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Evaluating Alzheimer Disease Biomarkers as Mediators of Age-Related Cognitive Decline

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Abstract

Age-related changes in cognition are partially mediated by the presence of neuropathology and neurodegeneration. This manuscript evaluates the degree to which biomarkers of Alzheimer's disease (AD) neuropathology and longitudinal changes in brain structure account for age-related differences in cognition. Data from the AD Neuroimaging Initiative (n=1012) were analyzed, including individuals with normal cognition and mild cognitive impairment. Parallel process mixed effects regression models characterized longitudinal trajectories of cognitive variables and time varying changes in brain volumes. Baseline age was associated with both memory and executive function at baseline (p's<0.001), and change in memory and executive function performance over time (p's<0.05). After adjusting for clinical diagnosis, baseline and longitudinal change in brain volume, and baseline levels of CSF biomarkers, age effects on change in episodic memory and executive function were fully attenuated, age effects on baseline memory were substantially attenuated, but an association remained between age and baseline executive function.

Results support previous studies that show that age effects on cognitive decline are fully mediated by disease and neurodegeneration variables but also show domain specific age effects on baseline cognition, specifically an age pathway to executive function that is independent of brain and disease pathways.

1. Introduction

Cognitively normal older adults show subtle cognitive decline with advancing age (Hayden et al., 2011), and at autopsy present with a variety of neuropathologies including neuritic plaques, neurofibrillary tangles, microscopic and macroscopic cerebrovascular lesions, and other non-Alzheimer's disease (AD) pathologies including hippocampal sclerosis, lewy bodies, and TDP-43 (Bennett et al., 2006). The common occurrence of subclinical cognitive decline and neuropathology has led to the hypothesis that age-related cognitive decline may be fully mediated by co-occurrence of various neuropathologies. That is, advancing age is associated with disease related neuropathologies that are the primary causes of cognitive decline. Evidence from the Religious Orders Study and Rush Memory and Aging Project has suggested that neuropathological burden at autopsy mediates the association between age and cognitive decline (Yu et al., 2014), although substantial cognitive variance remains unexplained (Boyle et al., 2013). This manuscript will seek to better understand the complex interplay between early brain changes and cognitive decline using a comprehensive set of *in vivo* biomarkers of brain status and disease.

A prominent model of AD progression hypothesizes that the pathological cascade of AD is precipitated by abnormal synthesis and/or failure to clear a toxic beta form of the amyloid protein (Aβ; Jack et al., 2010; Jack et al., 2013). There is accumulating evidence that Aβ-42 oligomers have neurotoxic effects that cause neuronal dysfunction and precipitate tau hyperphosphorylation; these tau changes result in degradation of the neuronal cytoskeleton and eventually cell death. Accumulating neuronal loss is associated with gray matter atrophy, especially in higher level association cortex, which eventually leads to the cognitive and functional decline that becomes the clinical expression of AD. This cascade suggests that measures of Aβ, tau, and neurodegeneration are important biomarkers for AD. Moreover, cerebrospinal fluid (CSF) levels of Aβ-42 and tau and magnetic resonance imaging (MRI) measures of brain gray matter volume and volume change have been demonstrated to be strong predictors of cognitive decline even in those who are cognitively normal at baseline (Fagan et al., 2007; Hedden et al., 2013; Risacher et al., 2009; Vemuri et al., 2009).

Due to the powerful predictive value of AD biomarkers, "preclinical" AD is often defined based on the presence or absence of amyloid and neurodegenerative biomarkers (Sperling et al., 2011). For example, the use of AD biomarkers in defining pre-clinical disease has led to the identification of an interesting subgroup of older adults with "suspected non-AD" pathology (SNAP; Jack et al., 2012; Jack, 2014) in which there is neuronal degeneration in the absence of Aβ-42 abnormalities. SNAP exemplifies the notion that non-AD disease mechanisms contribute to neurodegeneration, and ultimately, cognitive decline and dementia. Thus, there is a compelling body of evidence that the presence of AD and the

extent of neurodegeneration caused by AD and other age related diseases can be measured using currently available AD biomarkers and MRI based measures of structural brain integrity.

There remains an important question as to whether cognitive decline occurs in association with advancing age apart from AD and other age related disease pathways. That is, what are the "normal" age effects on cognition? Previous work has clearly demonstrated that both brain atrophy and decline in neuropsychological test performance are key features of normal aging (Lamar et al., 2003; Resnick et al., 2003), and that the earliest observed changes are in structural and functional measures of the brain (Clark et al., 2012; Saykin et al., 2006). Yet, it is less clear whether such brain changes, and the previously highlighted fluid AD biomarker changes, fully explain age-related cognitive decline. Moreover, it is unclear how concurrent brain changes relate to declining cognitive performance because the longitudinal trajectories of brain structure and cognition are rarely modeled in parallel.

The goal of this project was to decompose age effects on longitudinal cognitive trajectories into a component that could be explained by mediating effects of CSF biomarkers and longitudinal changes in brain structure and a "normal aging" component that is independent of these brain variables. Although fluid and structural biomarkers of AD are strong predictors of future cognitive decline, we hypothesized that additional variance in cognitive performance would remain after accounting for these powerful factors. The outcome of this work will highlight aspects of cognition that change in a manner that does not depend on the AD biomarker cascade and neurodegeneration.

2. Materials and Methods

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative launched in 2003 (ADNI; adni.loni.usc.edu). The initial goal of ADNI was to recruit 800 participants, but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, excluding serious neurological disease other than AD, history of brain lesion or head trauma, and history of psychoactive medication use (for full inclusion/exclusion criteria see www.adni-info.org). Informed written consent was obtained from all participants at each site.

2.1 Participants

We accessed publicly available data from ADNI on 5/10/2017. Participants were enrolled based on criteria outlined in the ADNI protocol (http://www.adni-info.org/Scientists/ AboutADNI.aspx). For the present analyses we included all participants who had a composite measures of memory and executive function, and CSF biomarker data (379 cognitively normal at baseline, 633 with mild cognitive impairment (MCI) at baseline).

2.3 CSF Biomarker Processing

ADNI's CSF protocol, including the quantification of Aβ-42 and tau, has been outlined in detail elsewhere (Jagust et al., 2009; Shaw et al., 2011). For the present analyses, we used the UPenn master dataset that was previously curated and made available for download on

the ADNI site. We used the first measure of total tau and Aβ-42 available for each participant. Biomarker levels were entered as continuous predictors in statistical models.

2.4 Composite Neuropsychological Measurements

The ADNI neuropsychological protocol has been reported in detail, including calculation of composite measures of episodic memory and executive function (Crane et al., 2012; Gibbons et al., 2012). We leveraged both the memory (ADNI-MEM) and the executive function (ADNI-EF) scores in the present analyses. Briefly, ADNI-MEM was derived from a factor model based on item level data from the Rey Auditory Verbal Learning Test, the AD Assessment Scale-Cognitive Subscale, the Mini-Mental State Examination, and the Logical Memory test. Item level data from the Trail Making Test (A and B), Digit Span Backwards, Digit Symbol, Animal Naming, Vegetable Naming, and the Clock Drawing Test were used in the calculation of the ADNI-EF score. These composite scores have been optimized in previous work for psychometric characteristics and sensitivity to AD related cognitive changes (Crane et al., 2012; Gibbons et al., 2012). These measures use all items available in ADNI for measuring these cognitive domains and also address form differences for ADNI memory measures.

2.5 Quantification of Brain Volume

The ADNI neuroimaging protocol has been reported in detail elsewhere (Jack et al., 2008). Images for the current study included original uncorrected 1.5T T1-weighted high-resolution three-dimensional structural data for ADNI-1 and 3T data for ADNI-2/GO. Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite version 4.3 in ADNI-1 and 5.1 in ADNI 2 (http://surfer.nmr.mgh.harvard.edu/ (Dale et al., 1999; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, et al., 1999). FreeSurfer processing in ADNI has been described in detail elsewhere (Mormino et al., 2009). Briefly, although manual edits were not completed, but all FreeSurfer scans were manually checked and given a QC score of pass, fail, or partial (such as only Hippocampus usable). For the present analyses, we only used scans which fully passed all QC procedures. An early version of the longitudinal image processing framework was used to process the sequential scans (Reuter et al., 2012).

We used regions of interest (ROIs) based on a structural network previously defined in ADNI using factor analysis of change in brain volume ROIs (Carmichael et al., 2013), based on granular ROIs defined by FreeSurfer (Desikan et al., 2006). The ROIs corresponded to the default mode network, frontal lobe, medial temporal cortex, sensory motor network, and hippocampus. The ROIs that made up each network are presented in Supplementary Materials A. All brain volume analyses also included a measurement of intracranial volume (ICV) and a variable for scanner strength as covariates.

2.6 Statistical Analyses

Data Processing—Raw brain ROI volumes were residualized for intracranial volume, gender, and the interaction of gender and intracranial volume. The baseline measure of intracrancial volume was used to adjust all longitudinal scans. CSF Aβ-42 and tau and the adjusted brain volumes were Blom transformed. The Blom transformation is an inverse

normal rank order transformation that is useful both for normalizing non-normally distributed variables, especially continuous variables, and for placing variables on a common metric, in this case a standard score metric. Baseline brain variables were Blom normalized, lookup tables were created that showed the minimum and maximum raw score that corresponded to each unique normalized value, and these lookup tables were then applied to the follow-up variables to generate normalized values. Descriptive analyses used analysis of variance to compare diagnosis group means of continuous variables and the chi-square test to evaluate group differences in categorical variables. This allows the direct comparison of observed effects.

Primary Analysis—We used the multi-level modeling framework of Mplus software (Muthén & Muthén, 1998) to estimate parallel process mixed effects regression models to characterize longitudinal trajectories of cognitive variables and time varying brain volumes. In the Within part of this multilevel model for a specific longitudinal outcome, the longitudinal values for that variable for a given individual are regressed on time (from baseline measurement for that individual) to estimate a person-specific intercept and a person-specific slope. These person-specific slopes and intercepts are combined into random effects that are represented by latent variables at the Between level of the model.

The Between part of the model addressed relations of these random effects, including cognitive change with brain change, as well as relations with external variables, specifically, age and baseline measures of CSF Aβ-42 and tau. These models estimated baseline levels (intercepts) as well as linear rates of change (slopes) of cognitive and longitudinal brain variables. A schematic of the modeling approach is presented in Figure 1.

We evaluated whether interpretability was improved by adding second order global intercept and slope factors to explain covariance among the random effects of the time varying variables. The multilevel modeling framework flexibly incorporates all data and is robust to patterns of missing data. It allows for a continuous measure of time and differing times between observations and across individuals can be accommodated.

We evaluated age effects on memory and executive function intercepts and slopes in three different models: 1) age explained cognitive intercepts and slopes along with covariates, gender and education, 2) age, covariates and diagnosis (MCI) were included, and 3) age, covariates, diagnosis, and brain variables were included. Brain variables in model 3 included intercepts and slopes of the time varying brain volumes along with baseline values of the CSF measures of Aβ-42 and total tau. A schematic of the Model 3 analysis is presented in Figure 1. The age effect in Model 1 was considered to represent the overall (simple) effect of age on cognitive trajectory components. The independent (direct) effect of age in Model 3 was considered to represent the contribution of age that cannot be explained by confounding associations of age with age-related disease and accumulation of brain injury. Thus, the age effect in Model 1 was used to estimate the age impact on cognition, Model 2 evaluated the effect of age after adjusting for clinical status, and the Model 3 estimated the "normal" aging effect – that not attributable to measured disease and brain effects.

We examined both linear and non-linear effects of age on the cognitive trajectory components. Non-linear effects were modeled by including a quadratic term for age, defined by age-squared, as a Within level independent variable. We used model fit indices, the Akaike's Information Criterion (AIC; Akaike, 1987), the Bayesian Information Criterion (BIC; Schwarz, 1978), and the Sample Adjusted BIC (SaBIC; Sclove, 1987) to evaluate whether linear or quadratic models for age effects provided better fit to the data and to evaluate if second order factors were useful for explaining covariance among brain intercept and slope random effects.

We compared the simple age effects on cognitive intercepts and slopes that were estimated in Model 1 with the direct (fully adjusted) effects estimated in Model 3, and in addition estimated indirect pathways that showed the magnitude of age effects mediated by specific brain variables and the combined influence of brain variables. This was done by an extension to Model 3. Direct regressions of the brain variables on age were included in this model, and in addition, age via brain indirect (mediated) paths were estimated. The path coefficient for a specific indirect path was calculated as the regression coefficient for the age effect on the brain variable multiplied by the regression coefficient for the effect of the brain variable on the cognitive dependent variable. The combined indirect effect for a cognitive outcome was defined as the sum across brain variables of the individual indirect effects for that outcome. The Mplus Model Constraint feature was used to calculate these effects and their standard errors and to evaluate statistical significance of the calculated, indirect paths. A specific indirect effect indicates the extent to which a one year difference in age impacts cognition (expressed in units of 1/15 s.d.) via the mediating effect of the brain variable. These indirect effects can be directly compared with the simple and direct age effects from Model 1 and Model 3.

We included effects in the Within part of the multilevel model to account for practice effects and differences in MRI scanner strength at different assessments. Practice was modeled using an indicator variable that was coded 0 for the first assessment and 1 for all subsequent assessments. Scanner strength was coded using an indicator variable that was 1 for 3 Tesla scans (ADNI Go and ADNI2) and 0 for 1.5 Tesla scans (ADNI1). We adjusted brain volumes for scanner strength in the Within part of the model by regressing the ROI volumes on the scanner strength variable. We also evaluated a model in which cognitive variables were regressed on ROI volumes, scanner strength, and ROI volumes by scanner strength interactions in the Within part of the model.

Secondary Analysis—We conducted a follow-up multiple group analysis that systematically evaluated whether results differed across the Normal and MCI subgroups. This multiple group analysis simultaneously estimated Model 3 in both groups, and then evaluated whether model fit was better when specific parameters were freely estimated in each group as opposed to being constrained to be equal. Nested models in which specific parameters were either constrained to equality or freely estimated were compared using a modified likelihood ratio test to assess if model fit was significantly better when the parameters of interest were freely estimated. In effect, this approach evaluates whether results significantly differ across the two groups. Specific comparisons of interest were identified *a priori*. We were particularly interested in associations of independent variables

(age, baseline CSF values, intercepts and slopes of time varying brain volumes) with dependent variables (ADNI-MEM and ADNI-EF intercepts and slopes). We started with a base model in which the coefficients for the regressions of cognitive intercepts and slopes regressed on the independent variables were freely estimated. We then systematically constrained a group of parameters to equality and compared fit of that model to the freely estimated model using the likelihood ratio test. We used separate sets of analyses to compare: 1) age effects on cognitive slopes, 2) age effects on cognitive intercepts, 3) CSF Aβ-42 and tau effects on cognitive intercepts and slopes, 4) brain volume intercept (baseline) effects on cognitive intercepts and slopes, and 5) brain volume slope effects on cognitive slopes.

3. Results

Sample characteristics are presented in Table 1. Results are presented by baseline clinical diagnosis group (Normal versus MCI) and for the full sample. The Normal group was about two years older on average ($F[1,1010] = 8.17$, $p = 0.004$). Gender differed across diagnosis groups ($\chi^2[1] = 12.14$, $p<0.001$); males were more frequently MCI cases, while slightly more female were Normals. The two groups did not differ in education level ($F[1,1010] = 3.38$, $p = 0.07$). Average scores at baseline for both cognitive outcomes were higher in the Normal group (ADNI-MEM - $F[1,1010] = 420.40$, $p < 0.001$; ADNI-EF - $F[1,1010] = 120.50$, $p < 0.001$). The MCI group had lower average Aβ-42 ($F[1,1010] = 72.59$, $p < 0.001$) and higher tau ($F[1,981] = 52.72$, $p < 0.001$). Residual brain volumes, adjusted for effects of gender, intracranial volume, and the interaction of gender with intracranial volume were larger in Normals for default mode ($F[1,793] = 22.45$, $p < 0.001$), medial temporal ($F[1,793] = 17.03$, $p < 0.001$), hippocampus ($F[1,793] = 81.51$, $p < 0.001$), and frontal ($F[1,793] = 5.72$, $p = 0.02$), but did not differ for sensory ($F[1,793] < 1.0$, $p = 0.72$).

3.1 Primary Analysis

The model with linear age effects fit the data better than that with quadratic age effects in the fully adjusted, Model 3 (values of AIC, BIC, and SaBIC were smaller for the linear model). Consequently, linear age effects are presented in subsequent results. Fit was better (smaller values of BIC, and SaBIC) for a model that included a second order factor to explain covariance among brain gray matter volume slopes but maintained individual intercepts (depicted in Figure 1). Loadings for gray matter slopes on the global slope factor were: Default Mode – 1.00 (reference), Frontal – 0.77, Medial Temporal – 0.85, sensory – 0.69, Hippocampus – 0.70. Practice effects were significant for both cognitive variables and so were retained in subsequent models. Average scores for the first assessment were about 0.10 SD lower than for subsequent assessments. Brain gray matter volumes for 3T scans were significantly larger than those for 1.5T scans for the four cortical ROIs (about 0.21 – 0.31 SD) but did not differ for hippocampus (0.02 SD). The effects on cognition of scanner strength by ROI volume interactions were not significant, indicating that the ROI volumes had the same effect on cognition for the two scanner strengths. Consequently, subsequent analyses did not include these interactions.

Table 2 shows the independent associations of baseline age with ADNI-MEM and ADNI-EF intercepts and slopes in the three models. The cognitive variables were scaled to have a mean of 100 and a standard deviation of 15. Consequently a 1.0 unit estimate in Table 2 would indicates that a 1-year difference in age was associated with a $1/15^{th}$ standard deviation difference in a cognitive intercept, or a $1/15^{th}$ standard deviation annual change in the cognitive variable. Age was related to both ADNI-MEM and ADNI-EF intercepts in Model 1. This effect was enhanced when diagnosis was added as an independent variable in Model 2. However, the age effect on ADNI-MEM was substantially attenuated when brain variables were added in Model 3. The age effect on ADNI-EF was smaller in Model 3 but was still a strong independent effect. Age was related to the ADNI-MEM and ADNI-EF slopes in Model 1 and Model 2 and age effects were larger in Model 2. Age was positively related to the ADNI-EF slope in Model 3 and a positive association with ADNI-MEM slope approached statistical significance (p=0.06). That is, after adjusting for both diagnosis and brain variables, older age was associated with less rapid ADNI-EF, and to a lesser degree, ADNI-MEM decline.

Figure 2 shows the independent effects of age on cognitive trajectories in the three models. This figure is based on the regression parameters estimated in Models 1, 2 and 3, and presents model derived estimates of the baseline value and expected change over 4 years for hypothetical individuals beginning at specific 5-year age values ranging from 60 to 90 years. This figure mimics the design of ADNI in that individuals entered the study at different ages and were followed for approximately 4 years. The unadjusted model in the lower pane of Figure 2 shows how age is related to baseline level and rate of change of ADNI-MEM and ADNI-EF when no independent variables other than gender and education were entered to explain cognitive trajectories. The middle pane shows the effects of age after adjusting for covariates and diagnosis, and essentially depicts expected trajectories for cognitively normal individuals. The upper pane shows age effects after adjusting for covariates, diagnosis and brain variables, and depicts average trajectories for cognitively normal individuals with brain variable values that were average for the Normal sub-group.

Several noteworthy results are presented in Figure 2. First, as would be expected since a substantial part of this sample had progressive mild cognitive impairment, there is robust overall decline in cognitive performance associated with age in the unadjusted model, and the amount of decline is substantially less in both the Normal cases (middle pane) and the Normal cases with normal brain values (upper pane). Second, the average ADNI-MEM and ADNI-EF slopes over the entire age span are significantly negative (see Table 3) in all three panes, indicating that memory is declining on average over the multiple within person ADNI assessments, even in cognitively normal individuals with average baseline brain values. Third, the average rate of within person decline in Model 3 does not vary by baseline age for ADNI-MEM but is significantly _**less**_ for older age for ADNI-EF. Fourth, baseline ADNI-EF scores are substantially lower in older individuals even for Normals with normatively average baseline brain measures. Overall, these results show dissociation of age effects on memory and executive function. Age was not associated with memory slopes after adjusting for diagnosis and brain variables and adjusted age effects on memory intercepts were weak. Executive function intercepts, in contrast, were strongly, negatively associated with "normal

aging", operationally defined as a clinical diagnosis of normal cognition and normatively average values on a number of brain and CSF measures, but executive function decline was slower in older individuals.

Table 3 presents statistically significant influences on cognitive intercepts and slopes identified using Model 3. All findings, non-significant as well as significant can be viewed in Supplemental Table 1. Memory and executive function declined independent of age, diagnosis, and brain variables. The reference values for the ADNI-MEM and ADNI-EF Slopes in Table 3 can be interpreted to indicate these variables declined 9 (ADNI-MEM, 0.6 SD) and 6 points (ADNI-EF 0.4 SD) over 10 years of follow-up in cognitively normal individuals with normatively average brain values. CSF Aβ-42 and tau had relatively robust effects on intercepts and slopes of both cognitive variables (tau was not related to executive intercepts). Global brain volume change was strongly related to cognitive change. Specific brain volume ROIs had more limited relations with cognition. The default mode ROI was related to intercepts and slopes of both ADNI-MEM and ADNI-EF, but cognitive effects of other ROIs were not reliably different from zero. Hippocampal volume was related to ADNI-MEM intercepts. A diagnosis of MCI was associated with lower baseline values of both cognitive outcomes and with faster decline of memory independent of the brain variables.

Table 4 shows strength of effects associated with simple, mediated/indirect, and direct paths from age to cognitive trajectory components. The simple age effect of ADNI-MEM indicated that ten years of additional age was associated with 0.24 s.d. lower memory score; after adjusting for effects of brain variables, this effect was reduced to 0.04 s.d., an 85% reduction. For ADNI-EF, 10 years of age was associated with 0.39 s.d. lower baseline score, and after adjusting for brain variables, this effect was 0.25 s.d., a 36% reduction. The total mediated effects of age by brain variables was larger for ADNI-EF change than the simple effect of age and equal to the simple effect for ADNI-MEM. Both direct effects were positive, though this was significant only for ADNI-EF. Baseline Default Mode ROI, tau, and Aβ were robust mediators of age effects on cognitive intercepts and slopes. The indirect age pathway to Memory intercept via baseline hippocampus was also significant.

3.2 Secondary Analysis

We performed a multiple group analysis based on Model 3 to evaluate how effects of age and brain variables differ in Normal and MCI subgroups. Age effects on cognitive intercepts and slopes did not significantly differ. The fit of a model in which age effects on cognitive intercepts were constrained to be the same in Normals and MCI was not significantly worse than fit of the freely estimated base model using the likelihood ratio test for nested models ($\chi^2[2] = 0.78$, p=0.68); age effects on slopes also did not differ ($\chi^2[2] = 1.93$, p=0.38). Model fit was significantly worse when effects on cognition of brain volume intercepts ($\chi^2[20] = 41.54$, p=0.003), global brain volume slope ($\chi^2[2] = 11.66$, p=.003), and CSF values ($\chi^2[8] = 27.63$, p<0.001) were constrained to equality. These effects subsequently were freely estimated in the two groups. Figure 3 shows average age trajectories for Normals and MCI in the fully adjusted Model 3. Age effects on intercepts were clearly present for ADNI-EF in both groups, and to a much smaller extent, age was negatively related to ADNI-

Mem intercepts. ADNI-MEM slopes were negative on average in both groups but did not differ across the 60+ year age range, while in contrast ADNI-EF slopes were negative in younger but less so in older individuals in both groups.

Complete results of effects of brain variables on cognitive trajectories in Normals and MCI can be viewed in Supplemental Table 2. As would be expected, intercepts of both cognitive variables were lower in the MCI group. The ADNI-MEM slope (the value associated with normatively average brain measures) was significantly and similarly negative in both groups; the ADNI-EF slopes also were negative in both groups. CSF Aβ-42 was related to the memory intercept in MCI and executive intercepts in both MCI and Normals; Aβ-42 was related to slopes of both variables in both groups. CSF tau was related to memory intercepts in MCI but not Normals, and was related to memory and executive slopes in MCI but not Normals. Brain volume change was related to memory and executive slopes in MCI but not Normals. The default mode ROI was related to memory intercepts in MCI and executive intercepts in both groups and to memory and executive slopes in MCI. Hippocampal volume was related to the memory intercepts in MCI and to both memory and executive slopes in Normals but not in MCI. In summary, age was equally related to cognitive intercepts and slopes in Normals and MCI. CSF tau, global brain volume change, and baseline default mode ROI volume had stronger effects on cognition in MCI. Hippocampal volume was a predictor of cognitive decline in Normals but not MCI. CSF Aβ-42 had relatively robust effects on memory and executive change in both groups with weaker effects on intercepts.

4. Discussion

This study showed that brain variables mediate some or all of the effects of age on late life cognition, but results varied across episodic memory and executive function domains and estimates of baseline cognitive level and rate of cognitive change. About 85% of the age effect on episodic memory intercepts was explained by brain variables including CSF biomarkers of AD and baseline and longitudinal measure of gray matter volumes. In contrast, these brain variables explained only 36% of the age effect on baseline executive function. But all of the negative effects of age on decline in both cognitive domains were mediated by brain variables, and for both memory and executive function, age had a net positive effect on cognitive slopes after adjusting for brain mediation effects. For executive function, this net positive effect was statistically significant.

We conceptualized "normal cognitive aging" as the age effect on cognition that was independent of the CSF and MRI measures included in this study. While we used a comprehensive set of brain measures that had robust effects on cognition, there most likely are other aspects of brain disease and neurodegeneration that our measures did not capture. In light of this limitation of our study, it is notable that all of the negative effects of age on cognitive decline were explained by brain variables and the vast majority of age effects on episodic memory baseline scores were attributable to brain variables. Only for executive function baseline scores was there evidence of substantial "normal aging" effects.

Past research has found that normal aging and AD are marked by differential effects on brain structure that only partially overlap (Bakkour et al., 2013), suggesting that these distinct

patterns may represent unique pathways to cognitive decline. However, previous work has also suggested that age effects on cognitive decline can be largely accounted for by the presence of neuropathologies at autopsy (Yu et al., 2014). The present findings provide additional evidence that variance in cognitive slopes is attributable to disease and brain variables, but also demonstrate substantial age effects on executive function that are not mediated by the measured brain variables.

Cognitive decline during normal aging has been well characterized (Harada et al., 2013), and is likely driven in part by the subtle brain atrophy that occurs over the course of normal aging (Resnick et al., 2003). Yet, even when accounting for the presence of AD biomarkers and measurement of gray matter volume change, there was still a pronounced age effect on executive function intercepts. The gradual process of age-related cognitive decline appears to begin in early to middle adulthood (Salthouse, 2009), and one possible explanation for the strong "normal aging" effect on executive function intercepts is that this represents the accumulation over decades of cognitive changes that are not tied to brain disease or neurodegeneration. Large age-related differences in aspects of executive function including processing speed (Salthouse, 2000) and visual attention (Madden, 2007) have been noted in the literature previously.

It also would be interesting to determine whether additional age-related variance may be subsumed by metrics of white-matter integrity that are known to degrade during normal aging and impact executive function (Madden et al., 2009). Other pathological processes observed during aging such as changes in brain function, reductions in cerebral blood flow, and reductions in white matter integrity merit consideration. A comprehensive model of normative and pathological aging will ultimately need to account for all of these various pathways to executive decline. Finally, cohort effects might contribute to age effects on executive function intercepts. It is possible that older individuals had less exposure to education and life experiences that might promote performance on executive function tasks.

Subgroup analyses within Normal and MCI participants are relevant to understanding normal and pathological aging effects. Age effects on slopes and intercepts did not differ across diagnosis groups. In contrast, brain variables had stronger effects on cognition in MCI individuals than in Normals. Of particular note, there was a stronger association between CSF AD biomarkers and cognition among MCI individuals. Significantly negative cognitive slopes were observed in Normals, but slopes were more pronounced in MCI (Figure 3), likely signaling greater neurodegeneration in the MCI group. Taken together, these findings support the general notion that neurodegeneration is the primary driver of cognitive decline in older adults. As the prodromal stages of AD progress, it is likely that the deleterious effects of AD neuropathology surpass and overwhelm the normal aging effects that are prevalent in the participants with normal cognition. Previous work has similarly found that progressive neurodegeneration and longitudinal alterations in AD biomarkers drive cognitive decline during MCI and AD (Dodge et al., 2014). The different patterns of age and AD biomarker effects in Normal and MCI individuals suggest a shift in the drivers of cognitive decline across the spectrum of normal aging and dementia.

Older age was associated with a slower rate of executive function decline in the model that controlled for brain variables. As illustrated in Figure 2, this appears to reflect a leveling off of age-related decline in executive function among the oldest old participants. This finding is somewhat surprising given the ubiquity of negative effects of age on cognition in late life. At face value, this finding suggests that, after controlling for AD biomarkers and MRI measures of neurodegeneration, older individuals decline less rapidly. Selection bias in the ADNI sample, (e.g., the selective recruitment of healthy older old participants) could contribute to this finding. This hypothesis is supported by the Normal group being older on average, and by the unexpected finding that brain ROI volumes were smaller in Normals, which was largely attributable to Normal-MCI age differences. It is also possible that the slight positive slope in the oldest old reflects a regression to the mean effect due to below average baseline performance, although retest effects were explicitly modeled in this study. This significance of this finding is not clear and requires confirmation in different samples.

This study has numerous strengths including the well-characterized ADNI sample, the comprehensive longitudinal assessment of cognition and brain structure, and the large sample of Normal and MCI participants to achieve the needed statistical power to detect group differences in cognitive trajectories. It is important to note some limitations of the study. Although our analyses included substantial longitudinal data, the CSF biomarker data was only evaluated at baseline, leaving open the possibility that changes in AD biomarker levels may explain additional variance in age-related cognitive decline. That said, baseline CSF biomarker levels were strong predictors of cognition, were associated with age, and were significant mediators of age effects on cognition. The ADNI cohort is not representative of the general population due to the skew towards white, highly educated individuals with limited vascular comorbidities. The healthy status of the Normal group and the selection bias toward memory impairment among the MCI group may introduce additional unmeasured confounders into the analysis. Despite these limitations, the results of the present study provide important findings to contribute to the body of research on normal and pathological cognitive aging, and specifically show that late life cognitive decline is largely attributable to brain disease and neurodegeneration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Age-related changes in memory and executive function were assessed

- Cerebrospinal fluid biomarkers of Alzheimer's disease were measured at baseline visit

- Longitudinal changes in brain structure were modeled in parallel with longitudinal cognition

- Biomarkers and structural volumes partially mediated the association between age and cognition
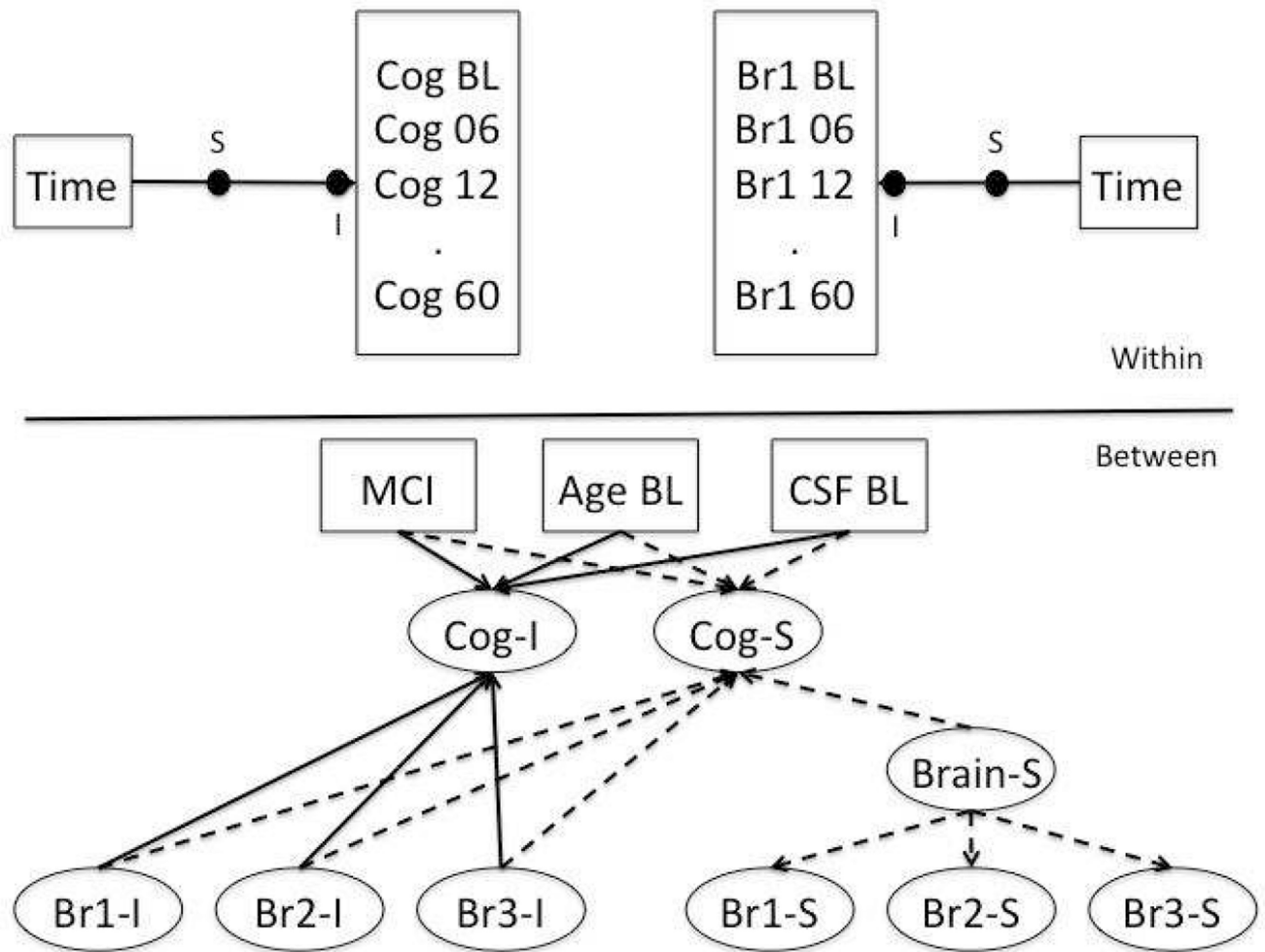
Figure 1. Schematic of Analytic Model - Multi-Level Modeling Framework
Longitudinal ADNI-MEM and ADNI-EF measures and time varying brain measures were simultaneously decomposed into individual random effects (intercepts and linear slopes) in the Within part of the multilevel model. Slopes from individual brain variables were decomposed into a second order global slope factor in the Between part of the model. Cognitive intercepts and slopes were regressed on Age, time invariant CSF measures (Abeta and Tau), clinical diagnosis (MCI), individual brain intercepts and global brain slope. The Within part of the model includes multiple cognitive and brain measures that are not shown for simplicity of presentation. The Between part of the model is also simplified for presentation purposes.
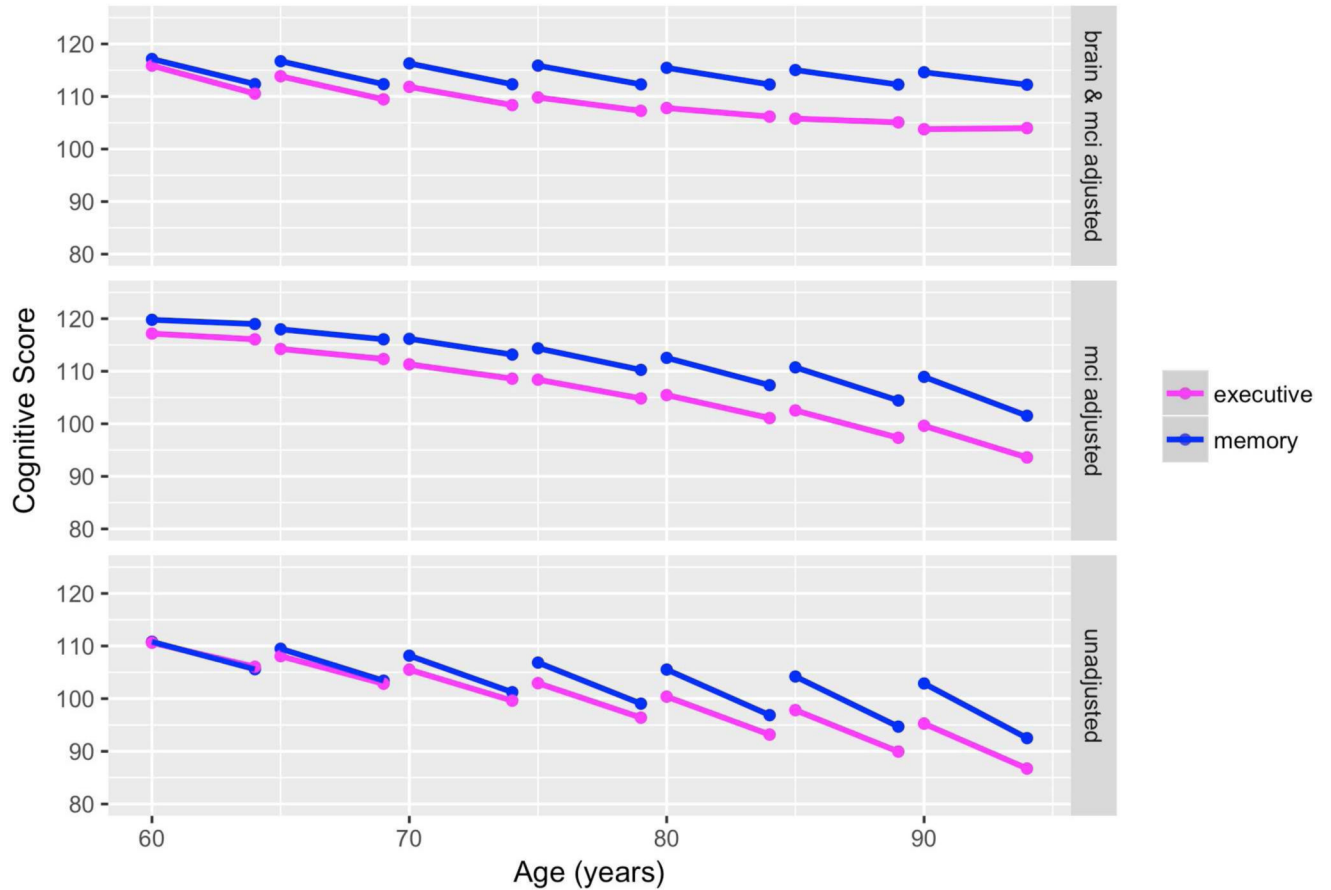
Figure 2. Age effects on cognitive trajectories - unadjusted and adjusted for diagnosis and brain effects (volume baseline and change and CSF baseline)

Estimated 4-year cognitive trajectories are shown for individuals starting in the study at different ages. Results show the estimated cognitive scores at the initial evaluation and the amount of change over 4 years. Brain variables were standardized based on the baseline scores of cognitively normal individuals.
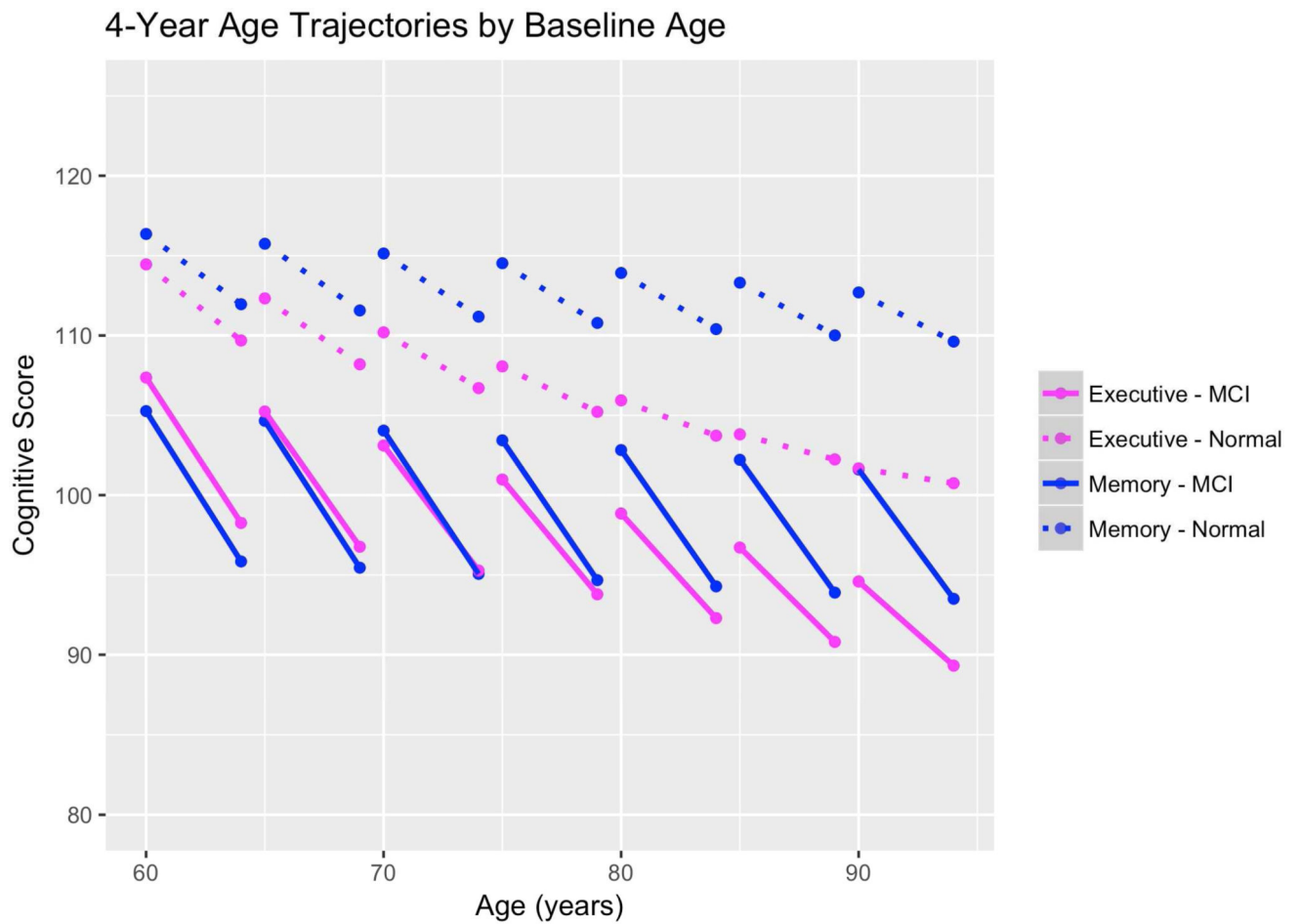
Figure 3. Age effects on cognitive trajectories in Normals and MCI
Estimated 4-year cognitive trajectories are shown for individuals starting in the study at different ages. Results show the estimated cognitive scores at the initial evaluation and the amount of change over 4 years and are from a multiple group analysis where brain variable effects on cognitive outcomes were allowed to differ in Normal and MCI groups. Brain variable values were set at the means for Normal and MCI groups.

Table 1

Characteristics of ADNI sample.

	Clinical Diagnosis, Baseline Evaluation		
	Normal	MCI	Total
Age			
Mean (SD)	73.9 (±5.9)	72.6 (±7.5)	73.1 (±7.0)
Gender			
Male	178 (47.0%)	370 (58.5%)	548 (54.2%)
Female	201 (53.0%)	263 (41.5%)	464 (45.8%)
Education (years)			
Mean (SD)	16.4 (±2.6)	16.1 (±2.8)	16.2 (±2.7)
Composite Memory Performance			
Mean (SD)	115.7 (±8.4)	103.0 (±10.2)	107.8 (±11.4)
Composite Executive Function Performance			
Mean (SD)	111.6 (±10.9)	103.3 (±12.1)	106.4 (±12.3)
CSF Aβ-42 (pg/mL)			
Mean (SD)	200.4 (±52.0)	171.3 (±53.1)	182.2 (±54.6)
CSF Total Tau (pg/mL)			
Mean (SD)	67.5 (±31.6)	90.1 (±52.2)	81.5 (±46.7)
Missing	5 (1.3%)	24 (3.8%)	29 (2.9%)
Default Mode ROI Volume Residual (mm3) [*]			
Mean (SD)	3170.1 (±13169.1)	−2037.0 (±16253.4)	0.0 (±15325.6)
Missing	68 (17.9%)	149 (23.5%)	217 (21.4%)
Frontal ROI Volume Residual (mm3) [*]			
Mean (SD)	1358.8 (±12155.4)	−873.1 (±13269.7)	−0.0 (±12883.7)
Missing	68 (17.9%)	149 (23.5%)	217 (21.4%)
Medial Temporal ROI Volume Residual (mm3) [*]			
Mean (SD)	470.7 (±2223.3)	−302.4 (±2782.1)	−0.0 (±2604.0)
Missing	68 (17.9%)	149 (23.5%)	217 (21.4%)
Sensory Cortex ROI Volume Residual (mm3) [*]			
Mean (SD)	113.0 (±6832.2)	−72.6 (±7396.7)	−0.0 (±7177.4)
Missing	68 (17.9%)	149 (23.5%)	217 (21.4%)
Hippocampus Volume Residual (mm3) [*]			
Mean (SD)	410.8 (±812.4)	−264.0 (±1145.8)	0.0 (±1079.3)
Missing	68 (17.9%)	149 (23.5%)	217 (21.4%)

[*] Deviation from volume predicted by gender, intracranial volume, and gender × intracranial volume

Table 2

Age Effects by Model

	Intercept			Slope		
	Model 1: *Age Only*	**Model 2:** *Age and Dx*	**Model 3:** *Age, Dx, Brain*	**Model 1:** *Age Only*	**Model 2:** *Age and Dx*	**Model 3:** *Age, Dx, Brain*
Memory	−0.26 ***	−0.36 ***	−0.08 *n.s.*	−0.043 ***	−0.055 ***	0.020 *n.s.*
Executive Function	−0.51 ***	−0.59 ***	−0.40 ***	−0.033 *n.s.*	−0.041 **	0.046 **

Note:

*** $p < 0.001$

** $p = 0.01$,

* $p < 0.05$,

ns $p > 0.05$

Table 3

Significant associations of age, diagnosis, baseline CSF biomarkers, and brain volume trajectory components with individual differences in cognitive intercepts and slopes

			Intercepts							
	Ref	**Age**	**Sex**	**Dx**	**Educ**	**CSF Tau**	**CSF Aβ-42**	**Hipp**	**Default**	**Practice**
Memory	115.87 ***	.	−5.40***	−9.07***	0.65 ***	−1.39***	0.89 **	1.55 ***	1.63 *	2.08 ***
Executive Function	109.81 ***	−0.40 ***	−1.86 **	−7.17 ***	0.72 ***		1.30 ***		2.35 ***	1.62 ***

			Slopes							
	Ref	**Age**	**Sex**	**Dx**	**Educ**	**CSF Tau**	**CSF Aβ-42**	**Hipp**	**Default**	**Brain Slope**
Memory	−0.89 ***			−0.33 *		−0.30***	0.47***		0.69 ***	7.49 ***
Executive Function	−0.64 ***	0.05 **				−0.32 **	0.48***		0.58 ***	7.83 ***

Table 4

Relative effects sizes of simple, mediated, and direct paths from age to Memory and Executive baseline values and rates of change.

Dependent Variable	Effect Type	Independent Variable	Estimate	Standard Error	p-value
Memory Intercept	Simple	Age	−0.362	0.045	0
Memory Intercept	Direct	Age	−0.056	0.045	0.216
Memory Intercept	Indirect	Age-Default Mode	−0.089	0.029	0.002
Memory Intercept	Indirect	Age-Hippocampus	−0.114	0.027	0
Memory Intercept	Indirect	Age-Tau	−0.036	0.01	0
Memory Intercept	Indirect	Age-Aβ-42	−0.017	0.007	0.014
Memory Intercept	Total Indirect	Age-Brain Combined	−0.277	0.028	0
Executive Function Intercept	Simple	Age	−0.585	0.049	0
Executive Function Intercept	Direct	Age	−0.377	0.056	0
Executive Function Intercept	Indirect	Age-Default Mode	−0.127	0.035	0
Executive Function Intercept	Indirect	Age-Aβ-42	−0.024	0.009	0.006
Executive Function Intercept	Total Indirect	Age-Brain Combined	−0.192	0.03	0
Memory Slope	Simple	Age	−0.055	0.012	0
Memory Slope	Direct	Age	0.012	0.012	0.314
Memory Slope	Indirect	Age-Default Mode	−0.037	0.009	0
Memory Slope	Indirect	Age-Tau	−0.008	0.002	0.001
Memory Slope	Indirect	Age-Aβ-42	−0.009	0.003	0.001
Memory Slope	Total Indirect	Age-Brain Combined	−0.055	0.012	0
Executive Function Slope	Simple	Age	−0.041	0.015	0.005
Executive Function Slope	Direct	Age	0.04	0.014	0.004
Executive Function Slope	Indirect	Age-Default Mode	−0.031	0.009	0.001
Executive Function Slope	Indirect	Age-Tau	−0.008	0.003	0.002
Executive Function Slope	Indirect	Age-Aβ-42	−0.009	0.003	0.001
Executive Function Slope	Total Indirect	Age-Brain Combined	−0.069	0.012	0