, possibly due to reduced statistical power. Overall, these results show support for ApoE status to be a significant predictor of rate of functional decline in amnestic MCI subjects.

Biomarkers and Neuroanatomy.

The use of biomarkers has become an integral part in the diagnosis of mild cognitive impairment, and advances in research have continually provided new opportunities to better identify pathology and predict progression to dementia. The abnormal accumulation of protein in the brain, such as beta-amyloid and phosphorylated tau, has been shown to occur decades before symptoms begin, and recent findings suggest that subtle changes in cognition are apparent even at the preclinical stage (Ho et al., 2018). Low beta-amyloid 42 and elevated total and phosphorylated tau in CSF was shown to predict progression from MCI to AD (Hansson et al., 2006; Mattsson et al., 2009; Shaw et al., 2009). Patients who convert from MCI to AD have been found to show reduced baseline glucose metabolism in brain areas such as the inferior parietal, temporoparietal, and cingulate cortices (Chetelat et al., 2003; Drzezga et al., 2003; Morbelli et al., 2010; Mosconi et al., 2004) compared to non-converters. Amyloid positive amnestic MCI patients have been shown to convert to AD more

frequently and more quickly compared to amyloid-negative MCI patients (Doraiswamy et al., 2012; Okello et al., 2009).

Overall, longitudinal studies have found that baseline atrophy in the MTL (hippocampal and entorhinal cortex volume), inferior temporal lobe, left lateral temporal lobe, temporo-parietal association neocortex, left parietal cortex, posterior cingulate, and frontal lobes was predictive of conversion to AD (Chetelat et al., 2005; Devanand et al., 2007; Karas et al., 2008; Whitwell et al., 2008). Voxelwise meta-analyses reported findings that suggest left MTL atrophy was the neuroanatomical abnormality that most consistently predicted conversion from amnestic MCI to AD (Ferreira, Diniz, Forlenza, Busatto, & Zanetti, 2011; Yang et al., 2012).

Rate of Decline in MCI

Although there has been much research on the cognitive profile of individuals with MCI due to AD and predictors of conversion to AD, there is less literature on rate of decline and predictors that may influence rate of decline and conversion to AD. A longitudinal study by Johnson et al. (2012) reported that MCI individuals declined at a faster rate on the memory factor compared to cognitively normal controls, and declined generally on non-memory factors overtime. In addition, within MCI individuals, executive functions were found to decline at a faster rate than memory, while the other domains declined at a slower rate than memory. A longitudinal study by Hodges, Erzinclioglu, & Patterson (2006) studied MCI individuals once a year over an average of 7 years and found that measures of episodic memory and category fluency were consistently impaired at baseline and steadily declined over time, whereas other aspects of cognition, such as semantic functioning, visuospatial abilities, and attention changed more variably over time. One study found that among MCI

subjects who later converted to AD, only episodic memory performance had significantly faster rates of decline compared to other MCI subjects, while executive functions, general knowledge, and spatial skills did not differ in rate of decline (Albert et al., 2007). Boyle et al. (2006) found that individuals with MCI declined more rapidly compared to those without cognitive impairment at an additional linear rate of 0.03 standard units per year on a global composite measure of cognitive functioning, although rates of decline were not determined within each cognitive domain. Boyle et al. also noted that demographic variables did not impact rate of global cognitive decline in MCI. Wilson, Leurgans, Boyle, & Bennett (2011) found rapid declines in global cognition (-0.21 units per year) and all cognitive domains tested (ranged from -0.15 to -0.25 units per year) for MCI subjects in the prodromal phase of AD, although predictors of rate of global and cognitive domain decline were not performed. Howieson and colleagues (2008) found that immediate and delayed recall of a story declined at a rate of 0.68 points per year, and performance on the animal fluency and block design subtests declined at rates of one point per year in MCI individuals who later converted to AD.

Regarding predictors, according to Petersen et al., 2008, those with more severe memory impairment would be expected to progress to AD more quickly, and those who are impaired in more than one cognitive domain may progress more rapidly than those who are purely amnestic. As discussed in earlier sections, neuropsychiatric symptoms (Somme, Fernandez-Martinez, Molano, & Zarranz, 2013) and ApoE ε4 carrier status (Aggarwal et al., 2005; Holland et al., 2013; Petersen et al., 1995) have been associated with faster cognitive decline, and baseline executive dysfunction (Cahn-Weiner et al., 2007), ApoE ε4 allele status (Okonkwo et al., 2010) and apathy (Copeland et al., 2003) have been associated with more

rapid iADL decline. Furthermore, in contrast to conversion to AD literature, sex, age, and education were found to not be predictive of faster decline on a global composite of 17 measures of cognition (Boyle et al., 2006), while Holland et al. (2013) found that women progressed more rapidly on dementia severity measures compared to men. This particularly highlights the variability and inconclusiveness in the literature on sociodemographic predictors of decline, which is likely attributed to different methodological procedures across studies.

Aims and Hypotheses

Aim 1: The first aim was to identify select sociodemographic (age), genetic (ApoE carrier status), and cognitive predictors of rate of cognitive decline in amnestic MCI patients.

Hypothesis 1: It was predicted that older individuals at baseline and carriers of the ApoE ε4 allele would have more rapid cognitive decline (as measured by dementia severity measures).

Hypothesis 2: It was predicted that poorer baseline performance on measures of episodic memory, executive functions, and overall cognitive status would be associated with more rapid cognitive decline (as measured by dementia severity instruments). Those with greater breadth and severity of episodic memory impairment at baseline were expected to decline more rapidly. Those who were impaired in more than one domain (multi-domain amnestic) at baseline were expected to progress more rapidly compared to single-domain amnestic patients. Those with poorer performance on a semantic fluency measure were expected to decline more rapidly.

Aim 2: The second aim was to identify neuropsychiatric predictors of rate of cognitive decline in amnestic MCI patients.

Hypothesis 3: It was expected that greater levels of overall neuropsychiatric symptom severity and depression would be related to more rapid decline on dementia severity measures.

Aim 3: A third aim was to identify select sociodemographic (age), genetic (ApoE carrier status), cognitive, and functional predictors of rate of functional decline in amnestic MCI patients.

Hypothesis 4: It was predicted that older individuals at baseline and carriers of the ApoE ε4 allele would have more rapid functional decline.

Hypothesis 5: Those with greater iADL impairment and poorer performance on memory, executive functions, and dementia severity measures at baseline would be related to more rapid decline in iADL functioning.

Aim 4: A fourth aim was to identify neuropsychiatric predictors of rate of functional decline in amnestic MCI patients.

Hypothesis 6: It was expected that greater levels of overall neuropsychiatric symptom severity and depression would be related to more rapid decline on iADL functioning.

Methods

Participants

This study included 151 participants enrolled in a longitudinal study at the Baylor College of Medicine Alzheimer's Disease and Memory Disorders Center (ADMDC). This study has long-standing approval by the Baylor Institutional Review Board, and approval was also obtained from the University of Houston Committee for the Protection of Human Subjects for utilization of the variables relevant for the current project. All participants in the study met diagnostic criteria for mild cognitive impairment due to AD (Petersen, 2004) at baseline. All had evidence of memory impairment, performing at least 1.5 SDs below cognitively normal older adults on at least one memory measure. Single-domain patients (n = 82, 54.3% of sample) did not exhibit significant additional impairments in other cognitive domains, and multiple-domain patients (n = 69, 45.7% of sample) did display such additional impairment. In many cases, participants later converted to an AD diagnosis (n = 109, 72.2% of sample). Since rate of decline may differ after change in diagnosis, subject visits after which the diagnosis changed from MCI to AD were excluded from analysis. Participants were excluded if their eventual dementia diagnosis was not probable AD, based on the NINCDS-ARDA diagnostic criteria (McKhann et al., 1984). In addition to the neuropsychological battery administered at baseline, every participant had to have at least one follow-up evaluation.

Of the 151 participants, 52.3% were women, and 94.0% were non-Hispanic Caucasians. The mean age of participants at their baseline visit was 71.58 (SD = 7.88; Range: 50.00 – 87.10). The average years of education was 15.42 years (SD = 2.69). ApoE ε4 status was obtained from 142 participants. Of these, 10.6% (n = 15) were homozygous for the

allele, 41.5% (*n* =59) were heterozygous for the allele, and 47.9% (*n* = 68) lacked the allele. Participants had a mean of 2.32 total visits (*SD* = 1.54, median = 2.00, maximum = 10) and a mean of 1.61 years of follow-up (*SD* = 1.88, maximum =10.16). Table 1 displays the total number of participants per number of visits.

A cognitively normal older adult sample was also utilized to develop normative data (see Procedures section below for more information). These 222 participants were 50 years of age or older, in stable general health, and did not exhibit significant memory or other cognitive problems.

Procedures

The archival data.

As mentioned above, this study used archival data from the Baylor ADMDC's database. This database, which began enrolling participants in 1989, has been utilized to investigate the clinical and psychometric correlates of Alzheimer's disease pathology and progression. Participants receive comprehensive evaluations, including clinical interviews, neurological and physical exams, blood work, genetic testing, neuroimaging, and a comprehensive neuropsychological assessment. The neuropsychological battery, which is repeated on a yearly basis, consists of standardized tests and questionnaires that assess cognitive and emotional functioning, such as memory, attention, executive functions, language, visuospatial abilities, motor functioning, mood, behavior, and everyday functioning. Patients can be self-referrals or from other sources (e.g. physicians, family members, Alzheimer's Association). Some participants do not return for follow-up evaluations, primarily due to difficulties traveling to Houston from distant locations.

A second archival database from Baylor's Healthy Aging Control Study that includes only healthy controls was also utilized in this study for the primary purpose of developing normative data that were used to derive z-scores for the MCI participants (see Appendix, Table 2 for raw scores). Participants underwent the same procedures as the participants in the ADMDC database. This healthy control study also has long-standing approval by the Baylor Institutional Review Board and approval has also been obtained by the University of Houston Committee for the Protection of Human Subjects for the utilization of relevant measures for this project.

Measures

Selected measures from the Baylor ADMDC standard neuropsychological battery were used to test research hypotheses. Participants were administered these tests at baseline evaluation and at all subsequent annual follow-ups. Raw scores were utilized from the dementia severity measures and for the specific neuropsychological measures, including Wechsler Adult Intelligence Scale (WAIS) scores. These scores were converted into standardized z-scores using normative data derived from the healthy controls, except for WAIS-IV Similarities subtest, which was derived from non-age-corrected WAIS normative information listed in Wisdom, Mignogna, & Collins (2012). Cognitive performances were calculated by combining and averaging z-score performances across a number of measures in memory and executive function cognitive domains (as per methods described in Wilson et al., 2002). Semantic fluency, a measure of language performance, was analyzed separately. Measures that were chosen to represent each cognitive domain were created based both on standard clinical practice and further supported by previous factor analyses (e.g. Albert et al., 2007). Cognitive measures included in each domain are listed below.

Dementia Severity

Mini Mental State Exam (MMSE). The MMSE (Folstein, Folstein, & McHugh, 1975) is a 30-point brief screening instrument for dementia, measuring orientation, memory, language, mental manipulation, and visuoconstruction.

Alzheimer's Disease Assessment Scale- Cognitive Subscale (ADAS-Cog). The ADAS-Cog (Mohs et al., 1997) is a measure of dementia severity that is widely used in clinical trials for Alzheimer's disease. Subtests include word recall, naming objects and fingers, responding to basic commands, drawing figures, completing steps involving sending a letter, assessment of orientation to time and place, word recognition, and examiner ratings of language ability (including expression, comprehension, and word finding difficulty). Scores range from 0 to 70, with higher scores indicating more impairment.

Clinical Dementia Rating- Sum of Boxes (CDR-SB). The CDR (Morris, 1993) is a measure of six categories of functioning, which include memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Information is obtained in the form of a semi-structured interview given separately to the patient and an informant. The CDR provides a global score of severity, as well as the sum of scores across the six category boxes (CDR-SB). This 'Sum-of-Boxes' score (range of possible scores from 0 to 18), with higher scores signifying greater impairment, was the primary measure utilized.

Episodic Memory

WMS-R Logical Memory (LM-I and LM-II). The LM subtest of the WMS-R (Wechsler & Stone, 1987) is a measure of immediate and delayed memory involving free recall of two short stories read aloud to subjects. Delayed recall follows 20-30 minutes after

immediate recall. Each story consists of 25 elements, each worth one point, yielding a total possible maximum score of 50 points for LM-I and LM-II.

WMS-R Visual Reproduction (VR-I and VR-II). The VR subtest of the WMS-R (Wechsler & Stone, 1987) is a test of non-verbal memory that consists of four cards with figures on them of increasing difficulty. The subject is requested to draw from memory each figure after it is presented for 10 seconds. Delayed recall follows 20-30 minutes after immediate recall. The total score for VR-I and II is based on the sum of points for all four stimuli, with a total possible maximum of 41 points.

The "Memory Domain" composite score was calculated as the mean of the following individual z-scores: LM-I, LM-II, VR-I, and VR-II. This study originally proposed that the Memory Domain composite score would also incorporate scores from the Hopkins Verbal Learning Test-Revised (HVLT-R; Benedict, Schretlen, Groninger, & Brandt, 1998). However, after conducting a missing data analysis (see Results section below), it was deemed that the missing data were excessive and therefore this variable was excluded from the composite. Also, a 'Memory Severity' index was calculated by summing the number of memory scores (on LM-I, LM-II, VR-I, and VR-II) that were 1.5 SDs or more below the normative mean.

Executive Functions

Trail Making Test, Part B (TMT-B). Part B of the TMT (Reitan, 1958) is a measure of set-shifting ability in which the participant is instructed to draw lines connecting numbers and letters in ascending, alternating order (1-A-2-B, etc.). Time to completion was the primary performance measure.

WAIS-R/III/IV Digit Span Backwards. The Digit Span Backwards subtest of the WAIS-R/III/IV (Wechsler, 1981, 1997, 2008) assesses working memory, executive functions, and mental manipulation by asking subjects to repeat back a string of numbers in reverse order. The raw score is based on the participant's longest backward span (LDSB). Different versions of the WAIS on this subtest were combined as one variable.

WAIS-R/III/IV Similarities. The Similarities subtest of the WAIS-R/III/IV (Wechsler, 1981, 1997, 2008) is a test of abstract verbal reasoning in which subjects are asked to identify similarities between two words. Each item is scored zero to two points with higher raw scores indicating better performance. Age-scaled scores were converted to z-scores and utilized in data analyses. Different versions of the WAIS on this subtest were combined as one variable (details below).

Stroop Color and Word Test, Color-Word Inhibition condition. The color-word inhibition condition of the Stroop task examines response inhibition by requiring participants to read the color of the ink while avoiding the incongruent word that the ink is printed in. Number of items completed in 45 seconds was the primary performance measure.

Letter Fluency (FAS). This test (Spreen & Benton, 1969; Spreen & Strauss, 1998) measures the individual's ability to spontaneously generate words that begin with the letters 'F', 'A', and 'S' in 1-min time periods.

The "Executive Functions Domain" composite score was calculated as the mean of the following individual z-scores: TMT-B time to completion, LDSB, WAIS Similarities total score, and Stroop Color-Word Inhibition items completed.

Language

Semantic Fluency (Animals). This test (Rosen, 1980) is designed to measure an individual's ability to spontaneously generate items belonging to a semantic category, in this case animals. Examinees are asked to say as many animals as possible in one minute.

Additional Neuropsychological Domains/Scores Utilized in the Single Versus Multiple Domain Designation

Language: Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983), in addition to Category/Semantic Fluency.

Attention: Verbal Series Attention Test (VSAT; Mahurin & Cooke, 1996), WAIS-R/III/IV Digit Span Forward (Wechsler, 1981, 1997, 2008), Trail Making Test, Part A (TMT-A; Reitan, 1958), and Color Naming and Word Reading Conditions of the Stroop Color and Word Test (Stroop, 1935).

Visuospatial Functioning: WAIS-R/III/IV Block Design (Wechsler, 1981, 1997, 2008) and Rey-Osterrieth complex figure test, copy (RCFT; Osterrieth, 1944).

iADLs

Lawton Brody Instrumental Activities of Daily Living (Lawton & Brody, 1969). The Lawton-Brody iADL scale is a rating scale consisting of eight domains of independent living, including ability to use a telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, ability to handle finances, and medication management. Informants rate the participant's level of independence within each domain. Higher scores indicate greater dependence, with a minimum possible score of 8 and maximum score of 31 points. A ratio score was calculated that adjusted for "Not Applicable" items (e.g. a subject who never

performed housekeeping or laundry tasks). This ratio was: Total Score / Number of Possible Points. The number of possible points was 31 minus the total number of possible points from the "Not Applicable" items.

Neuropsychiatric symptoms

Neuropsychiatry Inventory Questionnaire (NPI-Q; Kaufer et al., 2000). The NPI-Q is an informant-based questionnaire specifically assessing neuropsychiatric symptoms associated with dementia, and was adapted from an NPI questionnaire originally developed by Cummings et al. (1994). The questionnaire assesses 12 domains that are commonly seen in dementia patients, including delusions, hallucinations, agitation or aggression, depression or dysphoria, anxiety, elation or euphoria, apathy or indifference, disinhibition, irritability or lability, motor disturbance, nighttime behaviors, and appetite and eating. The informant assesses the presence and severity of each symptom in a participant over the past month, as well as the level of distress the informant experiences as a result of each symptom. If a symptom is present, the severity is rated on a 3-point scale (mild, moderate, and severe), and level of distress in the informant is rated on a 5-point scale. The total severity score was used in this study.

Geriatric Depression Scale **(GDS;** Yesavage et al., 1983***).*** The GDS is a self-report scale that was developed to specifically assess depression symptoms in geriatric individuals. It consists of 30 items in which the individual reports the presence or absence of a specific symptom. Higher scores indicate more depressive symptoms, with a total score of 30 possible points.

Analyses

Data analysis was performed using SPSS 25.0 for Mac. Linear mixed models were used to analyze the longitudinal data in this study, as this type of analysis allows for greater flexibility for data that is not collected at fixed time intervals (since the intervals between visits varied considerably in the current study), adjusts for non-independence of observations, and can simultaneously assess between- and within-subject variability (McCoach, 2010). Model fit was determined using the Aikake's Information Criterion (AIC) and Schwarz's Bayesion Information Criterion (BIC).

Missing data were dealt with using multiple imputation methods (MI; Sinharay, Stern, & Russell, 2001), and analysis interpretation was based on pooled data when available. In order to prevent excessive imputation of missing data, the extent of missing data values within each cognitive domain composite score was evaluated for each subject to determine inclusion in the analyses. All subjects were ultimately included in the analyses, since all subjects had at least half of the test scores present per domain composite (as per methods described in Wilson et al., 2002). If missing data on a given variable were found to be systematic and substantial, then the variable was removed from the analyses.

Potential covariates of baseline severity, age, education, sex, and ApoE allele status were examined. Age, education, time, and time-squared were centered, and ApoE allele and domain impairment status were dummy-coded. Model assumptions of normality, homoscedasticity, and multicollinearity were assessed through multiple linear regression. Principal-components factor analysis (PCA) was performed to determine whether the proposed measures for Memory and Executive Functions composite scores loaded together onto one factor per cognitive domain. All cognitive variables and the iADL ratio score were

converted from raw scores into standardized z-scores, while neuropsychiatric variables remained as raw scores. The CDR-SB and iADL ratio score were standardized based on the MCI sample due to lack of variability ($SD = 0$) of these measures in the Normal Control sample. The ADAS-Cog, CDR-SB, and iADL ratio scores were reverse-scored so that higher z-scores indicate better performance.

To examine whether WAIS subtest raw scores were comparable across the different test versions, one-way ANOVAs were performed for the Similarities and LDSB subtest scores (with a test version as the between-subjects factor).

Data analyses were performed separately to examine predictors of rate of cognitive and functional decline, though implemented steps (described it with details below) were nearly identical for aforementioned sets of predictors.

Aim 1 – Identifying Predictors of Rate of Cognitive Decline

Hypothesis 1

Before addressing Aim 1, Model 1 used Time and Time-squared to predict performance on each cognitive dependent variable (e.g. each dementia severity measure) in order to examine whether the cognitive dependent variables changed over time and to establish a model for comparison of fit of future models. Time-squared was included to evaluate whether there was a curvilinear component to the model, and if significant, was retained in future models for that particular DV.

While retaining Time and Time-squared variables from Model 1, Model 2 added covariates (age, education, genetic carrier status, and baseline dementia severity) to determine main effects, as well as the interactions between Time and age, Time and genetic

carrier status, and Time and baseline dementia severity to identify predictors of rate of change in each dementia severity measure.

Hypothesis 2

Baseline memory and executive domain composite scores, baseline semantic fluency score, and their interactions with Time were added to Model 2 to determine which variables were associated with rate of change in each dementia severity measure, after controlling for covariates and their interactions with Time. A separate model that included covariates, memory severity grouping, and its interaction with Time was formed to determine rate of decline for memory severity groups. In order to assess rate of cognitive decline in single versus multi-domain MCI subjects, a dummy-coded variable was created and included with its interaction with Time to a separate model, along with covariates.

Hypothesis 3

This model included overall neuropsychiatric symptom severity and depression scores, and their interactions with Time, along with significant covariates, to determine whether neuropsychiatric predictors were associated with rate of change on each dementia severity measure.

Aim 2 - Identifying Predictors of Rate of Functional Decline

Hypothesis 4

Before addressing Aim 2, Model 1 used Time and Time-squared to predict performance on the iADL ratio score in order to examine whether it changed over time and to establish a model for comparison of fit of future models. Time-squared was included to

evaluate whether there was a curvilinear component to the model, and if significant, was retained in future models.

While retaining Time and Time-squared variables from Model 1, Model 2 added age, age x time, genetic carrier status, genetic carrier status x time, baseline iADL ratio score, and baseline dementia severity measures to identify predictors of rate of change on the iADL ratio score.

Hypothesis 5

Baseline dementia severity measures, baseline memory and executive domain composite scores, baseline iADL ratio score and their interactions with Time were added to Model 2 to investigate whether cognitive and functional variables were associated with rate of change on the iADL ratio score.

Hypothesis 6

This separate model included overall neuropsychiatric symptom severity and depression scores and their interactions with Time, along with significant covariates to determine whether neuropsychiatric predictors were associated with rate of change on the iADL ratio score.

Results

Missing Data Analysis, Principal-Components Analysis, and Testing of Assumptions

Missing Data Analysis.

Across all variables, data missingness ranged from 0% (MMSE) to 56.8% (HVLT-R), with most variables having less than 5% missing data. After examination, it was deemed that the HVLT-R variable would no longer be imputed and included as a memory composite

measure due to excessive missingness. All other variables remained in the subsequent analyses and multiple imputation methods were used for all cognitive variables.

Correlations and Principal-Components Factor Analysis of Composite Measures.

A simple bivariate correlation matrix among the Memory and Executive Function composite measures is presented in Table 2, showing primarily correlations of small- to medium magnitude between measures within the same cognitive domain.

In order to provide additional empirical support for the measures proposed to be included within the Memory and Executive Functions composite scores, a principal-components factor analysis (PCA) with varimax rotation was performed. Results showed support for two factors, with measure loadings consistent with a Memory domain and an Executive Functions domain (see Table 3).

Testing Assumptions.

Multiple linear regression analyses with fixed predictor variables were performed for each dependent variable to examine normality and homoscedasticity of residuals per research hypothesis. Visual examination of P-P plots and scatterplots revealed that residuals were normally distributed without evidence of severe heteroscedasticity, and therefore met testing assumptions. In order to examine multicollinearity between the Geriatric Depression Scale (GDS) and Neuropsychiatric Inventory Questionnaire (NPI-Q) severity scale, a Pearson's correlation was performed. Results showed a significant but small positive correlation between the variables ($r = .17$, $p < .01$, two-tailed), providing evidence against significant multicollinearity. In addition, variance inflation factors (VIF) for all variables included in the

regression models ranged between 1.0 and 1.4, which were well below recommended cut-off scores for determining multicollinearity (O'Brien, 2007).

Neuropsychological Test Performances

Performances on neuropsychological tests at baseline are shown in Table 4. Regarding the extent of memory impairment on the four memory measures (LM I, LM II, VR I, and VR II) at baseline, 8.6% (n = 13) had no impairment, 5.3% (n = 8) had impairment on one measure, 18.5% (n = 28) had impairment on two measures, 33.8% (n = 51) had impairment on three measures, and 33.8% (n = 51) had impairment on all four measures.

To examine whether WAIS subtest scores were comparable across the different test versions, a one-way ANOVA was performed for each subtest (with test version as the between-subjects factor). As shown in the Appendix (Table 1), raw scores for the different versions of longest Digit Span Backwards did not differ significantly, but Similarities scores differ ($p < .001$). Fisher's LSD post-hoc analyses showed that all three versions of the WAIS were significantly different from one another at $p < .001$. Therefore, separate normative data were calculated and applied to each version of the Similarities subtest prior to combining them into one variable.

Examining Possible Covariates

The covariates of education and sex were considered as part of the linear mixed model analyses with other variables of interest. Age, ApoE status, and baseline severity status results were also included in this section to determine inclusion in models addressing Hypotheses 3 and 6 (neuropsychiatric predictors), and were automatically included in all other analyses due to the study's interest in these variables as predictors of rate of decline.

Bivariate correlations among continuous covariates were determined based on significance with the variable of interest at $p < .01$ in order to adjust for multiple comparisons. Table 5 is a summary of correlations between each covariate of interest with the dependent variables (dementia severity measures and iADL ratio score at Visit 1) and various independent variables used in the mixed model analyses. Although age was found to be non-significantly associated with most predictor variables, it was decided that age would remain in the subsequent models as a covariate due to its theoretical importance. Education and baseline dementia severity status were significantly associated with cognitive measures (*ps* < .01), but not with neuropsychiatric or functional measures. Baseline iADL ratio score was significantly associated with neuropsychiatric, functional, and select cognitive measures (*ps* < .01). The baseline iADL ratio score is used as a covariate only for Hypotheses 4 through 6.

A t-test and ANOVA were performed for the categorical covariates of sex and the number of ApoE ε4 alleles, respectively. Overall, women performed worse on the memory composite score compared to men, $t(438) = 5.33$, $p < .01$ and reported significantly greater levels of depression on the GDS $t(429) = -3.18$, $p < .01$. No other statistically significant differences among variables were found between men and women. Table 6 provides a summary of these results below. ANOVA results across ApoE ε4 allele groups revealed significant omnibus *F* values for the CDR-SB (($F(2, 401) = 3.37$, $p < .05$), MMSE (($F(2, 413) = 5.76$, $p < .01$), and baseline memory composite score (($F(2, 413) = 5.36$, $p < .01$). Fisher's LSD post-hoc analyses showed that baseline memory composite performance was worse ($p < .01$) for those with two ε4 alleles ($M = -2.43$, $SD = 0.79$) compared to noncarriers ($M = -1.96$, $SD = 0.93$), MMSE was worse (*ps* < .01) for those with two alleles ($M = -3.26$, $SD = 2.49$) compared to noncarriers ($M = -1.98$, $SD = 2.24$) and those with one allele ($M =$ -

2.04, *SD* = 2.21), and CDR-SB was worse ($p = .014$) for those with two alleles ($M = -0.32$, $SD = 1.13$) compared to non-carriers ($M = 0.08$, $SD = 0.95$). Neuropsychiatric severity scores, depression scores, and iADL ratio scores did not differ between carriers and non-carriers ($p > .05$). Overall, covariates included in the models for each hypothesis are summarized in Table 7.

Examining Predictors of Rate of Cognitive and Functional Change

Model Covariance Structures and AIC/BIC Values

A heterogeneous autoregressive covariance structure was used for models including the ADAS-Cog as the dependent variable, as this provided the best model fit. All remaining dependent variables, including MMSE, CDR-SB, and iADL ratio score, used Compound Symmetry covariance structures, as this provided the best model fit.

AIC and BIC values for each model are presented in Tables 8 – 15. Overall, in each case, AIC and BIC values for each model indicated better fit for more complex models (e.g., Model 2 compared to Model 1, or Model 3 compared to Model 2).

Hypothesis 1

Mixed effects models were used to identify predictors of rate of cognitive change on each dementia severity measure, and results for Hypotheses 1 and 2 are shown in Tables 8 through 10. Model 1 shows the effects of time and time-squared on each of the dependent variables. In this model, time was included as a random and fixed effect, and the intercept was a fixed effect. There was a significant fixed effect of time on all of the dependent variables (ps $< .01$), and a significant fixed effect of time-squared on the ADAS-Cog ($p = .03$) and CDR-SB ($p < .01$). There was a significant random effect of time for the ADAS-Cog dependent variable only (Wald $Z = 3.71$, $p < .01$). Subsequent, final models for the ADAS-

Cog and CDR-SB dependent variables included time-squared only as a main effect, as preliminary analyses showed non-significant interaction effects of time-squared with predictor variables of interest.

Model 2 added covariates to the model, including age, age x time, ApoE ε4 carrier status, ApoE ε4 carrier status x time, baseline dementia severity, baseline dementia severity x time, and, with the exception of the CDR-SB, education. For the ADAS-Cog, results showed significant main effects of education, age, and baseline dementia severity performance. Specifically, lower education ($\beta = 0.15$, $p < .01$), older age ($\beta = -0.43$, $p < .01$), and greater levels of dementia severity (e.g., lower dementia severity scores; $\beta = 0.42$, $p < .01$) predicted worse performance on the ADAS-Cog. For the MMSE, results showed significant main effects of ApoE ε4 carriers and baseline dementia severity performance as predictors of performance on the MMSE, such that carriers of the ε4 allele ($\beta = -0.71$, $p = .01$) and those with greater baseline dementia severity ($\beta = 0.56$, $p < .01$) had lower MMSE scores across all visits. Similarly, for CDR-SB, results showed significant main effects for ApoE ε4 carriers and baseline dementia severity performance as predictors of performance on the CDR-SB, with ε4 carriers ($\beta = -0.36$, $p = .01$) and those with greater dementia severity ($\beta = 0.14$, $p < .01$) having worse performance on the CDR-SB across all visits. In addition, there were significant interaction effects of ApoE ε4 carrier status and Time as a predictor of change on the MMSE ($\beta = -0.86$, $p = .01$), ADAS-Cog ($\beta = -0.87$, $p = .02$), and CDR-SB ($\beta = -0.50$, $p < .01$), such that carriers of the ε4 allele declined more quickly on dementia severity measures compared to non-carriers (see Figures 1 - 3). Interactions of Time with age and dementia severity status were non-significant for all cognitive dependent variables (*ps* > .05).

Hypothesis 2

Model 3 added the cognitive predictors (Memory composite, Executive Functions composite, and Semantic Fluency) and their interactions with Time. For the ADAS-Cog, MMSE, and CDR-SB, results showed significant main effects of memory (ADAS-Cog: $\beta = 0.65$, $p < .01$; CDR-SB: $\beta = 0.15$, $p < .01$; MMSE: $\beta = 0.63$, $p < .01$) and executive functions (ADAS-Cog: $\beta = 0.77$, $p < .01$; CDR-SB: $\beta = 0.25$, $p < .01$; MMSE: $\beta = 0.54$, $p < .01$), with lower scores at baseline being predictive of greater dementia severity. For the ADAS-Cog only, lower scores on the Semantic Fluency task at baseline were also found to be predictive of greater dementia severity ($\beta = 0.39$, $p = .03$). In addition, there were significant interaction effects of the Executive Functions composite score and Time as a predictor of change on the ADAS-Cog ($\beta = 0.39$, $p = .01$) and CDR-SB ($\beta = 0.25$, $p < .01$), with results trending towards significance for the MMSE ($\beta = 0.25$, $p = .07$), such that those with lower Executive Functions composite scores at baseline declined more quickly on dementia severity measures (see Figures 4 and 5). Interactions of Time with Memory composite and Semantic Fluency scores were non-significant for all cognitive dependent variables (*ps* > .05).

A separate model (see Table 11) was created that included covariates, domain impairment (single versus multiple domain impairment), and its interaction with Time as predictors of change on the dementia severity measures. Results showed non-significant main effects and interactions with Time of the domain impairment variable for all cognitive dependent variables (*ps* > .05).

An additional model (see Table 12) was created that included covariates, memory severity scores (ranging from zero to four impaired tests, with the reference group being four impaired memory scores), and their interactions with Time as predictors of change on the dementia severity measures. For the MMSE, results showed significant main effects for all

memory severity variables and two significant interaction effects between Time and those with zero impaired scores and those with one impaired score. Main effects showed that greater severity impairment at baseline was predictive of greater dementia severity on the MMSE (β's = 1.06 to 2.20, *ps* < .01). The interaction effects showed that those with four impaired memory scores declined more rapidly on the MMSE compared to those with zero (β = 1.18, *p* = .03) or one impaired score (β = 1.39, *p* = .04). Figure 6 depicts rate of decline on the MMSE for subjects with increasing memory impairment severity.

Similarly, for the ADAS-Cog, significant main effects were found for those with no impaired scores (β = 2.67, *p* < .01) and two impaired scores (β = 1.25, *p* = .03), with those with one impaired score trending towards significance (β = 1.98; *p* = .06). There was one significant interaction effect found between Time and those with zero impaired scores, such that those with four impaired memory scores declined more rapidly on the ADAS-Cog compared to those with zero impaired scores (β = 1.82; *p* < .01). For the CDR-SB, there were only two significant main effects found for those with no impaired memory scores (β = 0.75, *p* = .01) and two impaired memory scores (β = 0.62, *p* < .01), and no significant interactions.

Hypothesis 3

A mixed effects model included covariates, baseline Geriatric Depression Score (GDS), baseline Neuropsychiatric Inventory Questionnaire (NPI-Q) Severity Score, and their interactions with Time to determine neuropsychiatric predictors of change on dementia severity measures (see Table 13). Results showed a significant main effect of GDS on performance on the CDR-SB (β = 0.05, *p* = .04), and two significant interaction effects between the GDS and Time on the ADAS-Cog (β = 0.16, *p* = .01) and CDR-SB (β = 0.07, *p*

= .04) dependent variables. As depicted in Figures 7 and 8, those with lower depression scores (GDS ≤ 5) appeared to decline more quickly on dementia severity measures compared to those with higher depression scores. Additional post-hoc analyses were conducted to help rule-out possible explanations for these findings, as they are contradictory to current literature. Other than the previously-reported differences in sex, with women constituting a larger proportion of individuals within the more depressed group and men constituting a larger proportion of individuals within the less depressed group ($\chi^2 = 15.51$, $p < .01$), no significant differences were found between depression groups on age, education, number of follow-up visits, dementia severity scores, or proportion of individuals who were later diagnosed with probable AD (*ps* > .05). Results and conclusions remained unchanged when sex was added as a covariate. However, depression scores within the less depressed group gradually increased over time, while depression scores within the more depressed group gradually decreased over time (see Figure 9). The main effect of baseline NPI-Q severity and its interaction with Time were not significant ($p > .05$).

Hypothesis 4

Model 1 in Table 14 shows the effects of time and time-squared on the iADL ratio score dependent variable. In this model, time was included as a random and fixed effect, and the intercept was a fixed effect. There was a significant fixed effect of time on the dependent variable of the iADL ratio score only ($\beta = -0.32$, $p < .01$).

Model 2 added covariates to the model, including age, age x time, ApoE ε4 carrier status, ApoE ε4 carrier status x time, baseline iADL ratio score, and baseline dementia severity (see Table 14). Results showed significant main effects of age and baseline iADL ratio score. Specifically, older age ($\beta = -0.30$, $p < .01$) and greater levels of baseline

functional impairment (e.g., lower iADL ratio z-scores; β = 0.57, $p < .01$) predicted worse iADL functioning at each visit. There was a significant interaction effect of baseline age and Time as a predictor of change on the iADL ratio score (β = -0.35, $p < .01$), such that older individuals at baseline declined more rapidly on the iADL ratio score (see Figure 10). The main effects of baseline dementia severity and ApoE ε4 carrier status, as well as the interaction between Time and ApoE ε4 carrier status, on iADL ratio score were non-significant (*ps* > .05).

Hypothesis 5

Model 3 added the cognitive predictors (Memory composite, Executive Functions composite, all three baseline dementia severity scores), their interactions with Time, and baseline iADL ratio score x Time (see Table 14). There was a significant interaction effect of baseline iADL ratio score and Time as a predictor of change on the iADL ratio score (β = -0.52, $p < .01$). As depicted in Figure 11, participants with average baseline iADL ratio scores declined slightly more quickly compared to participants with below average (more impaired) or above average (less impaired) baseline iADL ratio scores. Results showed significant main effects of memory (β = 0.21, $p = .04$) and executive functions (β = 0.18, $p < .01$), with lower scores at baseline being predictive of greater functional impairment across visits. In addition, there were significant interaction effects of Time with the Executive Functions composite (β = 0.16, $p = .01$) and Memory composite (β = 0.29, $p < .01$) scores as predictors of change on the iADL ratio score. Particularly, those with lower Memory composite scores and higher Executive Functions scores at baseline declined more quickly on the iADL ratio score at each visit (see Figures 12 and 13). Main effects of all three baseline dementia severity scores and their interactions with Time were non-significant (*ps* > .05).

Hypothesis 6

A mixed effects model included covariates, baseline Geriatric Depression Score (GDS), baseline Neuropsychiatric Inventory Questionnaire (NPI-Q) Severity score, and their interactions with Time to determine neuropsychiatric predictors of change on the iADL ratio score (see Table 15). Results showed no significant main effects of the GDS or NPI-Q severity score or their interactions with Time on predicting iADL ratio scores (*ps* > .05).

Discussion

In summary, results revealed some differences in predictors of rate of decline for cognition and functional ability. Particularly, ApoE ε4 allele carriers declined more quickly on all three dementia severity measures, but not on instrumental activities of daily living (iADL) functioning, compared to non-carriers. Older individuals declined more rapidly on iADL functioning but not in dementia severity. Baseline executive functions appeared to be an important predictor of both rate of cognitive and functional decline, but with opposite effects. Baseline memory performance was also shown to be an important predictor of rate of decline in both cognition and iADL functioning, as lower memory composite scores at baseline predicted faster decline on iADL functioning, while greater memory impairment severity predicted faster decline on the MMSE in particular. Each hypothesis is discussed in more depth below.

Hypothesis 1

Research examining age as a predictor of rate of cognitive decline in MCI is lacking, and findings on age as a predictor of conversion to AD are inconsistent. Specifically, several studies reported that older age was predictive of conversion from MCI to AD (e.g., Amieva et al., 2004; Ganguli et al., 2004; Kryscio et al., 2006; Perri et al., 2007; Tifratene et al.,

2015), while one study by Fleisher et al. (2007) reported no influence of age as a predictor. Based on this limited research, the present study hypothesized that older individuals at baseline with MCI would decline more rapidly on dementia severity measures. Study findings did not support this hypothesis, as no significant interactions between age and Time were found for any of the dementia severity measures. Overall, these findings suggest that although older individuals with MCI may be more likely to convert to AD, they decline in general cognition at similar rates compared to younger individuals.

Previous research has found that ApoE ε4 status is a meaningful predictor of conversion to AD and that ε4 status may be associated with more rapid progression of dementia symptoms (Blom et al., 2009; Holland et al., 2013; Xu et al., 2013). Therefore, this study hypothesized that carriers of the ApoE ε4 allele would decline more rapidly on dementia severity measures. Results supported this hypothesis, as significant interactions were found between ApoE ε4 carrier status and Time for all three dementia severity measures. Overall, this study provides further evidence highlighting the impact of genetic vulnerability on the clinical progression of MCI due to AD.

Hypothesis 2

Previous literature has suggested that baseline dementia severity, memory, executive functions, and semantic fluency may be important predictors of decline from MCI to AD (Albert et al., 2007; Hodges, Erzinclioglu, & Patterson, 2006; Jack et al., 2008; Johnson et al., 2012). In addition, it has been proposed by Peterson et al. (2008) that MCI individuals with more severe memory impairment and multiple-domain MCI would be expected to decline more rapidly in cognition. Therefore, this study hypothesized that MCI individuals with poorer performance on dementia severity measures, memory, and executive functioning,

as well as those with more severe memory impairment and multiple-domain impairment would decline more quickly on dementia severity measures. Overall, results showed that worse baseline executive functioning, but not dementia severity, memory, or semantic fluency, predicted faster rate of cognitive decline. These results could suggest that amnestic MCI individuals with executive functioning (as well as memory impairment) may have more extensive neurodegeneration, which leads to quicker cognitive decline. However, the present study did not find multiple-domain impairment to be a predictor of rate of cognitive decline, which would contradict this hypothesis. A possible reason for this discrepancy in findings could be due to the operationalization of multiple-domain impairment, since this variable included individuals with impairment in domains including, but not limited to, executive functioning. Overall, 24 out of 69 (34%) multiple-domain MCI participants were identified as having impaired executive functioning scores at baseline, which highlights the variability in the multiple-domain MCI sample.

In addition, while overall memory performance was not found to be predictive of rate of cognitive decline, greater numbers of impaired memory scores (impaired memory severity) predicted faster cognitive decline, particularly on the MMSE. There may be several possible reasons for these discrepant findings. One possible reason is that because the immediate and delayed memory scores were both included in the composite score, some individuals' relatively good immediate memory scores may have obscured the evidence of memory dysfunction they showed on delayed recall. Second, the number of impaired memory scores may be indicative of more extensive neurodegeneration, particularly within the medial temporal lobe regions, and may also be a stronger predictor of decline in general, as greater levels of memory impairment may be more strongly associated with an AD

pathophysiological process. Third, although previous research has suggested that word lists may be the most sensitive measure to detect memory impairment in the MCI population and a strong predictor of conversion to AD, the HVLT-R was ultimately removed from the Memory Composite score because of excessive missing data. Therefore, results could have been different if a list-learning task were also included in the analysis.

Lastly, baseline dementia severity did not predict rate of cognitive decline on any of the dementia severity measures. There has been some criticism that dementia severity measures may not be sufficiently responsive to detecting cognitive impairment or change at the MCI stage (Ciesielska et al., 2016; Skinner et al., 2012), which could potentially contribute to these null findings. In addition, since individuals with an MCI diagnosis are not expected to have very impaired scores on dementia severity measures (especially at baseline), restriction of range in MMSE and the CDR-SB scores may have negatively impacted the predictive power of these measures.

Hypothesis 3

Several studies have found neuropsychiatric symptoms, including apathy and depression, to be predictive of conversion from MCI to AD and associated with faster progression to dementia (Copeland et al., 2003; Modrego & Fernandez, 2004; Palmer et al., 2010; Robert et al., 2006; Somme, Fernandez, & Cummings, 2007; Teng, Lu, & Cummings, 2007). Therefore, this study predicted that higher baseline neuropsychiatric symptom severity and depression scores would be associated with faster cognitive decline on dementia severity measures. However, although findings showed a significant interaction between the Geriatric Depression Scale and Time, the direction of the interaction was contrary to expectations. Specifically, those with higher levels of depression at baseline had a slower rate of decline

(on the ADAS-Cog and CDR-SB) compared to those with lower levels of depression. Post-hoc analyses were conducted to help determine a possible explanation for these contradictory findings. As discussed in the Results section, no significant differences were found between depression groups on age, education, number of follow-up visits, dementia severity scores, or proportion of individuals who were later diagnosed with probable AD. However, as depicted in Figure 9, depression scores within the less depressed group increased over time, while depression scores within the more depressed group decreased over time. While speculative, if individuals with higher levels of depression were more likely to be treated for their mood symptoms, perhaps these results are reflective of the positive cognitive effects associated with improved mood (e.g., Butters et al., 2000). Another possible reason for these contradictory findings could be reflective of lack of insight or anosognosia. Specifically, neuropsychiatric symptoms such as depression are common in MCI patients (Apostolova & Cummings, 2007), and being aware of one's cognitive deficits could reasonably be associated with worsened mood. Therefore, those who do not endorse depression symptoms may not appreciate the extent of their cognitive impairment. This inverse relationship between anosognosia and GDS has been reported in Alzheimer's disease patients (Kashiwa et al., 2005). Anosognosia has been associated with greater frontal dysfunction in those with AD (Michon, Deweer, Pillon, Agid, & Dubois, 1994). However, post-hoc analyses did not show a significant relationship between GDS and executive functioning, which would make this possible explanation for the results less likely.

Hypothesis 4

Similar to the literature on predictors of rate of cognitive decline, research examining age as a predictor of rate of functional decline in MCI is lacking. Nonetheless, the present

study hypothesized that, similar to Hypothesis 1, older individuals at baseline with MCI would decline more rapidly on iADL functioning. Results supported Hypothesis 4, as a significant interaction between age and Time was found, with older individuals at baseline declining more rapidly on iADL functioning. This finding adds to the literature on sociodemographic predictors of rate of functional decline in MCI.

One study has found that ApoE ε4 status in MCI individuals may be associated with more rapid iADL functional decline using the Functional Activity Questionnaire (FAQ; Okonkwo et al., 2010). Therefore, this study sought to replicate these findings in an MCI sample using the Lawton & Brody iADL Scale. Results were not replicated in this study, as a significant interaction was not found between ApoE ε4 carrier status and Time on the Lawton & Brody iADL Scale. One possible reason for this discrepancy in findings could be due to some research suggesting that the Lawton & Brody iADL Scale may not be sensitive enough to detect the subtle changes in functioning that occur within an MCI sample (Burton et al., 2009), while such distinctions have been made using the FAQ among older individuals with normal cognition, single domain amnestic MCI, and multiple domain amnestic MCI (Teng et al, 2010). Therefore, the FAQ may be preferable to the Lawton & Brody iADL scale when trying to detect subtle changes in functioning among MCI individuals over time.

Hypothesis 5

Based on existing, limited research on predictors of functional decline in normal older adults, MCI, and AD, it was hypothesized MCI participants with greater baseline iADL impairment, dementia severity, executive dysfunction, and memory impairment would decline more rapidly on iADL functioning. Results partially supported this hypothesis, as a significant interaction was found between Time and memory impairment, such that greater

baseline impairment predicted faster iADL decline. It appears that the effects of memory impairment on iADLs (e.g., remembering to pay bills and take medications on time) particularly impacts rate of functional decline and increases dependence on others. However, results were contrary to expectations between Time and executive functioning, as those with better baseline performance predicted faster iADL decline. While these results may seem contradictory at first, they may be reflective of loss of compensatory techniques. Since executive functioning is an important part of iADL functioning (e.g., organizing pills or managing money), those with greater levels of executive functioning may initially be better able to compensate for increasing struggles with iADLs. However, as the disease progresses and EF declines, iADL deficits become more apparent in the initially more high-functioning group. Overall, these results highlight the differential impact that deficits in memory and executive functioning have on iADLs. In contrast to domain impairment, there was no significant interaction found between Time and any of the baseline dementia severity measures. Similar to the previous discussion regarding null findings in Hypothesis 2, dementia severity measures may not be sensitive enough at the MCI stage to differentially predict rate of functional decline.

There was a significant interaction between baseline iADL and Time; however, the results were contrary to the hypothesis, showing that individuals who had average impairment in iADLs at baseline declined more rapidly compared to individuals who were within the below average or above average range of iADL functioning (compared to the overall MCI sample). Overall, while the results were statistically significant, Figure 11 shows that the slopes are minimally different from one another, which suggests that these differences among groups may not be clinically meaningful.

Hypothesis 6

Research on neuropsychiatric predictors of functional decline is limited. One study by Copeland et al. (2003) found that one specific neuropsychiatric symptom, apathy, may be associated with more rapid functional decline in MCI participants. Therefore, this study predicted that higher baseline neuropsychiatric symptom severity, including depression severity, would be associated with faster functional decline. Study results did not support this hypothesis, as no significant interactions between Time and both neuropsychiatric measures were found. Overall, it appears that neuropsychiatric symptom severity and depression do not significantly impact rate of functional decline in this MCI sample. Null findings for the NPI-Q may also be due to the non-specific nature of the measure, as it consists of a variety of behavioral symptoms. While it was expected that depression would have a negative impact on everyday functioning in an amnestic MCI sample and possibly accelerate functional decline, the vast majority of the participants (87%) were at levels at or below the recommended clinical threshold (≤ 9) for depression on the GDS. Therefore, most of these participants would be categorized as "not depressed," which could possibly explain the lack of significant findings.

Study Limitations, Future Directions, and Implications

One study limitation is the extensive missingness of data that was found in the verbal list-learning task, the HVLT-R, which precluded its inclusion in the Memory Composite score. The inclusion of the HVLT-R in the Memory Composite score could have led to different and more robust findings than those presented in this study.

As discussed above, the MMSE, CDR-SB, ADAS-Cog, Lawton & Brody iADL Scale, and the NPI-Q were all developed for the dementia population. While these measures

are regularly used in research and clinical practice to diagnose MCI, some research has suggested that these measures may not be optimal in detecting the subtle changes that occur in cognition and functional ability during the MCI prodromal stage. The present study was limited to the measures included in the Baylor ADMDC archival database, and therefore no substitutions or supplementing of measures were possible. Nonetheless, the use of these widely-used measures in this study can be more easily compared and interpreted relative to individuals with dementia and AD, MCI individuals within the clinic, and for clinical trial purposes. In the future, it would be beneficial to replicate these findings using alternative measures that were specifically designed to detect changes in cognition and functioning at the prodromal stages of dementia.

While all participants in this study had at least one follow-up visit, a majority of participants (52%) only had two time points. Therefore, the ability to detect rate of change in these individuals was limited. It would be beneficial to replicate findings in this MCI sample in the future once these participants accrue more visits.

This MCI sample was very homogenous in terms of race and ethnicity, since 94.0% of participants were non-Hispanic Caucasians. Therefore, future studies should focus on whether results replicate in more culturally and racially diverse samples to further understand the extent of generalizability of this study's findings.

Lastly, while the use of a control group to derive normative data has its benefits, the sample size for the WAIS-III Similarities subtest in the control group was small (N = 12). Therefore, the calculation of z-scores based on a small sample size is not ideal, but was still used for consistency purposes.

The aim of this study was to systematically and comprehensively examine predictors of rate of decline in a longitudinal sample of individuals with MCI. Overall, results suggest that there may a differential impact of genetic vulnerability on cognition but not on functional ability, while age may impact functional ability to a greater extent than cognitive ability over time. Identifying individuals with amnestic MCI who have more severe memory impairment and executive functioning impairment could be important prognostic indicators of both rate of cognitive and functional decline. Overall, this study contributes meaningfully to the literature by providing a better understanding of predictors of rate of decline in individuals with MCI who are at risk for conversion to AD, which could help guide clinical practice and research.

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Table 1

Number of Visits Per Participant

Number of Visits	Number of Participants
2	78
3	42
4	14
5	8
6	6
7	1
8	0
9	1
10	1

Note. Average Number of Visits = 2.32, *SD* = 1.54, Median = 2.00.

Table 2

Correlations Between Neuropsychological Test Scores [a]

	LM I	LM II	VR I	VR II	Similarities	LDSB	Stroop C-W	TMT-B
LM I	-							
LM II	.74*	-						
VR I	.32*	.32*	-					
VR II	.44*	.62*	.53*	-				
Similarities	.36*	.23*	.23*	.10	-			
LDSB	.14*	.02	.09	-.07	.29*	-	.	
Stroop C-W	.14*	-.03	.24*	.02	.22*	.24*	-	
TMT-B	.26*	.10	.36*	.09	.40*	.30*	.39*	-
FAS	.12	.03	.14*	-.04	.41	.32*	.26*	.30*

Note. [a] Correlations are based on z-scores *$p < .01$, two-tailed. Shaded values represent correlations within composites.

Table 3

Principal-Components Analysis of Composite Measures with Varimax Rotation

	Factor Loading [a]	
Measure	1	2
Memory:		
Logical Memory I	**.89**	.19
Logical Memory II	**.82**	-.12
Visual Reproduction I	**.78**	.34
Visual Reproduction II	**.64**	-.16
Executive Functions:		
Letter Fluency (FAS)	-.05	**.67**
WAIS [c] LDSB	-.16	**.59**
WAIS [c] Similarities	.32	**.65**
TMT, Part B	.22	**.73**
Stroop Task, C-W	.02	**.63**

Note: [a] Factor loadings of .50 or higher are in boldface and are based on z-score data.

Table 4
Test Performances for the MCI Sample [a]

Measure	Baseline (N = 151)	
	Raw Score *M* (*SD*)	z-score *M* (*SD*)
Dementia Severity:		
CDR-SB	1.91 (1.36)	0.17 [b] (0.78)
ADAS-Cog Total	10.07 (4.12)	-2.39 (1.95)
MMSE	27.38 (2.20)	-1.59 (1.92)
Memory:		
Logical Memory I	15.52 (5.93)	-2.15 (1.05)
Logical Memory II	7.63 (6.25)	-2.34 (0.90)
Visual Reproduction I	27.81 (7.04)	-1.34 (1.52)
Visual Reproduction II	11.44 (10.12)	-2.49 (1.38)
Memory Composite		-2.08 (0.92)
Semantic Fluency	15.23 (4.64)	-0.98 (1.07)
Executive Functions:		
Letter Fluency (FAS)	34.69 (11.01)	-0.61 (0.88)
WAIS [c] LDSB	4.59 (1.10)	-0.40 (0.86)
WAIS [c] Similarities	- -	-0.72 (1.26)
TMT, Part B	121.34 (65.00)	-1.57 (2.27)
Stroop Task, C-W	31.22 (10.07)	-0.85 (1.01)
EF Composite		-0.83 (0.84)

NPI-Q Severity	4.30
	(4.66)
GDS	5.60
	(3.93)
iADL Ratio Score	0.31
	(0.08)

Note: [a] Scores are based on imputed pooled values. [b] The CDR-SB z-score is derived from the MCI sample. All other standardized scores were derived from the Normal Control sample. [c] Score represents combined WAIS R/III/IV scores.

Table 5

Bivariate Correlations of Covariates of Interest at Baseline

	Age	Education	ADAS-Cog	MMSE	CDR-SB	iADL Ratio
ADAS-Cog	-.15*	.23*	-	.46*	.23*	.06
MMSE	-.07	.19*	.46*	-	.21*	.25*
CDR-SB	.01	.07	.23*	.21*	-	.20*
Memory Composite	-.27*	.18*	.23*	.36*	.28*	.18*
EF Composite	-.20	.27*	.37*	.25*	.18*	.20
iADL Ratio Score	-.15*	.02	.06	.25*	.20*	-
GDS	-.02	.01	.06	.00	.03	-.21*
NPI-Q Severity	-.10	-.11	.00	-.03	-.02	-.37*

Note. * $p < 0.01$. Cognitive variables and iADL Ratio Score are z-scores. The baseline iADL ratio score is used as a covariate only for Hypotheses 4 through 6.

Table 6

Comparisons Between Women and Men on Key Measures

Measures	Sex		*t*	*df*
	Women	Men		
Memory Composite	-2.28 (0.86)	-1.83 (0.92)	5.33*	438
EF Composite	-0.75 (0.90)	-0.79 (0.73)	-0.50	438
ADAS-Cog	-2.77 (2.69)	-2.60 (2.46)	-0.68	438
CDR-SB	-0.07 (1.01)	0.07 (0.97)	1.49	438
MMSE	-2.36 (2.36)	-1.92 (2.37)	1.96	438
NPI-Q Severity	3.70 (4.35)	4.58 (4.44)	1.60	263
GDS	6.43 (3.96)	5.12 (4.19)	-3.18*	429
iADL Ratio	.34 (.12)	.34 (.11)	.11	387

Note. Standard deviations appear in parentheses below means.

* $p < .01$.

Table 7

Covariates Included in the Models

Hypotheses	Dependent Variables	Covariates
Hypotheses 1 and 2	MMSE and ADAS-Cog	Age, education, ApoE status, and baseline dementia severity
	CDR-SB	Age, ApoE status, and baseline dementia severity
Hypothesis 3	MMSE, ADAS-Cog, CDR-SB	Age only
Hypothesis 4	iADL	Age, ApoE status, baseline iADL ratio score, and baseline dementia severity score (MMSE only)
Hypothesis 5	iADL	Age, baseline iADL ratio score, and baseline dementia severity scores (all three included)
Hypothesis 6	iADL	Age and baseline iADL ratio score

Table 8
Linear Mixed Models Identifying Predictors of Change on the ADAS-Cog Total Score: Fixed-Effects Estimations

	Model 1			Model 2			Model 3		
Variable	β	*SE*	*p*	β	*SE*	*p*	β	*SE*	*p*
Intercept	-3.09	0.22	**<.01**	-2.57	0.33	**<.01**	-0.18	0.50	.73
Time	-1.02	0.18	**<.01**	-1.33	0.31	**<.01**	0.16	0.46	.73
Time-Squared	-0.25	0.11	**.03**	-0.21	0.07	**<.01**	-0.09	0.07	.17
Education				0.15	0.05	**<.01**	0.06	0.05	.18
Age				-0.43	0.21	**.04**	0.04	0.18	.81
Age x Time				-0.20	0.19	.29	0.05	0.17	.77
ApoE ε4				-0.40	0.41	.32	-0.02	0.34	.94
ApoE ε4 x Time				-0.94	0.38	**.01**	-0.58	0.33	.08
MMSE				0.42	0.11	**<.01**	0.20	0.10	**.04**
MMSE x Time				0.11	0.10	.28	-0.03	0.10	.75
Memory							0.65	0.21	**<.01**
Memory x Time							0.35	0.19	.07
Executive Functions (EF)							0.77	0.16	**<.01**
EF x Time							0.39	0.15	**.01**
Semantic Fluency							0.39	0.18	**.03**
Semantic Fluency x Time							0.20	0.17	.24
AIC		1877.38			1709.00			1664.38	
BIC		1910.07			1765.42			1745.00	

Note. Bold text designates $p < .05$. AIC = Akaike's Information Criterion; BIC = Schwarz's Bayesian Criterion; MMSE = Mini Mental State Exam. Predictor variables (except time and time-squared) are from the baseline visit. A heterogeneous autoregressive covariance structure was used in this model, as this provided the best model fit. The full model initially included WAIS Version as a predictor. However, this predictor did not yield statistically significant results and was trimmed from the final model.

Table 9
Linear Mixed Models Identifying Predictors of Change on the MMSE: Fixed-Effects Estimations

	Model 1			Model 2			Model 3		
Variable	β	*SE*	*p*	β	*SE*	*p*	β	*SE*	*p*
Intercept	-2.37	0.15	**<.01**	-1.52	0.26	**<.01**	0.10	0.35	.77
Time	-0.62	0.18	**<.01**	-0.96	0.32	**<.01**	-0.14	0.43	.74
Time-Squared	0.13	0.20	.49	-	-	-	-	-	-
Education				0.07	0.04	.13	0.01	0.04	.73
Age				-0.07	0.14	.60	0.18	0.13	.16
Age x Time				-0.04	0.17	.83	0.05	0.15	.75
ApoE ε4 Carrier				-0.71	0.27	**.01**	-0.36	0.25	.14
ApoE ε4 x Time				-0.86	0.34	**.01**	-0.62	0.32	**.05**
ADAS				0.56	0.08	**<.01**	0.33	0.08	**<.01**
ADAS x Time				0.17	0.10	.08	0.04	0.10	.69
Memory							0.63	0.14	**<.01**
Memory x Time							0.25	0.17	.15
Executive Functions (EF)							0.54	0.13	**<.01**
EF x Time							0.25	0.14	.07
Semantic Fluency							0.07	0.13	.61
Semantic Fluency x Time							0.03	0.16	.87
AIC		1986.08			1749.00			1723.12	
BIC		2010.60			1797.37			1795.67	

Note. Bold text designates $p < .05$. AIC = Akaike's Information Criterion; BIC = Schwarz's Bayesian Criterion. Predictor variables (except time and time-squared) are from the baseline visit. A Compound Symmetry covariance structure was used in this model, as this provided the best model fit. The full model initially included WAIS Version as a predictor. However, this predictor did not yield statistically significant results and was trimmed from the final model.

Table 10
Linear Mixed Models Identifying Predictors of Change on the CDR-SB: Fixed-Effects Estimations

	Model 1			Model 2			Model 3		
Variable	β	*SE*	*p*	β	*SE*	*p*	β	*SE*	*p*
Intercept	-0.05	0.06	.42	-0.14	0.12	.25	0.63	0.19	**<.01**
Time	-0.50	0.09	**<.01**	-0.64	0.15	**<.01**	-0.23	0.23	.33
Time-Squared	-0.35	0.08	**<.01**	-0.13	0.03	**<.01**	-0.04	0.04	.27
Age				-0.12	0.08	.13	0.04	0.07	.52
Age x Time				-0.17	0.10	.09	-0.08	0.09	.35
ApoE ε4				-0.36	0.15	**.01**	-0.24	0.13	.06
ApoE ε4 x Time				-0.50	0.19	**<.01**	-0.42	0.16	**.01**
MMSE				0.14	0.04	**<.01**	0.07	0.04	.07
MMSE x Time				0.07	0.05	.17	0.03	0.05	.55
Memory							0.21	0.08	**<.01**
Memory x Time							0.08	0.10	.42
Executive Functions (EF)							0.32	0.06	**<.01**
EF x Time							0.25	0.06	**<.01**
Semantic Fluency							0.05	0.07	.41
Semantic Fluency x Time							-0.10	0.08	.23
AIC		1181.67			1068.68			1020.15	
BIC		1206.19			1117.05			1092.71	

Note. Bold text designates $p < .05$. AIC = Akaike's Information Criterion; BIC = Schwarz's Bayesian Criterion; MMSE = Mini Mental State Exam. Predictor variables (except time and time-squared) are from the baseline visit. A Compound Symmetry covariance structure was used in this model, as this provided the best model fit. The full model initially included WAIS Version as a predictor. However, this predictor did not yield statistically significant results and was trimmed from the final model.

Table 11

Linear Mixed Models with Single- vs. Multiple-Domain MCI Diagnosis as a Predictor of Change in Dementia Severity Measures: Fixed-Effects Estimations

	ADAS-Cog			MMSE			CDR-SB		
Variable	β	*SE*	*p*	β	*SE*	*p*	β	*SE*	*p*
Intercept	-2.59	0.38	**<.01**	-1.15	0.42	**<.01**	-0.19	0.17	.29
Time	-1.11	0.21	**<.01**	-0.78	0.20	**<.01**	-0.53	0.10	**<.01**
Time-Squared	-0.16	0.07	**.02**	-	-	-	-0.10	0.03	**<.01**
Age	-0.24	0.13	.07	-0.06	0.13	.61	-0.01	0.05	.90
Education	0.14	0.05	**<.01**	0.07	0.05	.13	-	-	-
Baseline Severity	0.32	0.07	**<.01**	0.51	0.08	**<.01**	0.10	0.03	**<.01**
ApoE ε4 Carrier	0.37	0.26	.16	-0.34	0.25	.16	-0.09	0.11	.44
Multi-Domain MCI	-0.24	0.25	.33	0.31	0.31	.32	0.11	0.13	.38
Multi-Domain MCI x Time	-0.24	0.25	.33	0.31	0.31	.32	0.11	0.13	.38
AIC		1713.11			1752.20			1073.23	
BIC		1761.47			1792.51			1113.53	

Note. Bold text designates $p < .05$. AIC = Akaike's Information Criterion; BIC = Schwarz's Bayesian Criterion. Predictor variables (except time and time-squared) are from the baseline visit.

Table 12

Linear Mixed Models with Memory Severity as a Predictor of Change in Dementia Severity Measures: Fixed-Effects Estimations

	ADAS-Cog			MMSE			CDR-SB		
Variable	β	*SE*	*p*	β	*SE*	*p*	β	*SE*	*p*
Intercept	-3.22	0.41	**<.01**	-2.46	0.34	**<.01**	-0.37	0.15	**.02**
Time	-1.67	0.34	**<.01**	-1.28	0.30	**<.01**	-0.68	0.16	**<.01**
Time-Squared	-0.19	0.69	**<.01**	-	-	-	-0.12	0.03	**<.01**
Age	-0.13	0.14	.33	0.10	0.13	.43	0.02	0.06	.67
Education	0.13	0.04	**<.01**	0.03	0.04	.42	-	-	-
Baseline Severity	0.26	0.07	**<.01**	0.42	0.08	**<.01**	0.07	0.03	**.02**
ApoE ε4 Carrier	0.49	0.26	.06	0.25	0.24	.29	0.05	0.11	.62
Impaired Memory[a]:									
No Scores	2.67	0.80	**<.01**	2.20	0.53	**<.01**	0.75	0.31	**.01**
One Score	1.98	1.07	.06	1.92	0.64	**<.01**	0.67	0.38	.08
Two Scores	1.25	0.59	**.03**	1.14	0.39	**<.01**	0.62	0.21	**<.01**
Three Scores	0.76	0.49	.12	1.06	0.32	**<.01**	0.17	0.18	.32
No Scores x Time	1.82	0.67	**<.01**	1.18	0.56	**.03**	0.57	0.33	.08
One Score x Time	1.45	0.90	.11	1.39	0.70	**.04**	0.70	0.41	.09
Two Scores x Time	0.62	0.53	.24	0.40	0.45	.37	0.28	0.25	.27
Three Scores x Time	0.85	0.48	.08	0.51	0.41	.21	0.18	0.22	.40
AIC		1686.47			1742.85			1072.13	
BIC		1763.06			1811.37			1140.65	

Note. [a] Reference Group = Four Impaired Memory Scores; Bold text designates $p < .05$. AIC = Akaike's Information Criterion; BIC = Schwarz's Bayesian Criterion. Predictor variables (except time and time-squared) are from the baseline visit.

Table 13

Linear Mixed Models with Neuropsychiatric Predictors of Change in Dementia Severity Measures: Fixed-Effects Estimations

	ADAS-Cog			MMSE			CDR-SB		
Variable	β	*SE*	*p*	β	*SE*	*p*	β	*SE*	*p*
Intercept	-4.00	0.54	**<.01**	-3.22	0.42	**<.01**	-0.54	0.18	**<.01**
Time	-1.74	0.43	**<.01**	-1.57	0.54	**<.01**	-0.89	0.23	**<.01**
Time-Squared	0.02	0.11	.881	-	-	-	-0.09	0.06	.15
Age	-0.55	0.21	**<.01**	-0.27	0.19	.16	-0.14	0.07	**.04**
NPI-Q Severity	-0.08	0.06	.23	-0.02	0.05	.72	-0.02	0.02	.29
NPI-Q x Time	-0.05	0.05	.33	0.03	0.07	.70	-0.02	0.03	.52
GDS	0.15	0.08	.06	0.11	0.06	.09	0.05	0.03	**.04**
GDS x Time	0.16	0.07	**.01**	0.09	0.08	.26	0.07	0.03	**.04**
AIC		1118.25			1189.08			704.12	
BIC		1161.03			1224.73			743.33	

Note. Bold text designates $p < .05$. AIC = Akaike's Information Criterion; BIC = Schwarz's Bayesian Criterion; GDS = Geriatric Depression Scale; NPI-Q = Neuropsychiatric Inventory Questionnaire. Predictor variables (except time and time-squared) are from the baseline visit.

Table 14
Linear Mixed Models Identifying Predictors of Decline on the iADL Ratio Score: Fixed-Effects Estimations

	Model 1			Model 2			Model 3		
Variable	β	*SE*	*p*	β	*SE*	*p*	β	*SE*	*p*
Intercept	-0.10	0.06	.11	-0.52	0.14	**<.01**	0.24	0.23	.31
Time	-0.32	0.08	**<.01**	-0.67	0.16	**<.01**	0.27	0.26	.30
Time-Squared	0.10	0.07	.16	-	-	**-**	-	-	-
Age				-0.30	0.10	**<.01**	-0.20	0.09	**.03**
Age x Time				-0.35	0.11	**<.01**	-0.23	0.11	**.03**
ApoE ε4				-0.18	0.18	.33	-	-	-
ApoE ε4 x Time				-0.24	0.20	.23	-	-	-
iADL Ratio				0.57	0.14	**<.01**	0.50	0.13	**<.01**
iADL x Time							-0.52	0.15	**<.01**
MMSE				0.00	0.02	.75	0.04	0.05	.40
MMSE x Time							0.06	0.06	.31
ADAS-Cog							-0.03	0.05	.50
ADAS-Cog x Time							-0.05	0.05	.35
CDR-SB							-0.04	0.11	.74
CDR-SB x Time							-0.05	0.13	.69
Memory							0.21	0.10	**.04**
Memory x Time							0.29	0.12	**.01**
Executive Functions (EF)							0.18	0.05	**<.01**
EF x Time							0.16	0.06	**<.01**
AIC		1048.67			725.78			730.37	
BIC		1072.46			771.97			804.52	

Note. Bold text designates $p < .05$. AIC = Akaike's Information Criterion; BIC = Schwarz's Bayesian Criterion. Predictor variables (except time and time-squared) are from the baseline visit. A Compound Symmetry covariance structure was used in this model, as this provided the best model fit. The full model initially included WAIS Version as a predictor. However, this predictor did not yield statistically significant results and was trimmed from the final model.

Table 15

Linear Mixed Models on Neuropsychiatric Predictors of Change in the iADL Ratio Score: Fixed-Effects Estimations

	Model 1			Model 2		
Variable	β	*SE*	*p*	β	*SE*	*p*
Intercept	-0.10	0.06	.11	-0.79	0.22	**<.01**
Time	-0.32	0.08	**<.01**	-1.02	0.24	**<.01**
Time-Squared	0.10	0.07	.16	-	-	-
Age				-0.02	0.05	.59
iADL Ratio				0.96	0.07	**<.01**
NPI-Q Severity				0.03	0.02	.26
NPI-Q x Time				0.04	0.03	.14
GDS				-0.01	0.03	.93
GDS x Time				0.00	0.04	.99
AIC		1048.67			492.31	
BIC		1072.46			530.73	

Note. Bold text designates $p < .05$. AIC = Akaike's Information Criterion; BIC = Schwarz's Bayesian Criterion; GDS = Geriatric Depression Scale; NPI-Q = Neuropsychiatric Inventory Questionnaire. Predictor variables (except time and time-squared) are from the baseline visit. A Compound Symmetry covariance structure was used in this model, as this provided the best model fit.

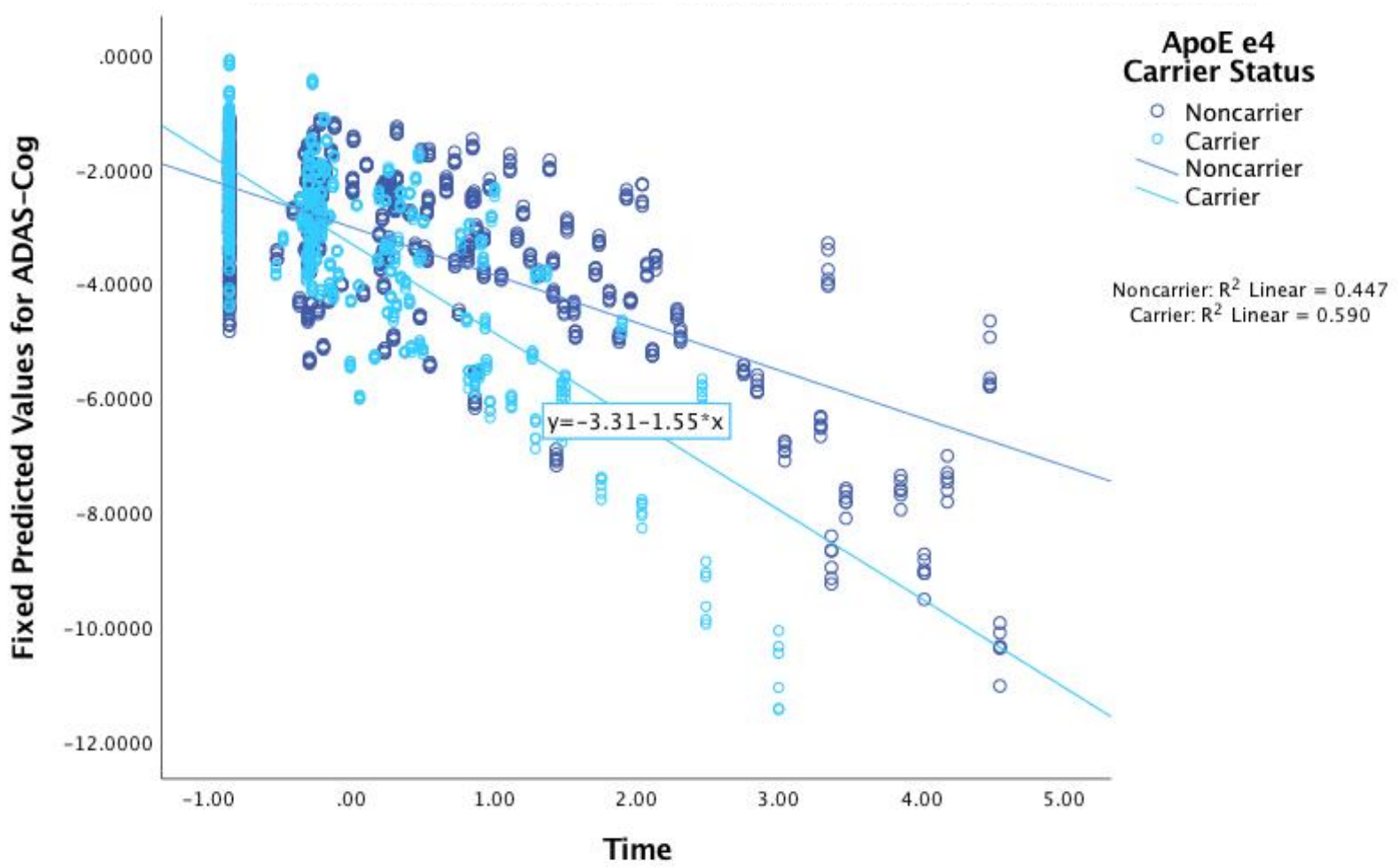

Figure 1. Rate of decline on the ADAS-Cog for carriers and non-carriers of the ApoE ε4 allele. Time is a centered variable and Fixed Predicted Values for the ADAS-Cog are presented as z-scores.

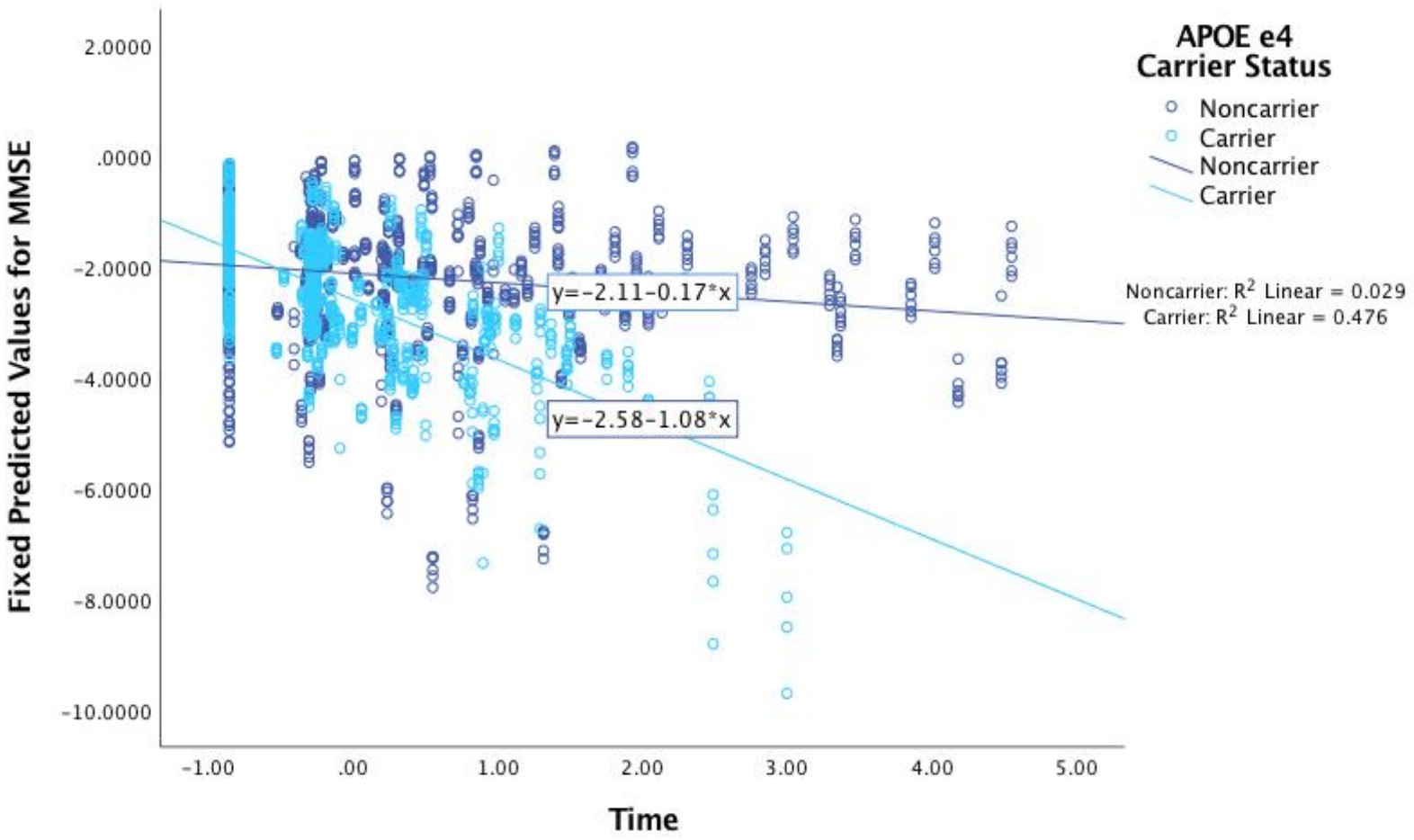

Figure 2. Rate of decline on the MMSE for carriers and non-carriers of the ApoE ε4 allele. Time is a centered variable and Fixed Predicted Values for the MMSE are presented as z-scores.

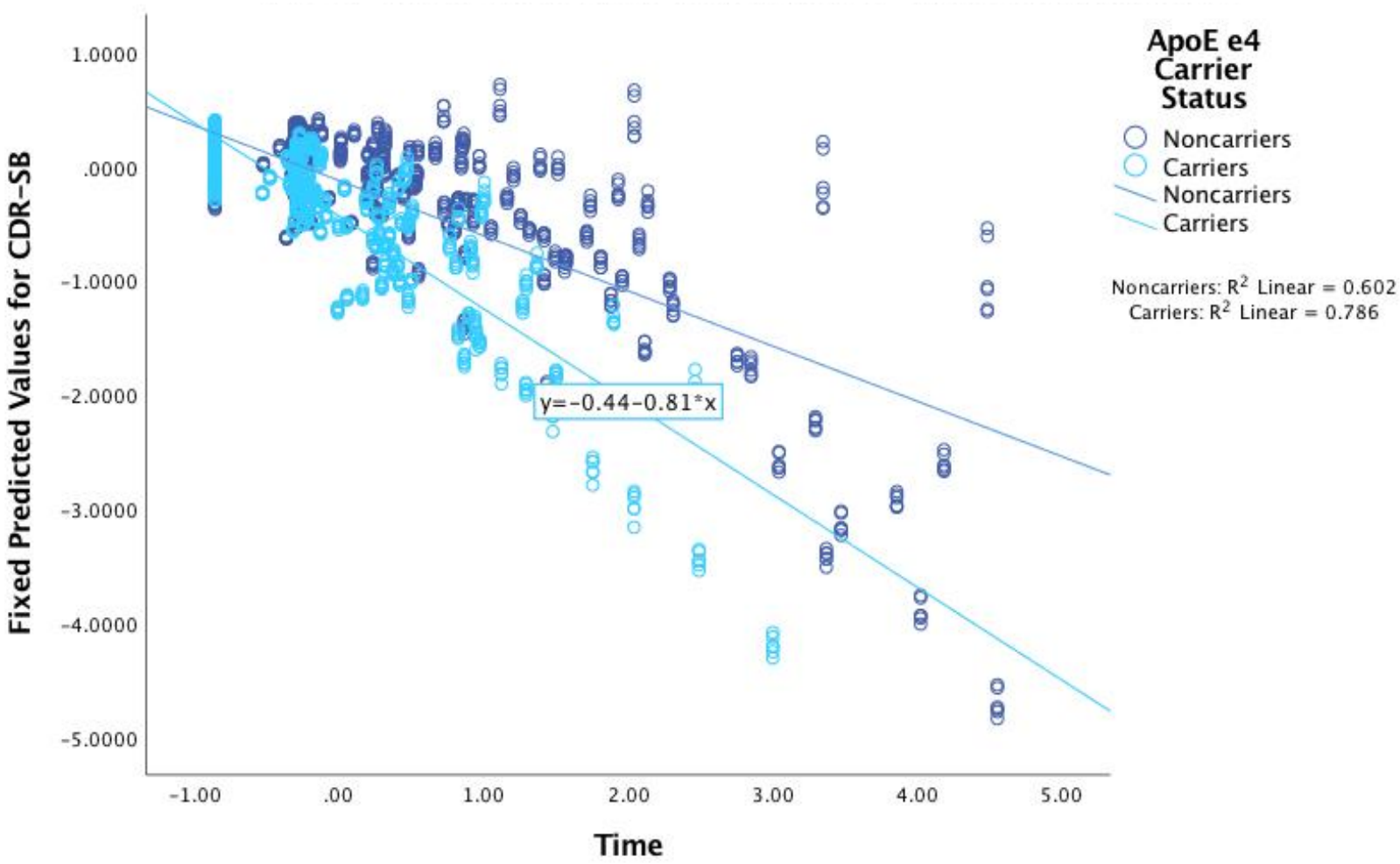

Figure 3. Rate of decline on the CDR-SB for carriers and non-carriers of the ApoE ε4 allele. Time is a centered variable and Fixed Predicted Values for the CDR-SB are presented as z-scores.

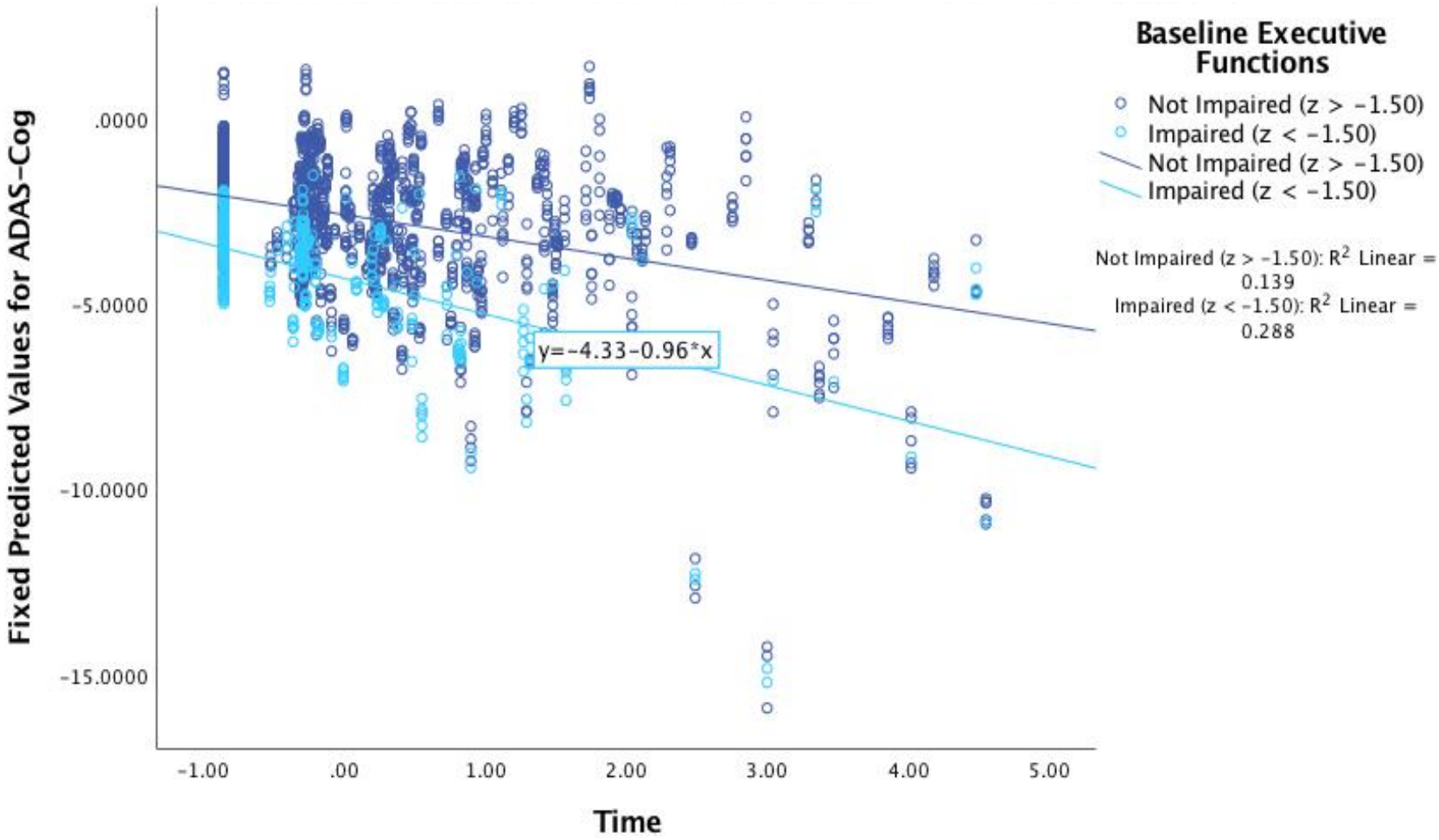

Figure 4. Rate of decline on the ADAS-Cog for impaired (z-scores ≤ -1.50) versus non-impaired (z-scores > -1.50) subjects on the Executive Functions composite score at baseline. Time is a centered variable and Fixed Predicted Values for the ADAS-Cog are presented as z-scores.

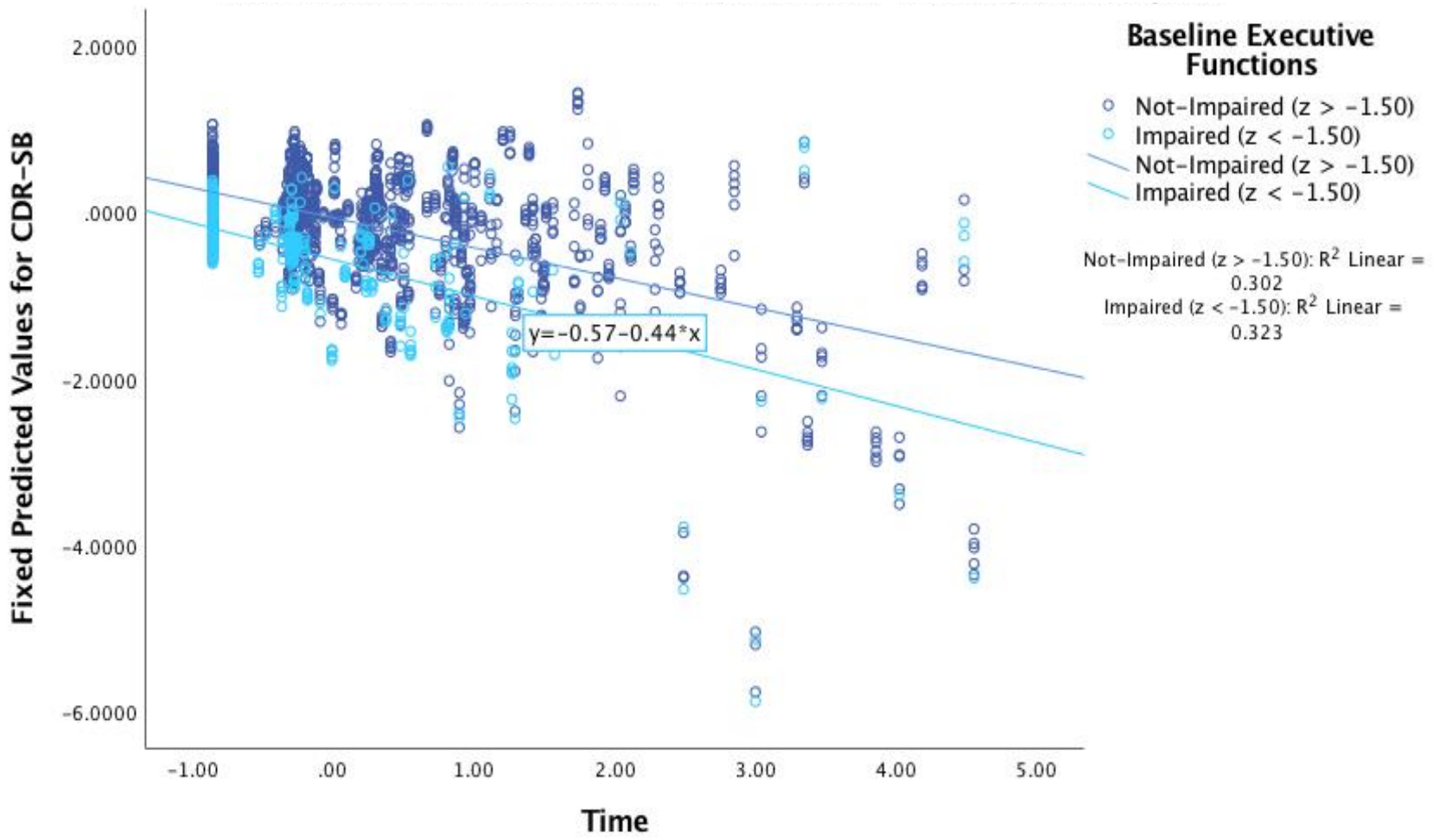

Figure 5. Rate of decline on the CDR-SB for impaired (z-scores ≤ -1.50) versus non-impaired (z-scores > -1.50) subjects on the Executive Functions composite score at baseline. Time is a centered variable and Fixed Predicted Values for the CDR-SB are presented as z-scores.

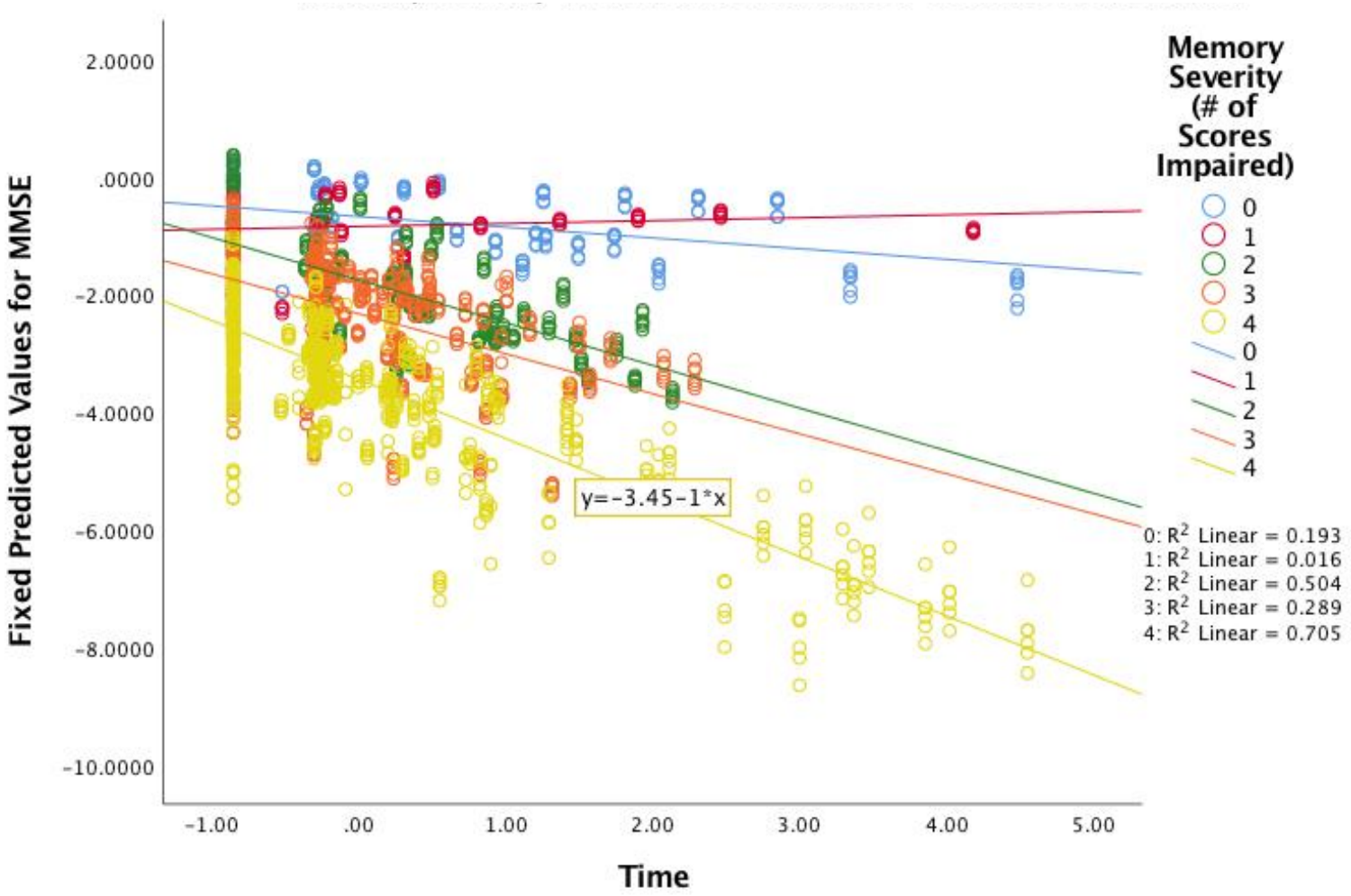

Figure 6. Rate of decline on the MMSE for subjects with increasing memory severity at baseline on the LM 1, LM 2, VR 1, and VR 2 (with z-scores ≤ -1.50). Time is a centered variable and Fixed Predicted Values for the MMSE are presented as z-scores.

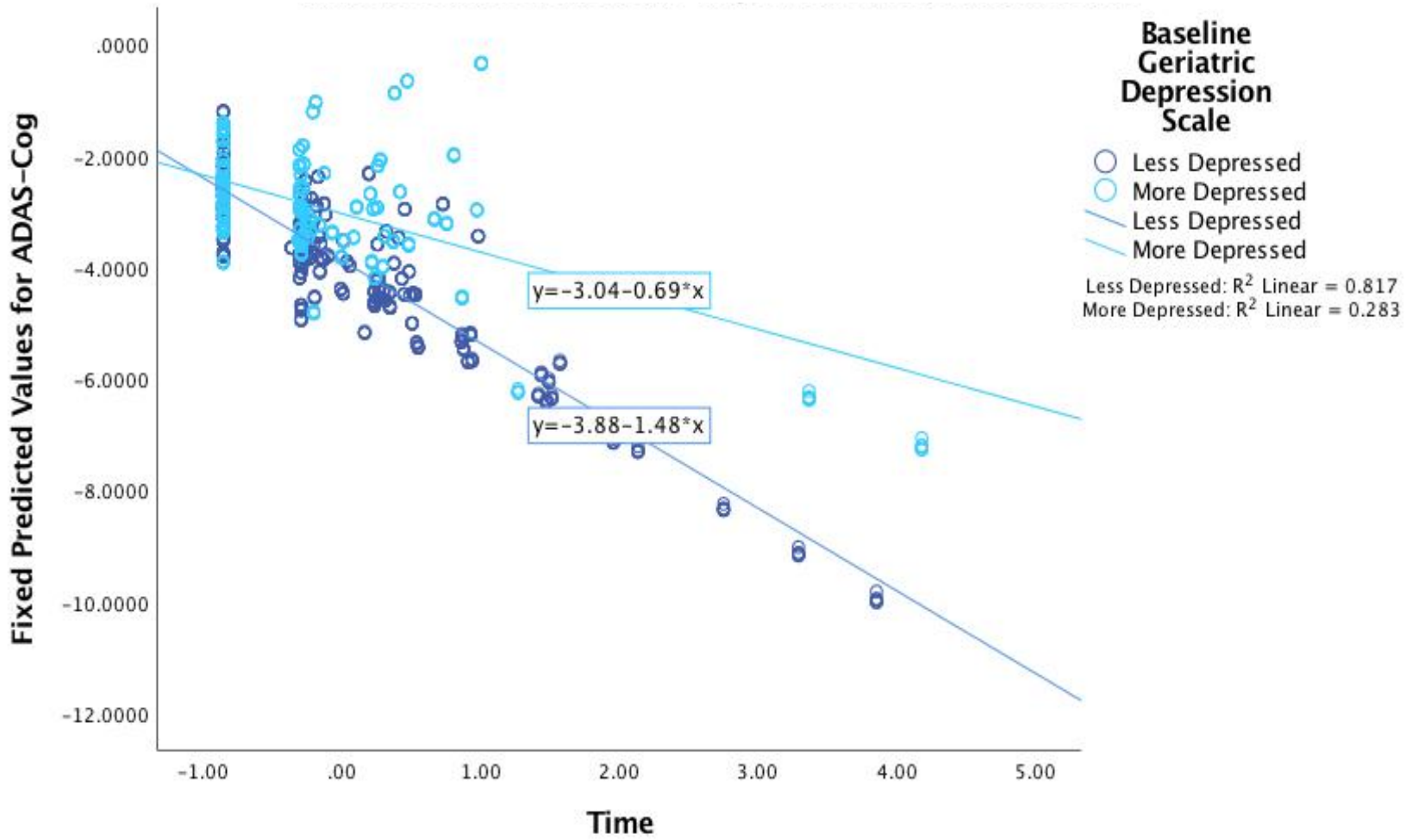

Figure 7. Rate of decline on the ADAS-Cog for subjects with lower baseline depression (GDS ≤ 5) versus higher baseline depression (GDS > 5). Time is a centered variable and Fixed Predicted Values for the ADAS-Cog are presented as z-scores.

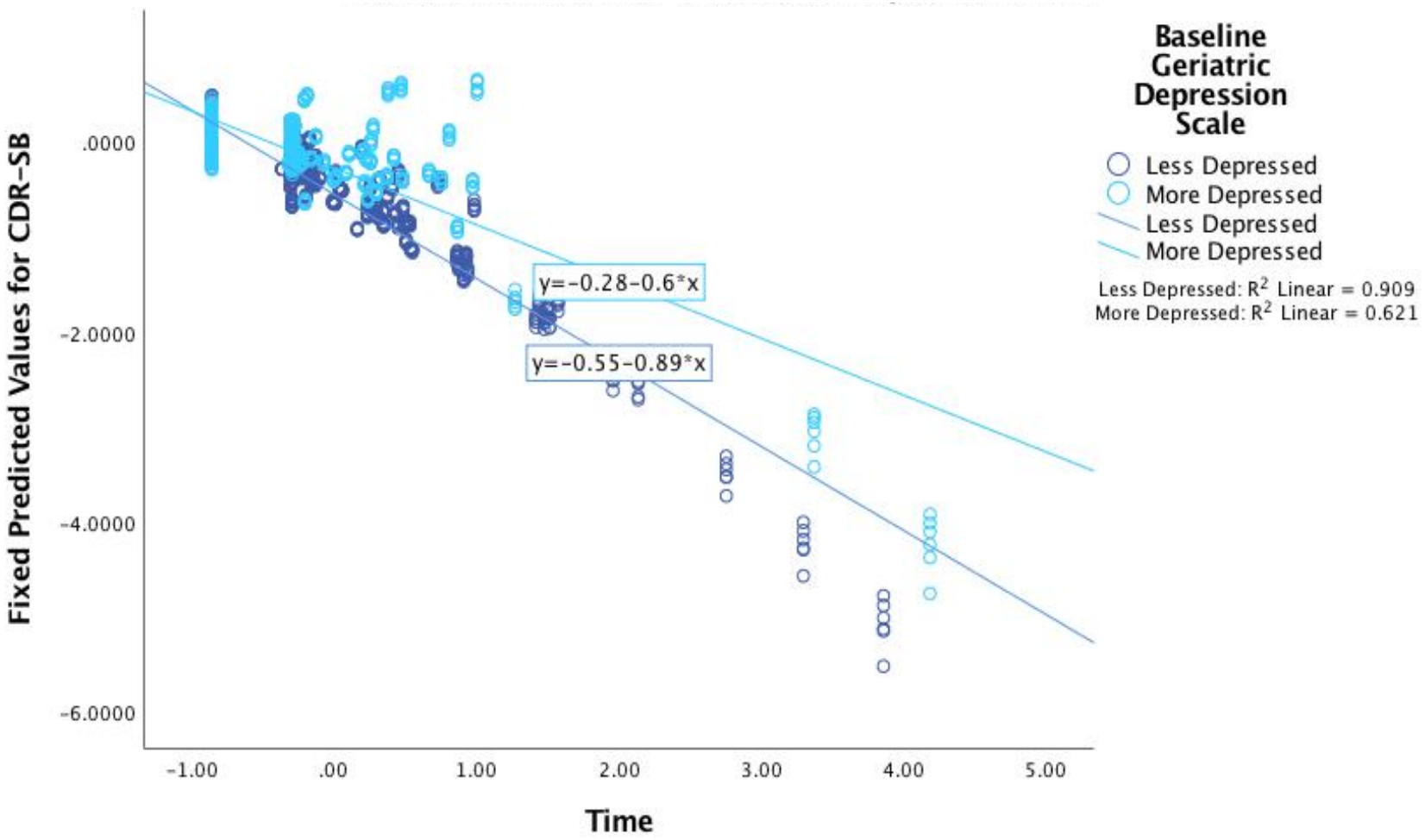

Figure 8. Rate of decline on the CDR-SB for subjects with lower baseline depression (GDS ≤ 5) versus higher baseline depression (GDS > 5). Time is a centered variable and Fixed Predicted Values for the CDR-SB are presented as z-scores.

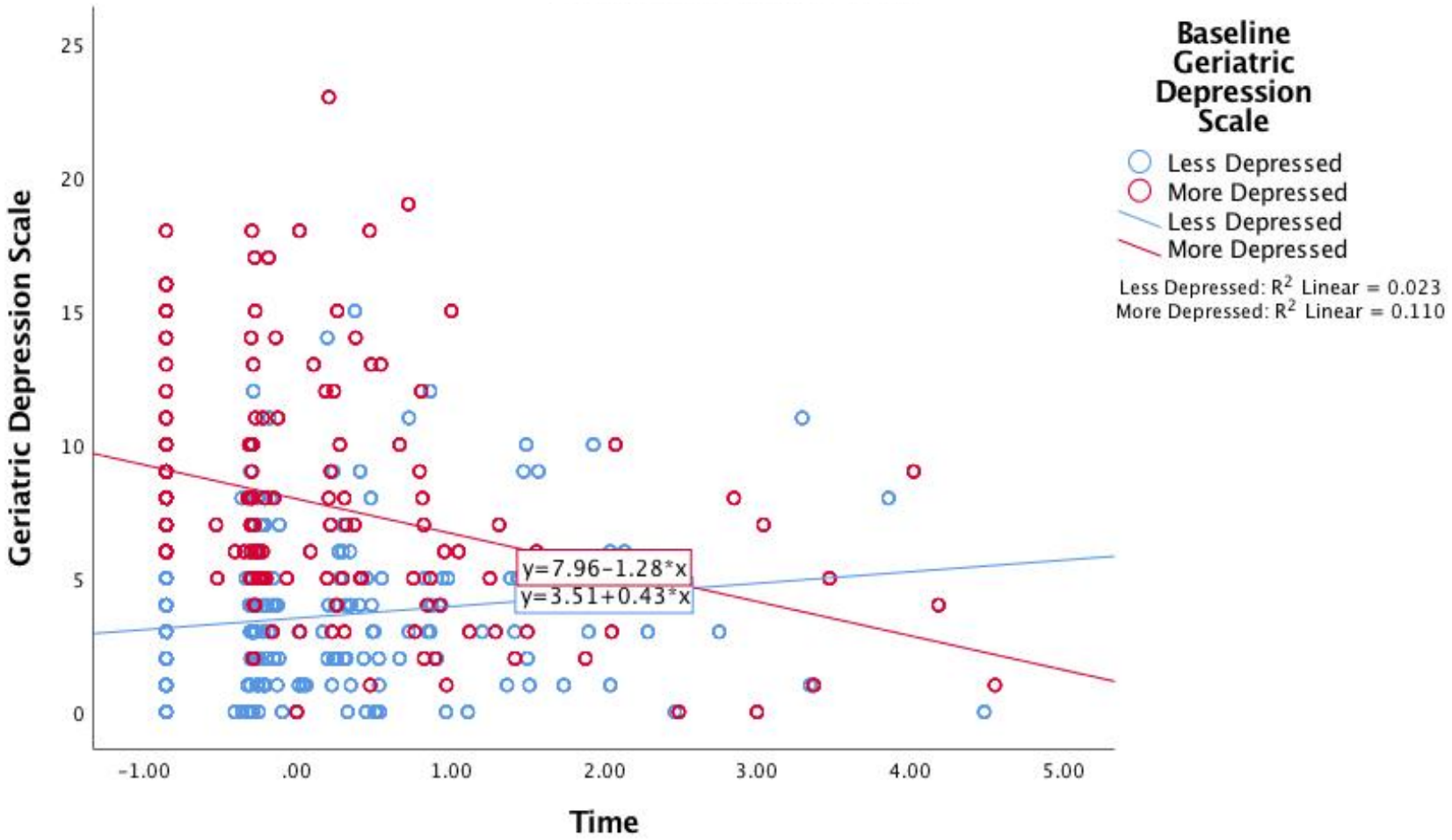

Figure 9. Changes on the GDS over time for subjects with lower baseline depression (GDS ≤ 5) versus higher baseline depression (GDS > 5). Time is a centered variable and GDS is presented as raw scores.

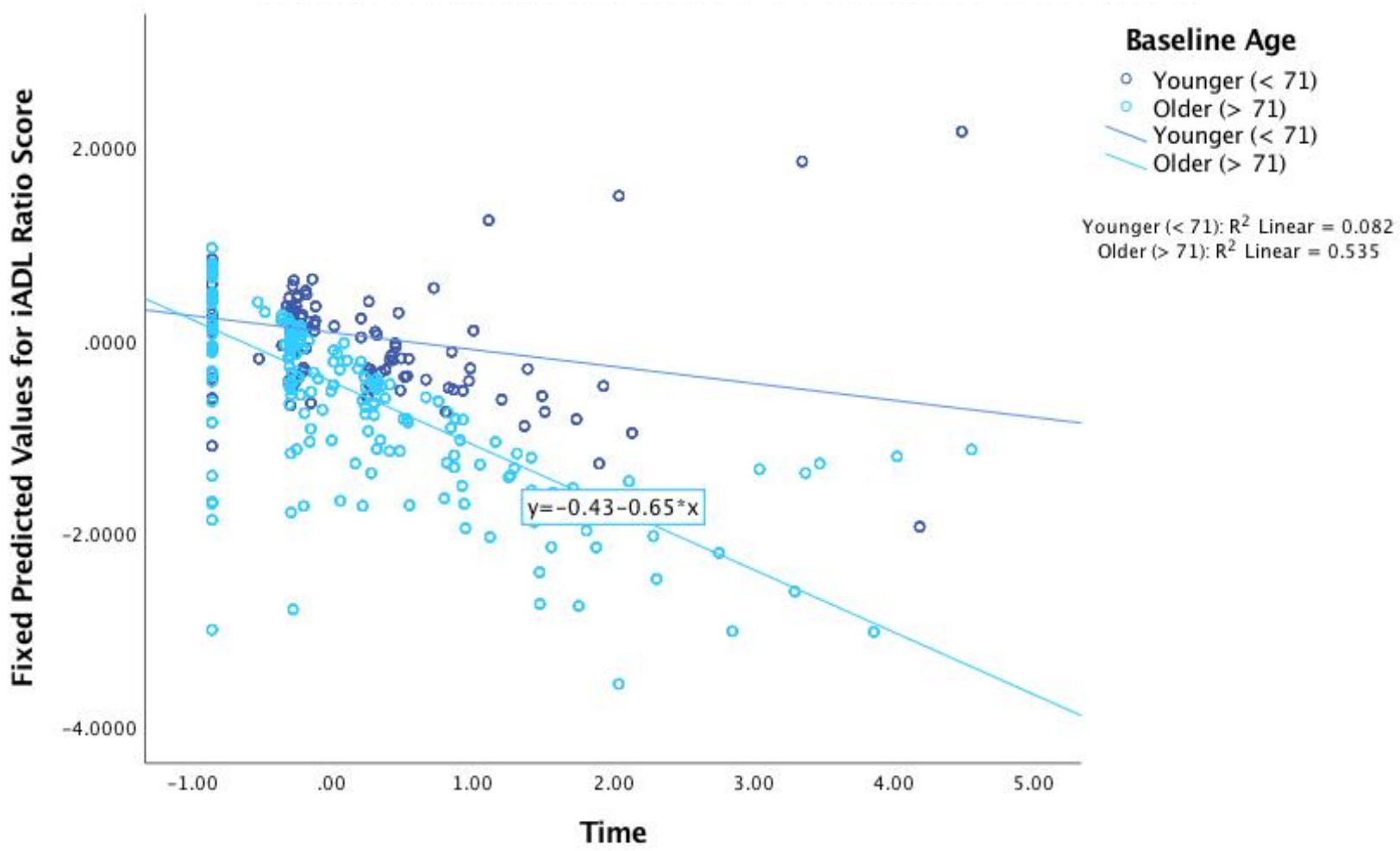

Figure 10. Rate of decline on the iADL Ratio Score for younger versus older subjects. Time is a centered variable and Fixed Predicted Values for the iADL Ratio Score are presented as z-scores.

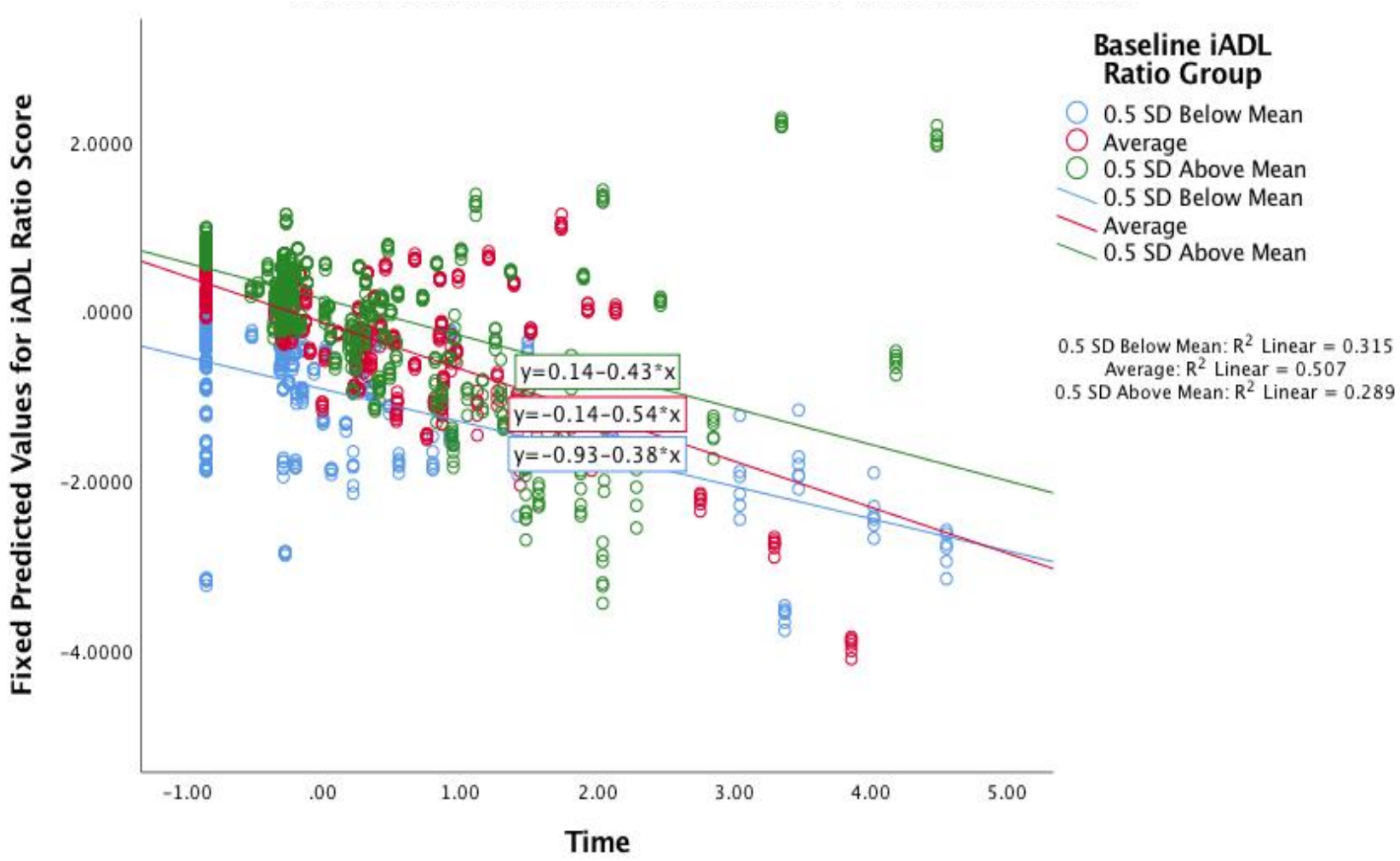

Figure 11. Rate of decline on the iADL ratio score for subjects with below average, average, and above average baseline iADL ratio Scores. Time is a centered variable and Fixed Predicted Values for the iADL Ratio Score are presented as z-scores.

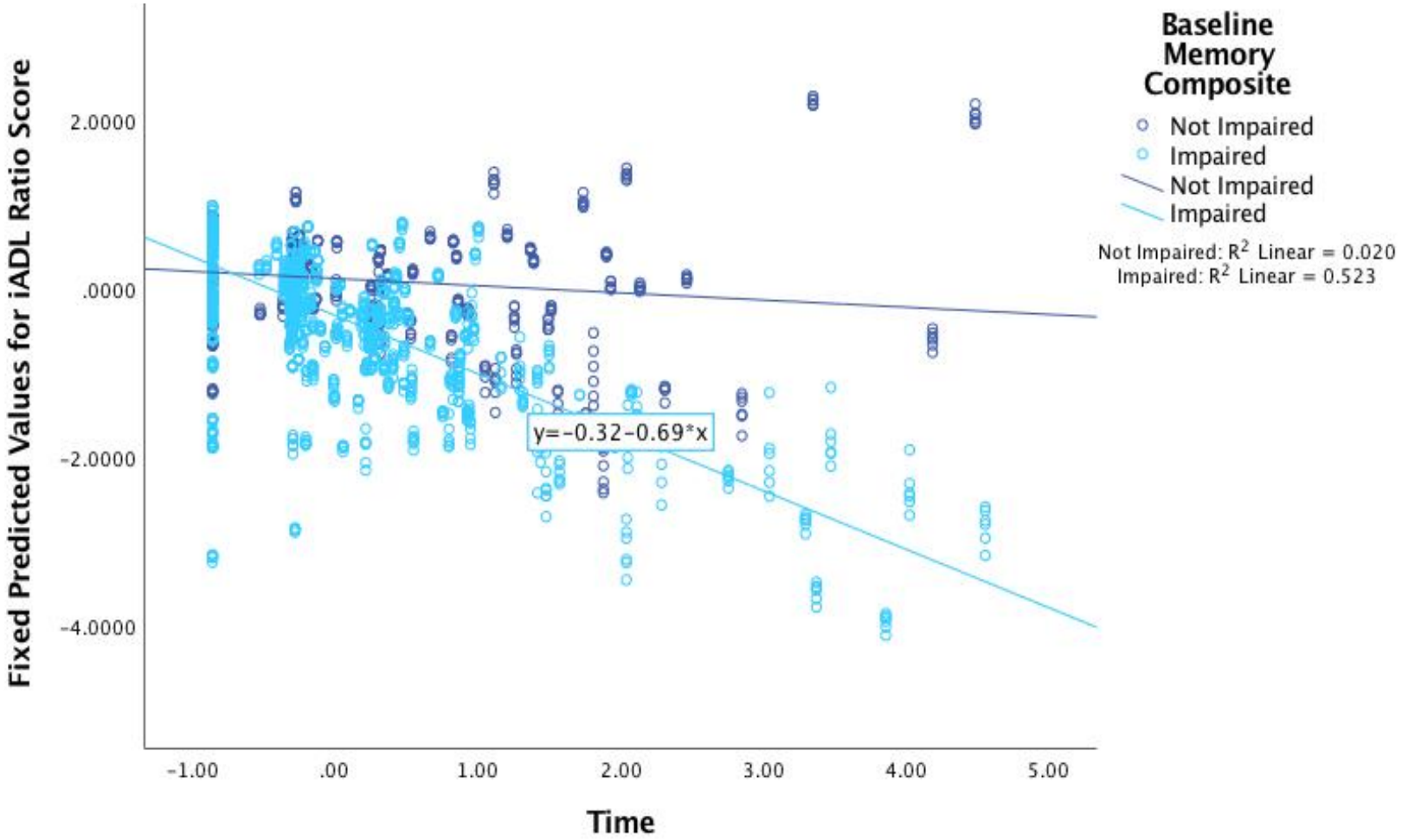

Figure 12. Rate of decline on the iADL ratio score for impaired (z-scores ≤ -1.50) versus non-impaired (z-scores > -1.50) subjects on the Memory composite score at baseline. Time is a centered variable and Fixed Predicted Values for the iADL ratio score are presented as z-scores.

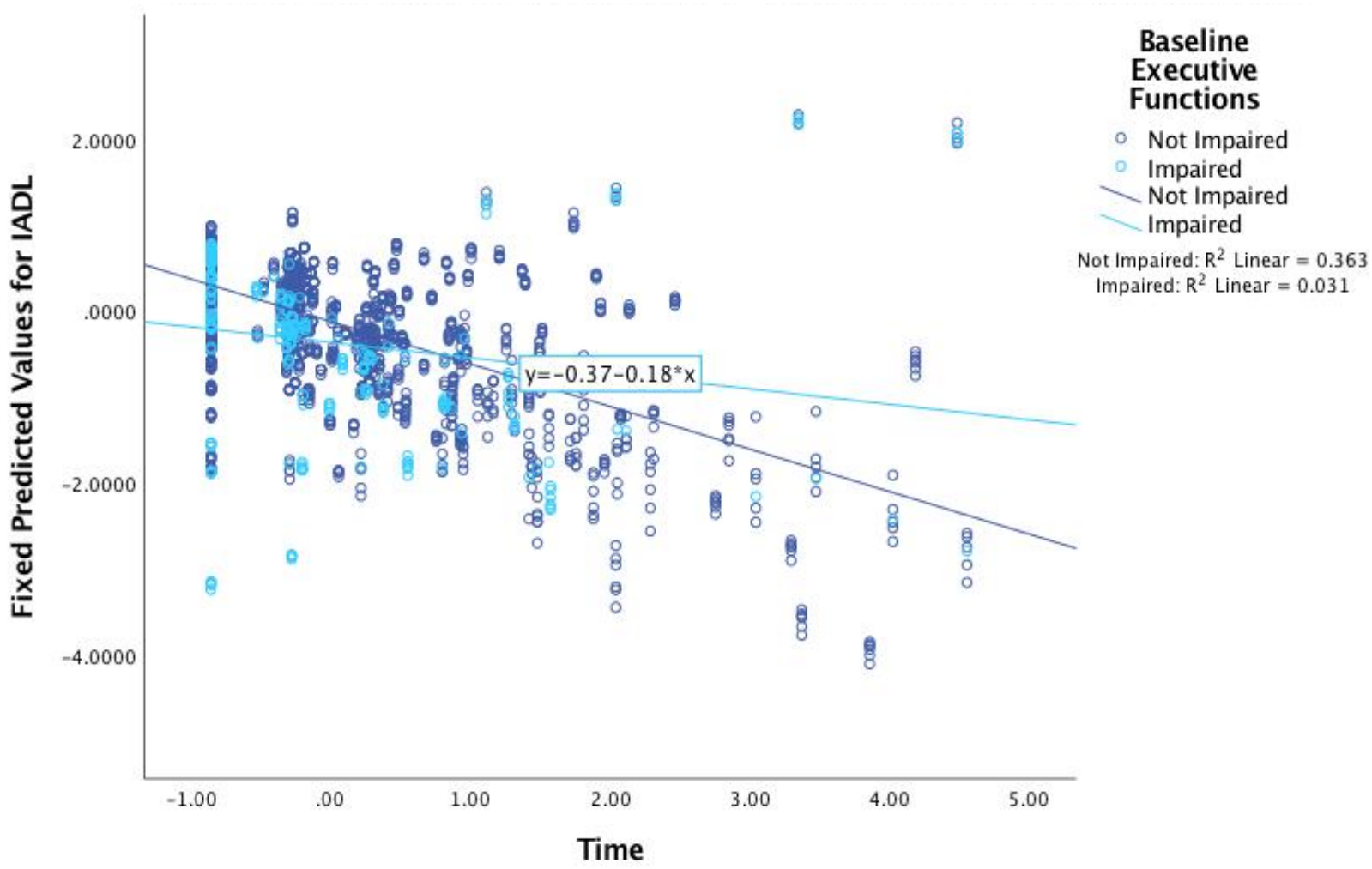

Figure 13. Rate of decline on the iADL ratio score for impaired (z-scores ≤ -1.50) versus non-impaired (z-scores > -1.50) subjects on the Executive Functions composite score at baseline. Time is a centered variable and Fixed Predicted Values for the iADL ratio score are presented as z-scores.

Appendix

Table 1

Descriptive Statistics and Comparisons of Different WAIS Versions of Subtests

WAIS Version		Mean Raw Scores (*SD's*) of WAIS Subtests	
		Similarities* (N = 437)	Digit Span LDSB (N = 437)
WAIS	R	18.35 (5.19) n = 118	4.56 (1.11) n = 119
	3	20.70 (6.26) n= 253	4.39 (1.09) n = 254
	4	25.27 (5.26) n = 66	4.69 (1.10) n = 64

Note. *Significance level = $p < .001$. Post-hoc analysis shows that all three versions of the WAIS were significantly different from one another at $p < .001$ significance level.

Table 2

Neuropsychological Test Performances of the Normal Control Sample

Measure	n	Mean	*SD*
Dementia Severity:			
ADAS-Cog Total	221	5.04	2.11
MMSE	222	29.20	1.14
Memory:			
Logical Memory I	123	27.70	5.65
Logical Memory II	122	23.85	6.90
Visual Reproduction I	222	34.03	4.64
Visual Reproduction II	221	29.70	7.32
Semantic Fluency	220	19.48	4.36
Executive Functions:			
Letter Fluency (FAS)	221	42.38	12.52
WAIS-R LDSB	125	5.29	1.34
WAIS-III LDSB	97	5.03	1.25
WAIS-R Similarities	92	25.60	4.39
WAIS-III Similarities	12	20.75	4.71
TMT, Part B	95	76.37	28.62
Stroop Task, C-W	82	39.74	10.01

Note: Mean raw scores are presented. CDR-SB scores had $M = 0$, $SD = 0$.