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Jae-Won Jang, Yeshin Kim, Seongheon Kim, Sang Won Park, Sung Ok Kwon, Young Ho Park, Jae-Sung Lim, Young Chul Youn, Sung Hun Kim, SangYun Kim, Alzheimer's Disease Neuroimaging Initiative,

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Dynamic association between AT(N) profile and cognition mediated by cortical thickness in Alzheimer's continuum

Jae-Won Jang[a,b], Yeshin Kim[a,b], Seongheon Kim[a,b], Sang Won Park[b], Sung Ok Kwon[c], Young Ho Park[d,e], Jae-Sung Lim[f], Young Chul Youn[g], Sung Hun Kim[a,b], SangYun Kim[d,e] and the Alzheimer's Disease Neuroimaging Initiative[1]

[a]Department of Neurology, Kangwon National University Hospital, Chuncheon, Republic of Korea

[b]Kangwon National University School of Medicine, Chuncheon, Republic of Korea

[c]Biomedical Research Institute, Kangwon National University Hospital, Chuncheon, Republic of Korea

[d]Department of Neurology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea

[e]Department of Neurology, Seoul National University College of Medicine, Seoul, Republic of Korea

[f]Department of Neurology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Republic of Korea.

[g]Department of Neurology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Republic of Korea

E-mail addresses:

Jae-Won Jang: light26@kangwon.ac.kr

Yeshin Kim: yeshins@gmail.com

Seongheon Kim: dr.kim94@gmail.com

Sang Won Park: chicwon229@kangwon.ac.kr

Sung Ok Kwon: kamelon@hanmail.net

Jae-Sung Lim: rophe.pneuma@gmail.com

Young Ho Park: kumimesy@snubh.org

Sung Hun Kim: marinen@kangwon.ac.kr

Young Chul Youn: neudoc@cau.ac.kr

Correspondence to:

SangYun Kim, MD, PhD, Department of Neurology, Seoul National University Bundang Hospital, 82, Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 13620, Korea. Tel.: +82 31 787 7462; Fax: +82 31 787 4059; E-mail: neuroksy@snu.ac.kr

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Abstract

Background: The recently-proposed National Institute on Aging and Alzheimer's Association research framework organizes Alzheimer's disease (AD) biomarkers based on amyloid/tau/neurodegeneration (AT(N)). This study investigated the mediating effect of structural change in brain MRI on changes in cognitive function according to initial AT(N) profiles.

Methods: We included 576 subjects (cognitively unimpaired (N=136), mild cognitive impairment (N=294), dementia (N=146)) from the Alzheimer's disease Neuroimaging Initiative study. The parallel-process latent growth curve model was applied to test the mediational effect of cortical thickness growth trajectory between the initial AT(N) profiles and cognitive growth trajectory.

Results: In Alzheimer's continuum, only the A+T+(N)+ profile showed a mediational effect of the cortical thickness growth trajectory. A+T-(N)- was not sufficient to induce direct or indirect effects on cognitive dysfunction, and A+T+(N)- showed a significant direct path from an altered cortical thickness to cognitive decline.

Conclusion: The sequential effect between changes in brain MRI and cognition varied by baseline AT(N) profile, suggesting the dynamic changes in the relationships among biomarkers in the current cascade model.

Keywords: Mild cognitive impairment, Alzheimer′s disease, CSF biomarkers, Brain MRI, Beta amyloid, Tau, Structural equation modeling, Parallel process latent growth curve model

1.Introduction

Alzheimer's disease (AD) is the most common cause of cognitive impairment among the elderly. Recently, the pathophysiologic sequential changes in amyloid-β (Aβ), pathologic tau, and neurodegeneration were conceptualized as the [AT(N)] system constituting a new biomarker definition of AD (Jack et al., 2018).

The cerebrospinal fluid (CSF) has been used to detect and track Aβ, pathologic tau, and neurodegeneration in AD across clinical stages (Olsson et al., 2016). The best identified example includes CSF measurement of the 42-aminoacid form of Aβ ($A\beta_{1-42}$), which is found at low concentration in subjects with AD because of cortical amyloid deposition, phosphorylated tau (P-tau) at high concentration reflecting cortical tangle formation (Seppälä et al., 2012), and total tau (T-tau) at high concentration due to cortical neuronal injury (de Souza et al., 2012). According to the AT(N) system, CSF Aβ abnormality reflects "Alzheimer's pathophysiologic change," CSF Aβ and P-tau abnormality reflects "AD," and the neurodegeneration is indicated by abnormal T-tau (Jack et al., 2018). The National Institute on Aging and Alzheimer's Association (NIA-AA) also adopted atrophy observed on structural MRI as a neurodegenerative marker of AD along with hypometabolism on [18F]-fluorodeoxyglucose (FDG)-positron emission tomography (PET) (Jack et al., 2018). Among the neurodegenerative markers, brain MRI has been consistently reported to be effective in detecting structural change in dementia (Jack et al., 1997) as well as predicting MCI progression (Visser et al., 1999), but the temporal effects of these biomarkers on cognitive decline have not been studied with the mediational hypothesis in a multimodal framework.

The "modified amyloid cascade hypothesis" involves sequential change from amyloidosis, pathologic tau, and neurodegeneration to cognitive decline (Jack and Holtzman, 2013). Some studies have attempted to explain the possible causal relationships between these biomarkers and their effect on cognition using longitudinal mediation models(Fletcher et al., 2018; Mattsson et al., 2015; Villeneuve et al., 2014). To test and explore the hypothesis on the role of biomarkers in terms of the AT(N)

system, these modeling approaches can be applied in the sequence of events. The current study used a parallel-process latent growth curve model (PPLGCM) (Cheong et al., 2003) to identify the mediating effects of change in an AD-signature cortical region of interest for pathways between AT(N) profiles determined by CSF components of Aβ, t-tau and p-tau and cognitive change, in each of the Alzheimer's continuum biomarker profiles (i.e. A+) in the AT(N) schema. Our hypothesis was that the mediating role of structural MRI in the assumed sequential chain would vary according to the different AT(N) profiles at baseline.

2.Methods

2.1. Subjects

Data used in this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was started in 2003 as a public-private partnership, by Principal Investigator Michael W. Weiner. The principal aim of ADNI has been to investigate whether serial MRI, PET, other biological markers, neuropsychological and clinical assessments can be combined to measure the progression of MCI and early AD. For the latest information, see www.adni-info.org.

Data used in this study were downloaded from the ADNI database on the 21th January, 2018. The population for this study included all subjects with brain MRI measures (up to the 24-month) and neuropsychological measures (up to the 36-month visit) for at least two time points and obtainable baseline CSF measures. Table 1 summarizes ADNI diagnostic criteria for subjective with cognitively unimpaired (CU), MCI and dementia(Petersen et al., 2010). Subjects with cognitively unimpaired (CU) are distinguished from MCI by Clinical Dementia Rating score of 0 versus 0.5, respectively. Diagnosis of MCI was made based on the presence of objective memory impairment without meeting the criteria for dementia. All participants had a Mini Mental State Examination (MMSE) score of 24 to 30, a global Clinical Dementia Rating (CDR) score of 0.5, a CDR memory score of 0.5 or higher, and a score that indicated impairment on the delayed recall of Story A of the Wechsler Memory Scale-Revised (≥16 years of education: <11; 8-15 years of education: ≤9; 0-7 years of education: ≤6).

Diagnosis of dementia was made based on the presence of objective memory impairment and all subjects had a MMSE score of between 20 and 24, CDR score of 0.5 or 1, and a score that indicated impairment on the delayed recall of Story A of the Wechsler Memory Scale-Revised (≥16 years of education: ≤8; 8-15 years of education: ≤4; 0-7 years of education: ≤2). A final total of 576 subjects from the ADNI-1/GO/2 cohort were included in this study.

2.2. MRI measures

All participants were imaged using a 1.5-T and 3-T MRI scanner (GE, Philips or Siemens). Data were collected at multiple sites with a standardized MRI protocol that was made by evaluating and comparing 3D T1-weighted sequences for morphometric analyses. As longitudinal mediator, MRI data were taken at five time points: baseline, month 6, month 12, month 18, month 24 and month 36. MRI acquisition and processing were performed according to standard protocol(Jack et al., 2008).

Regional volumes were estimated automatically by the Freesurfer image analysis tool obtainable freely for download (http://surfer.nmr.mgh.harvard.edu). The ADNI1 1.5 T MR data were run on Freesurfer version 4.3, and 3 T MR data of ADNI1 and ADNI2 were run on Freesurfer version 5.1. Each scan was segmented in accordance with an atlas defined by Freesurfer (Fischl and Dale, 2000). We calculated mean cortical thickness of the AD-signature area(Dickerson et al., 2009) that is composed of eight bilateral regions including the medial temporal gyrus, temporal pole, inferior temporal gyrus, and superior frontal gyrus. The average cortical thickness in these regions were computed that each subject had a single value representing AD-signature of cortical thickness(Busovaca et al., 2016).

2.3. CSF biomarker measures

The standardized protocol for CSF analysis and sample collection in ADNI is available elsewhere(Shaw, 2008). In brief, after executing the quality control studies and organizing the validity of the platform, the baseline CSF $A\beta_{1-42}$, t-Tau and p-Tau_{181p} were measured by Innogenetics (INNO-BIA AlzBio3, Ghent, Belgium) immunoassay kit and the multiplex xMAP Luminex platform. This system can measure the biomarkers simultaneously in the same sample in ADNI subjects and in an age-matched cohort of autopsy-confirmed AD cases (Shaw et al., 2009).

2.4. Classification of AT(N) profiles

In current study, AT(N) profiles were classified by CSF abnormality with CSF $A\beta_{1-42}$ of less than 192 pg/ml as A+, p-Tau_{181p} more than 23pg/ml as T+ and t-Tau more than 93 pg/ml as N+(Shaw et al., 2009). Baseline means and standard deviations for raw CSF variables and AT(N) profiles based on them are presented in Table 2.

2.5. Neuropsychological measures

Longitudinal neuropsychological data such as MMSE, Alzheimer's Disease Scale Cognitive Subscale (ADAS-cog) (Rosen et al., 1984), and CDR-Sum of Boxes score were evaluated at baseline. Among them, ADAS-cog was used as longitudinal outcome measure and taken at five time points: baseline, month 6, month 12, month 18, month 24 and month 36. Compared with the MRI mediation process, measured from baseline to month 24, the outcome changes of ADAS-cog increased to include another year to attenuated issues regarding concurrent causation (Salthouse, 2011).

2.6. Statistical analysis

As displayed in Fig. 1, the mediational process was modeled by associating baseline AT(N) profiles by CSF measures (predictors) and latent growth factors for MRI measures (mediator) and cognitive function also indexing changes over time(outcome). By baseline AT(N) profiles using initial CSF values, we compared each of Alzheimer's continuum profiles (A+T-(N)-, A+T+(N)-, A+T+(N)+) with normal AD biomarker (A-T-(N)-) as reference profile to calculate β coefficients. To improve the validity of the mediation analysis, all models were controlled for the following covariates: initial clinical diagnosis (normal control as the reference), gender, age at baseline, educational level, and *ApoE* status (coded as ε4 present versus absent).

A structural equation model approach to build and evaluate LGCMs (Meredith and Tisak, 1990; Muthén and Curran, 1997; Singer et al., 2003; Tucker-Drob and Salthouse, 2013) was used for differentiating the direct versus indirect effects of the initial AT(N) profiles by CSF abnormality(CSF $A\beta_{1-42}$ of less than 192 pg/ml as A+, p-Tau_{181p} more than 23pg/ml as T+ and t-Tau more than 93 pg/ml as N+) on the potential mediating effects of changes in cortical thickness and the rate of decline in cognitive function comprising the causal pathway of a parallel change process. The simultaneous modeling of the growth

trajectories of the mediator and outcome as well as of the mediational process was performed with the PPLGCM (Cheong et al., 2003; MacKinnon et al., 2004). The hypothesis regarding the mediational or indirect effects was tested by parameter estimates obtained from the effect of the initial AT(N) profiles on the growth rate of the cortical thickness and the growth rate of the cognition by a two-wave PPLGC mediation model (Fig. 1). The growth variables included vectors for the slope (Muthén and Curran, 1997) on the pathway of the AT(N) profiles→ AD-signature slope→ADAS-cog slope. By using the vector of repeated measures of individuals over the timepoints for the MRI mediator and the cognitive outcome, the mediational effect of the initial AT(N) profiles by CSF measures through the MRI slope was β_a*β_b and the direct effect on the cognitive slope was β_c. Both effects are representative of linear change over the study period and conditional on the combined effect of all the predictors in the model. LGC modeling can define changes over time with regard to unobserved latent factors, estimate parameters concurrently, and include measurement errors that result in complex multivariate modeling (Rovine and Molenaar, 2001; Singer et al., 2003). PPLGC modeling with a univariate two-factor LGCM was used to examine the presence of change in the MRI mediator and cognitive outcome and whether the AT(N) profile could change these trajectories. This latent growth model estimated MRI cortical thickness and cognitive measures with two latent factors defining the intercept and the slope of the "growth" curve, respectively. The control variables were also selected in these models. To explore the marginal growth trends and growth shape, subject-specific mean functions were plotted and time-based LGCM was adopted. After examining the shape of the trajectories and confirming growth, the models were combined to simultaneously incorporate two outcomes and the longitudinal mediational effects of MRI measures estimating the parameters.

The significance of the mediational effect was examined using 95% bias-corrected bootstrapped asymmetric confidence intervals (CIs) in the PPLGCMs (Preacher and Hayes, 2008). Bias-corrected bootstrapped asymmetric CIs do not require the mediational effect estimate sampling distribution to be normal (MacKinnon et al., 2004). All mediation was tested with 10,000 bootstrap replications. If the spectrum of the 95% bias-corrected CI for the given point estimate did not include 0, the effect was

considered significant. The normal approximation of the CIs was investigated for all single direct paths in the model.

The hypothesized models were assessed with multiple fit indexes including the root mean square error of approximation (RMSEA) (Bollen and Long, 1993), the comparative fist index (CFI) (Bentler and Bonett, 1980) and the Tucker-Lewis Index (TLI) (Tucker and Lewis, 1973). The models with RMSEA lower than 0.08 and with CFI and TLI values higher than 0.9 were regarded to adequately fit the data (Hoyle, 1995). Residual diagnostics procedures were performed to assess possible model misspecification (Wang et al., 2005). To analyzing longitudinal measurement change of ADAS-Cog across AT(N) profiles, factorial invariance was assessed using a confirmatory factor analysis (CFA). Establishing factorial invariance consists of a hierarchy of levels that include configural, weak, strong, strict and structural invariance, which are evaluated in a measurement model (Horn and McArdle, 1992; McArdle, 2009; Meredith, 1993; Muthen and Muthen, 2017; Widaman and Reise, 1997).

Evidence of invariance between the less restrictive model (e.g., configural invariance model) and more restrictive model (e.g., weak measurement invariance models) were based on recommendations from the literature (Chen, 2007; Cheung and Rensvold, 2002; Wang and Wang, 2019). The configural model was then used to compare against the more restrictive measurement invariance. The values of the change in CFI (△CFI) smaller than or equal to 0.01 indicates that the hypothesis of invariance should not be rejected. For △TLI, the critical value is 0.01. The Chi-square difference test was also reported for each comparison. Descriptive analyses were analyzed using R (Version 3.5.0, The R Foundation for Statistical Computing, Vienna, Austria; 64-bit platform). Growth curve model analyses were performed with Mplus, Version 8.3 (Muthen and Muthen, 2017) using a full information maximum likelihood estimator.

3. Results

As presented in Table 2, the final sample included 576 subjects with available data, diagnosed at study entry as CU (N = 136), MCI (N = 294), and Dementia (N = 146). The participants were mostly male

(58.3%), ranging in age from 55 to 90 years (M = 74.0, SD = 7.0), reported an average of 15.8 years of education (SD = 2.9; range, 4–20 years), and approximately 54% were carriers of more than one *APOE*-ε4 allele. Table 2 also shows global cognition at baseline measured by the MMSE (Folstein et al., 1975).

The bivariate correlations among baseline predictors (CSF measures), the longitudinal mediator (MRI), and longitudinal outcome (cognition) are reported in Fig. 2. MRI mediators and cognitive outcomes were negatively correlated across all data collection timepoints. Moreover, most CSF measures were correlated with both longitudinal MRI and cognitive measures. Because all variables appeared to be correlated with cognitive outcomes, it was appropriate to include them in the multiple comparison.

3.1. Univariate Latent growth curve model for the MRI mediator

Table 3 presents the results of the univariate LGCMs for the MRI mediator as an outcome measure. The models fit the data well according to the overall fit indices (CFI, range: 0.998–1.000; TLI, 0.998–1.002; RMSEA, 0.000–0.035). The linear LGCM showed good fit and appeared appropriate for the data.

The shape of the growth curve was also investigated using individual and mean plots. As a result, the mean of the slope growth factor of the unconditional models for the AD signature was negative and statistically significant (−0.049, $P < .001$). The negative rate of change in the slope suggested that the MRI scores decreased by approximately 0.04 points between each evaluation. The statistically significant variance of intercepts and slopes indicated that they had important individual variability around their mean values across five timepoints. Subjects varied in their initial MRI cortical thickness and their rates of change over time. The effect of baseline CSF measures on initial and longitudinal changes in cortical thickness varied by AT(N) profile. The A+T+(N)+ profile by CSF measures revealed a significant negative regression coefficient for the MRI measure slope growth factor compared to those with normal AD biomarker profile (A-T-(N)-). That is, AD with an A+T+(N)+ CSF profile was associated with faster decline in AD-specific cortical thickness.

3.2. Univariate latent growth curve model for cognitive outcome

The results for each univariate LGCM, including ADAS-Cog13 as the cognitive outcome, are reported in Table 4. All models yielded a good fit based on established criteria (Hoyle, 1995); the CFI and TLI values ranged between 0.983–0.995 and 0.977–0.993, respectively, and the RMSEA values varied between 0.029–0.053. The mean growth trajectory for the unconditional (without covariates) model was positive and significant (2.346, $P < .001$) for an average decline of approximately 2.3 points/year in the ADAS-cog-13 score. In the conditional model, the variances of the intercept and growth factors showed statistically significant variability at baseline and change in cognition over time ($P < .05$). All Alzheimer's continuums, (A+T-(N)-, A+T+(N)-, and A+T+(N)+), revealed positive and significant effects on the baseline status and change in cognitive function over time except for the intercept of A+T-(N)- (0.994, $P = .270$). The effect of Alzheimer's pathophysiologic change (A+T-(N)-) on the intercept was statistically insignificant although significant on the slope.

3.3. Mediation tests and parallel process LGCMs

One of the primary goals of this study was to test the mediational effect of changes in MRI measures on the relationship between baseline AT(N) profiles by CSF biomarkers and changes in cognitive performance. That is, we tested the hypothesis that different AT(N) stages by CSF measures would result in structural changes in the brain and that these changes could increase cognitive decline over a 3-year period.

To this end, the MRI mediator LGCM was combined with the cognitive outcome growth model in a PPLGCM and regressed on the initial AT(N) profile, sex, education, age, *APOE*, and diagnosis at entry. The relationships among predictors and the latent growth factors describing the mediational process were estimated separately for each analyte and hypothesized as shown in Fig. 1. The values of the point estimates of these relationships and 95% CIs are presented by the AT(N) profiles in Fig. 3. The role of decline in MRI cortical thickness as a process variable mediating the effects of the initial AT(N) profiles on changes in cognitive function varied even in the Alzheimer's continuum, and the mediating effect of changes in cortical thickness on changes in cognition was statistically significant only for the A+T+(N)+ profile (1.373, $P = .024$). That is, only in the A+T+(N)+ profile, a decreased

slope of cortical thickness mediated the initial CSF profiles and cognitive decline over time. Additionally, the direct path from the initial CSF profile to the MRI slope was also significant only for the A+T+(N)+ profile (-0.026, $P < .001$) and the direct paths from the longitudinal changes of MRI measures to those of cognitive performance were significant for AD (e.g., A+T+(N)- and A+T+(N)+ profiles) (Fig. 3).

3.4. Evaluation of longitudinal factorial (measurement and structural) invariance

The weak invariance model (M1), fit the data well (Supplementary Table1). When the weak invariance model is compared with the configural invariance model (M0), changes of CFI and TLI were within acceptable values (△CFI = -0.002, △TLI = 0.001 for A+T-(N)-, △CFI = -0.008, △TLI = -0.005 for A+T+(N)-, △CFI = -0.011, △TLI < 0.001 for A+T+(N)+). This indicates that the metric of factor scores was invariant across AT(N) profiles. The next restrictive model, the strong invariance model (M2) also fit the data well. This constrained the factor loadings and item intercept to create the strong invariance model, resulted in the demonstration of strong invariance (△CFI = -0.005, △TLI = 0.000 for A+T-(N)-, △CFI = -0.014, △TLI = -0.001 for A+T+(N)-, △CFI = -0.02, △TLI = 0.001 for A+T+(N)+). This indicates that both factor loadings and intercept are invariant across AT(N) profiles. The last more restrictive model, which constrained the factor loadings, intercept, and residual variances, to produce the strict invariance model (M3) was then inspected. The changes of the fit indices were within the recommended values (△CFI = -0.031, △TLI = -0.025 for A+T-(N)-, △CFI = -0.011, △TLI = -0.006 for A+T+(N)-, △CFI = -0.038, △TLI = -0.025 for A+T+(N)+). When comparing structural invariance model (M4) with the less restrictive model (M2) (i.e., strong measurement invariance model), the differences of several fit indices are within the acceptable values (△CFI = -0.029, △TLI = -0.032 for A+T-(N)-, △CFI = -0.034, △TLI = -0.038 for A+T+(N)-, △CFI = -0.025, △TLI = -0.0027 for A+T+(N)+). In longitudinal factorial invariance

across AT(N) profiles, at least the third level of factorial invariance, strong factorial invariance, must be met. The overall conclusion is that there is a reasonable level of longitudinal factorial invariance for the CFA model of AD spectrum across AT(N) profiles group.

4. Discussion

This study attempted to examine the dynamic association between the initial AT(N) profiles by CSF and longitudinal change in brain MRI and cognitive function after controlling for demographic variables, baseline clinical diagnosis, and *APOE* status in Alzheimer's continuum. Adopting a simultaneous longitudinal scheme, the sequential effect between brain MRI and cognition according to the AT(N) profiles was analyzed. It was tested whether the relationship between the initial AT(N) profiles and the growth trajectory for cognitive decline was mediated by the growth trajectory of cortical thickness. In the A+T+(N)- profile, a direct path from an altered level of cortical thickness was hypothesized to result in cognitive decline. Only in the A+T+(N)+ profile, the initial CSF measures appeared to result in cognitive decline mediated by cortical thickness in addition to the direct path from the initial CSF profile to brain MRI as well as from brain MRI to cognitive decline. To our knowledge, this is the first study using PPLGCM to test the biomarker sequence hypothesis based on the AT(N) system.

These findings suggested a dynamic causal sequence that identifies change in cortical thickness as a mediator between antecedent change in the AT(N) profile by CSF and subsequent cognitive decline. Based on the new biomarker profiles by the NIA-AA research framework (Jack et al., 2018), there was different sequential change among the A+T-(N)-, A+T+(N)-, and A+T+(N)+ profiles compared to the normal AD biomarker (A-T-(N)-). At the category of Alzheimer's pathologic change (A+T-(N)-), there were no significant direct or indirect paths among the initial CSF profile, MRI slope, and cognitive slope. From the category of AD (A+T+(N)- and A+T+(N)+), a relationship was observed between the brain MRI and cognition slopes (Fig. 3). Another direct path between the initial CSF profile and the brain MRI slope became significant in the A+T+(N)+ profile in addition to the indirect path mediated by the MRI slope. Although the A+T+(N)- and A+T+(N)+ profiles are both categorized as "Alzheimer's disease" in NIA-AA research framework, the A+T+(N)+ profile is distinct from the A+T+(N)- profile because the former contains (N) positivity, which is an indicator of neurodegeneration or neuronal injury

of varying causality. This implies that the A+T+(N)+ profile might be related to other possible comorbid conditions as well as to AD pathology and that these combined pathologies may increase the possibility of activation of other biomarker pathways. Consequently, these findings provide support for the NIA-AA research framework model that defines biomarker profiles based on the AT(N) system where the presence of more abnormal biomarker groups represents more advanced pathologic stages (Mormino et al., 2014). In addition to sequential change in AD biomarkers by "modified amyloid cascade hypothesis" (Jack et al., 2013), our results suggested another relationship among biomarkers and cognition. Consistent with the findings of previous studies, primarily cross-sectional (Vemuri et al., 2010), an initial pathologic CSF profile such as the A+T-(N)- did not directly affect the cognitive or MRI slope in our study. However, the MRI slope began to affect the cognitive slope starting at the A+T+(N)- profile, then mediational test modeling changes in brain MRI, as a mediator of the effect of the CSF profile on cognitive change across time, were significant at the A+T+(N)+ profile in addition to the direct effect from the initial CSF profile to the MRI slope. This finding extended the scope of research from sequential ordering of events (Petrella et al., 2019; Young et al., 2014) to longitudinal mediation using the PPLGCM, which considered changes in structural MRI and cognitive function across time. Investigation using this model has only been performed for FDG uptake using PET as a mediator between CSF profiles and cognitive change (Dowling et al., 2015). Although structural MRI and FDG PET are placed in the same (N) biomarker group, there is some difference because atrophy on MRI reflects loss of the neuropil (Barkhof et al., 2007), while FDG PET shows functional impairment of neurons in addition to shrinkage of the neuropil (Chételat et al., 2016). Additionally, brain MRI is more widely used in clinical practice according to the diagnostic guidelines of dementia (Wang et al., 2017) that we used the AD signature of cortical thickness including the eight bilateral regions (Busovaca et al., 2016). According to recent mediation model, sequence of Aβ, tau, atrophy and cognitive change vary by brain region and disease state for nondemented cohort (Fletcher et al., 2018). Another study found the mediational effect of neurodegenerative marker such as FDG-PET or brain MRI between initial Aβ pathology and episodic memory for MCI (Mattsson et al., 2015) and this effect can be

affected by vascular risk and brain region (Villeneuve et al., 2014). These studies using mediational model gave insight for causal relationship among AD biomarkers based on cognitive stage, and our study investigated another mediational effect focused on AT(N) system with PPLGC model that consider time-dependent effects of biomarkers. Additionally, one of the big differences between previous mediational studies and ours is that they used individual CSF measurement ($A\beta_{1-42}$, $pTau_{181p}$, t-Tau) as continuous variables but we used them as categorical variables for ATN profiles. When we performed mediational analysis using CSF measures as continuous variables, $A\beta_{1-42}$ showed significant effects for all of the direct and indirect pathways while Tau did not reveal significant direct effect from CSF ($pTau_{181p}$, t-Tau) to MRI slope (Supplementary Table2).

Our study adopted PPLGC modeling to validate the newly-developed biological definition of AD by the NIA-AA research framework (Jack et al., 2018). One of the main changes of the research framework was that it defined AD biologically, separating cognitive impairment as a subsequent symptom of the preceding AD pathology. In line with this notion, we examined longitudinal ADNI data representing the whole range of the AD continuum from CU to dementia to investigate temporal change based on the initial AT(N) profiles. In the research framework, CSF biomarkers and brain imaging are placed into common groups but fundamental difference and discordance between them should be recognized (Gordon et al., 2016a; Vos et al., 2016) because CSF biomarkers measure the concentration of protein at a given timepoint, while imaging measures the neuropathologic or neurodegenerative loading accumulated over time (Alexopoulos et al., 2014; Blennow and Hampel, 2003; Gordon et al., 2016b). This discordance was also observed in our study where the A+T+(N)- profile by CSF measures without neurodegeneration already showed a direct effect between the MRI slope (i.e., another (N) marker) and cognitive slope. However, initial CSF did not directly affect the cognitive slope across the entire Alzheimer's continuum even in the A+T+(N)+ profile. Taking together these observations, the hypothetical biomarker sequence might be appropriate because the number of significant direct and indirect pathways between biomarkers increased across Alzheimer's continuum, but detailed effects between biomarkers across time must be considered in the future. Our study showed that sequential changes of AT(N) profiles by initial CSF measures according to research

framework did not reflect sequential changes of biomarkers and cognition although the number of significant direct or indirect pathways increased across Alzheimer's continuum. Presently, the AT(N) biomarker system of the research framework does not include the notion of time-dependent effects of biomarkers because it is an unbiased system for grouping biomarkers and classifying participants (Jack et al., 2016). So our finding will be useful for designing detailed clinical trials using NIA-AA Research Framework based on AT(N) profiles in the future.

This study has several limitations. First, Alzheimer's continuum included the A+T-(N)+ profile, which was not included in our study because there were no subjects with this profile in the ADNI data. This was not in line with previous studies that reported approximately 35 (8.0%) of 435 subjects (Jack et al., 2017) and 19 (2.3%) of 814 subjects (Soldan et al., 2019) with this profile for CU individuals, and this discrepancy according to study cohorts may be the target of a future study. Second, we defined the AT(N) classification based on initial CSF biomarkers, but it could also be defined by imaging markers that validation of mediational effects using this image-based AT(N) classification may be necessary to strengthen our results. Third, a better model for assessing the temporal sequence of events and reducing concurrent causation might have been achieved by using longitudinal CSF biomarkers rather than initial categorization by the AT(N) classification. Although using biomarkers as continuous measures might be better for research purposes, denoting abnormal cutoff points is necessary to support decision making for individual patients in the clinic as well as subject selection in clinical trials. This study attempted to prove causal inference by mediation analysis investigating the effect of changes in cortical thickness on changes in cognition according to the initial AT(N) classification, and this was consistent with the supposition of the research framework that the presence of more biomarker abnormalities denotes more advanced stages of the disease (Mormino et al., 2014). More appropriate modeling approaches employed by longitudinal studies are required to validate the complex sequence of events that results in neurodegeneration and cognitive dysfunction in AD.

5. Conclusions

Our findings demonstrate the hypothetical biomarker sequence related to mediation effect is different according to AT(N) profile. These suggest the need to consider dynamic changes in the relationship among biomarkers in current cascade model.

Abbreviations

Aβ: Amyloid-β1-42; AD: Alzheimer's disease; ADNI: Alzheimer's Disease Neuroimaging Initiative; ADAS-cog: Alzheimer's Disease Assessment Scale-cognitive subscale; APOE: Apolipoprotein E; AT(N): Amyloid/tau/neurodegeneration; CDR-SOB: Clinical Dementia Rating Sum of Boxes; CSF: Cerebrospinal fluid; CFI: Comparative fist index; FDG:[18F]-fluorodeoxyglucose; MCI: Mild cognitive impairment; MMSE: Mini Mental State Examination; MRI: Magnetic resonance imaging; NIA-AA : National Institute on Aging and Alzheimer's Association; PET: Positron emission tomography; PPLGCM: Parallel-process latent growth curve model; RMSEA: Root mean square error of approximation; TLI: Tucker-Lewis Index

Declarations

Ethical approval, consent to participate, and consent for publication

The study procedures were approved by the institutional review board of all participating centers (http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf) and written informed consent was obtained from all participants or authorized representatives.

Availability of data and material

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JWJ, and SYK designed the study and participated in data analysis and interpretation. JWJ, SOK and SHK participated in data analysis and interpretation, drafted the manuscript, and revised the manuscript for important intellectual content. JSL, YHP, YSK, SHK, SWP and YCY participated in data analysis. All authors read and approved the final manuscript.

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Fig. 1. Schematic figure of the parallel process growth curve model to test the effect of CSF measures on the rate of cognitive change via rate of change in cortical thickness over time. The subscripts for AD-signature and ADAS cog refer to the months collected in the ADNI data. Latent variable slopes (circles) were regressed on the observed variables (squares) of the CSF adjusted by age, sex, *APOE*, educational level, and initial clinical diagnosis. Residual error variances are represented by two-headed curved arrows for observed and latent variables.

Fig. **2.** Bivariate correlation matrix between variables.

The red color indicates a positive correlation, whereas the yellow indicates a negative correlation.

Fig. 3. Mediational effects of brain magnetic resonance imaging (MRI) on baseline cerebrospinal fluid (CSF) to cognitive slope

The diagram of the mediation model pathways is presented above the table.

Showing direct pathways among initial CSF, MRI slope, and cognitive slope (i.e., a, b, and c).

The strength of the mediation pathway (i.e., i) is the multiplication product of the component edge weights in these pathways (i.e., $\beta_a * \beta_b$).

Abbreviations: CSF, cerebrospinal fluid, CI, confidential interval

NOTE. Regression coefficients are computed by bootstrap sampling with 10,000 iteration after adjusted for age, gender, education, ApoE and diagnosis at entry.

In the table, β coefficients and 95% confidence intervals are displayed. Coefficients significance at 95% confidence level are in bold.

Table1

Classification of ADNI to distinguish CU, MCI and dementia

		CU	**MCI**	
Subjective memory complaint	None	Yes		Yes

	CU	MCI	
MMSE score	≥24	≥24	Betw and 2 years
Logical memory score	≥9 for 16 or more years of education	≤8 for 16 or more years of education	≤8 fo
	≥5 for 8-15 years of education	≤4 for 8-15 years of education	≤4 fo
	≥3 for 0-7 years of education	≤2 for 0-7 years of education	≤2 fo
CDR	CDR=0 Memory Box score must be 0	CDR=0.5 Memory Box score of at least 0.5	CDR
General cognition and functional status	Cognitively normal based on the absence of significant impairment in cognitive functions or activities of daily living	General cognition and functional performance sufficiently preserved such that a diagnosis of dementia cannot be made	NINC AD

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; CU, cognitively unimpaired; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; CDR, The Clinical Dementia Rating Scale; NINCDS/ADRDA, National Institute of Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders Association. This table was adapted and modified from the procedure manuals for ADNI1, ADNI GO, and ADNI 2 available at http://adni.loni.usc.edu/methods/documents/.

Table2

Descriptive statistics of study variables at baseline

	CU (N=136)	MCI (N=294)	Dementia (N=146)	Total (N=576)	p
Demographic characteristics					
Age	74.7 ± 5.5	73.4 ± 7.2	74.4 ± 7.8	74.0 ± 7.0	0.776
Male, n(%)	71 (52.2)	184 (62.6)	81 (55.5)	336 (58.3)	0.092
Education in years	16.0 ± 2.8	15.9 ± 2.9	15.3 ± 3.0	15.8 ± 2.9	0.034
APOE ε4 carrier, n(%)	37 (27.2)	166 (56.5)	118 (73.9)	311 (54.0)	< 0.001
Cognition					
ADAS-cog-13	10.0 ± 4.6	17.2 ± 6.8	29.5 ± 7.9	18.6 ± 9.6	< 0.001
CSF biomarkers					
Aβ	190.9 ± 54.7	158.3 ± 48.3	134.8 ± 33.7	160.0 ± 50.6	< 0.001
p-Tau	25.4 ± 14.8	39.7 ± 23.4	49.5 ± 27.5	38.8 ± 24.4	< 0.001
t-Tau	64.7 ± 28.8	98.2 ± 57.1	126.7 ± 60.8	97.5 ± 57.1	< 0.001
AT(N) profiles, n(%)					< 0.001
- A-T-(N)-	65 (47.8)	63 (21.4)	5 (3.4)	133 (23.1)	
- A+T-(N)-	28 (20.6)	26 (8.8)	10 (6.9)	64 (11.1)	
- A+T+(N)-	25 (18.4)	82 (27.9)	33 (22.6)	140 (24.3)	
- A+T+(N)+	18 (13.2)	123 (41.8)	98 (67.1)	239 (41.5)	
Mean cortical thickness					
AD signature	2.60 ± 0.16	2.44 ± 0.20	2.27 ± 0.22	2.44 ± 0.22	< 0.001

Abbreviations: CU, cognitively unimpaired; MCI, mild cognitive impairment; *APOE*, apolipoprotein E; MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's Disease Assessment Scale Cognitive subscale; CDR-SB, The Clinical Dementia Rating Scale Sum of Boxes; CSF, cerebrospinal fluid; Aβ, beta amyloid; p-Tau, phosphorylated tau; t-Tau, total tau

Values are presented as mean ± SD unless otherwise stated.

1 Table3. Univariate Latent growth curve model results for AD signature as outcome (n=576)

	Model 1[a]		Model 2[b]		Model 3[b]
AD signature	RMSEA=0.035 (0.000, 0.064), CFI=0.998, TLI=0.998	*p*	RMSEA=0.017 (0.000, 0.057) , CFI=0.999 , TLI=0.998	*p*	RMSEA=0.000 (0.000, 0.042), CFI=1.000 , TLI=1.000
Intercept	2.483	0.000	3.549	0.000	3.504
Slope	-0.049	0.000	0.051	0.198	-0.038
Variance (intercept)	0.050	0.000	0.024	0.000	0.028
Variance (slope)	0.002	0.000	0.000	0.057	0.001
Covariance (intercept and slope)	0.004	0.000	0.000	0.790	0.002
ATN (A-T-(N)- vs. A+T-(N)-)					
Intercept on AD signature			-0.006	0.817	
Slope on AD signature			-0.008	0.243	
ATN (A-T-(N)- vs. A+T+(N)-)					
Intercept on AD signature					-0.037
Slope on AD signature					-0.012
ATN (A-T-(N)- vs. A+T+(N)+)					
Intercept on AD signature					
Slope on AD signature					

2 a. Unconditional latent growth curve model (model with no covariates).
3 b. Models also included all control variables, namely, age, education, gender, *ApoE* status, and
4 diagnosis at baseline.
5 RMSEA, Root Mean Standardized Error of Approximation; CFI, Confirmatory Fit Index; TLI, Tucker
6 Lewis Index
7

Table4. Univariate Latent growth curve model results for ADAS-Cog 13 as outcome (n=576)

	Model 1[a]		Model 2[b]		Model 3[b]
ADAS-Cog 13	RMSEA=0.053 (0.033, 0.074), CFI=0.993, TLI=0.993	*p*	RMSEA=0.049 (0.019, 0.073), CFI= 0.983, TLI=0.977	*p*	RMSEA=0.044 (0.020, 0.064), CFI=0.989, TLI=0.985
Intercept	18.419	0.000	-1.723	0.734	6.535
Slope	2.346	0.000	-1.112	0.542	0.166
Variance (intercept)	85.693	0.000	24.268	0.000	28.983
Variance (slope)	10.688	0.000	1.126	0.039	2.327
Covariance (intercept and slope)	20.821	0.000	2.619	0.004	5.201
ATN (A-T-(N)- vs. A+T-(N)-)					
Intercept on ADAS-Cog			0.994	0.270	
Slope on ADAS-Cog			0.815	0.011	
ATN (A-T-(N)- vs. A+T+(N)-)					
Intercept on ADAS-Cog					2.221
Slope on ADAS-Cog					1.164
ATN (A-T-(N)- vs. A+T+(N)+)					
Intercept on ADAS-Cog					
Slope on ADAS-Cog					

a. Unconditional latent growth curve model (model with no covariates).
b. Models also included all control variables, namely, age, education, gender, *ApoE* status, and diagnosis at baseline.
RMSEA, Root Mean Standardized Error of Approximation; CFI, Confirmatory Fit Index; TLI, Tucker Lewis Index

Highlights

- PPLGCM was used to test the biomarker sequence hypothesis based on AT(N) profiles.
- Alzheimer's pathologic change (e.g. A+T-(N)-) was insufficient to induce effects on cognitive dysfunction.

- There was a significant direct path from altered cortical thickness to cognitive decline in A+T+(N)- profile.
- Only the A+T+(N)+ profile showed significant mediation effect of cortical thickness.
- Sequential effects between brain MRI and cognition changes varied by AT(N) profile.
- Dynamic changes in biomarker relations in the cascade model should be considered.

Credit author statement

Jae-Won Jang, SangYun Kim: Conceptualization, Methodology, Software. **Jae-Won Jang, Sung OK Kwon**: Data curation, Writing-Original draft preparation. **Jae-Won Jang, Young Ho Park**: Visualization, **Yeshin Kim, Sang Won Park, Seongheon Kim**: Investigation. **Jae-Sung Lim**: Resources. **Young Chul Youn**, **Sung Hun Kim***:* Supervision.**: SangYun Kim:** Supervision, Writing-Reviewing and Editing