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Research Article

A longitudinal study using latent curve models of groups with mild cognitive impairment and Alzheimer's disease

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ABSTRACT

Background: This study explores how mild cognitive impairment (MCI) and Alzheimer's disease (AD) develop over time.
New method: this study involves a new application of latent curve models (LCM) to examine the development trajectory of a healthy, MCI, and AD groups on a series of clinical and neural measures. Multiple-group latent curve models were used to compare the parameters of the trajectories across groups.
Results: LCM results showed that a linear functional form of growth was adequate for all the clinical and neural measures. Positive and significant differences in initial levels were seen across groups on all of the clinical and neural measures. In all groups, the following measures increased slightly, or considerably, over time: Clinical Dementia Rating, Alzheimer's disease Cognitive Assessment, and Montreal Assessment Test for Dementia. In contrast, a slight or a greatly decreasing trajectory was observed on the following measures: Fluorodeoxyglucose, Mini-Mental State Exam, Rey Auditory Verbal Learning Test as well as Hippocampus, Fusiform and Entorhinal Cortex volume measures. However, a constant mean trajectory was seen on Cognition Self Report Memory and languages scores.
Comparision with existing methods: there are no prior studies that applied LCM on large AD datasets.
Conclusions: cognitive decline occurs in the cognitively normal (CN), MCI, and AD groups but at different rates. Further, some important cognitive, neural, and clinical variables that (a) best differentiate between CN, MCI, and AD as well as (b) differentially change over time in MCI and AD, which may explain disease progression.

1. Introduction

The Alzheimer's Disease Neuroimaging Initiative (ADNI; Jack et al., 2008) has collected longitudinal data from individuals aged 55–90 with normal cognition, mild cognitive impairment, and Alzheimer's disease (AD) at 0, 6, 12, 24, and 36-month intervals. The goal of the ADNI project is to use biomarkers to assess the trajectory of AD to promote early detection and to identify effective interventions, preventative measures, and treatments. Understanding the trajectory and progression of neurodegenerative diseases such as Alzheimer's disease is important to provide early diagnosis and limit the effects of cognitive impairments associated with the AD (e.g., memory decline, learning difficulties, and reduced decision-making capacity). However, as cognitive decline is a normal aging process (Harada et al., 2013; Malpetti et al., 2019; Salthouse, 2011), it can be difficult to differentiate between normal cognitive decline, mild cognitive impairment, and AD (Pietrzak et al., 2015). Therefore, identifying differences in trajectories can aid our understanding of how biomarkers and neurocognitive assessments change over time for these three groups (i.e., cognitively normal, mild cognitive impairment, and AD).

Cognitive decline is part of the normal aging process and is

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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characterized by a significant deterioration in cognitive tasks such as reasoning, spatial orientation, memory, and processing speed (Salthouse, 2009, 2010). Findings suggest cognitive decline can begin in healthy people aged 20–30 (Salthouse, 2009). However, others have shown that cognitive decline before the age of 65 is often small (Cornelis et al., 2019). Further, age-related cognitive decline seems to be task-specific. For example, compared to younger controls, older people tend to show significantly poorer performance for visual memory (Cornelis et al., 2019), episodic memory (Lundervold et al., 2014), decision making (Boyle et al., 2012) and processing speed tasks (Cornelis et al., 2019); but not for reasoning or prospective memory tasks (Cornelis et al., 2019). Mild-cognitive impairment is characterized as cognitive decline greater than what can be expected due to age and educational level but does not cause impairments is normal daily functioning (Gauthier et al., 2006; R. C. Petersen et al., 1999). However, some research has shown that mild-cognitive impairment does produce some dysfunction in the performance of daily activities, such as cleaning, shopping, driving, and finances (e.g., Marshall et al., 2011). Alzheimer's disease is defined as a neurodegenerative disease which progressively deteriorates cognitive functions (e.g., memory, learning, language, judgment, decision making, processing speed, and emotion regulation; Alzheimer Association, 2019) which produces marked impairments in daily functioning.

Declines in cognitive performance can occur due to the normal aging process, mild cognitive impairment, or AD. As all three groups demonstrate a significant decline in cognitive abilities when compared to controls, it can be difficult to differentiate between the prognoses of people presenting with different types of cognitive impairment, especially during the early stages (Gross, Inouye, et al., 2012; McArdle et al., 2005; Pietrzak et al., 2015). Indeed, as AD develops slowly over time, symptoms may occur well-before a diagnosis is reached (Haaksma, Calderón-Larrañaga, Olde Rikkert, Melis, & Leoutsakos, 2018; Ji et al., 2003; Royall and Palmer, 2012). During the early stages of AD, cognitive decline might be subtle and indistinguishable from normal cognitive decline or mild cognitive impairment (Buckley et al., 2015; Jacobs et al., 2012; MacAulay et al., 2018; Perrin et al., 2009). However, it is not necessarily the decline in cognitive impairment but the difference between the steepness (i.e., severity) and the longitudinal trajectory of the decline associated with normal aging, mild cognitive impairment, and Alzheimer's Disease which might help differentiate these groups (Johnson et al., 2012; Mungas et al., 2010).

Latent class modeling can be used to identify groups with different Alzheimer's disease progression; for example, those with slow, moderate, and rapid progression (Haaksma et al., 2018). Then latent growth curve models can be applied to determine the trajectories of Alzheimer's Disease for the different classes (Anstey et al., 2003; Garre-Olmo, López-Pousa, Vilalta-Franch, De Gracia Blanco, & Vilarrasa, 2010; Haaksma et al., 2018; Johnson et al., 2012; MacAulay et al., 2018; McArdle et al., 2005). For example, in a group already diagnosed with Alzheimer's disease, baseline measures of neuropsychological assessments (e.g., the mini-mental state exam and the clinical dementia rating) can successfully predict the rate and progression of cognitive decline at multiple follow-ups (e.g., 12, 24, and 36 months; Haaksma et al., 2018). While a majority of people with Alzheimer's disease are likely to experience slow progression, a subset of those with poor neuropsychological assessment at baseline are more likely to experience a rapid progression (Haaksma et al., 2018). These studies reliably distinguish between different classes of Alzheimer's disease. However, as their main focus is Alzheimer's disease, the research does not aid our understanding or ability to distinguish between groups with age-related cognitive decline, mild cognitive impairment, and AD. As such, the predictive power to identify groups at risk of developing AD during the early stages of cognitive decline is inadequate.

Johnson et al. (2012) utilized latent growth modeling to estimate the difference in the trajectories of cognitive changes in a group with mild cognitive impairment and healthy controls. Longitudinal neuropsychological assessment data from the ADNI project was included in their analysis (i.e., at baseline, 6-, 12-, 18-, and 36-months). Their results showed that cognitive decline was noticeable for both healthy controls and a group with mild cognitive impairment. However, cognitive decline was more rapid for those with mild cognitive impairment. Specifically, there was a steeper decline for measures of memory, processing speed, language, attention, and visuospatial tasks — healthy controls did not show a decline in any of these domains. The authors indicate that processing speed showed the largest effect and can better differentiate between healthy people and a group with mild cognitive impairment.

The Johnson et al. (2012) results show that latent curve modeling can be used to identify the trajectories of cognitive decline between a group with mild cognitive decline and healthy controls. While outside of the scope of their study, the trajectory of cognitive decline associated with AD was not assessed. For that reason, it is difficult to generalize these findings to AD. As there is a high-risk of people with mild cognitive impairment progressing to AD (Gauthier et al., 2006; Hansson et al., 2006; Michaud et al., 2017; Mitchell and Shiri-Feshki, 2009; Petersen, 2009; Roberts et al., 2005), it is important to distinguish the trajectories for cognitively normal, mild cognitive impairment, and AD patients. Another drawback of these studies is their reliance on neuropsychological assessments (e.g., Alzheimer's Disease assessment scale, mini-mental state examination, and the clinical dementia rating) to predict the trajectory of Alzheimer's.

In addition to neuropsychological assessments, biomarkers such as Amyloid-β, total tau (t-tau), phosphorylated tau (p-tau), hippocampal volume, ventricular volume, fluorodeoxyglucose positron emission tomography (PET), and genetic carriers (i.e., Apolipoprotein E4 gene or APOE) have improved our understanding of the progression of cognitive decline due to the normal aging process, mild-cognitive impairment, and AD (Deary et al., 2009; Dowling et al., 2015; Gross et al., 2012a, 2012b; Han et al., 2012; Pietrzak et al., 2015; Rabin et al., 2017; Thibeau et al., 2017; Vemuri et al., 2019). Latent growth curve models have identified that high levels of Amyloid-β, the APOE gene, and tau are predictive of rapid memory decline in AD (Dowling et al., 2015; Pietrzak et al., 2015). Other findings have implicated lower levels of Amyloid-β, tau, and a loss of Hippocampal volume as predictors of cognitive decline during early-stages of an AD diagnosis (Dowling et al., 2015; Perrin et al., 2009; Shaw et al., 2009). Indeed, low levels of Amyloid-β are predictive of the progression from normal cognitive functioning to mild cognitive impairment; and from mild cognitive impairment to AD (Fagan et al., 2007; Hansson et al., 2006; Li, 2007; Perrin et al., 2009).

Malpetti et al. (2019) assessed the longitudinal progression of cognitive decline in a group with mild cognitive impairment ($N = 14$), probable AD ($N = 12$), and cognitively normal individuals ($N = 26$). The study aimed to identify if neuroimaging biomarkers (i.e., using PET and structural Magnetic resonance imaging, MRI) such as tau pathology, neuroinflammation, and brain atrophy are predictive of cognitive decline in AD. Further, they aimed to determine if PET or MRI imaging is a more robust assessment of cognitive decline. Latent growth curve modeling determined that the AD group had a more rapid decline in cognitive performance over the three year period compared to mild-cognitive impairment, and cognitively normal controls. Their results also confirmed that lower baseline scores were predictive of a more rapid decline in cognitive performance (Haaksma et al., 2018). In terms of neurological biomarkers, tau, neuro-inflammation, and atrophy all predicted longitudinal cognitive decline. Further, structural MRI (i.e., atrophy) was more predictive of longitudinal cognitive decline compared to PET imaging (i.e., tau and neuroinflammation). The results also suggest that the trajectory (i.e., slope) of cognitive decline differed significantly between healthy controls, mild cognitive impairment, and AD. However, the authors do caution that their result should be replicated in a larger sample to confirm the effects of multiple predictors of cognitive decline.

The literature has established that there is a decline in cognitive performance in AD patients and this might be predicted by baseline neuropsychological assessment and neurological biomarkers (Haaksma et al., 2018; Johnson et al., 2012). With latent growth curve modeling showing some differences in the trajectory of cognitive decline in groups

with slow, moderate, or rapid AD (Haaksma et al., 2018; Malpetti et al., 2019). However, latent growth curve modeling has not been applied to assess the longitudinal changes within neurological biomarkers of AD for cognitively normal, mild cognitive impairment, or AD groups. Understanding the trajectories associated with neuropsychological assessments and neurological biomarkers of AD could assist in the development of assessments for early detection, identify effective interventions, preventative measures, and treatments(Jack et al., 2008). Measuring changes using more objective neurological biomarkers of cognitive decline (i.e., Amyloid-β, tau, and Hippocampal volume) could also contribute to the earlier detection of AD; or to identify if the trajectory of people during the earlier stages of cognitive decline will predict if they are experiencing age-related cognitive decline, mild cognitive impairment, or the early-stages AD. The goals of the present study are to identify the development trajectories[1] of three groups (i.e., cognitively normal, mild cognitive impairment, and AD) on the clinical and neural measures. Second, our goal is to also identify whether these three cognitively normal, mild cognitive impairment and AD groups differ significantly in their trajectories.

2. Method

2.1. ADNI dataset

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. 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).

The ADNI dataset includes 2132 participants: 512 controls, and 353 with early-MCI (EMCI), 621 with late-MCI (LMCI), and 279 with subjective memory complaints (SMC), and 367 CE patients. Data were collected over a 3-year persion, at 0, 6, 12, 24, and 36 months. The ADNI dataset includes the following measures for all participants: APOE4 = Apolipoprotein E4 gene (it is either 0 or 1, which refers to having the gene polymorphism or not); FDG = Fluorodeoxyglucose (refers to Average FDG-PET of angular, temporal, and posterior cingulate); CDRSB = Clinical Dementia Rating Sum of Boxes (takes a value from 0 to 6, which higher values mean more dementia symptoms); ADAS11 = Alzheimer's Disease Assessment Scale (11 item version,which measure degree of cognitive decline); MMSE = Mini-Mental State Examination (30 questions to measure cognitive impairment); RAVimD = Rey Auditory Verbal Learning Test (Immediate word recall score, which measuers short term memory and rate of learning using list of words); MOCA = The Montreal Cognitive Assessment (30 items to test cognitive impairment); EcPtMm = Everyday Cognition-Participant Self Report (8 memory items, which measures functional and cognitive factors related to daily living activities by the participant themselves); EcPtLg = Everyday Cognition-Participant Self Report (9 language items, which measures language processes in everyday livig by the participant themselves); EcSPM = Everyday Cognition- Participant Study Partner Report (8 Memory items, which measures functional and cognitive factors related to daily living activities by the partner of the participant); EcSPLg = Everyday Cognition- Participant Study Partner Report (9 Language items, which measures language processes in everyday livig by the partner of the participant); Hipc = Hippocampus volume (measure of hippocampus volume as indicated by imaging studies); Entor = entorhinal cortex volume (measure of entorhinal cortex volume as indicated by imaging studies) ; Fusif = fusiform gyrus volume (measure of fusiform gyrus volume as indicated by imaging studies).

2.2. Statistical analysis

Latent curve model in the structural equation modeling framework also referred to as growth curve model, latent trajectory model, or random-effects modeling was used to estimate the development trajectories of the three groups of patients on the clinical and neural measures. Latent curve model analysis changes in a construct over time by explicitly modeling growth and group differences in growth over time.

2.2.1. Latent curve models (LCM) specification

LCM are used to analyze multiwave longitudinal data when population homogeneity is assumed for the estimated population parameters and global shape of the growth trajectories. Assuming a linear model for the repeated measures, for an individual i at time t $(t = 1, 2, ..., T)$, the within-person longitudinal LGM with Time-varying Covariate (TVC) is represented as:

$$y_{it} = \alpha_i + \beta_i . \lambda_t + \varepsilon_{it}$$

where y_{it} is the repeated measure outcome variable, λ_t is the time score, α_i is the intercept growth factor, β_i is the linear slope growth factor, and $\varepsilon_{it} \sim N(0, \theta_t)$ is the normally distributed residual for y_{it}. Growth is represented by imposing constraints on the time scores (λ_t) reflecting the passage of time. LCM generally assumes that the growth factors and the time specific residuals are mutually independent and multivariate normal.The between person LCM model is specified as:

$$\alpha_i = \mu_\alpha + \zeta_{\alpha i}$$
$$\beta_i = \mu_\beta + \zeta_{\beta i}$$

where μ_α, μ_β are the means of the growth factors; and $\zeta_{\alpha i}$ and $\zeta_{\beta i}$ are the multivariate normal residuals of growth factors with a zero mean vector, $Var(\alpha) = Var(\zeta_{\alpha i}) = \psi_{\alpha_y}\alpha_y$, $Var(\beta) = Var(\zeta_{\beta i}) = \psi_{\beta_y}\beta_y$, and $Cov(\alpha, \beta) = Cov(\zeta_{\alpha i}, \zeta_{\beta i}) = \psi_{\alpha_y}\beta_y$.

Further development on latent trajectory analysis is presented in elsewhere (e.g., Diallo and Morin, 2015; Diallo et al., 2014; Diallo and Lu, 2016; Duncan and Duncan, 1994; McArdle, 1988; McArdle and Epstein, 1987; Meredith and Tisak, 1984, 1990; Muthén and Curran, 1997; Willett and Sayer, 1994).

2.2.2. LCM estimation

The Maximum Likelihood Estimation (ML) method, the most used method to estimate parameters in Structural equation modeling (SEM), is also used for estimating LCM parameters as it provides many desirable statistical proprieties under multivariate normality assumption. The starting point of the ML estimation is the likelihood function (or the density function) of the data, viewed as a function of the unknown parameters. Maximizing the likelihood function determines the parameters that are most likely to produce the observed data. ML estimator minimizes the fitting function

$$F_{ML} = tr\left(S\widehat{\Sigma}^{-1}\right) + \ln|\widehat{\Sigma}| - \ln|S| - (p+q)$$

Where S is the to the (actual) covariance matrix based on the empirical data, $\widehat{\Sigma}$the implied covariance matrix produced by the specified model, q is the number of *independent* variables in the model and p is the number of *dependent* variables in the model.

Assuming large sample sizes, the ML estimates are asymptotically normally distributed with the asymptotic covariance matrix equal to the inverse of the Fisher information matrix, computed as the negative Hessian of the log-likelihood. The asymptotic standard errors of the ML estimates are then obtained as the square root of the diagonal element of the asymptotic covariance matrix.

Furthermore, the null hypothesis (H0) that the population total covariance matrix is equal to the model implied covariance matrix can be evaluated using the likelihood ratio statistic, T_{ML}:

$$T_{ML} = F_{ML}(\widehat{\theta}) - F_{ML}(\widehat{\theta}_S)$$

where $F_{ML}(\widehat{\theta})$ denotes the fitting function for the hypothesized model and $F_{ML}(\widehat{\theta}_S)$ denotes the fitting function for the saturated model. Assuming that the null hypothesis holds, the likelihood ratio statistic T_{ML} asymptotically follows a central chi-square distribution with degree of freedom (df) equals to the difference in the number of parameters between the saturated model and the hypothesized model. It's important to note that the test statistic T_{ML} follows a central chi-square distribution under various conditions including proper model specification,

Table 1
Goodness-of-fit indices for the Latent Growth Curve Analysis. Our results show that a linear functional form of growth provided the best fit to the data.

Groups	χ^2	df	p-value	CFI	TLI	RMSEA	(90 % CI)
Fluorodeoxyglucose							
AD	13.59	9	0.14	0.99	0.99	0.05	(0.00–0.09)
CN	14.65	10	0.15	0.99	0.99	0.04	(0.00–0.07)
MCI	7.14	10	0.71	1.00	1.00	0.00	(0.00–0.03)
Clinical Dementia Rating Scale- Sum of Boxes							
AD	21.93	10	0.02	0.96	0.96	0.05	(0.02–0.09)
CN	47.79	10	0.00	0.93	0.93	0.06	(0.05–0.09)
MCI	26.56	10	0.00	0.99	0.99	0.04	(0.02–0.06)
Alzheimer'sDiseaseAssessmentScale							
AD	34.10	10	0.00	0.95	0.95	0.08	(0.05–0.11)
CN	38.54	10	0.00	0.95	0.95	0.06	(0.04–0.08)
MCI	24.63	10	0.01	0.99	0.99	0.04	(0.02–0.06)
Mini Mental State Exam							
AD	24.68	10	0.01	0.95	0.95	0.06	(0.03–0.10)
CN	24.06	10	0.01	0.94	0.94	0.04	(0.02–0.06)
MCI	39.83	10	0.00	0.98	0.98	0.05	(0.04–0.07)
Rey Auditory Verbal Learning Test							
AD	28.42	10	0.00	0.96	0.96	0.07	(0.04–0.10)
CN	18.87	10	0.04	0.99	0.99	0.03	(0.01–0.07)
MCI	17.99	10	0.06	1.00	1.00	0.03	(0.00–0.05)
Montreal Cognitive Assessment Test for Dementia							
AD	25.07	10	0.01	0.92	0.92	0.09	(0.09–0.14)
CN	16.23	12	0.18	0.99	0.99	0.03	(0.00–0.05)
MCI	20.89	10	0.02	0.99	0.99	0.04	(0.01–0.07)
Cognition Self Report (Memory)							
AD	5.62	11	0.90	1.00	1.00	0.00	(0.00–0.04)
CN	4.81	9	0.85	1.00	1.00	0.00	(0.00–0.03)
MCI	9.82	9	0.37	1.00	1.00	0.01	(0.00–0.05)
Cognition Self Report (Language)							
AD	5.76	11	0.89	1.00	1.04	0.00	(0.00–0.04)
CN	7.92	10	0.64	1.00	1.00	0.00	(0.00–0.04)
MCI	8.16	10	0.61	1.00	1.00	0.00	(0.00–0.04)
Cognition Partner Report (Memory)							
AD	9.56	11	0.57	1.00	1.00	0.00	(0.00–0.07)
CN	12.33	10	0.26	1.00	1.00	0.02	(0.00–0.05)
MCI	25.07	10	0.01	1.00	1.00	0.05	(0.03–0.08)
Cognition Partner Report (Language)							
AD	9.50	10	0.49	1.00	1.00	0.00	(0.00–0.08)
CN	17.24	10	0.07	0.98	0.98	0.04	(0.00–0.06)
MCI	25.45	10	0.00	0.99	0.99	0.05	(0.03–0.08)
Hippocampus							
AD	39.00	9	0.00	0.98	0.98	0.09	(0.07–0.13)
CN	38.87	10	0.00	0.99	0.99	0.07	(0.05–0.10)
MCI	25.17	10	0.01	1.00	1.00	0.01	(0.02–0.06)
Entorhinal cortex							
AD	12.47	10	0.26	1.00	1.00	0.03	(0.00–0.07)
CN	20.70	10	0.02	0.99	0.99	0.05	(0.02–0.08)
MCI	9.75	10	0.46	1.00	1.00	0.00	(0.00–0.04)
Fusiform							
AD	25.63	10	0.00	0.99	0.99	0.07	(0.04–0.11)
CN	8.71	10	0.56	1.00	1.00	0.00	(0.00–0.04)
MCI	30.79	10	0.00	1.00	1.00	0.05	(0.03–0.07)

multivariate normality at both levels, and sufficiently large sample sizes. Iterative numerical methods are often used to get the ML estimates.

The ML function to be minimized is distributed as follows:

$(N\text{-}1)^* F_{ML} \sim \chi^2 [(p + q)(p + q+1)\text{-}t]$, where t is the number of free parameters and N is the sample size. For a technical detail on this estimation process, we refer the reader to (Bollen and Curran, 2006).

2.2.3. Multiple group analysis

Multiple-group latent curve model (Bollen and Curran, 2006) also known as a multiple-sample latent curve model, was then employed to test whether the three groups of patients with AD, cognitively normal (CN) and MCI differ significantly in their trajectories. This analytical technique imposes a series of nested equality constraints on the parameters of the growth trajectories across the different groups. The multiple-group latent curve model was conducted in three steps. First, a latent curve model that best described the data was estimated in each group separately. Second, a joint analysis of all groups with the parameters of the trajectories estimated freely was carried out. Third, a joint analysis of all groups and tests of invariance was conducted through equality restrictions.

2.2.4. Analytical steps

A series of latent curve models were estimated to specify the optimal functional form of growth of the clinical and neural measures across groups. Different forms of growth including linear, quadratic and free-loading models were estimated and the fit of these models was compared. A linear function was found to be optimal for all the measures considered in this paper. Residuals were freely estimated across time and were allowed to correlate. Because we did not have hypotheses about the order in which parameters of the latent curve models should be tested, we followed the hierarchy suggested in Bollenand Curran (2006). We first tested whether the means of growth trajectories parameters (i.e., intercept and linear slope) were equal (invariant) across groups. Then, growth trajectories variances (i.e, random intercepts and random linear slopes variances) invariance across groups was

Table 2
Multi-group Analysis Results. The results showed that among several models, the linear functional form of growth was optimal for the three groups and for all clinical and neural measures.

	χ^2	df	p-value	CFI	TLI	RMSEA	(90 % CI, RMSEA)	$\Delta\chi^2$	df	P difference
Fluorodeoxyglucose										
Baseline Model: No Invariance	35.38	29	0.19	1.00	1.00	0.03	(0.00−0.05)			
Intercept and Slope Mean Invariance	360.23	33	0.00	0.84	0.86	0.16	(0.14−0.17)	324.85	4	< 0.0001
Intercept Mean Invariance	270.89	31	0.00	0.88	0.89	0.14	(0.14−0.17)	235.51	2	< 0.0001
Slope Mean Invariance	47.44	31	0.03	1.00	1.00	0.04	(0.01−0.06)	12.06	2	0.00
Partial Slope Invariance: (NC = MCI)	39.04	30	0.03	1.00	1.00	0.03	(0.00−0.05)	3.66	1	0.06
Intercept Variance Invariance	77.45	33	0.00	1.00	1.00	0.05	(0.04−0.07)	38.41	3	< 0.0001
Slope Variance Invariance	89.86	33	0.00	0.99	0.99	0.06	(0.04−0.07)	50.82	3	< 0.0001
Clinical Dementia Rating Scale- Sum of Boxes										
Baseline Model: No Invariance	96.28	30	0.00	0.98	0.98	0.06	(0.04−0.07)			
Intercept and Slope Mean Invariance	1576.27	34	0.00	0.42	0.49	0.25	(0.24−0.26)	1479.99	4	< 0.0001
Intercept Mean Invariance	1154.48	32	0.00	0.58	0.61	0.22	(0.21−0.23)	1058.20	2	< 0.0001
Slope Mean Invariance	124.53	32	0.00	0.97	0.97	0.06	(0.05−0.08)	28.25	2	< 0.0001
Partial Slope Invariance: (NC = MCI)	105.42	31	0.00	0.97	0.97	0.06	(0.05−0.07)	9.14	1	0.00
Intercept Variance Invariance	1055.98	32	0.00	0.62	0.64	0.21	(0.20−0.22)	959.70	2	< 0.0001
Slope Variance Invariance	389.59	32	0.00	0.87	0.87	0.13	(0.12−0.14)	293.31	2	< 0.0001
Alzheimer'sDiseaseAssessmentScale										
Baseline Model: No Invariance	97.27	30	0.00	0.98	0.98	0.06	(0.04−0.07)			
Intercept and Slope Mean Invariance	1083.66	34	0.00	0.66	0.67	0.21	(0.20−0.22)	986.39	4	< 0.0001
Intercept Mean Invariance	852.32	32	0.00	0.73	0.75	0.19	(0.18−0.20)	755.05	2	< 0.0001
Slope Mean Invariance	131.24	32	0.00	0.97	0.97	0.07	(0.06−0.08)	33.97	2	< 0.0001
Partial Slope Invariance: (AD = MCI)	109.02	31	0.00	0.97	0.97	0.06	(0.05−0.07)	11.75	1	< 0.001
Intercept Variance Invariance	492.62	32	0.00	0.85	0.86	0.14	(0.13−0.15)	395.35	2	< 0.0001
Slope Variance Invariance	218.73	32	0.00	0.94	0.93	0.09	(0.08−0.10)	121.46	2	< 0.0001
Mini Mental State Exam										
Baseline Model: No Invariance	88.58	30	0.00	0.97	0.97	0.05	(0.04−0.07)			
Intercept and Slope Mean Invariance	1210.45	34	0.00	0.42	0.48	0.22	(0.21−0.23)	1121.87	4	< 0.0001
Intercept Mean Invariance	949.19	32	0.00	0.54	0.57	0.20	(0.19−0.21)	860.61	2	< 0.0001
Slope Mean Invariance	115.92	32	0.00	0.96	0.96	0.06	(0.05−0.07)	27.34	2	< 0.0001
Partial Slope Invariance: (AD = MCI)	100.21	31	0.00	0.97	0.97	0.06	(0.06−0.07)	11.63	1	< 0.001
Intercept Variance Invariance	448.72	32	0.00	0.79	0.81	0.14	(0.13−0.15)	360.14	2	< 0.0001
Slope Variance Invariance	341.13	32	0.00	0.85	0.86	0.12	(0.11−0.13)	252.55	2	< 0.0001
Rey Auditory Verbal Learning Test										
Baseline Model: No Invariance	65.28	30	0.00	0.99	0.99	0.04	(0.03−0.05)			
Intercept and Slope Mean Invariance	1238.58	34	0.00	0.73	0.73	0.22	(0.21−0.24)	1173.30	4	< 0.0001
Intercept Mean Invariance	1086.47	32	0.00	0.77	0.78	0.22	(0.21−0.23)	1021.19	2	< 0.0001
Slope Mean Invariance	74.32	32	0.00	0.99	0.99	0.04	(0.03−0.06)	9.04	2	0.01
Partial Slope Invariance: (CN = MCI)	66.20	31	0.00	0.99	0.99	0.04	(0.03−0.05)	0.92	1	0.34
Intercept Variance Invariance	131.89	33	0.00	0.98	0.99	0.07	(0.05−0.08)	65.69	2	< 0.0001
Slope Variance Invariance	68.10	33	0.00	0.99	0.99	0.04	(0.03−0.05)	1.90	2	0.39
Montreal Cognitive Assessment Test for Dementia										
Baseline Model: No Invariance	62.19	32	0.00	0.98	0.98	0.05	(0.03−0.06)			
Intercept and Slope Mean Invariance	570.42	36	0.00	0.64	0.70	0.18	(0.17−0.20)	508.23	4	< 0.0001
Intercept Mean Invariance	513.82	34	0.00	0.68	0.73	0.18	(0.16−0.19)	451.63	2	< 0.0001
Slope Mean Invariance (AD = MCI)	71.29	33	0.00	0.97	0.98	0.05	(0.04−0.07)	9.10	1	0.00
Intercept Variance Invariance	280.11	34	0.00	0.84	0.85	0.13	(0.11−0.14)	217.92	2	< 0.0001
Slope Variance Invariance (AD = MCI)	63.17	33	0.00	0.98	0.98	0.05	(0.03−0.06)	0.98	1	0.32
Cognition Self Report (Memory)										
Baseline Model: No Invariance	20.25	29	0.88	1.00	1.01	0.00	(0.00−0.02)			
Intercept and Slope Mean Invariance	343.38	33	0.00	0.77	0.79	0.15	(0.13−0.16)	323.13	4	< 0.0001
Intercept Mean Invariance	268.17	31	0.00	0.83	0.83	0.13	(0.12−0.15)	247.92	2	< 0.0001
Partial Intercept Mean Invariance (AD = MCI)	20.37	30	0.91	1.00	1.01	0.00	(0.00−0.02)	0.12	1	0.73
Slope Mean Invariance	24.47	32	0.83	1.00	1.01	0.00	(0.00−0.02)	4.10	2	0.13
Intercept Variance Invariance	53.91	34	0.02	0.99	0.99	0.04	(0.02−0.05)	29.44	2	< 0.0001
Slope Variance Invariance: (CN = MCI)	28.02	33	0.71	1.00	1.00	0.00	(0.00−0.03)	3.55	1	0.06
Cognition Self Report (Language)										
Baseline Model: No Invariance	21.85	31	0.89	1.00	1.01	0.00	(0.00−0.02)			
Intercept and Slope Mean Invariance	220.64	35	0.00	0.86	0.88	0.11	(0.10−0.12)	198.79	4	< 0.0001
Intercept Mean Invariance	180.87	33	0.00	0.89	0.90	0.10	(0.09−0.12)	159.02	2	< 0.0001
Partial Intercept Mean Invariance (AD = MCI)	22.26	32	0.90	1.00	1.01	0.00	(0.00−0.02)	0.41	2	0.81
Slope Mean Invariance	22.56	34	0.93	1.00	1.01	0.00	(0.00−0.01)	0.71	2	0.70
Intercept Variance Invariance	113.40	36	0.00	0.94	0.95	0.07	(0.05−0.08)	90.84	2	< 0.0001
Slope Variance Invariance	31.36	36	0.70	1.00	1.00	0.00	(0.00−0.03)	8.80	2	0.01
Cognition Partner Report (Memory)										
Baseline Model: No Invariance	46.95	31	0.03	0.99	0.99	0.03	(0.01−0.05)			
Intercept and Slope Mean Invariance	868.51	35	0.00	0.54	0.61	0.23	(0.22−0.25)	821.56	4	< 0.0001
Intercept Mean Invariance	839.37	33	0.00	0.56	0.60	0.23	(0.22−0.25)	792.42	2	< 0.0001
Slope Mean Invariance	62.64	33	0.00	0.98	0.98	0.05	(0.03−0.06)	15.69	2	< 0.001
Partial Slope Mean Invariance (AD = MCI)	46.97	32	0.04	0.99	0.99	0.03	(0.01−0.05)	0.02	1	0.89
Intercept Variance Invariance	277.82	34	0.00	0.87	0.88	0.13	(0.13−0.14)	230.85	2	< 0.0001
Slope Variance Invariance: (CN = MCI)	58.12	33	0.00	0.99	0.99	0.04	(0.02−0.06)	11.15	1	< 0.001
Cognition Partner Report (Language)										
Baseline Model: No Invariance	52.19	30	0.01	0.99	0.99	0.04	(0.02−0.06)			

(*continued on next page*)

Table 2 (*continued*)

	χ^2	df	p-value	CFI	TLI	RMSEA	(90 % CI, RMSEA)	$\Delta\chi^2$	df	P difference
Intercept and Slope Mean Invariance	588.48	34	0.00	0.65	0.69	0.19	(0.18−0.21)	536.29	4	< 0.0001
Intercept Mean Invariance	524.70	32	0.00	0.69	0.71	0.19	(0.17−0.20)	472.51	2	< 0.0001
Slope Mean Invariance	62.58	32	0.00	0.98	0.98	0.05	(0.03−0.06)	10.39	2	0.01
Partial Slope Mean Invariance (AD = MCI)	53.71	31	0.01	0.99	0.99	0.04	(0.02−0.06)	1.52	1	0.22
Intercept Variance Invariance	496.26	33	0.00	0.71	0.74	0.18	(0.16−0.19)	442.55	2	< 0.0001
Slope Variance Invariance	92.54	33	0.00	0.96	0.97	0.06	(0.05−0.08)	38.83	2	< 0.0001
Hippocampus										
Baseline Model: No Invariance	103.04	29	0.00	0.99	0.99	0.07	(0.05−0.08)			
Intercept and Slope Mean Invariance	503.01	33	0.00	0.95	0.96	0.16	(0.15−0.17)	399.97	4	< 0.0001
Intercept Mean Invariance	477.19	31	0.00	0.96	0.96	0.16	(0.15−0.17)	374.15	2	< 0.0001
Slope Mean Invariance	251.55	30	0.00	0.97	0.97	0.12	(0.10−0.13)	148.51	2	< 0.0001
Partial Slope Mean Invariance (AD = MCI)	109.37	31	0.00	0.99	0.99	0.07	(0.05−0.08)	6.33	2	0.04
Intercept Variance Invariance	133.95	31	0.00	0.99	0.99	0.08	(0.06−0.09)	30.91	2	< 0.0001
Slope Variance Invariance	114.95	31	0.00	0.99	0.99	0.07	(0.06−0.08)	11.91	2	0.00
Entorhinal cortex										
Baseline Model: No Invariance	42.91	30	0.00	1.00	1.00	0.03	(0.00−0.05)			
Intercept Mean Invariance	402.24	34	0.00	0.92	0.93	0.14	(0.13−0.16)	359.33	4	< 0.0001
Partial Intercept Mean Invariance	359.42	32	0.00	0.93	0.93	0.14	(0.13−0.15)	316.51	2	< 0.0001
Slope Mean Invariance	49.08	32	0.03	1.00	1.00	0.03	(0.01−0.05)	6.17	2	0.04
Intercept Variance Invariance	73.73	34	0.00	0.99	0.99	0.05	(0.03−0.06)	30.82	4	< 0.0001
Slope Variance Invariance	54.79	34	0.01	0.99	0.99	0.03	(0.02−0.05)	11.88	4	0.02
Fusiform										
Baseline Model: No Invariance	65.12	30	0.00	1.00	1.00	0.05	(0.03−0.06)			
Intercept and Slope Mean Invariance	256.37	34	0.00	0.97	0.98	0.11	(0.10−0.12)	191.25	4	< 0.0001
Intercept Mean Invariance	221.15	32	0.00	0.98	0.98	0.11	(0.09−0.12)	156.03	2	< 0.0001
Partial Intercept Mean Invariance (CN = MCI)	74.58	31	0.00	0.99	0.99	0.05	(0.04−0.07)	9.46	1	0.00
Slope Mean Invariance	86.62	32	0.00	0.99	0.99	0.06	(0.04−0.07)	21.50	2	< 0.0001
Intercept Variance Invariance	77.39	32	0.00	0.99	0.99	0.05	(0.04−0.07)	12.27	2	0.00
Slope Variance Invariance	89.86	32	0.00	0.99	0.99	0.06	(0.04−0.07)	24.74	2	< 0.0001

investigated. Finally, when full invariance did not hold a partial invariance was performed.

To avoid bias due to attrition in the sample, all the models were estimated using direct maximum likelihood procedure available in Mplus V8.3 (Muthén and Muthén, 2002, 2011). The direct maximum likelihood also known as Full Information Maximum Likelihood utilized all available information during the estimation process and provided consistent and efficient population parameters (Enders, 2010). The adequacy of model fit was evaluated using the comparative fit index (CFI; Bentler, 1990), the Tucker-Lewis index (TLI; Tucker and Lewis, 1973), for which values of 0.95 or greater were considered adequate (Yu and Muthén, 2002; Hu and Bentler, 1999; Marsh et al., 2004). The root mean squared error of approximation (RMSEA) and its 90 % CI (Browne and Cudeck, 1993), for which values of 0.05 or less indicating adequate model fit, were also considered. Nested χ^2 methods were used to evaluate equality across groups imposed on the parameters of the latent trajectories.

3. Results

3.1. Bivariate analysis

Strong and positive correlation both within and across waves of

Table 3
Multi-group Analysis Results using the No invariance: Baseline Model. This figure provides a comparison among groups for all studied variales.

	InterceptMean	SlopeMean	Intercept Variance	Slope Variance
Fluorodeoxyglucose	No Invariance : CN > MCI > AD	No Invariance : | AD| > |MCI| > |CN|	No Invariance : AD > MCI > CN	No Invariance : AD > MCI > CN ns
Clinical Dementia Rating Scale- Sum of Boxes	No Invariance : AD > MCI > CN	No Invariance : AD > MCI > CN	No Invariance : AD > MCI > CN	No Invariance : AD > MCI > CN
Alzheimer'sDiseaseAssessmentScale	No Invariance : AD > MCI > CN	No Invariance : AD > MCI > CN	No Invariance : AD > MCI > CN	No Invariance : AD > MCI > CN
Mini Mental State Exam	No Invariance : CN > MCI > AD	No Invariance : | AD| > |MCI| > |CN| ns	No Invariance : AD > MCI > CN	No Invariance: AD > MCI > CN ns
Rey Auditory Verbal Learning Test	No Invariance : CN > MCI > AD	Partial Invariance: |AD| > |CN| = |MCI|	No Invariance : MCI > CN > AD	Invariance : AD ns = CN ns = MCI ns
Montreal Cognitive Assessment Test for Dementia	No Invariance : CN > MCI > AD	No Invariance : AD > MCI > CN ns	No Invariance : AD > MCI > CN	Partial Invariance : AD = MCI and CN@0
Cognition Self Report (Memory)	Partial Invariance: AD = MCI > CN	Invariance : AD ns = CN ns = MCI ns	No Invariance : MCI > AD > CN	No Invariance MCI > CN ns and AD@0
Cognition Self Report (Language)	Partial Invariance: AD = MCI > CN	Invariance : AD ns = CN ns = MCI ns	No Invariance : AD > MCI > CN	Partial Invariance : AD > MCI ns = CN ns
Cognition Partner Report (Memory)	No Invariance : AD > MCI > CN	Partial Invariance: |AD| = |MCI| > CN ns	No Invariance : MCI > AD > CN	No Invariance : MCI > CN and AD@0
Cognition Partner Report (Language)	No Invariance : AD > MCI > CN	Partial Invariance: |AD| = |MCI| > CN ns	No Invariance MCI > AD > CN	No Invariance : MCI > AD > CN ns
Hippocampus	No Invariance : CN > MCI > AD	No Invariance : |MCI| > |AD| > |CN|	No Invariance : MCI > AD > CN	No Invariance : AD > MCI > CN
Entorhinal cortex	No Invariance : CN > MCI > AD	No Invariance : |MCI| > |CN| > |AD| ns	No Invariance : MCI > AD > CN	No Invariance : MCI > AD > CN
Fusiform	No Invariance : CN > MCI > AD	No Invariance : |AD| > |MCI| > |CN|	No Invariance : MCI > AD > CN	No Invariance : AD > MCI > CN ns

Note. |.|= absoute value, AD = Alzheimer's disease, CN = cognitively normal, MCI = mild cognitive impairment.

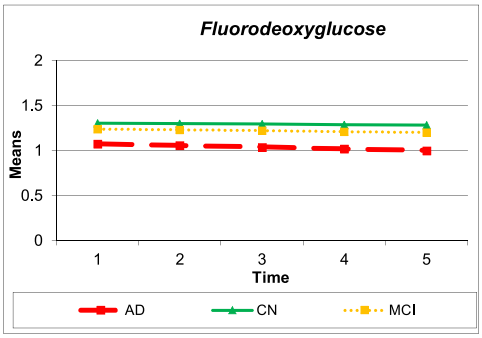

Fig. 1. PET Neuroimaging Marker Variable. The x axis represents time points of testing at 0, 6, 12, 24, and 36 months. AD = alzheimer's disease, CN = cognitively normal, MCI = mild cognitive impairment. The multiple-group analysis revealed that the CN group had higher initial levels of Fluorodeoxyglucose, followed by MCI group and by patients with AD. Patients with AD decreased more on their score of Fluorodeoxyglucose over time, followed by MCI and by the CN group. Patients with AD had more variability in both intercept and slope, followed by MCI and then the CN group.

measurement was seen for the clinical and neural measures across groups of patients. These results showed that patients with high clinical and neural measure scores at Time 1 tended to have high scores at the subsequent waves across groups. Means, standard deviations, zero-order correlations, and sample sizes for the clinical and neural measures are provided in Tables A1–A3 of the appendix.

3.2. Latent curve model and multiple-group analysis

As shown in Table 1, for each group, a linear functional form of growth was found to fit the observed data quite well. The CFI ranged from 0.92 to 1.00, the TLI from 0.92 to 1.01, the RMSEA from 0.00 to 0.09. Parameter estimates and asymptotic standard errors of the latent curve models are provided in the appendix accompanying this manuscript. The multiple-group analysis results are presented in Table 2. We will now discuss individual results in the following paragraphs by groups of clinical and neural measures. Parameter estimates and asymptotic standard errors of latent curve models of the clinical and neural measures are provided in Tables A4–A16 of the appendix. Table 3 provides a summary of the multi-group results.

3.3. PET neuroimaging marker

The results showed that, on average, the three groups of CN, MCI, and AD started with positive and significant levels of Fluorodeoxyglucose (with an intercept factor mean: AD = 1.08, CN = 1.31, MCI = 1.24) but their score of Fluorodeoxyglucose decreased slightly over time (with a slope factor mean: AD = -0.02, CN = -0.01, MCI = -0.02). Variance component in both the intercept (AD = 0.03, CN = 0.01, MCI = 0.02) and the slope (AD = 0.02, CN = 0.01 ns, MCI = 0.01) factors was significant, suggesting that there were meaningful group differences in both initial levels and growth in Fluorodeoxyglucose scores over time for patients with AD and MCI group. Meaningful individual variability for the intercept, but not for the slope, was found for the CN group. Non-significant correlation coefficients between the intercept and slope factors ($r = 0.01$) were found for the three groups. The latent curve models estimated for the three groups of patients are shown in Fig. 1. Finally, the multiple-group analysis revealed that the CN group had higher initial levels of Fluorodeoxyglucose, followed by MCI group and by patients with AD. Patients with AD decreased more on their score of Fluorodeoxyglucose over time, followed by MCI and by the CN group. Patients with AD had more variability in both intercept and slope, followed by MCI and then the CN group.

3.4. Psychological tests

3.4.1. Clinical dementia rating scale- sum of boxes

The intercept mean was significant and positive across groups (AD = 5.08, CN = 0.10, MCI = 1.95). A significant positive mean for the slope factor (AD = 0.32, CN = 0.02, MCI = 0.09) indicated that, overall, the three groups of patients increased in their Clinical Dementia Rating scores over time. Group differences in both initial levels and growth in Clinical Dementia Rating scores over time were significant across groups for the intercept (AD = 4.63, CN = 0.01, MCI = 3.89) and for the slope (AD = 0.69, CN = 0.02, MCI = 0.29). A significant negative correlation between the intercept and slope factors (AD = -0.72, CN = -0.02, MCI = -0.65) indicated that there was an inverse relationship between initial status and change over time (i.e., patients who reported lower levels Clinical Dementia Rating scores at Time 1 tended to report steeper increases in score over time). Finally, a higher initial level of Clinical Dementia Rating scores with steeper slope and more variability in both intercept and slope was seen for patients with AD, followed by MCI and by then the CN group.

3.4.2. Alzheimer's disease assessment scale

The intercept mean was significant and positive across groups (AD = 21.59, CN = 6.81, MCI = 11.41). A positive and significant mean slope factor was seen for patients with AD and MCI but negative for the CN group (AD = 0.85, CN = -0.13, MCI = 0.15), indicating increasing average trajectories in Alzheimer's Disease Assessment scores over time for patients with AD and MCI, but decreasing trajectories for the CN group. A significant variance component in both the intercept (AD = 64.75, CN = 6.25, MCI = 35.01) and the slope factors (AD = 7.54, CN = 0.20, MCI = 1.58) indicated that there were significant group differences in both initial levels and growth over time in Alzheimer's Disease Assessment scores across groups. Patients with lower levels of Alzheimer's Disease Assessment scores at Time 1 had a steeper increase over time across groups (AD = -8.53, CN = -0.33, MCI = -2.41). The multiple-group results were similar to those found for the Clinical Dementia Rating Scale. A higher initial level of Alzheimer's Disease Assessment scores with steeper slope and more variability in both intercept and slope were seen for patients with AD, followed by MCI and then the CN group.

Mini-Mental State Exam. The intercept mean was significant and positive across groups (AD = 22.32, CN = 28.98, MCI = 26.91). A significant negative mean for the average slope factor was seen for patients with AD and MCI but a non-significative mean slope factor for the CN group (AD = -0.46, CN = 0.00 ns, MCI =-0.10) indicated decreasing trajectories in Mini-Mental State Exam scores over time for patients with AD and MCI, but constant trajectories for the CN group. A significant variance component in both the intercept and the slope factors indicated that there were significant group differences in both initial levels and growth over time in Mini-Mental State Exam scores for patients with AD and MCI for the intercept (AD = 8.82, CN = 0.56, MCI = 6.61) and for the slope (AD = 2.17, CN = 0.01, MCI = 0.50). Meaningful variability of the intercept, but not of the slope, was found in the CN group. Patients with AD and the MCI group with lower levels of Mini-Mental State Exam scores at Time 1 had a steeper increase over time (AD = -1.85, MCI = -0.65). However, a non-significant correlation coefficient between the intercept and slope factors ($r = -0.02$ ns) was found for the CN group. The CN group showed higher initial levels of Mini-Mental State Exam scores at Time 1, followed by MCI and then patients with AD. Patients with AD decreased more over time, followed by the MCI group. In contrast, the CN group tended to have a constant trajectory over time. Patients with AD had more variability in both intercept and slope, followed by MCI and then CN group. Patients with AD had more variability in both intercept and slope, followed by MCI group.

3.4.3. Montreal cognitive assessment test for dementia

The intercept mean was significant and positive across groups (AD = 14.99, CN = 26.04, MCI = 22.49). Increasing mean trajectory over time was found for patients with AD ($M = 0.71$) and MCI group ($M = 0.24$), but a nonsignificant mean trajectory for the CN group ($M = 0.01$).

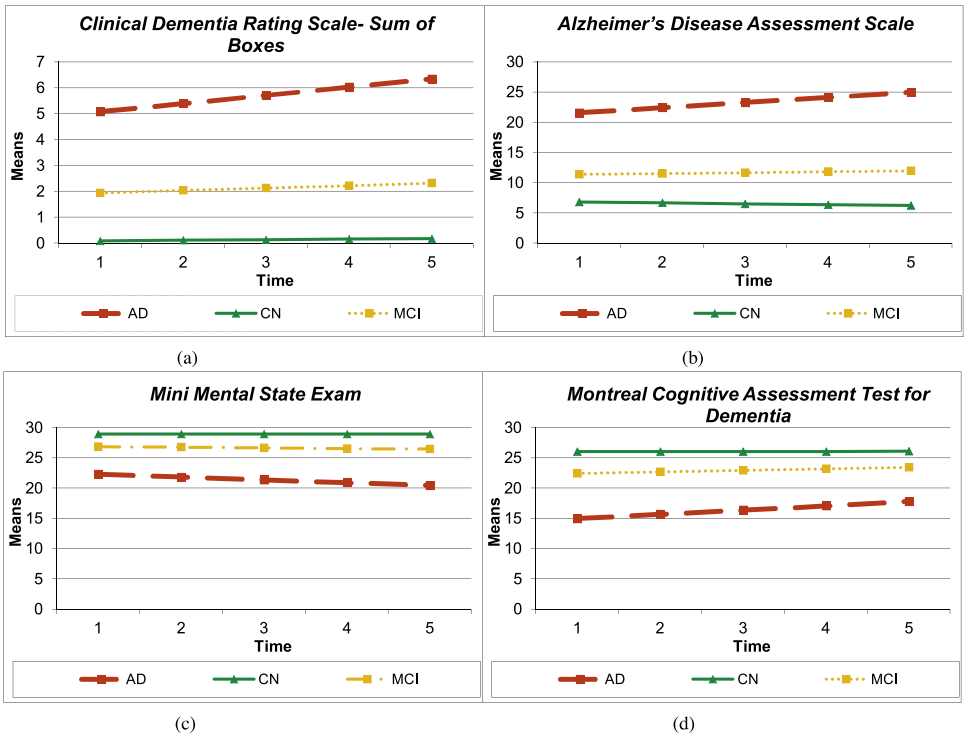

Fig. 2. Psychological Test Variables. The x axis represents time points of testing at 0, 6, 12, 24, and 36 months. (a) The intercept mean was significant and positive across groups. A significant positive mean for the slope indicated that, overall, the three groups increased in their Clinical Dementia Rating scores over time. Group differences in both initial levels and growth in Clinical Dementia Rating scores over time were significant across groups for the intercept and for the slope. (b) The intercept mean was significant and positive across groups. A positive and significant mean slope factor was seen for patients with AD and MCI but negative for the CN group, indicating increasing average trajectories in Alzheimer's Disease Assessment scores over time for patients with AD and MCI, but decreasing trajectories for the CN group. (c) The intercept mean was significant and positive across groups. A significant negative mean for the average slope factor was seen for patients with AD and MCI but a non-significative mean slope factor for the CN group indicated decreasing trajectories in Mini-Mental State Exam scores over time for patients with AD and MCI, but constant trajectories for the CN group. A significant variance component in both the intercept and the slope factors indicated that there were significant group differences in both initial levels and growth over time in Mini-Mental State Exam scores for patients with AD and MCI for the intercept and for the slope. (d) The intercept mean was significant and positive across groups. Increasing mean trajectory over time was found for patients with AD and MCI group, but a nonsignificant mean trajectory for the CN group. Intercept variance component was significant across groups, whereas the slope variance component for the CN group was slightly negative and thus fixed at zero. Patients with AD and MCI group, with lower levels of Montreal Cognitive Assessment Test for Dementia scores at Time 1, had a steeper increase over time.

Intercept variance component was significant across groups (AD = 28.20, CN = 3.69, MCI = 17.10), whereas the slope variance component for the CN group was slightly negative and thus fixed at zero (AD = 0.83, CN = @0, MCI = 0.44). Patients with AD and MCI group, with lower levels of Montreal Cognitive Assessment Test for Dementia scores at Time 1, had a steeper increase over time (AD = -2.73, MCI = -1.76). Because the slope variance for CN group was fixed at zero, no growth trajectory correlation was estimated for this group. The CN group showed higher initial levels of Montreal Cognitive Assessment Test for Dementia scores at Time 1, followed by MCI and by the AD group. Patients with AD showed a steeper increase in the Montreal Cognitive Assessment Test for Dementia scores over time, followed by MCI and CN who have a similar rate of decline over time. Similarly, patients with AD had more variability in the intercept factor, followed by MCI and by the CN group. A comparable amount of variability was seen in the slope for groups AD and MCI. The latent curve models estimated for the three groups of patients for the four psychological tests are shown in Fig. 2.

3.4.4. *Rey auditory verbal learning test*

Significant and positive intercept mean was seen across groups (AD = 21.49, CN = 45.05, MCI = 33.03). A decreasing mean trajectory in Rey Auditory Verbal Learning Test scores over time was seen across groups (AD = -0.62, CN = -0.19, MCI = -0.22). Furthermore, a significant variance intercept component but a non significant slope variance component and a non significant growth factor correlation were found for the three groups (AD = 44.70, CN = 83.17, MCI = 116.78; for the intercept AD =1.10 ns, CN = 0.98 ns, MCI =1.01 ns; for the slope AD = -1.49 ns, CN = -2.22 ns, MCI = -1.47 ns for correlation). The CN group showed higher initial levels of Rey Auditory Verbal Learning Test scores at Time 1, followed by MCI and by patients with AD. Patients with AD showed a steeper decline over time, followed by MCI and CN, who have a similar rate of decline over time. Similarly, the MCI group had more variability in the intercept factor, followed by the CN group and by patients with AD. No slope variability was significant across groups. Fig. 3 displays the latent curve models for the three groups of patients on the Rey Auditory Verbal Learning Test.

3.4.5. *Multi-domain neuropsychological and functional assessment*

Cognition Self Report (Memory). Significant and positive intercept mean in Cognition Self Report Memory scores were found across groups (AD = 2.28, CN = 1.67, MCI = 2.25). On average, the Cognition Self Report Memory trajectories were constant across groups over time (AD =0.03 ns, CN = -0.01 ns, MCI = -0.01 ns).The results also showed significant group differences in initial levels in Cognition Self Report Memory scores across groups (AD = 0.25, CN = 0.21, MCI = 0.41). Significant group differences in growth over time as well as significant negative factor correlation were found for MCI group only (AD = @0, CN = 0.00 ns, MCI

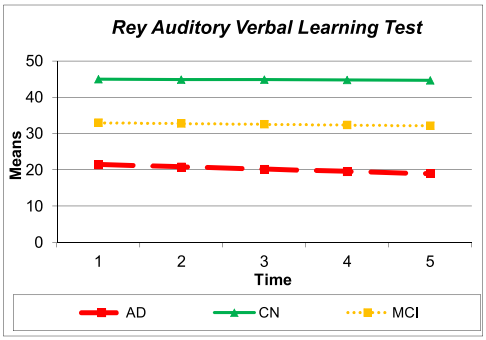

Fig. 3. Verbal Learning Test Variable. The x axis represents time points of testing at 0, 6, 12, 24, and 36 months. Significant and positive intercept mean was seen across groups. A decreasing mean trajectory in Rey Auditory Verbal Learning Test scores over time was seen across groups. Furthermore, a significant variance intercept component but a non significant slope variance component and a non significant growth factor correlation were found for the three groups.

= 0.01 for slope; AD = @0, CN = -0.01 ns, MCI = -0.02 ns for correlation). The slope variance for AD patients was fixed at zero because of small negative variance. The multiple-group analysis results showed that patients with AD had higher but comparable initial levels of Montreal Cognitive Assessment Test for Dementia scores with MCI at Time 1, followed by the CN group. In contrast, the MCI group had more variability in the intercept factor, followed by patients with AD and by the CN group. Higher differences in growth over time were seen in MCI.

3.4.6. *Cognition self report (language)*

Significant and positive intercept means in Cognition Self Report Language scores were found across groups (AD = 1.44, CN = 1.02, MCI = 1.86). On average, the Cognition Self Report Language trajectories were constant over time across groups (AD =0.02 ns, CN = 0.01 ns, MCI = 0.01 ns).Differences in initial levels in Cognition Self Report Language scores were significant across groups (AD = 0.56, CN = 0.13, MCI = 0.29). However, differences in growth on Cognition Self Report Language over time, as well as factor correlation (negative),were significant for AD patients only (AD : = 0.03, CN = 0.01 ns, MCI = 0.01 for slope; AD : = -0.08, CN = 0.00 ns, MCI = -0.01 ns for correlation). Finally, patients with AD showed higher, but comparable, initial levels of Cognition Self Report Language scores with MCI at Time 1, followed by the CN group. Non-significant and comparable average slope means were found across groups. Yet, patients with AD had more variability in the intercept factor, followed by MCI and then by the CN group. Higher differences in growth over time were seen for AD patients, followed by MCI and CN groups, with both non-significant.

3.4.7. *Cognition partner report (memory)*

Intercept means in Cognition Partner Report (Memory) scores were positive and significant across groups (AD = 3.40, CN = 1.36, MCI = 2.34). Decreasing mean trajectories over time were seen for patients with AD and the MCI group but the non-significant mean trajectory for the CN group (AD = -0.04, CN = -0.01 ns, MCI = -0.04). Moreover, significant differences in initial levels in Cognition Partner Report (Memory) scores were found across groups (AD = 0.30, CN = 0.14, MCI = 0.77). Significant differences in growth over time were seen for MCI and CN groups (AD = @0, CN = 0.02, MCI = 0.03). MCI group with lower levels of Cognition Partner Report (Memory) scores at Time 1 had a steeper increase over time. Lastly, patients with AD showed higher initial levels of Cognition Partner Report (Memory) scores at Time 1, followed by the MCI group. Patients with AD decreased more over time, followed by the MCI group. Similarly, the MCI group had more variability in initial levels and growth over time for Cognition Partner Report (Memory) scores, followed by the CN group (with the exception that the slope variance of AD was fixed to zero).

3.4.8. *Cognition partner report (language)*

Intercept means in Cognition Partner Report (Language) scores were significant and positive across groups (AD = 2.70, CN = 1.17, MCI = 1.83). The mean trajectory was decreasing over time for AD and MCI group, but there was a non-significant mean trajectory for the CN group (AD = -0.05, CN = 0.01 ns, MCI = -0.03). Furthermore, differences in initial levels of Cognition Partner Report (Language) scores were significant across groups (AD = 0.63, CN = 0.05, MCI = 0.68). However, differences in growth over time were significant for AD and MCI group (AD = 0.02, CN = 0.01 ns, MCI = 0.03). MCI group with lower levels of Cognition Partner Report (Language) scores at Time 1 showed a steeper increase over time. Similar to the

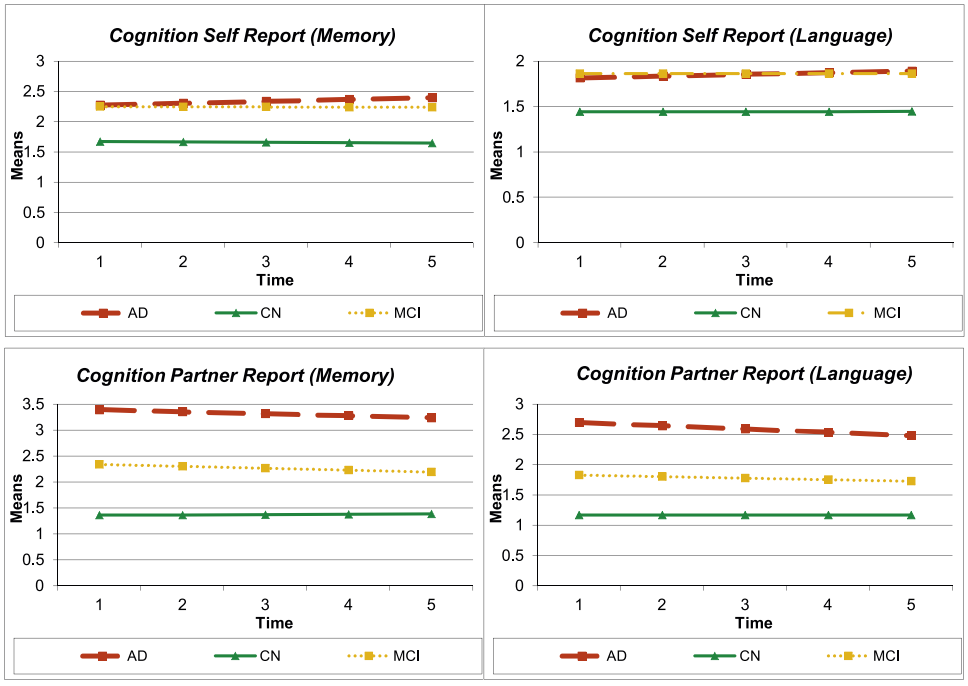

Fig. 4. Multi-domain Neuropsychological and Functional Assessment Variables. The x axis represents time points of testing at 0, 6, 12, 24, and 36 months. The Cognition Self Report Memory trajectories were constant across groups over time. The results also showed significant group differences in initial levels in Cognition Self Report Memory scores across groups. Significant group differences in growth over time as well as significant negative factor correlation were found for MCI group only.

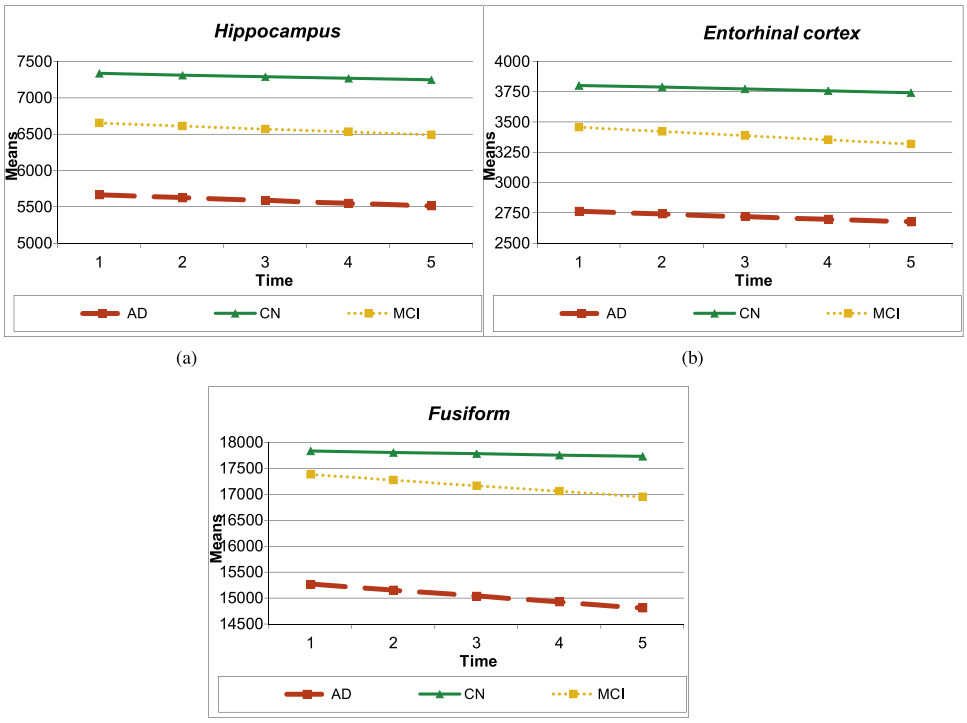

Fig. 5. Neuroimaging Variables. The x axis represents time points of testing at 0, 6, 12, 24, and 36 months. (a) Intercept means in Hippocampus volume measures were positive and significant across groups. And the trajectories means decreased over time across groups. Furthermore, differences in initial levels and growth over time in Hippocampus volume measure were significant across groups for the intercept and slope. (b) Intercept means in Entorhinal cortex measures were significant and positive across groups. Trajectories means of Entorhinal cortex measure decreased over time for the CN and MCI groups but was constant for patients with AD. Moreover, differences in initial levels in Entorhinal cortex measure were significant across groups. (c) The results showed significant and positive intercepts means in Fusiform measure across groups of patients. The results also showed decreasing mean trajectories over time across groups. In addition, significant differences in initial levels in Fusiform measure were seen across groups. Yet, significant differences in growth over time in Fusiform measure were seen for AD and MCI group, but the constant mean trajectory for CN group. The growth factor correlation coefficient was non-significant across groups.

results for the Cognition Partner Report (Memory), patients with AD showed higher initial levels of Cognition Partner Report (Language) scores at Time 1, followed by MCI and then by the CN group. Patients with AD decreased more over time, followed by MCI and then by CN. Finally, the MCI group had more variability in initial levels and growth over time in cognition Partner Report (Language) scores, followed by patients with AD and by the CN group. The latent curve models estimated for the three groups of patients for the four Multi-domain Neuropsychological and Functional Assessment measures are shown in Fig. 4.

3.5. Neuroimaging

3.5.1. Hippocampus

Intercept means in Hippocampus volume measures were positive and significant across groups (AD = 5667.60, CN = 7338.06, MCI = 6655.96). And the trajectories means decreased over time across groups (AD = -38.13, CN = -21.60, MCI = -40.64). Furthermore, differences in initial levels and growth over time in Hippocampus volume measure were significant across groups for the intercept (AD = 1165237.20, CN = 856372.20, MCI = 1365323.13) and slope (AD = 17781.52, CN = 7890.51, MCI = 11365.01). AD patients with lower levels of Hippocampus volume measure at Time 1 had a steeper increase over time. The CN group showed higher initial levels of Hippocampus volume measure at Time 1, followed by MCI and by patients with AD. The MCI group decreased more over time, followed by patients with AD and by the CN group. The MCI group had more variability in hippocampus volume measures at Time 1, followed by patients with AD and by the CN group. Finally, patients with AD had more variability in growth over time for Hippocampus volume measure, followed by MCI and then by the CN group.

3.5.2. Entorhinal cortex

Intercept means in Entorhinal cortex measures were significant and positive across groups (AD = 2765.06, CN = 3804.46, MCI = 3458.69). Trajectories means of Entorhinal cortex measure decreased over time for the CN (M = -15.15) and MCI (M = -34.52) patients but was constant for patients with AD (M = -21.73 ns). Moreover, differences in initial levels in Entorhinal cortex measure were significant across groups (AD = 378724.60, CN = 331352.03, MCI = 530292.30). However, differences in growth over time in Entorhinal cortex measure were significant for MCI group but non-significant for AD patients and CN group (AD =2839.92 ns, CN = 203.33 ns, MCI = 3862.41). Non-significant growth factor correlation coefficient was found across groups (AD =7242.86 ns, CN = 1003.20 ns, MCI =637.21 ns). Similar to the results with Hippocampus volume measure to some extent, CN group showed higher initial levels of Entorhinal cortex measure at Time 1, followed by MCI and by patients with AD. The MCI group decreased more over time, followed by the CN group and by patients with AD (non-significant variability for AD patients). Lastly, the MCI group had more variability in initial levels and growth over time, followed by patients with AD and by the CN group.

3.5.3. Fusiform

The results showed significant and positive intercepts means in Fusiform measure across groups of patients (AD = 15271.58, CN = 17832.74, MCI = 17385.25). The results also showed decreasing mean trajectories over time across groups (AD = -114.99, CN = -26.11, MCI = -108.57). In addition, significant differences in initial levels in Fusiform measure were seen across groups (AD = 6458500, CN = 5440045.30, MCI = 7339949.20). Yet, significant differences in growth over time in Fusiform measure were seen for AD and MCI group, but the constant mean trajectory for the CN group (AD = 102973.60, CN = 13024.40 ns, MCI = 47627.70). The growth factor correlation coefficient was non-significant across groups (AD = -23106.40 ns, CN = 10525.70 ns, MCI =40563.60 ns). Similarly, the CN group showed higher initial levels of Fusiform measure at Time 1, followed by MCI and by patients with AD. Patients with AD decreased more over time, followed by MCI and then by the CN group. The MCI group had more variability in Fusiform measure at Time 1, followed by patients with AD and by the CN group. Finally, patients with AD had more variability in growth over time in Fusiform measure, followed by MCI and by the CN group. The latent curve models estimated for the three groups of patients for the three Neuroimaging measures are shown in Fig. 5.

3.6. Summary

In summary, the three groups of patients showed, on average,

positive and significant differences in initial levels on all the clinical and neural measures.

3.6.1. Decreasing mean trajectory

The results showed a slight decrease, on average, in Fluorodeoxyglucose over time across groups with significant differences in growth for patients with AD and MCI. The CN group tended to have the same growth trajectories over time. The CN group had higher initial values of Fluorodeoxyglucose, followed by the MCI and AD groups. Patients with AD decreased more than the MCI group, followed by CN. Patients with AD had more variability in both intercept and slope, followed by the MCI and CN groups.

Similarly, the average trajectory of Mini-Mental State Exam scores was decreasing over time with significant differences in growth for patients with AD and the MCI group. But constant trajectory with the same growth trajectories was seen for the CN group. Those patients with AD and the MCI group who had lower levels of Mini-Mental State Exam scores at Time 1 tended to increase steeply over time. Higher initial level of Alzheimer's Disease Assessment score with steeper slope and more individual differences in both intercept and slope were seen for patients with AD, followed by the MCI and CN groups.

The average trajectory in Rey Auditory Verbal Learning Test scores was decreasing over time across groups. The same growth trajectories were seen within each group of patients. The CN group had higher levels of Rey Auditory Verbal Learning Test scores at Time 1, followed by MCI and by patients with AD. Patients with AD declined faster over time, followed by MCI and CN, who were comparable in their rate of decline. More differences at initial levels were seen for MCI, followed by CN and by patients with AD. No slope variability was significant across groups.

The average trajectories of Cognition Partner Report in Memory and Language were decreasing over time with significant differences in growth for patients with AD and MCI. In contrast, a constant average trajectory was seen for the CN group. The MCI with CN groups had meaningful differences in growth over time in Cognition Partner Report (Memory) scores, whereas patients with AD and the MCI group had meaningful differences in growth over time in Cognition Partner Report (Language) scores. MCI group with lower levels of Cognition Partner Report at Time 1 showed a steeper increase in Cognition Partner Report in both Memory and Language scores over time. Patients with AD had higher initial levels of Cognition Partner Report both in Memory and Language scores at Time 1, followed by MCI. Patients with AD decreased more over time on both Memory and Language scores, followed by the MCI group. The MCI group had more variability in initial levels and growth over time on both Memory and Language scores, followed by the CN group on Memory scores but by patients with AD on Language scores.

As for neuroimaging measures, the average trajectory decreased over time across groups for Hippocampus and Fusiform measures. The average trajectory in Entorhinal cortex decreased over time for CN and MCI groups but was constant for patients with AD. Differences in growth over time were seen across groups for Hippocampus volume measure, but only for MCI group in Ethorhinal measure, and only for AD and MCI group for Fusiform measures. Alzheimer's Disease patients with lower initial levels of Hippocampus volume measure had a steeper increase over time. The CN group had higher initial levels of neuroimaging measures (Hippocampus, Entorhinal Cortex & Fusiform) at Time 1, followed by the MCI group. The MCI group decreased more over time in Hippocampus and Entorhinal cortex measures. But patients with AD decreased more over time on Fusiform measures. Finally, patients with AD had more differences in growth over time for Hippocampus and Fusiform measures, followed by MCI. But the MCI group had more differences in growth over time in Entorhinal cortex measures, followed by patients with AD.

3.6.2. Increasing mean trajectory

The three groups of patients increased, on average, in their Clinical Dementia Rating scores over time with significant differences in growth for the three groups of patients. Patients with lower levels of Clinical Dementia Rating scores at Time 1 tended to report steeper increases in Clinical Dementia Rating scores over time. A higher initial level of Clinical Dementia Rating scores with steeper slope and more variability in both intercept and slope was seen for patients with AD, followed by the MCI and CN groups.

Increasing average trajectories in Alzheimer's Disease Assessment scores over time with significant variability was seen for patients with AD and MCI, but decreasing trajectories for the CN group. Patients with lower levels of Alzheimer's Disease Assessment scores at Time 1 had a steeper increase over time across groups. A higher initial level of Alzheimer's Disease Assessment scores with steeper slope and more variability in both intercept and slope was seen for patients with AD, followed by the MCI and CN groups.

In the same manner, the average trajectories of Montreal Cognitive Assessment Test for Dementia scores increased over time for AD and MCI group, but a non-significant mean trajectory was seen for the CN group. The results showed meaningful variability in growth over time in the Montreal Cognitive Assessment Test for Dementia scores for patients with AD and the MCI group. People with lower levels of Montreal Cognitive Assessment Test for Dementia scores at Time 1 among the AD MCI groups increased steeply over time. Patients with AD exhibited more variability in both intercept and slope, followed by MCI and by the CN group.

3.6.3. Constant mean trajectory

The constant average trajectory in Cognition Self Report Memory scores over time was seen across groups. Only the MCI group had significant differences in growth over time. Higher and compared initial levels of Montreal Cognitive Assessment Test for Dementia scores were found for patients with AD and the CN group. More differences in initial levels of Montreal Cognitive Assessment Test for Dementia scores were seen for MCI group, followed by patients with AD.

Similarly, the average trajectory in Cognition Self Report Language scores was constant across groups. However, patients with AD had significant differences in growth over time, while the other two groups (MCI and CN) of patients grew the same way within each group. AD patients with lower levels of Cognition Self Report Language score at Time 1 had steeper increases over time. Higher and compared initial levels of Cognition Self Report Language scores were found for patients with AD and the MCI group. Patients with AD had more differences in initial levels of Cognition Self Report Language score and growth over time.

4. Discussion

The study aimed to identify the trajectories of CN, MCI, and AD groups on neuropsychological assessments and neurological biomarkers associated with dementia. In addition, we examined whether the trajectories of cognitive decline differed between CN MCI, and AD groups. The results showed that there were generally strong correlations in the clinical and neural measures with respect to different time points. While a correlation is not sufficient to infer a causal relationship, the high scores in measures at time 1 could help us expect that the subsequent scores will be also high. All correlation values were larger than 0.85.

To find the most adequate model of growth of both clinical and neural measures, we used the Latent Curve Model (LCM). To the best of our knowledge, this is the first study to use LCM on a large longitudinal dataset that include controls, MCI, and AD patients. The results showed that among several forms of growth, including linear, quadratic, and freeloading models, the linear functional form of growth was optimal for the three groups and for all clinical and neural measures as shown in Table 1. The main indices of the goodness-of-fit such as CFI, TLI, and RMSEA were significantly in the range of optimal fit. In line with other research (e.g., Anstey et al., 2003; Garre-Olmo et al., 2010; Haaksma et al., 2018; Johnson et al., 2012; MacAulay et al., 2018; McArdle et al., 2005), we have shown that LCM can be used to identify and differentiate between groups with different cognitive decline trajectories. However, where previous research has typically identified different classes of AD (e.g., Haaksma et al., 2018), we here have shown that this method can also be applied to three different classes for CN, MCI, and AD groups.

The LCM was also used to examine the developmental trajectory of several neuropsychological assessments and AD biomarkers. The trajectories of these measures are distinguishable in all models. From the different graphs, there were generally no two trajectories that intersected at any time. Therefore, measurements can generally be differentiating between CN, MCI, and AD. We can also notice that the slope of the AD patients is relatively steeper than the slope of CN and MCI. These findings confirm previous research which suggested the longitudinal trajectory of cognitive decline might be different across normal age-related decline, MCI, and AD (Johnson et al., 2012; Mungas et al., 2010). Our research findings confirm Johnson et al., (2010) results by showing that latent curve modeling can be used to differentiate between groups with MCI and normal age-related decline. However, we have extended these findings by showing that LCM can be used to also differentiate the trajectory of cognitive decline associated with AD. That is, the trajectories and steepness of cognitive decline in neurocognitive measure scores can be used to differentiate between CN (i.e., normal age-related cognitive decline), MCI, and AD groups.

In terms of intercept and slope variances. The AD and MCI groups show higher variance values. This suggests that differentiating between MCI and AD groups could be difficult for some measurements. For example, in the Cognition Self Report (Language) the values of mean lines of AD and MCI are close. Therefore, based on scores on the Cognition Self Report (Language) it would be difficult to differentiate between groups presenting with AD and MCI. Instead, we suggest depending on more spread out or distinguishable lines as such Cognition Partner report (Language). These results showed that there is a significant difference in the trajectories for some of these measures between the three groups. Hippocampus and Fusiform measures decreased significantly for groups with AD compared to CN and MCI, supporting previous research that hippocampal volume is a reliable predictor of AD (e.g., Dowling et al., 2015; Perrin et al., 2009; Shaw et al., 2009). Further, our results show that the longitudinal progression of hippocampal and fusiform volume can be used to differentiate between CN, MCI, and AD groups (Fagan et al., 2007; Hansson et al., 2006; Li, 2007; Perrin et al., 2009).

While AD patients showed lower baseline levels of Hippocampus volume measure, over time they presented with a more rapid and steeper increase. On average, all three groups showed an increase in their Clinical Dementia Rating scale, Alzheimer's disease Cognitive Assessment scale, and Montreal Assessment Test for Dementia scale. The increase in Montreal Assessment Test for Dementia scale over time in all three groups is counterintuitive, as it expected that as people get older, their cognitive performance deteriorates. It is possible that these results are due to having a small number of participants at follow-up tests (around 60 participants and even fewer at later testing times). In contrast to these variables, there was a decrease in other neuropsychological and neurological biomarkers (i.e., Fluorodeoxyglucose, Mini-Mental State Exam scores, Rey Auditory Verbal Learning Test scores, Cognition Partner Report in Memory and Language, Hippocampal volume, Fusiform and Entorhinal cortex measures). This suggests that cognitive decline occurs within all three groups, emphasizing the difficulty to differentiate between these three groups of patients. We confirm that indicators of cognitive decline differed significantly between healthy controls, mild cognitive impairment, and AD, as found by measures of tau pathology, neuroinflammation, and brain atrophy (Malpetti et al., 2019). However, a novel finding of our study was that all three groups produced different trajectories across the clinical and neural measures. Accordingly, while all three groups show a decline in cognitive performance, the trajectory of the decline is often worse for those with MCI and AD, compared to CN groups.

5. Conclusion

Our study has shown that LCM can be used to reliably distinguish CN, MCI, and AD groups. Further, we have identified that the longitudinal trajectory and steepness of cognitive decline within these three groups differ significantly on multiple neuropsychological assessment and biomarkers. While the measures can classify people within the correct class, not all measures were able to clearly distinguish between the MCI and AD groups. This further emphasizes the complexity and difficulty to identify AD during the early stages. Our study has identified that LCM can be used to identify the longitudinal trajectory of patients with different levels of cognitive impairment (i.e., CN, MCI, and AD). Indeed, our findings showed that LCM can provide a more accurate prognosis by observing the trajectories, slopes, and variance of cognitive decline to differentiate if a person is experiencing cognitively normal age-related decline, MCI, or AD. Considering the neurodegenerative nature of AD (Alzheimer Association, 2019), clinicians need to identify the possible trajectory of cognitive decline of their patients to provide early intervention. Using LCM can provide clinicians with a tool to better identify the trajectory of cognitive decline for patients presenting with cognitive impairment. LCM shows promising results and should be considered as a method for classifying and differentiating between healthy, MCI, and AD groups by assessing the trajectories, slopes, and variance of multiple neuropsychological assessment and biomarkers.

CRediT authorship contribution statement

Ahmed A. Moustafa: Conceptualization, Data curation, Project administration, Writing - original draft, Writing - review & editing. **Richard Tindle:** Conceptualization, Writing - original draft, Writing - review & editing. **Hany Alashwal:** Conceptualization, Data curation, Project administration, Writing - original draft, Writing - review & editing. **Thierno M.O. Diallo:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing - original draft, Writing - review & editing.

Declarations of Competing Interest

None.

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Appendix A

Table A1
Means, Standard Deviations, Sample Size and Zero Order Correlation of the Dependent Variables for the AD patients.

	1	2	3	4	5
Fluorodeoxyglucose					
1. FDG 1	1				
2. FDG 2	0.90**	1			
3. FDG 3	0.87**	0.91**	1		
4. FDG 4	0.83**	0.88**	0.87**	1	
5. FDG 5	0.71**	0.84**	0.89**	0.78**	1
Mean	1.08	1.03	1.02	1.03	1.04
SD	0.15	0.13	0.14	0.15	0.18
n	127	103	91	81	46
Clinical Dementia Rating Scale- Sum of Boxes					
1. CDRSB 1	1				
2. CDRSB 2	0.61**	1			
3. CDRSB 3	0.48**	0.65**	1		
4. CDRSB 4	0.30**	0.54**	0.55**	1	
5. CDRSB 5	0.24**	0.29**	0.61**	0.79**	1
Mean	4.91	5.54	5.77	5.89	6.61
SD	2.46	2.54	2.81	2.84	3.69
n	298	270	215	154	97
Alzheimer'sDiseaseAssessmentScale					
1. ADAS11 1	1				
2. ADAS11 2	0.77**	1			
3. ADAS113	0.62**	0.72**	1		
4. ADAS11 4	0.47**	0.54**	0.69**	1	
5. ADAS11 5	0.35**	0.45**	0.79**	0.92**	1
Mean	21.29	22.20	22.64	23.35	25.79
SD	8.38	8.44	9.67	9.83	10.27
n	292	268	216	153	97
Mini Mental State Exam					
1. MMSE 1	1				
2. MMSE 2	0.53**	1			
3. MMSE 3	0.39**	0.61**	1		
4. MMSE 4	0.11	0.41**	0.62**	1	
5. MMSE 5	0.24**	0.34**	0.77**	0.84**	1
Mean	22.50	21.73	21.22	20.98	20.44
SD	3.06	4.19	4.69	4.76	4.99
n	292	270	217	154	98
Rey Auditory Verbal Learning Test					
1. RAVIMD 1	1				
2. RAVIMD 2	0.69**	1			
3. RAVIMD 3	0.67**	0.70**	1		
4. RAVIMD 4	0.67**	0.66**	0.72**	1	
5. RAVIMD 5	0.52**	0.63**	0.64**	0.76**	1
Mean	22.01	19.62	21.02	19.55	19.46
SD	7.85	7.84	8.21	7.76	8.45
n	288	265	210	150	92
Montreal Cognitive Assessment Test for Dementia					
1. MOCA 1	1				
2. MOCA 2	0.83**	1			
3. MOCA 3	0.78**	0.92**	1		
4. MOCA 4	0.66**	0.84**	0.85**	1	
5. MOCA 5	0.32**	0.64**	0.65**	0.89**	1
Mean	15.65	15.77	17.11	17.11	15.89
SD	5.41	5.28	5.45	4.50	4.61
n	97	81	57	66	44
Cognition Self Report (Memory)					
1. ECPTMM 1	1				
2. ECPTMM 2	0.60**	1			
3. ECPTMM 3	0.46*	0.45*	1		
4. ECPTMM 4	0.53**	0.47*	0.87**	1	
5. ECPTMM 5	0.29*	0.39*	0.39*	0.36*	1
Mean	2.29	2.29	2.17	2.42	2.41
SD	0.77	0.72	0.71	0.72	0.66
n	96	82	56	70	43
Cognition Self Report (Language)					
1. ECPTLG 1	1				
2. ECPTLG 2	0.91**	1			
3. ECPTLG 3	0.65**	0.75**	1		
4. ECPTLG 4	0.53**	0.57**	0.59**	1	
5. ECPTLG 5	0.18	0.53**	0.47*	0.45*	1
Mean	1.81	1.75	1.76	1.92	1.90
SD	0.74	0.70	0.73	0.74	0.72
n	94	81	55	70	43

*$p < 0.05$; ** $p < 0.01$.

Table A2
Means, Standard Deviations, Sample Size and Zero Order Correlation of the Dependent Variables for the CN group.

	1	2	3	4	5
Fluorodeoxyglucose					
1. FDG 1	1				
2. FDG 2	0.79**	1			
3. FDG 3	0.85**	0.87**	1		
4. FDG 4	0.76**	0.79**	0.87**	1	
5. FDG 5	0.81**	0.86**	0.86**	0.91**	1
Mean	1.30	1.29	1.27	1.27	1.28
SD	0.12	0.11	0.12	0.12	0.12
n	205	149	131	105	95
Clinical Dementia Rating Scale- Sum of Boxes					
1. CDRSB 1	1				
2. CDRSB 2	0.41**	1			
3. CDRSB 3	0.21*	0.53**	1		
4. CDRSB 4	0.12*	0.49**	0.67**	1	
5. CDRSB 5	0.10	0.13*	0.41**	0.57**	1
Mean	0.10	0.15	0.14	0.17	0.20
SD	0.43	0.45	0.37	0.54	0.60
n	763	402	395	353	313
Alzheimer'sDiseaseAssessmentScale					
1. ADAS11 1	1				
2. ADAS11 2	0.54**	1			
3. ADAS113	0.51**	0.51**	1		
4. ADAS11 4	0.55**	0.55**	0.52**	1	
5. ADAS11 5	0.47**	0.48**	0.54**	0.64**	1
Mean	6.99	5.81	5.74	5.71	5.91
SD	3.22	3.07	3.08	3.25	3.26
n	762	404	401	357	316
Mini Mental State Exam					
1. MMSE 1	1				
2. MMSE 2	0.36**	1			
3. MMSE 3	0.30**	0.17	1		
4. MMSE 4	0.38**	0.50**	0.30**	1	
5. MMSE 5	0.28**	0.24**	0.31**	0.30**	1
Mean	28.96	29.01	29.00	28.99	28.93
SD	1.28	1.20	1.28	1.28	1.26
n	766	405	401	357	318
Rey Auditory Verbal Learning Test					
1. RAVIMD 1	1				
2. RAVIMD 2	0.71**	1			
3. RAVIMD 3	0.71**	0.71**	1		
4. RAVIMD 4	0.68**	0.70**	0.70**	1	
5. RAVIMD 5	0.63**	0.68**	0.67**	0.69**	1
Mean	45.22	43.49	43.84	45.05	43.88
SD	10.56	10.41	10.81	10.69	10.09
n	762	401	401	355	315
Montreal Cognitive Assessment Test for Dementia					
1. MOCA 1	1				
2. MOCA 2	0.50**	1			
3. MOCA 3	0.53**	0.58**	1		
4. MOCA 4	0.59**	0.57**	0.64**	1	
5. MOCA 5	0.61**	0.52**	0.71**	0.51**	1
Mean	26.10	25.91	25.66	26.16	25.84
SD	2.57	2.70	2.56	2.38	2.70
n	527	183	190	201	171
Cognition Self Report (Memory)					
1. ECPTMM 1	1				
2. ECPTMM 2	0.67**	1			
3. ECPTMM 3	0.64**	0.62**	1		
4. ECPTMM 4	0.68**	0.67**	0.71**	1	
5. ECPTMM 5	0.55**	0.57**	0.64**	0.64**	1
Mean	1.68	1.80	1.69	1.70	1.72
SD	0.54	0.60	0.54	0.56	0.58
n	541	185	190	206	173
Cognition Self Report (Language)					
1. ECPTLG 1	1				
2. ECPTLG 2	0.64**	1			
3. ECPTLG 3	0.53**	0.57**	1		
4. ECPTLG 4	0.67**	0.69**	0.70**	1	
5. ECPTLG 5	0.60**	0.64**	0.64**	0.70**	1
Mean	1.45	1.52	1.49	1.45	1.49
SD	0.48	0.49	0.48	0.44	0.46
n	539	185	190	206	173
Cognition Partner Report (Memory)					
1. ECSPM 1	1				
2. ECSPM 2	0.65**	1			
3. ECSPM 3	0.61**	0.71**	1		
4. ECSPM 4	0.47**	0.65**	0.58**	1	
5. ECSPM 5	0.47**	0.61**	0.51**	0.64**	1
Mean	1.36	1.43	1.41	1.39	1.45
Standard deviation	0.47	0.47	0.51	0.49	0.54
n	522	181	186	199	169
Cognition Partner Report (Language)					
1. ECSPLG 1	1				
2. ECSPLG 2	0.50**	1			
3. ECSPLG 3	0.52**	0.64**	1		
4. ECSPLG 4	0.23**	0.48**	0.48**	1	
5. ECSPLG 5	0.46**	0.61**	0.61**	0.45**	1
Mean	1.17	1.18	1.19	1.17	1.19
SD	0.33	0.30	0.30	0.32	0.34
n	522	181	185	200	170
Hippocampus					
1. HIPC 1	1				
2. HIPC 2	0.96**	1			
3. HIPC 3	0.94**	0.96**	1		
4. HIPC 4	0.93**	0.94**	0.96	1	
5. HIPC 5	0.91**	0.94**	0.96**	0.97**	1
Mean	7278.04	7285.86	7289.11	7245.74	7227.75
SD	944.33	955.37	900.77	945.82	994.46
n	392	352	345	319	243
Entorhinal cortex					
1. ENTORC 1	1				
2. ENTORC 2	0.81**	1			
3. ENTORC 3	0.81**	0.80**	1		
4. ENTORC 4	0.84**	0.81**	0.79**	1	
5. ENTORC 5	0.80**	0.84**	0.83**	0.83**	1
Mean	3812.67	3767.56	3820.53	3751.22	3718.20
SD	667.59	630.18	657.80	630.25	646.17
n	366	333	329	303	245
Fusiform					
1. FUSIF1	1				
2. FUSIF 2	0.95**	1			
3. FUSIF 3	0.95**	0.96**	1		
4. FUSIF 4	0.94**	0.94**	0.95**	1	
5. FUSIF 5	0.93**	0.93**	0.95**	0.94**	1
Mean	17654.25	17630.35	17587.13	17764.19	17594.06
SD	2502.56	2431.90	2392.85	2350.87	2482.07
n	366	333	329	303	245

*$p < 0.05$; ** $p < 0.01$.

Table A3
Means, Standard Deviations, Sample Size and Zero Order Correlation of the Dependent Variables for the MCI group.

	1	2	3	4	5
Fluorodeoxyglucose					
1. FDG 1	1				
2. FDG 2	0.92**	1			
3. FDG 3	0.87**	0.90**	1		
4. FDG 4	0.90**	0.90**	0.91**	1	
5. FDG 5	0.87**	0.86**	0.88**	0.93**	1
Mean	1.24	1.19	1.19	1.19	0.18
SD	0.13	0.13	0.14	0.15	0.15
n	403	222	242	206	202
Clinical Dementia Rating Scale- Sum of Boxes					
1. CDRSB 1	1				
2. CDRSB 2	0.75**	1			
3. CDRSB 3	0.61**	0.78**	1		
4. CDRSB 4	0.40**	0.60**	0.70**	1	
5. CDRSB 5	0.25**	0.46**	0.58**	0.68**	1
Mean	1.97	2.19	2.12	2.29	2.45
SD	2.18	1.99	1.83	2.02	2.06
n	909	670	705	615	569
Alzheimer'sDiseaseAssessmentScale					
1. ADAS11 1	1				
2. ADAS11 2	0.73**	1			
3. ADAS113	0.69**	0.74**	1		
4. ADAS11 4	0.61**	0.66	0.73**	1	
5. ADAS11 5	0.49**	0.60**	0.68**	0.70**	1
Mean	11.40	12.08	11.37	12.06	12.39
SD	6.75	6.68	6.32	7.76	7.34
n	896	663	706	622	570
Mini Mental State Exam					
1. MMSE 1	1				
2. MMSE 2	0.64**	1			
3. MMSE 3	0.50**	0.65**	1		
4. MMSE 4	0.43**	0.60**	0.67**	1	
5. MMSE 5	0.31**	0.56**	0.55**	0.69**	1
Mean	26.93	26.50	26.69	26.59	26.23
SD	3.13	3.12	2.98	3.39	3.58
n	900	665	707	622	571
Rey Auditory Verbal Learning Test					
1. RAVIMD 1	1				
2. RAVIMD 2	0.82**	1			
3. RAVIMD 3	0.81**	0.82**	1		
4. RAVIMD 4	0.78**	0.82**	0.81**	1	
5. RAVIMD 5	0.77**	0.80**	0.83**	0.85**	1
Mean	33.36	30.83	32.29	32.15	31.01
SD	11.76	11.67	11.49	12.37	11.88
n	895	663	705	614	561
Montreal Cognitive Assessment Test for Dementia					
1. MOCA 1	1				
2. MOCA 2	0.81**	1			
3. MOCA 3	0.74**	0.78**	1		
4. MOCA 4	0.69**	0.74**	0.74	1	
5. MOCA 5	0.60**	0.70**	0.71**	0.75**	1
Mean	22.76	22.33	23.42	23.68	22.82
SD	4.52	4.31	3.48	3.72	3.75
n	485	273	339	281	282
Cognition Self Report (Memory)					
1. ECPTMM 1	1				
2. ECPTMM 2	0.68**	1			
3. ECPTMM 3	0.70**	0.71**	1		
4. ECPTMM 4	0.58**	0.66**	0.69**	1	
5. ECPTMM 5	0.61**	0.63**	0.70**	0.72**	1
Mean	2.26	2.28	2.26	2.18	2.30
SD	0.75	0.75	0.74	0.71	0.72
n	495	280	343	283	284
Cognition Self Report (Language)					
1. ECPTLG 1	1				
2. ECPTLG 2	0.65**	1			
3. ECPTLG 3	0.66**	0.73**	1		
4. ECPTLG 4	0.59	0.65**	0.68**	1	
5. ECPTLG 5	0.63**	0.69**	0.70**	0.69**	1
Mean	1.87	1.87	1.85	1.84	1.89
SD	0.67	0.68	0.65	0.65	0.66
n	492	279	342	280	285
Rey Auditory Verbal Learning Test					
1. RAVIMD 1	1				
2. RAVIMD 2	0.82**	1			
3. RAVIMD 3	0.81**	0.82**	1		
4. RAVIMD 4	0.78**	0.82**	0.81**	1	
5. RAVIMD 5	0.77**	0.80**	0.83**	0.85**	1
Mean	33.36	30.83	32.29	32.15	31.01
SD	11.76	11.67	11.49	12.37	11.88
n	895	663	705	614	561
Montreal Cognitive Assessment Test for Dementia					
1. MOCA 1	1				
2. MOCA 2	0.81**	1			
3. MOCA 3	0.74**	0.78**	1		
4. MOCA 4	0.69**	0.74**	0.74	1	
5. MOCA 5	0.60**	0.70**	0.71**	0.75**	1
Mean	22.76	22.33	23.42	23.68	22.82
SD	4.52	4.31	3.48	3.72	3.75
n	485	273	339	281	282
Cognition Self Report (Memory)					
1. ECPTMM 1	1				
2. ECPTMM 2	0.68**	1			
3. ECPTMM 3	0.70**	0.71**	1		
4. ECPTMM 4	0.58**	0.66**	0.69**	1	
5. ECPTMM 5	0.61**	0.63**	0.70**	0.72**	1
Mean	2.26	2.28	2.26	2.18	2.30
SD	0.75	0.75	0.74	0.71	0.72
n	495	280	343	283	284
Cognition Self Report (Language)					
1. ECPTLG 1	1				
2. ECPTLG 2	0.65**	1			
3. ECPTLG 3	0.66**	0.73**	1		
4. ECPTLG 4	0.59	0.65**	0.68**	1	
5. ECPTLG 5	0.63**	0.69**	0.70**	0.69**	1
Mean	1.87	1.87	1.85	1.84	1.89
SD	0.67	0.68	0.65	0.65	0.66
n	492	279	342	280	285
Cognition Partner Report (Memory)					
1. ECSPM 1	1				
2. ECSPM 2	0.86**	1			
3. ECSPM 3	0.79**	0.84**	1		
4. ECSPM 4	0.73**	0.76**	0.80**	1	
5. ECSPM 5	0.71**	0.71**	0.77**	0.80**	1
Mean	2.34	2.42	2.21	2.20	2.27
Standard deviation	0.94	0.96	0.91	0.88	0.89
n	494	283	344	275	280
Cognition Partner Report (Language)					
1. ECSPLG 1	1				

(*continued on next page*)

Table A3 (*continued*)

	1	2	3	4	5
2. ECSPLG 2	0.83**	1			
3. ECSPLG 3	0.76**	0.79**	1		
4. ECSPLG 4	0.74**	0.77**	0.79**	1	
5. ECSPLG 5	0.60**	0.71**	0.70**	0.78**	1
Mean	1.82	1.95	1.75	1.75	1.77
SD	0.83	0.92	0.76	0.78	0.74
n	496	283	343	275	281
Hippocampus					
1. HIPC 1	1				
2. HIPC 2	0.98**	1			
3. HIPC 3	0.97**	0.98**	1		
4. HIPC 4	0.96**	0.97**	0.93**	1	
5. HIPC 5	0.92**	0.93**	0.95**	0.97**	1
Mean	6664.01	6578.21	6565.86	6528.40	6500.56
SD	1144.29	1187.08	1262.11	1227.95	1239.22
n	606	605	578	447	431
Entorhinal cortex					
1. ENTORC 1	1				
2. ENTORC 2	0.87**	1			
3. ENTORC 3	0.85**	0.86**	1		
4. ENTORC 4	0.85**	0.88**	0.88**	1	
5. ENTORC 5	0.83**	0.85**	0.85**	0.89**	1
Mean	3449.21	3390.38	3383.53	3365.32	3339.33
SD	771.79	802.95	821.22	790.43	811.13
n	592	577	532	432	420
Fusiform					
1. FUSIF1	1				
2. FUSIF 2	0.96**	1			
3. FUSIF 3	0.96**	0.97**	1		
4. FUSIF 4	0.94**	0.96**	0.96**	1	
5. FUSIF 5	0.93**	0.93**	0.95**	0.96**	1
Mean	17190.63	17081.81	17046.37	16952.98	17094.35
SD	2726.22	2748.42	2816.96	2818.56	2885.17
n	592	577	532	432	420

*$p < 0.05$; ** $p < 0.01$.

Table A4
Parameter Estimates and Asymptotic Standard Errors of Latent Curve Model for Fluorodeoxyglucose Variablefor AD, CN, and MCI groups.

AD Group			CN Group		
Parameter	Estimate	SE	Parameter	Estimate	SE
Variances			***Variances***		
ψ_α	0.03***	0.00	ψ_α	0.01***	0.00
ψ_β	0.02*	0.00	ψ_β	0.01	0.01
Covariance			***Covariance***		
$\psi_{\alpha\beta}$	0.01	0.01	$\psi_{\alpha\beta}$	0.01	0.01
Means			***Means***		
Intercept μ_α	1.08***	0.01	Intercept μ_α	1.31***	0.01
Linear Slope μ_β	−0.03***	0.00	Linear Slope μ_β	−0.01***	0.00
Residual variances			***Residual variances***		
Var(ε_1)	0.02*	0.01	Var(ε_1)	0.03**	0.00
Var(ε_2)	0.02*	0.01	Var(ε_2)	0.02**	0.00
Var(ε_3)	0.02*	0.01	Var(ε_3)	0.02**	0.00
Var(ε_4)	0.03*	0.01	Var(ε_4)	0.02**	0.00
Var(ε_5)	0.02	0.03	Var(ε_5)	0.02	0.01

MCI group		
Parameter	Estimate	SE
Variances		
ψ_α	0.02***	0.00
ψ_β	0.01**	0.00

Table A4 (*continued*)

MCI group		
Parameter	Estimate	SE
Covariance		
$\psi_{\alpha\beta}$	0.01	0.01
Means		
Intercept μ_α	1.24***	0.01
Linear Slope μ_β	−0.02***	0.00
Residual variances		
Var(ε_1)	0.01**	0.00
Var(ε_2)	0.02***	0.00
Var(ε_3)	0.02***	0.00
Var(ε_4)	0.02**	0.00
Var(ε_5)	0.02**	0.00

Note. μ_α = intercept mean, μ_β = linear slope mean, ψ_α = intercept variance, ψ_β = linear slope variance, $\psi_{\alpha\beta}$ = intercept and slope covariance, Var(ε_i) =residual variance at time point i.
*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table A5
Parameter Estimates and Asymptotic Standard Errors of Latent Curve Model for Clinical Dementia Rating Scale- Sum of BoxesVariablefor AD CN and MCI groups.

AD group			CN group		
Parameter	Estimate	SE	Parameter	Estimate	SE
Variances			***Variances***		
ψ_α	4.63***	0.54	ψ_α	0.10***	0.01
ψ_β	0.69**	0.12	ψ_β	0.02***	0.00
Covariance			***Covariance***		
$\psi_{\alpha\beta}$	−0.72***	0.21	$\psi_{\alpha\beta}$	−0.02***	0.00
Means			***Means***		
Intercept μ_α	5.08***	0.14	Intercept μ_α	0.10***	0.02
Linear Slope μ_β	0.32***	0.06	Linear Slope μ_β	0.02*	0.01
Residual variances			***Residual variances***		
Var(ε_1)	1.79**	0.40	Var(ε_1)	0.09***	0.01
Var(ε_2)	2.32***	0.30	Var(ε_2)	0.10***	0.01
Var(ε_3)	2.76***	0.38	Var(ε_3)	0.06***	0.01
Var(ε_4)	2.58***	0.946	Var(ε_4)	0.09***	0.01
Var(ε_5)	3.31**	0.67	Var(ε_5)	0.18***	0.02

MCI group		
Parameter	Estimate	SE
Variances		
ψ_α	3.89***	0.01
ψ_β	0.29***	0.00
Covariance		
$\psi_{\alpha\beta}$	−0.65***	0.06
Means		
Intercept μ_α	1.95***	0.07
Linear Slope μ_β	0.09***	0.02
Residual variances		
Var(ε_1)	1.35***	0.11
Var(ε_2)	0.56***	0.06
Var(ε_3)	0.76***	0.06
Var(ε_4)	1.37***	0.11
Var(ε_5)	1.09***	0.14

Note. μ_α = intercept mean, μ_β = linear slope mean, ψ_α = intercept variance, ψ_β = linear slope variance, $\psi_{\alpha\beta}$ = intercept and slope covariance, Var(ε_i) =residual variance at time point i.
*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table A6
Parameter Estimates and Asymptotic Standard Errors of Latent Curve Model for Alzheimer's Disease Assessment ScaleVariablefor AD CN and MCI groups.

AD group			CN group		
Parameter	Estimate	SE	Parameter	Estimate	SE
Variances			***Variances***		
ψ_α	64.75***	6.22	ψ_α	6.25***	0.58
ψ_β	7.54***	1.04	ψ_β	0.20**	0.07
Covariance			***Covariance***		
$\psi_{\alpha\beta}$	−8.53***	1.93	$\psi_{\alpha\beta}$	−0.33*	0.17
Means			***Means***		
Intercept μ_α	21.59***	0.47	Intercept μ_α	6.81***	0.11
Linear Slope μ_β	0.85***	0.19	Linear Slope μ_β	−0.13**	0.04
Residual variances			***Residual variances***		
Var(ε_1)	9.12**	3.39	Var(ε_1)	4.03***	0.47
Var(ε_2)	20.50***	2.80	Var(ε_2)	4.66***	0.42
Var(ε_3)	22.47***	3.23	Var(ε_3)	4.83***	0.44
Var(ε_4)	22.75***	6.17	Var(ε_4)	4.36***	0.47
Var(ε_5)	2.46	8.22	Var(ε_5)	4.38***	0.64

MCI group		
Parameter	Estimate	SE
Variances		
ψ_α	35.01***	2.06
ψ_β	1.58**	0.18
Covariance		
$\psi_{\alpha\beta}$	−2.41***	0.47
Means		
Intercept μ_α	11.41***	0.21
Linear Slope μ_β	0.15*	0.06
Residual variances		
Var(ε_1)	11.79***	1.08
Var(ε_2)	10.40***	0.83
Var(ε_3)	9.20***	0.72
Var(ε_4)	19.31***	1.40
Var(ε_5)	12.87**	1.54

Note. μ_α = intercept mean, μ_β = linear slope mean, ψ_α = intercept variance, ψ_β = linear slope variance, $\psi_{\alpha\beta}$ = intercept and slope covariance, Var(ε_i) =residual variance at time point i.
*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table A7
Parameter Estimates and Asymptotic Standard Errors of Latent Curve Model for Mini Mental State ExamVariable for AD, CN, and MCI groups.

AD group			CN group		
Parameter	Estimate	SE	Parameter	Estimate	SE
Variances			***Variances***		
ψ_α	8.82***	1.24	ψ_α	0.56***	0.09
ψ_β	2.17***	0.28	ψ_β	0.01	0.01
Covariance			***Covariance***		
$\psi_{\alpha\beta}$	−1.85***	0.48	$\psi_{\alpha\beta}$	−0.02	0.03
Means			***Means***		
Intercept μ_α	22.32***	0.18	Intercept μ_α	28.98***	0.04
Linear Slope μ_β	−0.46***	0.10	Linear Slope μ_β	0.00	0.02
Residual variances			***Residual variances***		
Var(ε_1)	1.01	0.96	Var(ε_1)	1.06***	0.10
Var(ε_2)	10.04***	1.06	Var(ε_2)	0.93***	0.08
Var(ε_3)	8.89***	1.10	Var(ε_3)	1.18***	0.10
Var(ε_4)	5.61***	1.57	Var(ε_4)	1.10***	0.10
Var(ε_5)	@0.00	0	Var(ε_5)	1.11***	0.14

MCI group		
Parameter	Estimate	SE
Variances		
ψ_α	6.61***	0.44
ψ_β	0.50***	0.05
Covariance		
$\psi_{\alpha\beta}$	−0.65***	0.12
Means		
Intercept μ_α	26.91***	0.10
Linear Slope μ_β	−0.10**	0.03
Residual variances		
Var(ε_1)	3.64***	0.31
Var(ε_2)	2.66***	0.22
Var(ε_3)	3.35***	0.24
Var(ε_4)	3.53***	0.29
Var(ε_5)	3.66***	0.42

Note. μ_α = intercept mean, μ_β = linear slope mean, ψ_α = intercept variance, ψ_β = linear slope variance, $\psi_{\alpha\beta}$ = intercept and slope covariance, Var(ε_i) =residual variance at time point i.
*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table A8
Parameter Estimates and Asymptotic Standard Errors of Latent Curve Model for Montreal Cognitive Assessment Test for Dementia Variable for AD, CN, and MCI groups.

AD group			CN group		
Parameter	Estimate	SE	Parameter	Estimate	SE
Variances			***Variances***		
ψ_α	28.20***	4.01	ψ_α	3.69***	0.32
ψ_β	0.83*	0.39	ψ_β	@0.00	0.00
Covariance			***Covariance***		
$\psi_{\alpha\beta}$	−2.73**	0.92	$\psi_{\alpha\beta}$	@0.00	0.00
Means			***Means***		
Intercept μ_α	14.99***	0.47	Intercept μ_α	26.04***	0.11
Linear Slope μ_β	0.71***	0.14	Linear Slope μ_β	0.01	0.04
Residual variances			***Residual variances***		
Var(ε_1)	6.77**	2.40	Var(ε_1)	3.00***	0.30
Var(ε_2)	2.17	1.19	Var(ε_2)	3.45***	0.45
Var(ε_3)	4.49**	1.31	Var(ε_3)	2.40***	0.35
Var(ε_4)	2.83	1.68	Var(ε_4)	2.39***	0.34
Var(ε_5)	4.00	2.52	Var(ε_5)	2.90***	0.42

MCI group		
Parameter	Estimate	SE
Variances		
ψ_α	17.10***	1.29
ψ_β	0.44***	0.08
Covariance		
$\psi_{\alpha\beta}$	−1.76***	0.25
Means		
Intercept μ_α	22.49***	0.19
Linear Slope μ_β	0.24***	0.05
Residual variances		
Var(ε_1)	4.79***	0.59
Var(ε_2)	2.67***	0.42
Var(ε_3)	3.30***	0.37
Var(ε_4)	3.84***	0.49
Var(ε_5)	2.60***	0.58

Note. μ_α = intercept mean, μ_β = linear slope mean, ψ_α = intercept variance, ψ_β = linear slope variance, $\psi_{\alpha\beta}$ = intercept and slope covariance, Var(ε_i) =residual variance at time point i.
*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table A9
: Parameter Estimates and Asymptotic Standard Errors of Latent Curve Model for Rey Auditory Verbal Learning Test Variable for AD, CN, and MCI groups.

AD group			CN group		
Parameter	Estimate	SE	Parameter	Estimate	SE
Variances			***Variances***		
ψ_α	44.70***	5.13	ψ_α	83.17***	5.91
ψ_β	1.10	0.80	ψ_β	0.98	0.46
Covariance			***Covariance***		
$\psi_{\alpha\beta}$	−1.49	1.43	$\psi_{\alpha\beta}$	−2.22	1.33
Means			***Means***		
Intercept μ_α	21.49***	0.43	Intercept μ_α	45.05***	0.37
Linear Slope μ_β	−0.62***	0.14	Linear Slope μ_β	−0.19*	0.10
Residual variances			***Residual variances***		
Var(ε_1)	18.58***	3.48	Var(ε_1)	29.87***	3.62
Var(ε_2)	20.89***	2.63	Var(ε_2)	33.04***	3.19
Var(ε_3)	20.41***	2.76	Var(ε_3)	35.31***	3.27
Var(ε_4)	15.73***	3.92	Var(ε_4)	36.79***	3.70
Var(ε_5)	21.90**	7.44	Var(ε_5)	32.46***	4.62

MCI group		
Parameter	Estimate	SE
Variances		
ψ_α	116.78***	6.27
ψ_β	1.01	0.79
Covariance		
$\psi_{\alpha\beta}$	−1.47	0.99
Means		
Intercept μ_α	33.03***	0.37
Linear Slope μ_β	−0.22**	0.08
Residual variances		
Var(ε_1)	23.40***	2.26
Var(ε_2)	24.29***	1.90
Var(ε_3)	25.05***	1.78
Var(ε_4)	26.16***	2.11
Var(ε_5)	17.82***	2.39

Note. μ_α = intercept mean, μ_β = linear slope mean, ψ_α = intercept variance, ψ_β = linear slope variance, $\psi_{\alpha\beta}$ = intercept and slope covariance, Var(ε_i) =residual variance at time point i.
*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table A10
Parameter Estimates and Asymptotic Standard Errors of Latent Curve Model for Cognition Self Report (Memory) Variable for AD, CN, and MCI groups.

AD group			CN group		
Parameter	Estimate	SE	Parameter	Estimate	SE
Variances			***Variances***		
ψ_α	0.25***	0.05	ψ_α	0.21***	0.02
ψ_β	@0.00	0.00	ψ_β	0.00	0.00
Covariance			***Covariance***		
$\psi_{\alpha\beta}$	@0.00	0.00	$\psi_{\alpha\beta}$	−0.01	0.01
Means			***Means***		
Intercept μ_α	2.28***	0.06	Intercept μ_α	1.67***	0.02
Linear Slope μ_β	0.03	0.02	Linear Slope μ_β	−0.01	0.01
Residual variances			***Residual variances***		
Var(ε_1)	0.31***	0.07	Var(ε_1)	0.08***	0.02
Var(ε_2)	0.28***	0.06	Var(ε_2)	0.12***	0.02
Var(ε_3)	0.27***	0.07	Var(ε_3)	0.10***	0.02
Var(ε_4)	0.27***	0.07	Var(ε_4)	0.08***	0.01
Var(ε_5)	0.25**	0.08	Var(ε_5)	0.12***	0.02

MCI group		
Parameter	Estimate	SE
Variances		
ψ_α	0.41***	0.04
ψ_β	0.01**	0.00
Covariance		
$\psi_{\alpha\beta}$	−0.02*	0.01
Means		
Intercept μ_α	2.25***	0.01
Linear Slope μ_β	−0.01	0.01
Residual variances		
Var(ε_1)	0.16***	0.02
Var(ε_2)	0.19***	0.02
Var(ε_3)	0.14***	0.02
Var(ε_4)	0.17***	0.02
Var(ε_5)	0.13***	0.02

Note. μ_α = intercept mean, μ_β = linear slope mean, ψ_α = intercept variance, ψ_β = linear slope variance, $\psi_{\alpha\beta}$ = intercept and slope covariance, Var(ε_i) =residual variance at time point i.
*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table A11
Parameter Estimates and Asymptotic Standard Errors of Latent Curve Model for Cognition Self Report (Language) Variable for AD, CN, and MCI groups.

AD group			CN group		
Parameter	Estimate	SE	Parameter	Estimate	SE
Variances			***Variances***		
ψ_α	0.56***	0.07	ψ_α	0.13***	0.02
ψ_β	0.03*	0.01	ψ_β	0.01	0.01
Covariance			***Covariance***		
$\psi_{\alpha\beta}$	−0.08***	0.02	$\psi_{\alpha\beta}$	0.00	0.00
Means			***Means***		
Intercept μ_α	1.44***	0.07	Intercept μ_α	1.02***	0.01
Linear Slope μ_β	0.02	0.02	Linear Slope μ_β	0.01	0.01
Residual variances			***Residual variances***		
Var(ε_1)	@0.00	0.00	Var(ε_1)	0.09***	0.01
Var(ε_2)	0.09***	0.02	Var(ε_2)	0.08***	0.01
Var(ε_3)	0.22***	0.06	Var(ε_3)	0.09***	0.01
Var(ε_4)	0.26***	0.07	Var(ε_4)	0.04***	0.01
Var(ε_5)	0.23*	0.10	Var(ε_5)	0.07***	0.01

MCI group		
Parameter	Estimate	SE
Variances		
ψ_α	0.29***	0.03
ψ_β	0.01	0.01
Covariance		
$\psi_{\alpha\beta}$	−0.01	0.01
Means		
Intercept μ_α	1.86***	0.03
Linear Slope μ_β	0.01	0.01
Residual variances		
Var(ε_1)	0.17**	0.02
Var(ε_2)	0.15***	0.02
Var(ε_3)	0.12***	0.01
Var(ε_4)	0.15***	0.02
Var(ε_5)	0.13***	0.02

Note. μ_α = intercept mean, μ_β = linear slope mean, ψ_α = intercept variance, ψ_β = linear slope variance, $\psi_{\alpha\beta}$ = intercept and slope covariance, Var(ε_i) =residual variance at time point i.
*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table A12
Parameter Estimates and Asymptotic Standard Errors of Latent Curve Model for Cognition Partner Report (Memory) Variable for AD, CN, and MCI groups.

AD group			CN group		
Parameter	Estimate	SE	Parameter	Estimate	SE
Variances			***Variances***		
ψ_{α}	0.30***	0.04	ψ_{α}	0.14***	0.01
ψ_{β}	@0.00	0.00	ψ_{β}	0.02*	0.01
Covariance			***Covariance***		
$\psi_{\alpha\beta}$	@0.00	0.00	$\psi_{\alpha\beta}$	−0.01	0.01
Means			***Means***		
Intercept μ_{α}	3.40***	0.05	Intercept μ_{α}	1.36***	0.02
Linear Slope μ_{β}	−0.04*	0.02	Linear Slope μ_{β}	0.01	0.01
Residual variances			***Residual variances***		
Var(ε_1)	0.10**	0.04	Var(ε_1)	0.08***	0.01
Var(ε_2)	0.29***	0.05	Var(ε_2)	0.05***	0.01
Var(ε_3)	0.20***	0.05	Var(ε_3)	0.09***	0.01
Var(ε_4)	0.11***	0.03	Var(ε_4)	0.09***	0.01
Var(ε_5)	0.11**	0.04	Var(ε_5)	0.10***	0.02

MCI group		
Parameter	Estimate	SE
Variances		
ψ_{α}	0.77***	0.05
ψ_{β}	0.03***	0.01
Covariance		
$\psi_{\alpha\beta}$	−0.05***	0.01
Means		
Intercept μ_{α}	2.34***	0.04
Linear Slope μ_{β}	−0.04***	0.01
Residual variances		
Var(ε_1)	0.12**	0.02
Var(ε_2)	0.13***	0.02
Var(ε_3)	0.15***	0.02
Var(ε_4)	0.20***	0.02
Var(ε_5)	0.13***	0.03

Note. μ_{α} = intercept mean, μ_{β} = linear slope mean, ψ_{α} = intercept variance, ψ_{β} = linear slope variance, $\psi_{\alpha\beta}$ = intercept and slope covariance, Var(ε_i) =residual variance at time point i.
*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table A13
Parameter Estimates and Asymptotic Standard Errors of Latent Curve Model for Cognition Partner Report (Language) Variable for AD, CN, and MCI groups.

AD group			CN group		
Parameter	Estimate	SE	Parameter	Estimate	SE
Variances			***Variances***		
ψ_{α}	0.63***	0.10	ψ_{α}	0.05***	0.01
ψ_{β}	0.02*	0.01	ψ_{β}	0.01	0.01
Covariance			***Covariance***		
$\psi_{\alpha\beta}$	−0.05	0.03	$\psi_{\alpha\beta}$	−0.01	0.01
Means			***Means***		
Intercept μ_{α}	2.70***	0.07	Intercept μ_{α}	1.17***	0.01
Linear Slope μ_{β}	−0.05*	0.02	Linear Slope μ_{β}	0.01	0.01
Residual variances			***Residual variances***		
Var(ε_1)	0.11	0.06	Var(ε_1)	0.06***	0.01
Var(ε_2)	0.22***	0.01	Var(ε_2)	0.03***	0.00
Var(ε_3)	0.26***	0.01	Var(ε_3)	0.03***	0.01
Var(ε_4)	0.07	0.04	Var(ε_4)	0.07***	0.01
Var(ε_5)	0.07	0.07	Var(ε_5)	0.04***	0.01

MCI group		
Parameter	Estimate	SE
Variances		

(*continued on next page*)

Table A13 (*continued*)

MCI group		
Parameter	Estimate	SE
ψ_{α}	0.68***	0.04
ψ_{β}	0.03***	0.00
Covariance		
$\psi_{\alpha\beta}$	−0.06***	0.01
Means		
Intercept μ_{α}	1.83***	0.04
Linear Slope μ_{β}	−0.03***	0.01
Residual variances		
Var(ε_1)	0.09***	0.02
Var(ε_2)	0.14***	0.02
Var(ε_3)	0.15***	0.02
Var(ε_4)	0.14***	0.02
Var(ε_5)	0.09***	0.02

Note. μ_{α} = intercept mean, μ_{β} = linear slope mean, ψ_{α} = intercept variance, ψ_{β} = linear slope variance, $\psi_{\alpha\beta}$ = intercept and slope covariance, Var(ε_i) =residual variance at time point i.
*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table A14
Parameter Estimates and Asymptotic Standard Errors of Latent Curve Model for Hippocampus Variable for AD, CN, and MCI groups.

AD group			CN group		
Parameter	Estimate	SE	Parameter	Estimate	SE
Variances			***Variances***		
ψ_{α}	1165237.20***	98588.10	ψ_{α}	856372.20***	55977.10
ψ_{β}	17781.52***	3323.95	ψ_{β}	7890.51***	1121.60
Covariance			***Covariance***		
$\psi_{\alpha\beta}$	−2690.58*	1267.66	$\psi_{\alpha\beta}$	−4903.40	5700.50
Means			***Means***		
Intercept μ_{α}	5667.60***	63.53	Intercept μ_{α}	7338.06***	41.84
Linear Slope μ_{β}	−38.13**	11.69	Linear Slope μ_{β}	−21.60***	5.77
Residual variances			***Residual variances***		
Var(ε_1)	21253.70	15115.50	Var(ε_1)	32454.40***	6570.34
Var(ε_2)	58682.50***	11503.90	Var(ε_2)	34177.62***	4614.27
Var(ε_3)	50670.90***	11226.02	Var(ε_3)	37991.08***	4209.23
Var(ε_4)	14970.90	8076.31	Var(ε_4)	31546.65***	4702.94
Var(ε_5)	28385.70	17841.10	Var(ε_5)	18653.95**	5672.78

MCI group		
Parameter	Estimate	SE
Variances		
ψ_{α}	1365323.13***	68361.37
ψ_{β}	11365.01***	1050.72
Covariance		
$\psi_{\alpha\beta}$	5978.11	6113.64
Means		
Intercept μ_{α}	6655.96***	40.69
Linear Slope μ_{β}	−40.64***	5.10
Residual variances		
Var(ε_1)	16307.28***	3748.96
Var(ε_2)	23523.52***	2646.44
Var(ε_3)	29998.21***	2787.52
Var(ε_4)	14040.65***	2881.77
Var(ε_5)	69376.66***	8163.48

Note. μ_{α} = intercept mean, μ_{β} = linear slope mean, ψ_{α} = intercept variance, ψ_{β} = linear slope variance, $\psi_{\alpha\beta}$ = intercept and slope covariance, Var(ε_i) =residual variance at time point i.
*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table A15
Parameter Estimates and Asymptotic Standard Errors of Latent Curve Model for the Entorhinal Cortex Variable for AD, CN and MCI groups.

AD group			CN group		
Parameter	Estimate	SE	Parameter	Estimate	SE
Variances			***Variances***		
ψ_α	378724.60***	40971.30	ψ_α	331352.03***	26635.40
ψ_β	2839.92	3076.73	ψ_β	203.33	1135.64
Covariance			***Covariance***		
$\psi_{\alpha\beta}$	7242.86	8970.63	$\psi_{\alpha\beta}$	1003.20	4114.60
Means			***Means***		
Intercept μ_α	2765.06****	41.17	Intercept μ_α	3804.46***	28.92
Linear Slope μ_β	−21.73	11.59	Linear Slope μ_β	−15.15**	5.67
Residual variances			***Residual variances***		
Var(ε_1)	84698.50***	18942.03	Var(ε_1)	82078.80***	10266.60
Var(ε_2)	116107.30***	16314.50	Var(ε_2)	72452.70***	7973.80
Var(ε_3)	73078.80***	12132.10	Var(ε_3)	87088.70***	9008.50
Var(ε_4)	62446.70***	15364.90	Var(ε_4)	72630.40***	8400.01
Var(ε_5)	59275.40***	25457.30	Var(ε_5)	72022.50***	11560.90

MCI group		
Parameter	Estimate	SE
Variances		
ψ_α	530292.30***	30846.70
ψ_β	3862.41**	1112.60
Covariance		
$\psi_{\alpha\beta}$	637.21	4415.90
Means		
Intercept μ_α	3458.69***	27.67
Linear Slope μ_β	−34.52***	5.40
Residual variances		
Var(ε_1)	78133.90***	8840.10
Var(ε_2)	81351.80***	6935.40
Var(ε_3)	100807.50***	7950.60
Var(ε_4)	61267.40***	6797.20
Var(ε_5)	82949.21***	9859.70

Note. μ_α = intercept mean, μ_β = linear slope mean, ψ_α = intercept variance, ψ_β = linear slope variance, $\psi_{\alpha\beta}$ = intercept and slope covariance, Var(ε_i) =residual variance at time point i.
*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table A16
: Parameter Estimates and Asymptotic Standard Errors of Latent Curve Model for FusiformVariable for AD, CN, and MCI groups.

AD group			CN group		
Parameter	Estimate	SE	Parameter	Estimate	SE
Variances			***Variances***		
ψ_α	6,458,500***	576908.30	ψ_α	5440045.30***	364,198
ψ_β	102973.60***	26,523	ψ_β	13024.40	5767.40
Covariance			***Covariance***		
$\psi_{\alpha\beta}$	−23106.40	83946.90	$\psi_{\alpha\beta}$	10525.70	31992.20
Means			***Means***		
Intercept μ_α	15271.58***	156.43	Intercept μ_α	17832.74***	107.88
Linear Slope μ_β	−114.99***	33.92	Linear Slope μ_β	−26.11*	13.17
Residual variances			***Residual variances***		
Var(ε_1)	288362.10**	92683.30	Var(ε_1)	250250.20***	38638.60
Var(ε_2)	288190.60***	64,084	Var(ε_2)	293825.40***	32457.40
Var(ε_3)	220833.10***	54698.70	Var(ε_3)	229140.80***	27712.60
Var(ε_4)	589875.30***	135172.20	Var(ε_4)	347332.50***	40506.10
Var(ε_5)	229825.10	202,550	Var(ε_5)	414321.70***	61514.50

MCI group		
Parameter	Estimate	SE
Variances		
ψ_α	7339949.20***	381783.60
ψ_β	47627.70***	6592.20
Covariance		
$\psi_{\alpha\beta}$	40563.60	36,998

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Table A16 (*continued*)

AD group			CN group		
Parameter	Estimate	SE	Parameter	Estimate	SE
Means					
Intercept μ_α	17385.25***	97.21			
Linear Slope μ_β	−108.57***	13.02			
Residual variances					
Var(ε_1)	252981.60***	34842.60			
Var(ε_2)	285051.40***	26585.60			
Var(ε_3)	261,099***	24948.10			
Var(ε_4)	227195.50***	27993.60			
Var(ε_5)	395483.20***	50902.90			

Note. μ_α = intercept mean, μ_β = linear slope mean, ψ_α = intercept variance, ψ_β = linear slope variance, $\psi_{\alpha\beta}$ = intercept and slope covariance, Var(ε_i) =residual variance at time point i.
*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jneumeth.2020.109040.

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