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Beta Amyloid, Tau, Neuroimaging, and Cognition: Sequence Modeling of Biomarkers for Alzheimer's Disease

S. Duke Han[1,2], **Jonathan Gruhl**[3], **Laurel Beckett**[4], **Hiroko H. Dodge**[5], **Nikki H. Stricker**[6,7], **Sarah Farias**[8], **Dan Mungas**[8], and **the Alzheimer's Disease Neuroimaging Initiative**[*]

[1]Department of Behavioral Sciences, Rush University Medical Center, Chicago, IL

[2]Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL

[3]Department of Statistics, University of Washington, Seattle, WA

[4]Department of Public Health Sciences, University of California Davis, Davis, CA

[5]Department of Neurology, Oregon Health and Sciences University, Portland, OR

[6]Psychology Service, VA Boston Healthcare System, Boston, MA

[7]Department of Psychiatry, Boston University School of Medicine, Boston, MA

[8]Department of Neurology, University of California Davis, Davis CA

Abstract

Alzheimer's disease (AD) is associated with a cascade of pathological events involving formation of amyloid-based neuritic plaques and tau-based neurofibrillary tangles, changes in brain structure and function, and eventually, cognitive impairment and functional disability. The precise sequence of when each of these disease markers becomes abnormal is not yet clearly understood. The present study systematically tested the relationship between classes of biomarkers according to a proposed model of temporal sequence (Jack et al., 2010). We examined temporal relations among four classes of biomarkers: CSF Aβ, CSF tau, neuroimaging variables (hippocampal volume, ventricular volume, FDG PET), and cognitive variables (memory and executive function). Random effects modeling of longitudinal data obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) was used to test hypotheses that putative earlier markers of AD predicted change in later markers, and that intervening markers reduced effects of earlier on later markers. Specifically, we hypothesized that CSF tau would explain CSF Aβ's relation to neuroimaging and cognitive variables, and neuroimaging variables would explain tau's relation to cognitive variables. Consistent with hypotheses, results indicated that CSF Aβ effects on cognition change were substantially attenuated by CSF tau and measures of brain structure and function, and CSF tau effects on cognitive change were attenuated by neuroimaging variables. Contrary to hypotheses, CSF Aβ and CSF tau were observed to have independent effects on neuroimaging and CSF tau had a direct effect on baseline cognition independent of brain structure and function. These results have implications for clarifying the temporal sequence of AD changes and corresponding biomarkers.

Corresponding Author: S. Duke Han, PhD, Department of Behavioral Sciences, 1645 W. Jackson Blvd. Ste. 400, Chicago, IL 60612; 312-942-2893 (phone), 312-942-4990 (fax), Duke_Han@rush.edu..

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Keywords

Beta Amyloid; Tau; Memory; Executive Functions; Neuroimaging

INTRODUCTION

Alzheimer's disease (AD) is a condition marked by progressive deterioration in episodic memory and other cognitive domains such as executive function (EF) abilities in old age. Characteristic neuropathological signs of AD include beta amyloid (Aβ) plaque and tau tangle pathology, with greater accumulation of these often corresponding, but not always, with clinical severity (Negash et al., 2011). AD currently affects an estimated 4.5 million persons in the US (Hebert et al., 2003), and by the year 2050, it is predicted to affect more than 13.5 million persons (Alzheimer's Association, 2009). Because of the great personal and societal health costs AD poses, the early identification of individuals at risk of developing a clinical diagnosis of AD is a paramount endeavor, particularly for the testing and development of any pharmaceutical or behavioral intervention program. Understanding the sequence of changes in measurable biomarkers is an important prerequisite for development of procedures for early identification of AD.

A variety of approaches have been utilized to identify predictive biomarkers for AD (Sperling et al., 2011). In particular, assays that measure levels of Aβ and tau in the cerebral spinal fluid (CSF) have proven to be useful in the discrimination of early AD from other age-related conditions (Hampel et al., 2003). Low concentrations of CSF $A\beta_{42}$ have been shown to correspond with Aβ neuropathology at autopsy (Strozyk et al., 2003). Higher levels of CSF tau are associated with general neuronal injury, and while nonspecific to AD, CSF tau is elevated in response to neurofibrillary tangle pathology (Buerger et al., 2006). Structural and functional neuroimaging biomarkers such as changes in hippocampal or ventricular volumetry and [^{18}F]fluorodeoxyglucose PET (FDG-PET) have also advanced our understanding of the progression of AD (Habeck et al., 2008; Jagust et al., 2010).

Clearly there are a number of biological brain changes at both the cellular and gross structural and functional level that are associated with AD. More recently interest has turned to better understanding the temporal relationship between these biomarkers. That is, which are the earliest abnormalities to appear and which occur later on and are driven by those earlier changes. Jack et al. (2010) proposed a cascade of biomarkers such that Aβ precedes tau-mediated neuronal injury; Aβ- and tau-mediated abnormalities precede neuroimaging biomarkers; and all of these precede cognitive change. Studies have confirmed high levels of Aβ are found in cognitively intact individuals, supporting the notion that Aβ deposition precedes cognitive change (e.g., Savva et al., 2009). CSF tau appears to predict cognitive decline in AD patients (Kester et al., 2009) suggesting that it possibly precedes cognitive decline. Evidence also suggests that FDG-PET changes (de Leon et al., 2001) and even structural brain changes such as hippocampal atrophy and increases in ventricular size (Jack et al., 2004) may precede cognitive changes in AD. Finally, while neuroimaging biomarkers and CSF tau are associated with cognition in a group spanning from normal to AD (normal, MCI, AD), only neuroimaging biomarkers are associated with cognition in a more advanced group (MCI and AD; Vemuri et al., 2009). This finding suggests that the effect of tau on cognition may be mediated by structural and functional brain changes as measured by neuroimaging.

In summary, there is indirect evidence to support the model suggesting that CSF markers (particularly Aβ) are among the earliest abnormalities associated with AD, followed by brain functional changes (e.g. PET), and structural changes (e.g. hippocampal atrophy and

ventricular enlargement), followed by declines in cognition. However, few studies have attempted to examine the inter-relationships between changes at all of these levels. We sought to test a proposed biomarker sequence by using longitudinal data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Specifically, we hypothesized that (1) CSF Aβ would relate to CSF tau, and would predict change in neuroimaging biomarkers (hippocampal volume, ventricular volume, and FDG-PET) and cognitive variables (memory and executive functioning) because the latter are all hypothesized to be downstream to (i.e. occur later than) amyloid aggregation; (2) CSF tau would predict change in neuroimaging biomarkers and cognitive variables, again because tau is presumably upstream from the brain imaging and cognitive changes; (3) change is neuroimaging biomarkers would explain change in cognitive variables because these variables are hypothesized to be proximate to cognitive decline, and finally (4) that the effects of upstream events would not be related to downstream events after accounting for intermediate steps. Specifically, we hypothesized that Aβ would not be related to neuroimaging and cognitive variables independent of tau, and tau would not be related to cognition independent of neuroimaging variables.

METHOD

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, to participate in the research, approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years and 200 people with early AD to be followed for 2 years.” For up-to-date information, see www.adni-info.org.

Clinical characterization, CSF biomarker acquisition, imaging acquisition and processing, and cognitive measurements for ADNI are described in detail elsewhere (e.g, Petersen et al., 2010; Jagust et al., 2010). A total of 819 individuals received baseline ADNI evaluations that included structural MRI scans and neuropsychological testing. A subset agreed to lumbar puncture to obtain a CSF sample, and a different subset received an FDG PET scan. CSF measures for this study were cross-sectional, from the baseline evaluation. MRI measures of brain structure and neuropsychological measures of cognition were longitudinal, as was FDG PET for the PET subsample. We selected an analysis subsample of cases that had baseline CSF variables and longitudinal measures of cognition, structural MRI, and FDG PET. This yielded a sample of 172 individuals (41 had a clinical syndrome diagnosis on normal cognition, 85 had mild cognitive impairment (MCI), and 46 had Alzheimer's disease (AD)).

Measures of Aβ and total tau were obtained from CSF. CSF and neuroimaging protocols are described in detail at http://www.loni.ucla.edu/ADNI/Research/Cores/. Two T1-weighted volumes were acquired for each participant. Volumetric (Fischl et al., 2002; Fischl, Salat et al., 2004) and cortical surface reconstruction (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999; Fischl, van der Kouwe et al., 2004) methods based on FreeSurfer software, optimized for use on large, multi-site datasets, were used. FDG PET was an average of mean PET counts, normalized to cerebellum, in five regions of interest: left and right temporal lobes, left and right angular gyrus, and posterior cingulate. Structural MRI measures of ventricular volume and hippocampal volume were also used. We considered two different cognitive outcome measures. We used a composite score from the Rey Audio Verbal Learning Test (AVLT, Ivnik et al., 1990) as a measure of episodic memory. This score was the sum of number of words recalled on trial 2, trial 3, trial 4, trial 5, short delay free recall, and long delay free recall. To gauge executive function, we relied on a latent variable model-derived quantity. The latent variable model utilized participant responses to Clock Drawing, Digit Span, Trail-Making Test and Category Fluency in order to derive a composite measure of executive function, labeled as “ADNI-EF”.

All variables (CSF biomarkers, neuroimaging variables, cognition) were normalized using the Blom function (Blom, 1958). In order to explore the hypothesized temporal sequence for different sets of biomarkers, we fitted a sequence of linear mixed effects models to the longitudinal ADNI data. Linear mixed effects models (Diggle et al., 2002) represent longitudinal data by including individual-specific random effects that accommodate the correlation among observations from the same individual. Each model included a random intercept and a random coefficient for time. The random intercept estimates the baseline value of the longitudinal dependent variable and the random time coefficient estimates annual rate of change. Random time coefficients account for divergence of longitudinal trajectories from baseline values, a common finding in longitudinal studies of cognitive aging (Mungas et al., 2010; Wilson et al., 2002).

A hypothesis based sequential model development process was followed with additional independent variables added at each stage (Table 1): 1) CSF variables were independent variables (Aβ in Model 1a, Tau in Model 1b) and neuroimaging and cognition variables (baseline and change) were dependent variables, 2) CSF Aβ and Tau were jointly entered as independent variables predicting neuroimaging and cognition, 3) CSF Aβ and Tau, and baseline values of FDG PET and structural MRI (hippocampus and ventricle volumes) were joint independent variables predicting cognition measures, and 4) CSF Aβ and Tau, and baseline and change in FDG PET and structural MRI (hippocampus and ventricle volumes) were joint independent variables predicting cognition measures. The PET and MRI change measures were time varying independent variables and were coded as the value for a given follow-up scan minus the value for the initial scan. Main effects of baseline independent variables in these models estimated their effects on the baseline value of the dependent variable. Interactions of these baseline independent variables with time were also included to estimate effects on change in the dependent variable. The time varying independent variables in Model 4 estimated the change in dependent variables associated with change in the independent variables. We compared the coefficients of terms involving CSF Aβ across models 1-4 to test our primary hypotheses. Specifically we expected that Aβ effects on neuroimaging in Model 2 (Aβ + Tau) compared to Model 1a (Aβ alone) would be diminished. Diminishing Aβ effects on cognition from Model 1a (Aβ) to Model 4 (Aβ, Tau, neuroimaging) were expected with non-significant contribution of Aβ independent of Tau and neuroimaging variables. Similarly, we hypothesized a diminishing effect of CSF tau on cognition from Model 2 (Tau + Aβ) to Model 4 (Tau, Aβ, neuroimaging) and non-significant Tau effects independent of neuroimaging variables.

All models controlled for gender, education, age at baseline, and time elapsed since the baseline observation in years. Additionally, for the models with AVLT score as an outcome, we included a time varying covariate to account for which of two alternate forms of the AVLT was administered. Models that included structural MRI variables also included baseline intracranial volume as a covariate. Models were fitted using maximum likelihood estimation implemented in the nlme package in R. We compared models with different sets of random effects using the Akaike Information Criterion and Bayesian Information Criterion as a guide. In comparing two models, the model with the lower values for these information criteria is preferred. Both information criteria supported the inclusion of a random slope along with a random intercept in our model as compared to a model with a random intercept only (Verbeke & Molenberghs, 2000).

RESULTS

Demographics

Out of 819 participants in ADNI, 172 met inclusion criteria for this study. Clinical characterization of ADNI participants is detailed in a previous report (Petersen et al., 2010). Table 2 displays the baseline mean and accompanying standard error of demographic, biomarker, and cognitive measures for the participants by diagnosis.

Neuroimaging Outcomes

There were 728 observations for the 172 cases that had complete data at all evaluations for measures of hippocampal volume (HC), ventricle volume (VV), and FDG PET (PET). Table 3 shows results from Model 2 in which baseline Aβ and tau were joint predictors of longitudinal change of HC, VV, and PET. Aβ and tau had independent effects that were similar in magnitude on baseline and change for both HC and VV. Both Aβ and tau were independently related to baseline PET, but only tau was associated with PET change. We compared the magnitude of Aβ coefficients in Model 1a (Aβ alone) and Model 2 (Aβ and tau) to determine if there was evidence that tau mediates some of the effect of Aβ. The Aβ effect on baseline HC declined 19% from Model 1a to Model 2 (0.286 to 0.231), and the effect on HC change declined 33% (0.026 to 0.017). The Aβ effect on baseline VV increased by 37% (-0.110 to -0.150) and the effect on VV change decreased 25% (-0.027 to -0.020). The Aβ effect on baseline PET decreased by 17% (-0.276 to -0.228), but Aβ was not related to PET change in either analysis (p's =0.14, 0.60). To summarize, these results show that Aβ and tau have independent effects on brain structure and function. The magnitude of Aβ effects declined by 17-33% after controlling for tau. The Aβ effect on baseline VV actually increased after accounting for tau.

Cognition Outcomes

Table 4 shows results for Model 4, where Aβ, tau, and baseline and change for neuroimaging variables all were predictors of baseline cognition and cognitive change. The pattern of results associated with Aβ and tau was similar for AVLT and ADNI-EF. Tau was related to the baseline estimates of cognitive variables after controlling for Aβand baseline and change in neuroimaging variables. In contrast, Aβ was not independently related to baseline cognition and neither Aβ nor tau was related to AVLT or ADNI-EF change independent of the other independent variables in Model 4.

Figure 1 presents magnitude of effects on AVLT for all biomarker independent variables in all models, and Figure 2 shows the same results for ADNI-EF. The magnitude of the association of CSF Aβ with baseline memory and executive function decreased sharply as additional independent variables were added in Models 2, 3, and 4, dropping by about 35% with the addition of CSF tau and by over 90% with the further inclusion of MRI and FDG-

PET biomarkers. In contrast, tau still was associated with baseline estimates of both cognitive variables in Model 4. However, the tau effect on baseline did diminish nearly 43% for AVLT and 23% for ADNI-EF after controlling for Aβ and neuroimaging variables. The Aβ effect on AVLT change was diminished by 79% by tau and neuroimaging variables, and for ADNI-EF, was diminished by nearly 72%. Tau effects were diminished by 60% for AVLT change and 90% for ADNI-EF.

To summarize results from these sequential models, both Aβ and tau were related to cognitive baseline score and subsequent cognitive change when they were entered alone. Effects of Aβ and tau on longitudinal trajectories of cognitive variables were not significant in models that involved both CSF measures and baseline and change for the neuroimaging variables. Tau continued to have significant effects on baseline values of both cognitive measures. Figure 3 illustrates the impact of CSF Aβ on longitudinal trajectories for AVLT before and after controlling for CSF tau and neuroimaging variables. Figure 4 similarly presents the same results for CSF Tau. These graphs compare a hypothetical participant with average CSF Aβ (Figure 3) or CSF tau (Figure 4) to a participant with one standard deviation less CSF Aβ or one standard deviation greater CSF tau who is average on other variables in the model.

Our primary analyses were performed using a combined ADNI sample that included cognitively normal individuals and patients with MCI and clinical AD. We were interested in evaluating the relations among various biomarkers of AD across a broad spectrum from absence of clinical symptoms to clear presence of clinical impairment. In addition, there was considerable overlap of distributions of all study variables across the three diagnostic groups, which provides support for the notion that they are measuring continuous processes that quantitatively differ as a function of clinical severity but are not qualitatively different processes. However, to address the potential concern that relations among variables are primarily determined by non-specific diagnostic group difference, we did perform secondary analyses in which clinical diagnosis at baseline evaluation was added as a covariate to analytic models, and the overall pattern of results did not substantially differ (results not shown).

DISCUSSION

We utilized longitudinal models of different classes of biomarkers to test hypotheses derived from the Jack model (Jack et al., 2010) about the temporal sequence of biomarkers. As expected, CSF Aβ and tau were independently associated with brain structure and function, and all classes of biomarkers that we investigated (CSF Aβ, CSF tau, neuroimaging) were independently associated with the cognitive outcomes of episodic memory and executive functioning. The focus of our analysis strategy was to examine how these individual relations changed as additional explanatory variables, downstream in the Jack model, were added. Results generally supported hypotheses derived from the Jack model. CSF Aβ effects on neuroimaging and cognitive outcomes were significantly diminished by controlling for CSF tau and independent effects on cognitive outcomes were not present after accounting for neuroimaging variables. Similarly, CSF tau effects on cognitive change were attenuated substantially by effects of neuroimaging variables. Results deviated from expectations generated by the Jack model in that CSF Aβ had effects on brain structure and function that were independent of CSF tau, and CSF tau had effects on baseline cognition that were independent of neuroimaging measures. There were some minor differences in the pattern of results for neuroimaging measures as outcomes, where CSF tau was more specifically related to FDG PET.

The Jack model derives from a substantial foundation of research that identifies production of Aβ as a critical step in the causal sequence leading to brain degeneration and cognitive impairment. Aβ is posited to have a direct neurotoxic effect, leading to impaired tau processing, impaired cell function presumably reflected at an aggregate level by FDG PET, to cell death reflected at an aggregate level by brain atrophy, and eventually to impaired cognition resulting from the structural and functional changes occurring in the brain. This is a causal model in which tau mediates effects of Aβ, and neuroimaging variables mediate effects of tau (and Aβ through tau). The sequence of analyses in this study was designed to examine relations among CSF Aβ and tau and longitudinal trajectories of brain structure, brain function, and cognition to test mediation effects predicted by the Jack model.

Longitudinal studies have major advantages for studying causal mediation. Cross-sectional studies are limited by correlations obtained at one point in time, and can provide misleading information about true longitudinal relationships in causal pathways (Maxwell & Cole, 2007). An important advantage of longitudinal studies is that they can utilize information about temporal precedence, an important criterion for causal inference (MacKinnon et al., 2007). Studies in which proposed mediator variables are measured longitudinally are especially valuable because they can be used to evaluate how change in the final outcome is mediated by change in intervening variables (Cole & Maxwell, 2003, MacKinnon et al., 2007, Maxwell & Cole, 2007). However, there are complex issues that impact how effective a specific study will be for testing causal hypotheses. The amount of follow-up time and the lag between predictors and outcomes in particular are important considerations that apply to this specific study and present limitations with respect to conclusions about causal mediation.

The overall duration of this study was only 36 months, and it seems likely that changes in Aβ impact cognition, brain structure and function, and even changes in tau, with a lag of more than three years. For example, there are recent estimates that Aβ production in AD may begin decades before clinical changes (Negash et al., 2011). It is also conceivable that cognitive changes could lag brain function and structure changes by more than three years. FDG PET studies have shown reduced cortical metabolism in genetically at risk, cognitively normal individuals who are substantially younger than the typical age of onset of the earliest clinical symptoms of AD (Reiman et al., 2005). Consequently, the relatively short duration of follow-up in this study could limit ability to detect the full effects of earlier variables in the hypothesized sequence on later variables. Despite this important limitation, CSF Aβ and CSF tau individually had robust relations with brain imaging and cognitive measures. This indicates that a cross-sectional snapshot of the Aβ and tau profile at baseline is informative about the baseline values of the other variables and about change in those variables, and shows that this study was able to detect biological and cognitive effects of Aβ and tau. However, Aβ and tau did not explain cognitive change beyond effects of brain function and structure. The observed pattern of results provides evidence to support mediation of Aβ and tau effects on cognition by brain function and structure. That is, Aβ and tau individually were related to cognition and were related to brain function and structure, brain function and structure were related to cognition, but Aβ and tau were not related to cognitive change independent of brain function and structure. While these results are consistent with hypothesized mediation effects, research with substantially longer follow-up that corresponds to the time frame for transition from normal levels of Aβ and tau to clinical AD would provide a more definitive test.

One proposed mechanism for the association between increased Aβ and neuronal death involves a greater neural susceptibility to oxidative stress (Butterfield et al., 2002). These results are also consistent with CSF Aβ's hypothesized role as one of the earliest biomarkers for AD. However, while it is certainly plausible that Aβ precipitates the clinicopathological

symptom cascade of AD, it is clear that elevated levels of Aβ are not sufficient to produce clinical AD since many nondemented, cognitively-intact older adults show CSF, neuroimaging, and autopsy evidence of elevated levels of Aβ (Negash et al., 2011). Therefore, models of Aβ 's role in AD neuronal degeneration and cognitive deterioration must also address the lack of cognitive deterioration in nondemented cases. Results of this study suggest that the most likely explanation is that Aβ in isolation does not cause cognitive impairment, but does initiate a cascade of brain changes that leads to subsequent cognitive impairment; Aβ in the absence of downstream changes is not sufficient to cause cognitive decline.

The observations from this study that CSF Aβ and CSF tau made independent contributions to brain changes and that tau had effects on baseline cognition that could not be explained by brain structure and function are not entirely consistent with the Jack (2010) model. The level of analysis that was possible in this study could impact these findings. Our measures of Aβ and tau were aggregate measures, summed across the whole brain, that likely represent complex effects of multiple production and clearance mechanisms. Similarly, our measures of ventricle volume and FDG PET were aggregates involving the whole brain. Much of the earlier research supporting the amyloid hypothesis and the Jack model is based on molecular and cellular changes, and it is possible that such changes, occurring as hypothesized, might not show the same temporal relations when applied to the whole brain. This clearly is an issue that warrants further research. While the CSF measures of Aβ and tau are inherently aggregate measures, a high level of specificity of neuroimaging variables by brain regions and functional systems is possible within ADNI, and these measures might be useful for more refined studies of how AD progresses. For example, the highly influential Braak and Braak model for staging of AD neuropathology (Braak, Braak, & Bohl, 1993) could be tested using longitudinal, in-vivo data to address progression of changes in region-specific medial temporal and neocortical brain measures, how they relate to CSF Aβ and tau, and how they correspond to predicted domain-specific changes in episodic memory and executive function.

The effect of CSF tau on baseline cognition independent of brain structure and function also merits comment. Human and animal models have implicated tau's potentially greater role than Aβ in cognitive impairment (e.g., Oddo et al., 2006; Dowling et al., 2010); however, few studies have directly compared the contribution of imaging biomarkers and tau upon cognition over time. Baseline values in a study using a sample that is heterogeneous with respect to disease progression (normal, MCI, clinical AD) represent a cross-sectional snapshot of the accumulated effects of any biological changes that have occurred prior to the initial assessment. It is possible that the tau effects on baseline cognitive measures represent a cumulative effect of tau over a longer time frame than was covered by the longitudinal part of this study, and consequently, this may provide a more sensitive indicator of the effect of tau on longitudinal change. If this is the case, one might expect independent tau effects on longitudinal change in a study with longer follow-up. The inherent problems of using cross-sectional data to make inferences about longitudinal relationships (Maxwell & Cole, 2007) temper any conclusions that can be made about this finding, and this clearly is an open question for further research.

The well-documented heterogeneity in longitudinal trajectories as people age (Mungas et al., 2010, Wilson et al., 2002) presents a challenge in terms of finding variables that explain and predict who will and will not lose cognitive ability. This study included a diverse sample that, by design, incorporated heterogeneous trajectories; that is many MCI and most AD cases would be expected to decline at relatively rapid rates, while most normals and some MCI would likely show lesser to no cognitive decline. The basic approach in this study was to use continuous measures of CSF and neuroimaging biomarkers as measures of AD

severity that would be useful for explaining this heterogeneity. Underlying this approach is the notion that AD severity is an important determinant not only of who does and doesn't decline cognitively, but also of rate of decline. Our study used linear models to characterize and explain trajectories, and this presents a limitation to the extent that non-linear trends are present.

A number of other studies have taken a somewhat different approach to explaining variability in longitudinal trajectories. These studies generally have compared non-demented individuals who develop MCI or dementia during follow-up with individuals who do not develop dementia, and have used change point analyses to model non-linear trends (Howieson et al., 2008; Jacqmin-Gadda, Commenges, & Dartigues, 2006; Johnson et al., 2009; Yu & Ghosh, 2010). Change in clinical diagnoses over time has been used in these studies to identify more homogenous subgroups, time to diagnosis has guided modeling of differential linear and non-linear trends in these groups, and ultimately, these studies explain heterogeneity of cognitive trajectories. Variables like CSF Aβ and tau might prove to be similarly useful for identifying more homogenous subgroups within the general heterogeneity of cognitive trajectories. For example, studies of differential trajectories within homogenous groups defined by CSF Aβ and tau could contribute to understanding the overall biological sequence across the spectrum of AD related changes. ADNI is ideally suited to this type of study, and this is a logical next step to follow this study.

There are important limitations of the present study. Representativeness of the ADNI sample is an important concern. The sample is a highly selected cohort of well-educated participants and it is not a community-based sample. Therefore, caution must be exercised in generalizations of implications drawn from the ADNI sample to more diverse community populations. A second limitation, previously identified, is that the duration of longitudinal follow-up in this study was relatively brief in comparison with current estimates of the temporal progression of AD related changes, which may limit our ability to characterize longitudinal relationships. A third, related limitation is the use of linear models to characterize and explain longitudinal change. Non-linear models might be more appropriate for describing the development of AD related change over longer periods, but the short follow-up time in this study limits the use of non-linear models. A fourth limitation is the restricted age range of the sample. There is some evidence that biomarkers may be sensitive at even earlier age ranges, and this could not be investigated with the current data. Finally, the lack of comprehensiveness of biomarkers investigated in the present study is a limitation. Amyloid imaging might be especially relevant, but has been collected on only a limited number of ADNI participants to date. Neuroimaging of tau is potentially important but currently is not available.

Despite these limitations, this study makes unique contributions. The use of a large multidimensional and longitudinal dataset afforded the opportunity to systematically test hypotheses about the temporal relationships among multiple biomarkers. To our knowledge, this is the first systematic, longitudinal assessment of the temporal sequencing of biomarker classes in AD. Future studies are needed to clarify the broader implications of this study for understanding and measuring AD progression in clinical and community samples.

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ABBREVIATIONS

CEHR	crown ether host-rotaxane
Boc	*t*-butoxycarbonyl

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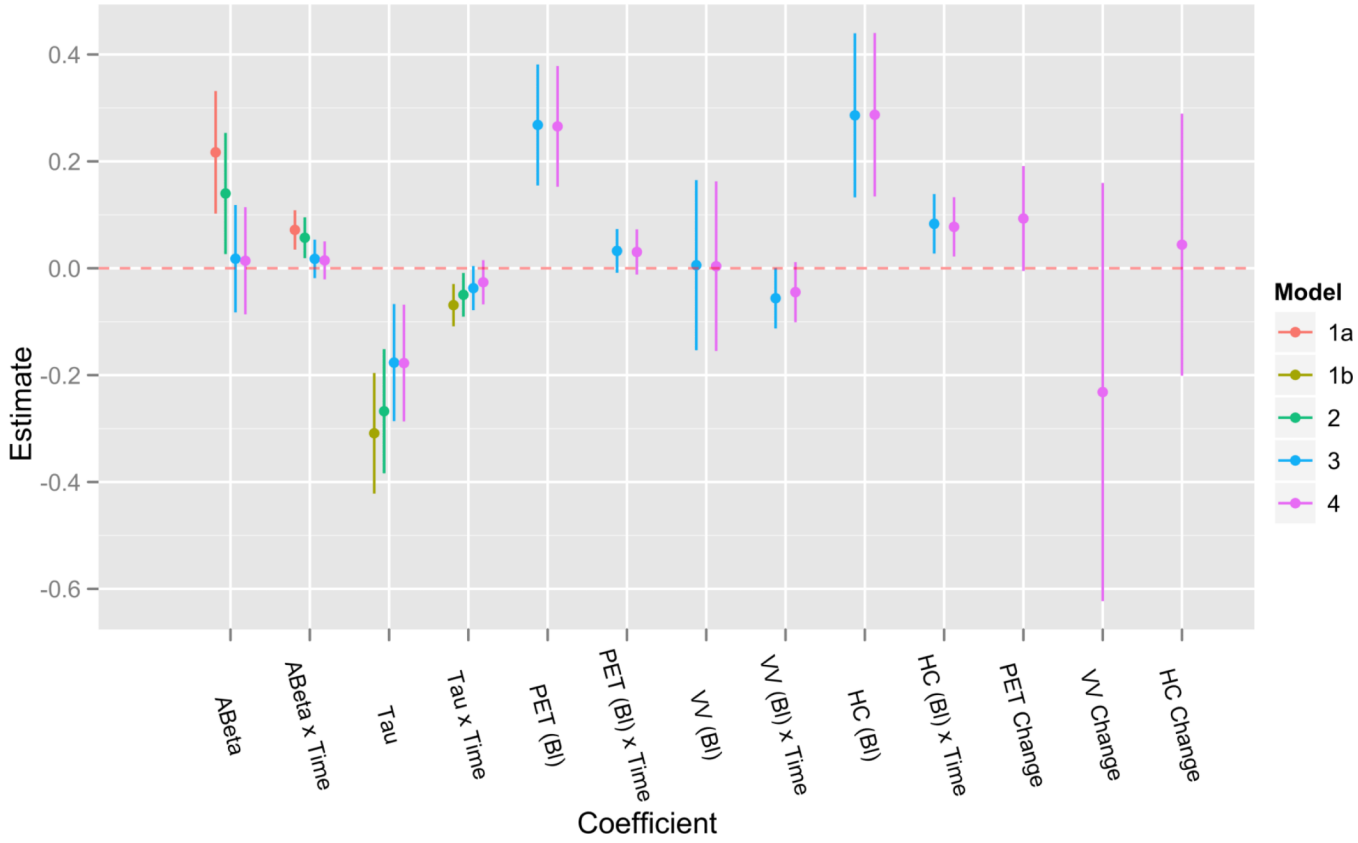

Figure 1.
Estimated biomarker coefficients with 95% confidence intervals presented for Models 1-4 with memory (AVLT) as an outcome.

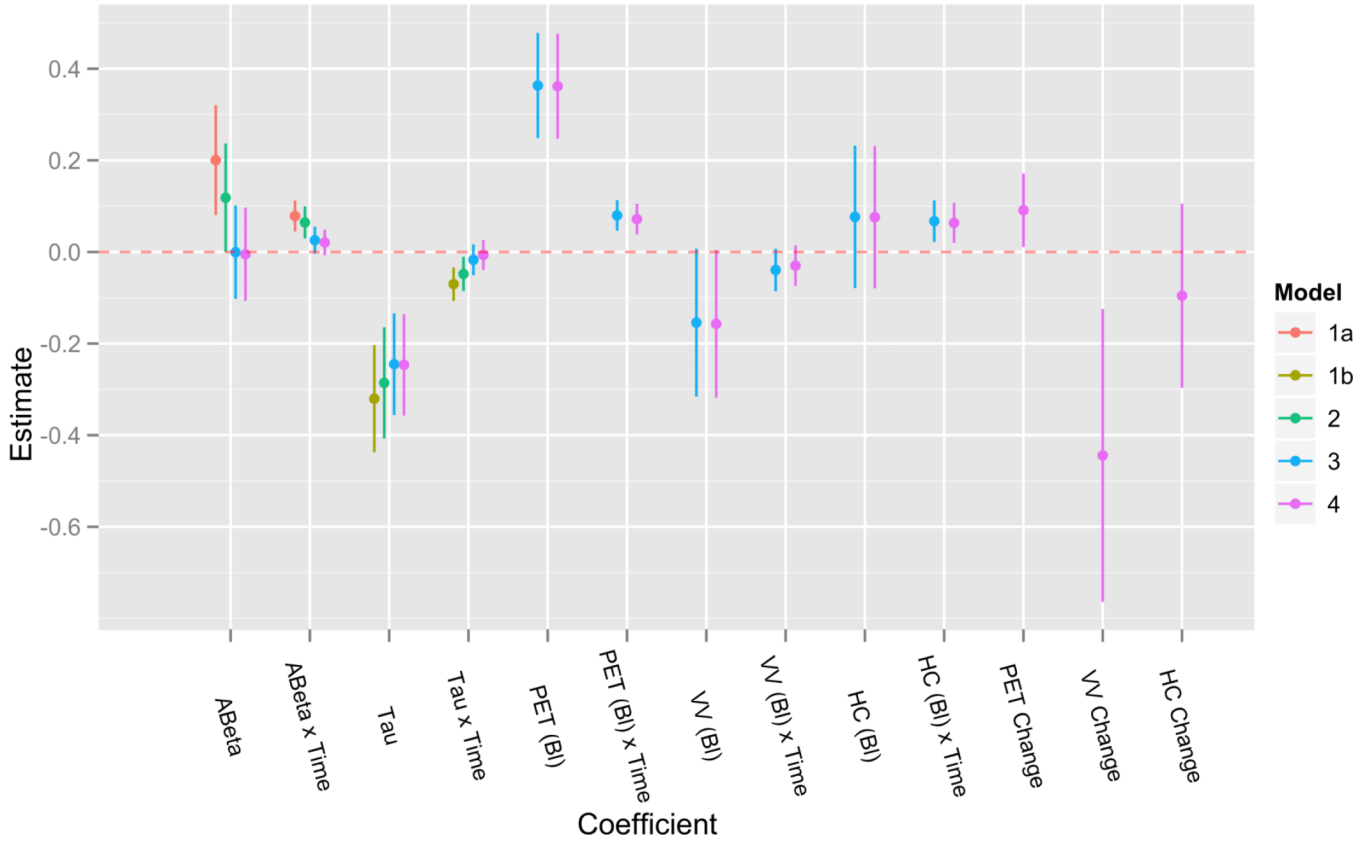

Figure 2.
Estimated biomarker coefficients with 95% confidence intervals presented for Models 1-4 with executive function as an outcome.

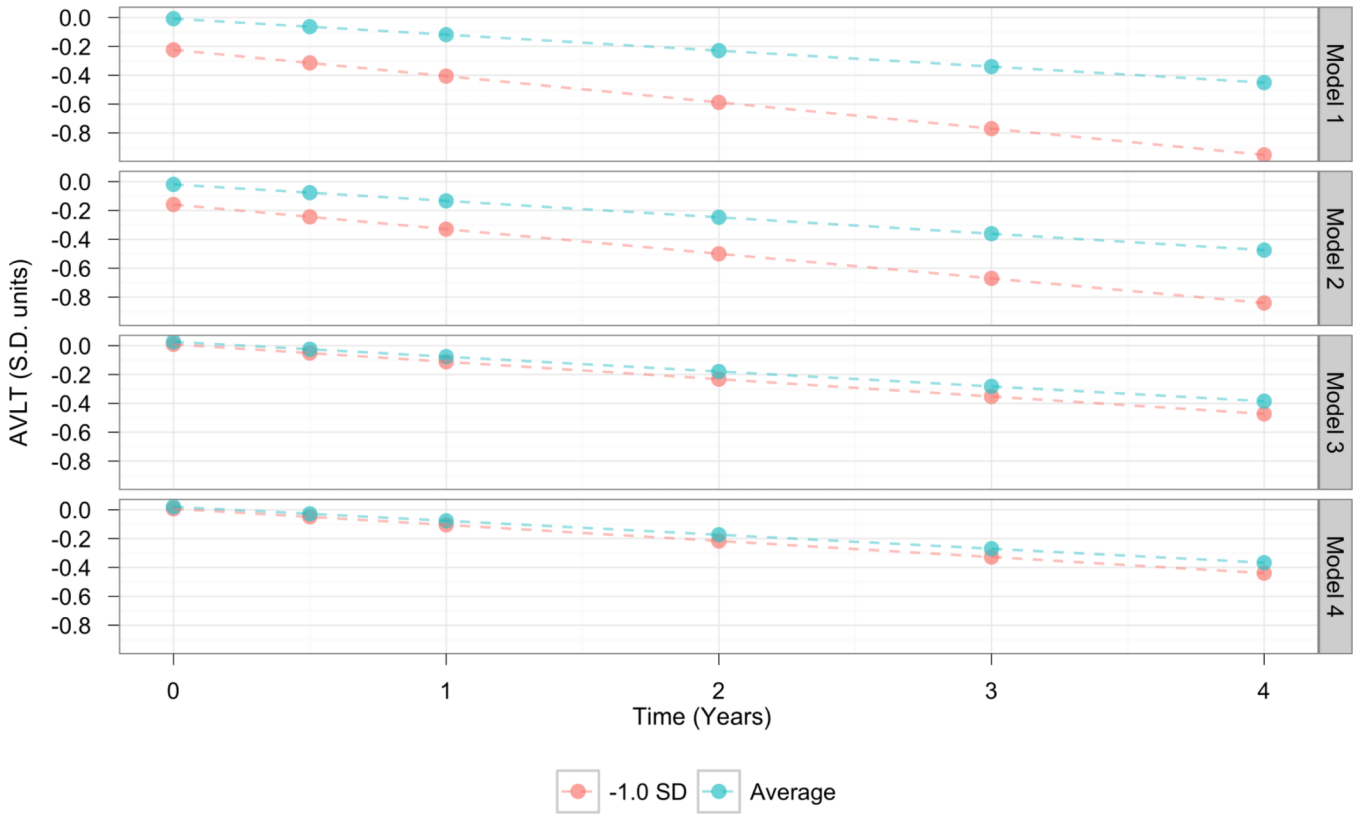

Figure 3.
Expected standardized memory (AVLT) scores across Models 1-4 for typical study participant and study participant with one standard deviation less Aβ but otherwise typical.

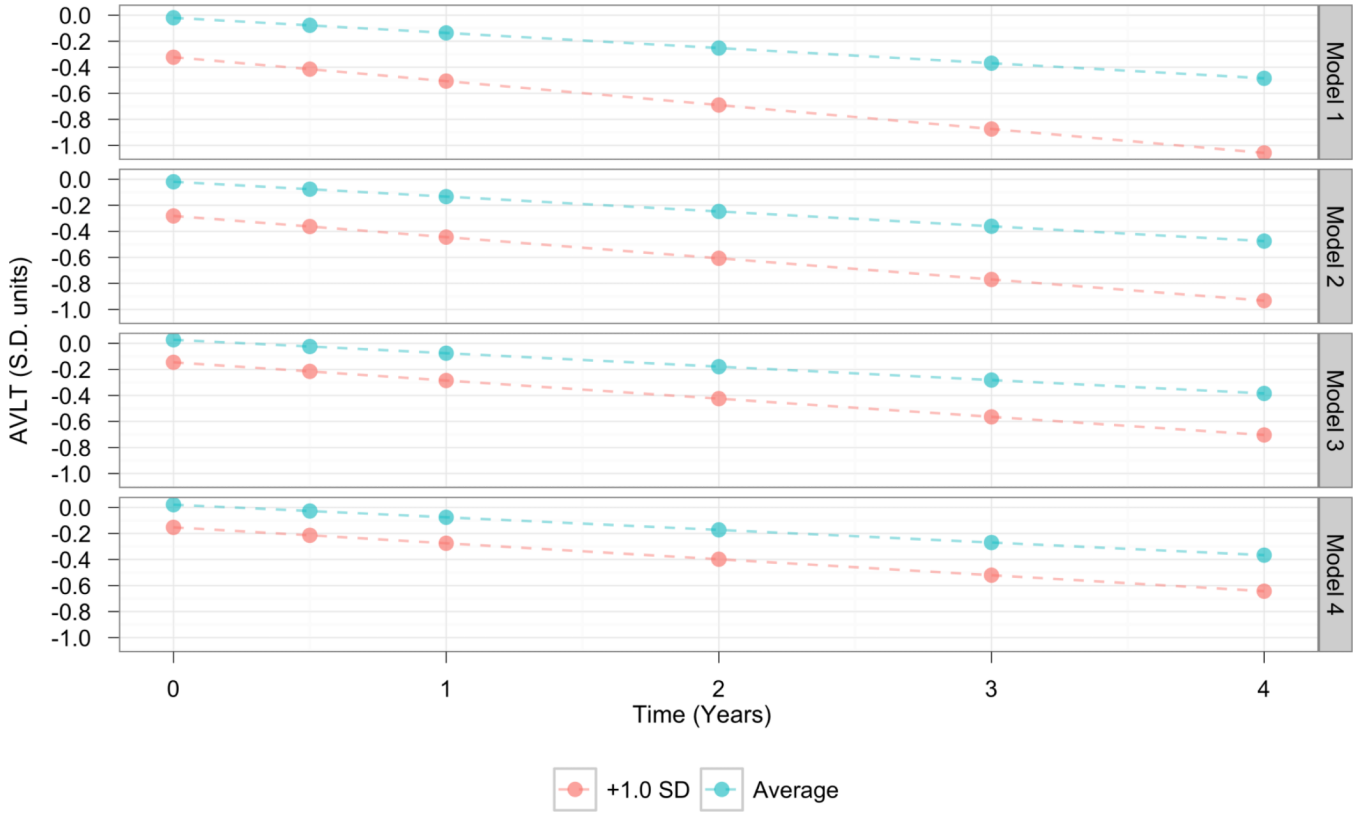

Figure 4.
Expected standardized memory (AVLT) scores across Models 1-4 for typical study participant and study participant with one standard deviation additional tau but otherwise typical.

Table 1

Analytic Models (BL=baseline; CH=change).

Model	Independent Variable	Outcomes
1a	Aβ	Cognition, Neuroimaging (BL & CH)
1b	Tau	Cognition, Neuroimaging (BL & CH)
2	Aβ, Tau	Cognition, Neuroimaging (BL & CH)
3	Aβ, Tau, Hippocampus (BL), Ventricle (BL), PET (BL)	Cognition (BL & CH)
4	Aβ, Tau, Hippocampus (BL & CH), Ventricle (BL & CH), PET (BL & CH)	Cognition (BL & CH)

Table 2

Summary statistics by diagnosis group. For gender, the male count is displayed and the quantities in the parentheses are the percentage of the diagnosis group population. For all other variables, we present the mean by diagnosis group. The standard errors are presented in the parentheses. SUVR=standardized uptake value ratio.

		Diagnosis		
Category	**Description**	**AD (N=41)**	**MCI (N=85)**	**Normal (N=46)**
Demographics	Gender (male)	26 (63.41%)	55 (64.71%)	29 (63.04%)
	Education (years)	14.90 (0.54)	16.24 (0.30)	15.41 (0.47)
	Age (years)	74.90 (1.10)	75.16 (0.81)	75.35 (0.76)
Biomarkers	CSF Beta Amyloid (pg/ml)	136.90 (5.97)	157.58 (5.63)	203.93 (8.15)
	CSF Tau (pg/ml)	125.83 (9.89)	99.82 (5.21)	65.35 (3.64)
	Hippocampal volume (mm^3)	2,637 (71.37)	2,893 (56.32)	3,360 (60.30)
	Ventricular volume (mm^3)	25,433 (1,875)	22,156 (1,266)	20,060 (1,625)
	FDG PET (SUVR)	1.08 (0.02)	1.19 (0.01)	1.30 (0.02)
Cognitive	Memory (# words on AVLT)	21.17 (1.18)	32.69 (1.37)	52.50 (2.01)
	Derived Executive Function	-1.05 (0.11)	-0.06 (0.08)	0.56 (0.09)

Table 3

Effects of CSF variables on neuroimaging variables. Main effects (e.g. Aβ and Tau) show how a 1.0 s.d difference in the independent variable affects baseline neuroimaging outcome (s.d. units). Interactions with Time show how a 1.0 s.d. difference relates to annual change in neuroimaging outcome (s.d.units). Bolded estimate are significantly different from 0.0 ($p<.05$).

Outcome	Effect	Estimate	SE	p value
Hippocampal Volume	Intercept	0.12	0.11	0.27
	Aβ	**0.23**	0.06	<0.01
	Tau	**-0.19**	0.06	<0.01
	Time	**-0.15**	0.01	<0.01
	Time X Aβ	**0.02**	0.01	0.03
	Time X Tau	**-0.03**	0.01	<0.01
Ventricle Volume	Intercept	-0.04	0.10	0.69
	Aβ	**-0.15**	0.06	0.01
	Tau	**-0.14**	0.06	0.03
	Time	**0.14**	0.01	<0.01
	Time X Aβ	**-0.02**	0.01	<0.01
	Time X Tau	**0.02**	0.01	<0.01
PET Average	Intercept	0.14	0.12	0.24
	Aβ	**0.23**	0.07	<0.01
	Tau	**-0.17**	0.08	0.03
	Time	**-0.14**	0.09	<0.01
	Time X Aβ	0.01	0.02	0.60
	Time X Tau	**-0.05**	0.02	<0.01

Table 4

Effects of CSF and neuroimaging variables on cognitive variables. Main effects (e.g. Aβ and Tau) show how a 1.0 s.d difference in the independent variable affects baseline cognitive outcome (s.d. units). Interactions with Time show how a 1.0 s.d. difference relates to annual change in cognitive outcome (s.d.units). Bolded estimate are significantly different from 0.0 ($p<.05$).

Outcome	Effect	Estimate	SE	p value
Memory (AVLT)	Intercept	-0.10	0.07	0.16
	Aβ	0.01	0.05	0.79
	Tau	**-0.18**	0.06	<0.01
	FDG PET	**0.27**	0.06	<0.01
	Ventricle Volume	0.00	0.08	0.96
	Hippocampus Volume	**0.29**	0.08	<0.01
	Time	-0.05	0.03	0.12
	Time X Aβ	0.01	0.02	0.43
	Time X Tau	-0.03	0.02	0.22
	Time X FDG PET (BL)	0.03	0.02	0.16
	Time X Ventricle			
	Volume (BL)	-0.04	0.03	0.13
	Time X Hippocampus			
	Volume (BL)	**0.08**	0.03	<0.01
	FDG PET CH	0.09	0.05	0.07
	Ventricle Volume CH	-0.23	0.20	0.25
	Hippocampus Volume			
	CH	0.04	0.13	0.73
Executive Function	Intercept	-0.11	0.07	0.12
	Aβ	0.00	0.05	0.93
	Tau	**-0.25**	0.06	<0.01
	FDG PET	**0.36**	0.06	<0.01
	Ventricle Volume	-0.16	0.08	0.06
	Hippocampus Volume	0.08	0.08	0.34
	Time	**-0.06**	0.03	0.03
	Time X Aβ	0.02	0.01	0.15
	Time X Tau	-0.01	0.02	0.70
	Time X FDG PET	**0.07**	0.02	<0.01
	Time X Ventricle Volume	-0.03	0.02	0.19
	Time X Hippocampus Volume	**0.06**	0.02	<0.01
	FDG PET CH	**0.09**	0.04	0.03
	Ventricle Volume CH	**-0.44**	0.17	<0.01
	Hippocampus Volume CH	-0.10	0.10	0.36