

An amyloid sensitive composite model to determine subtle cognitive differences in preclinical Alzheimer's disease

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Abstract

Background: Recently, the focus of Alzheimer's disease (AD) research has shifted from the clinical and symptomatic stage to the preclinical and asymptomatic stage. However, studies on the distinctive neuropsychological features of preclinical AD with adjusted measurement errors are insufficient. The present study aimed to investigate the distinctive cognitive features of preclinical AD and develop a cognitive composite model that can sensitively distinguish between the amyloid positive ($A\beta+$) and amyloid negative ($A\beta-$) status in cognitively normal (CN) elderly participants. **Methods:** A total of 423 CN elderly participants with amyloid positron emission tomography (PET) images were recruited. Using the multiple-indicator multiple-cause (MIMIC) model, sensitive cognitive domains to the $A\beta+$ group were found. Then, several cognitive tests were selected to create the cognitive composite model as a result of the multivariate analysis of covariance (MANCOVA). **Results:** The MIMIC model revealed that the domains of episodic memory (verbal and visual) and executive functions were significantly different between $A\beta-$ and $A\beta+$ ($p < 0.05$) participants. According to MANCOVA, the Seoul Verbal Learning Test-Elderly's version (SVLT-E) and the Rey-Osterrieth Complex Figure Test (RCFT) both distinguished between the $A\beta+$ group and the $A\beta-$ group on the delayed recall tests in terms of episodic memory ($p < 0.1$). Furthermore, on tests of executive functions, the $A\beta+$ group performed worse than the $A\beta-$ group in color reading of the Korean-Color Word Stroop test (K-CWST) and the animal naming of the Controlled Oral Word Association Test (COWAT) ($p < 0.1$). Consequently, the Preclinical Amyloid Sensitive Composite (PASC) model was comprised of SVLT-E delayed recall, RCFT delayed recall, K-CWST color reading, COWAT-animal, and the Korean Mini-Mental State Examination (K-MMSE) according to the results from our study and previous studies. **Conclusions:** In the present study, we developed our own composite PASC model with the distinctive cognitive profiles of $A\beta+$ CN individuals. Hence, this composite model can eventually contribute to not only early detection but also early interventions for AD.

Background

With the advancement of amyloid- β ($A\beta$) positron emission tomography (PET), the focus of research on Alzheimer's disease (AD) has shifted from the clinical and symptomatic stages to the preclinical and asymptomatic stages of AD [1]. Consequently, approximately 20 to 30% of cognitively normal (CN) elderly population is expected to be preclinical AD with amyloid positivity [2–4]. These CN individuals with elevated amyloidosis are considered to be more vulnerable to AD progression. This can be demonstrated by the subtle cognitive difference between CN individuals with amyloid positivity and those without $A\beta$ biomarkers in the late preclinical stage [5]. Furthermore, several reports have claimed that approximately 25% of preclinical AD converts to prodromal AD or AD dementia in approximately 3 years [6, 7].

Due to the high cost and health risks of $A\beta$ PET, it is usually challenging to obtain a large number of participants with PET data. Thus, it becomes pragmatic and essential for clinicians to predict who might be at high risk of having an $A\beta+$ biomarker with the expectation that future treatment may target $A\beta$. Given that several prevention trials are currently being conducted in preclinical AD, we need to investigate

the distinctive neuropsychological features of preclinical AD, which may help clinicians predict preclinical AD by reducing screen failures and monitoring the therapeutic efficacy of prevention.

Despite attempts to investigate the distinctive neuropsychological features of preclinical AD, the results were inconsistent among studies to date. This may be because previous studies did not consider the effects of measurement errors, although there is always a possibility for the presence of measurement errors in psychometrics [8]. However, by using the principle of factor analysis, the multiple-indicator multiple-cause (MIMIC) model can control for these measurement errors to estimate the latent values. That is, MIMIC may empower a composite model to sensitively detect subtle cognitive differences between A β + and A β - in CN elderlies. However, to our knowledge, no preclinical AD studies have developed a cognitive composite model using this factor structure method for identifying preclinical AD in the elderly population.

In the present study, we aimed to determine if there are any distinct cognitive domains and cognitive measures of preclinical AD using the MIMIC model, which may yield lower background noise in measurements. We also developed and validated the Preclinical Amyloid Sensitive Composite (PASC), a composite model that precisely distinguishes A β + and A β - in CN individuals. Considering that subtle deficits in episodic memory and executive functions appear to be critical in preclinical AD due to their strong association with AD progression [9], we hypothesized that memory and executive functions would be the cognitive domains with a significant difference between A β + CN and A β - CN individuals.

Methods

Study participants

A total of 423 CN participants were recruited from September 2015 to December 2018 at the Samsung Medical Center in Seoul, South Korea. All the participants met the following criteria to be qualified as CN: (a) the Korean Mini-Mental State Examination (K-MMSE) \geq 24 or above - 1.5 standard deviation (SD) from the age-, sex-, and education-adjusted norms if the education period was less than 9 years; (b) above - 1 SD from the age-, sex-, and education-adjusted norms on the delayed recall of the Seoul Verbal Learning Test-Elderly's version (SVLT-E); (c) above - 2 SD from the age-, sex-, and education-adjusted norms on the Korean version of the Boston Naming Test (K-BNT), the Rey-Osterrieth Complex Figure Test (RCFT) copy, and the Korean-Color Word Stroop test (K-CWST) color reading; and (d) an absence of other neurological disorders. The screenings were conducted by trained clinicians and neuropsychologists. Brain MRI confirmed the absence of structural lesions, including territorial cerebral infarction, brain tumors, hippocampal sclerosis, vascular malformation, and cerebral amyloid angiopathy (CAA).

¹⁸F-labeled amyloid PET acquisition and analysis

A total of 423 CN participants underwent ^{18}F -labelled amyloid PET; 219 underwent ^{18}F -florbetaben PET, 203 underwent ^{18}F -flutemetamol PET, and 1 underwent ^{18}F -florbetapir PET scanning at the Samsung Medical Center. The scanning was performed using a Discovery Ste PET/CT scanner (GE Medical Systems, Milwaukee, WI, USA) with a 3D scanning mode that examined 47 slices of 3.3 mm thickness spanning the entire brain. Prior to a 20-minute emission PET scan with dynamic mode consisting of 4×5 min frames, 311.5 MBq ^{18}F -florbetaben, 197.7 MBq ^{18}F -flutemetamol, and 370 MBq ^{18}F -florbetapir were injected. The scan was performed 90 minutes after the injection. 3D PET images were reconstructed in a $128 \times 128 \times 48$ matrix with a $2 \times 2 \times 3.27$ mm voxel size using the ordered-subsets expectation-maximization algorithm (^{18}F -florbetaben, iteration = 4 and subset = 20; ^{18}F -flutemetamol, iteration = 4 and subset = 20; ^{18}F -florbetapir, iteration = 4 and subset = 16).

All PET images were reviewed by trained nuclear medicine physicians who were blinded to patient information and dichotomized as A β -positive or negative using visual reads. The visual assessments for ^{18}F -florbetaben PET, ^{18}F -flutemetamol PET, and ^{18}F -florbetapir PET were performed with the scoring system that was used in the previous studies [10–14].

Neuropsychological assessments

The second edition of the Seoul Neuropsychological Screening Battery (SNSB-II) was administered to all the participants to assess their cognitive functions [15]. The SNSB-II was standardized on 1,067 CN elderly individuals in South Korea. The normative data for the individual neuropsychological test was established based on a representative of South Korean population with age between 45 and 90 and the education level over 18 years. In our study, we used the following tests that are included in SNSB-II: Digit Span Test (DST) forward and backward for attention; K-BNT for language; the Clock Drawing Test (CDT) and the RCFT for visuospatial function and visual memory; the SVLT-E for verbal memory; and phonemic and semantic Controlled Oral Word Association Test (COWAT), K-CWST, Digit Symbol Coding (DSC), and the Korean Trail Making Test-Elderly's version (K-TMT-E) for executive functions. The RCFT involved copying, immediate recall, 20-minute delayed recall, and recognition tests. Similarly, the SVLT-E was composed of immediate recall trials, delayed recall, and recognition tests. In addition to the tests mentioned above, the K-MMSE was also used for the global mental state assessments of the participants [16].

Statistical analyses

Demographic characteristics were compared between the A β + and A β - groups using the independent sample t-test if the variables were continuous and the chi-square test if the variables were categorical.

Confirmatory factor analysis (CFA) was yielded to validate the structure of the five cognitive domains. CFA is one of the multiple forms of structural equation modeling (SEM), which confirms whether a pre-specified factor structure fits the data well [8]. We validated the CFA model for the neuropsychological test battery to control for measurement errors. The tests included in each cognitive domain were the same as those described earlier, and the language domain consisted of a single test score. The subtests

of the SVLT-E and the RCFT in the memory domain were measured respectively using the same method. Therefore, it was considered acceptable to add an error covariance between the residual variances associated with SVLT-E immediate and delayed recalls and RCFT immediate and delayed recalls. Since our factor structure included both reflective and causal indicators, we used the MIMIC model to compare the latent means in the cognitive domains between the A β + and A β - groups (Fig. 1).

Multivariate analysis of covariance (MANCOVA) was performed to see if any neuropsychological tests showed a significant difference between the two groups. Since the measurement errors were not treated in the MANCOVA, we deliberately set the cutoff for significance to be less conservative in order to increase the power and reduce the risk of type II errors. Thus, the tests with p-value < 0.1 were selected to be included in the composite model. Lastly, the MIMIC model was repeated to identify whether these tests were sensitive to differences between A β + and A β - in CN elderlies as a composite.

Raw scores were used in each test in all statistical analyses. The K-TMT-E part B was log-transformed for accuracy of the estimate due to its large range (0-300) and non-normality. Multiple imputation and full information maximum likelihood estimations were used to treat missing values.

IBM SPSS (version 25.0, SPSS Statistics/IBM Corp, Armonk NY, USA) was used for demographic analysis and MANCOVA. For comparisons of latent means between the groups, maximum likelihood estimation was analyzed by Mplus (version 8.0) [17]. However, due to the violation of normality, bias-corrected bootstraps were performed together.

Results

Demographic characteristics of participants

The demographic and neuropsychological characteristics of the study participants are presented in Table 1. The overall mean age of the participants was 69.9 years. Among the 423 participants, 75 were A β + (17.7%). The frequency of APOE ϵ 4 carriers was 24.6%.

The A β + group was significantly older than the A β - group (71.5 ± 6.8 years vs. 69.5 ± 8.4 years, $p < 0.05$). The A β + group also displayed a higher percentage of APOE ϵ 4 carriers compared with the A β - group (53.3% vs. 16.4%, $p < 0.001$). However, the two groups did not significantly differ in education level and proportion of female participants.

Table 1^a				
Demographic and neuropsychological characteristics of the study participants (N = 423)				
	All	A β - (N = 348)	A β + (N = 75)	p value
Demographics ^b				
Age, years [*]	69.9 (8.1)	69.5 (8.4)	71.5 (6.8)	0.034
Education, years	11.8 (4.8)	11.9 (4.8)	11.3 (4.5)	0.327
Female, N(%)	267 (63.1)	219 (62.9)	48 (64)	0.862
APOE ϵ 4 carrier N (%) ^{d**}	97 (24.6)	57 (17.5)	40 (58.0)	< 0.001
Neuropsychological Tests ^c				
Attention				
Digit Span Forward	6.3 (1.4)	6.3 (1.4)	6.2 (1.3)	
Digit Span Backward	4.1 (1.3)	4.1 (1.4)	4.0 (1.1)	
Language				
K-BNT	48.6 (6.7)	48.8 (6.6)	47.7 (7.2)	
Visuospatial Functions				
RCFT copy	32.7 (3.6)	32.7 (3.7)	32.5 (3.1)	
CDT	2.8 (0.5)	2.8 (0.5)	2.8 (0.4)	
Memory				
SVLT-E immediate recall	21.4 (4.6)	21.6 (4.6)	20.4 (4.4)	
SVLT-E delayed recall	7.0 (2.1)	7.1 (2.1)	6.4 (2.0)	
SVLT-E recognition	21.2 (2.0)	21.3 (1.9)	20.8 (2.0)	
RCFT immediate recall	14.9 (7.2)	15.3 (7.2)	13.1 (7.4)	
RCFT delayed recall [*]	14.8 (6.8)	15.2 (6.7)	12.9 (7.1)	
RCFT recognition	19.6 (2.2)	19.7 (2.2)	19.2 (2.2)	
Frontal/Executive Functions				
COWAT animal	15.9 (4.8)	16.1 (4.9)	14.7 (4.3)	
COWAT phonemic total	27.2 (11.8)	27.6 (11.8)	25.4 (12.0)	
K-CWST color reading [*]	87.1 (21.2)	88.6 (21.2)	80.7 (20.3)	

Table 1^a			
DSC	53.1 (19.5)	54.2 (19.8)	48.3 (17.1)
K-TMT-E-A time, seconds	24.6 (13.1)	24.1 (13.3)	26.9 (11.9)
K-TMT-E-B time, seconds	56.5 (54.1)	55.2 (54.3)	62.7 (53.1)
Others			
K-MMSE	28.1 (1.8)	28.2 (1.8)	27.7 (1.5)
* $p < 0.05$; ** $p < 0.001$			
^a Values are presented as mean (standard deviation) or number (%)			
^b The Independent sample t-test was used for continuous variables, and the chi-square test was used for categorical variables.			
^c Analysis of covariance was conducted as a statistical analysis to see the difference in test scores of each group. Age, education, and sex were adjusted as covariates in the analysis.			
^d APOE $\epsilon 4$ genotyping N = 395			
Abbreviations: N, number; APOE $\epsilon 4$, Apolipoprotein E; A β , amyloid- β ; K-BNT, the Korean version of the Boston Naming Test; CDT, the Clock Drawing Test; RCFT, the Rey-Osterrieth Complex Figure Test; SVLT-E, the Seoul Verbal Learning Test-Elderly's version; COWAT, the Controlled Oral Word Association Test; K-CWST, the Korean Color Word Stroop Test; DSC, Digit Symbol Coding; K-TMT-E-A, the Korean Trail Making Test-Elderly's version part A; K-TMT-E-B, the Korean Trail Making Test-Elderly's version part B; K-MMSE, the Korean Mini-Mental State Examination.			

MIMIC model for latent mean analysis

The CFA model was successfully validated to control measurement errors. Accordingly, error covariance was added between the residual variances associated with SVLT-E immediate and delayed recalls and RCFT immediate and delayed recalls. The CFA model with added error covariance fit the data well ($\chi^2 = 212.181$, $df = 78$, $p < .001$; RMSEA = .064; CFI = .957; TLI = .942; SRMR = .056). All factor loadings in the model were significant between .49 and .89.

Next, a latent mean difference between A β + and A β - for each cognitive domain was verified. The latent mean model fit the data well ($\chi^2 = 359.481$, $df = 128$, $p < .001$; RMSEA = .065; CFI = .944; TLI = .919; SRMR = .048).

The result revealed that the difference between the A β + and A β - groups in attention, visuospatial function, and language function were not significant, but the latent means in the A β + group were significantly lower than the A β - group in the three domains of verbal memory, visual memory, and executive functions (Table 2).

Table 2			
Latent mean difference between amyloid positive and negative groups for neuropsychological domains			
Neuropsychological domains	Estimate	SE	Bias-corrected bootstrap percentile (95% CI)
Amyloid positivity -> Attention	0.040	0.114	(-0.168, 0.282)
Amyloid positivity -> Visuospatial function	0.159	0.375	(-0.657, 0.814)
Amyloid positivity -> K-BNT	-0.017	0.782	(-1.961, 1.122)
Amyloid positivity -> Verbal memory	-0.809	0.345	(-1.662, -0.213)
Amyloid positivity -> Visual memory	-1.449	0.724	(-3.004, -0.233)
Amyloid positivity -> Frontal EF	-0.440	0.213	(-1.109, -0.094)

Sex, education, and age were adjusted as covariates in the analyses.
Abbreviations: K-BNT, the Korean Boston Naming Test; Frontal EF, Frontal Executive Functions; SE, Standard Error.

MANCOVA

Based on the results above, further statistical analyses were conducted for each neuropsychological assessment within the episodic memory and executive functions. MANCOVA was used to see the score differences of the tests under episodic memory and executive functions between the Aβ+ and Aβ- groups when sex, education, and age were controlled. The result of the MANCOVA is shown in Table 3.

Few neuropsychological subtests showed meaningful differences between the groups. Primarily, we set the level of significance at 0.1. Regarding episodic memory, SVLT-E delayed recall showed a difference in score between the Aβ+ and Aβ- groups ($F(1, 418) = 3.666, p = 0.056$). For RCFT, the Aβ+ group performed worse, not only on the delayed recall ($F(1, 418) = 4.036, p = 0.045$), but also on the immediate recall ($F(1, 418) = 2.898, p = 0.089$). However, due to the extremely high correlation between the two subtests ($r = 0.935$), we considered that it would be reasonable to use only one subset in our composite model. Based on the clinical and statistical significance, RCFT delayed recall was favored over RCFT immediate recall for the PASC. In terms of executive functions, K-CWST color reading ($F(1, 418) = 4.745, p = 0.030$) and COWAT animal showed worse performance in the Aβ+ group compared to that in the Aβ- group ($F(1, 418) = 3.152, p = 0.077$).

Table 3				
MANCOVA with neuropsychological tests in Memory and Executive Functions				
	Wilks' Lambda	Mean Square	F	p-value
Verbal Memory	0.991		1.274	0.283
SVLT-E immediate recall		31.149	2.007	0.157
SVLT-E delayed recall*		11.700	3.666	0.056
SVLT-E recognition		4.760	1.564	0.212
Visual Memory	0.989		1.595	0.190
RCFT immediate recall*		110.640	2.898	0.089
RCFT delayed recall*		132.980	4.036	0.045
RCFT recognition		5.195	1.263	0.262
Executive Functions	0.981		1.602	0.161
COWAT animal*		57.491	3.152	0.077
COWAT phonemic total		40.766	0.416	0.560
K-CWST color reading*		1305.356	4.745	0.030
DSC		436.424	2.303	0.178
K-TMT-E-B time		100.874	0.052	0.843
*p < 0.1				
Abbreviations: RCFT, the Rey-Osterrieth Complex Figure Test; SVLT-E, the Seoul Verbal Learning Test-Elderly's version; COWAT, the Controlled Oral Word Association Test; K-CWST, the Korean Color Word Stroop Test; DSC, Digit Symbol Coding; K-TMT-E-B, the Korean Trail Making Test-Elderly's version part B.				

Preclinical Amyloid Sensitive Composite (PASC)

Based on the MANCOVA results and clinical significance, the following 5 tests were finally selected: the SVLT-E delayed recall; the RCFT delayed recall; the K-CWST color reading; the COWAT animal; and the K-MMSE. The K-MMSE was added for examining global cognition. The PASC model presented a good fit with the data ($\chi^2 = 4.757$, $p = .933$; RMSEA = .000; CFI = 1.000; TLI = 1.001; SRMR = .014). All factor loadings in the model were significant between .56 and .73 (Fig. 2).

The MIMIC model was used to ensure that the PASC distinguished between A β + and A β - (Fig. 3). Our model for PASC fit the data well ($\chi^2 = 55.184$, $df = 17$, $p < .001$; RMSEA = .073; CFI = .952; TLI = .930; SRMR

= .039). The result showed that the latent mean in the A β + group was significantly lower than the A β -group (Table 4).

Table 4			
Latent mean difference between amyloid positive and negative groups for PASC			
Latent mean difference	Estimate	SE	Bias-corrected bootstrap percentile (95% CI)
Amyloid positivity -> PASC	-0.429**	0.131	(-0.675, -0.177)
** $p < 0.001$ Education and age were adjusted as covariates in the analyses. Abbreviations: PASC, the Preclinical Amyloid Sensitive Composite; SE, Standard Error.			

Discussion

We investigated the distinctive neuropsychological features of A β + CN elderlies in a carefully phenotyped, CN cohort that underwent detailed neuropsychological tests, MRI, and amyloid PET scans with the standardized protocols. Accordingly, there were several significant neuropsychological findings in this study. First, the MIMIC model found a difference in the latent mean between the A β + and A β -groups in the domains of verbal memory, visual memory, and executive functions. Furthermore, MANCOVA showed that the A β + group performed worse in the RCFT delayed recall, SVLT-E delayed recall, COWAT animal, and K-CWST color reading within the three cognitive domains. Lastly, based on our results and clinical significance, we developed the PASC with the RCFT delayed recall, SVLT-E delayed recall, COWAT animal, K-CWST color reading, and K-MMSE that were found to be critical for amyloid deposition and global cognition. Hence, the PASC can be used to develop a composite score for detecting A β positivity in CN individuals, which can eventually help with early intervention of AD.

The demographic profile of our participants was extremely close to that of the previously reported Asian society profile. The CN A β + percentage in Asian countries is known to be lower than that in western countries. The percentage of CN amyloid positivity in the Asian population ranged between 18% and 25% according to the Korean Brain Aging Study for the Elderly Diagnosis and Prediction of Alzheimer's disease (KBASE) and J-ADNI [18, 19]. On the other hand, the western population, represented by ADNI, was reported to range approximately from 25 to 45% A β positivity rate [20, 21]. Our study exhibited approximately 18% A β positivity in the 423 CN individuals, which was in line with that in the Asian population. The discrepancy between our results and that of the western society may be explained by the differences in the frequency of APOE ϵ 4 and the age of the study participants. Our cohort seemed to have a lower percentage of APOE ϵ 4 (23%) than that reported by ADNI (27%) [22]. Moreover, the younger age of our cohort (mean, 69.9 years) compared to that of the ADNI CN individuals (mean, 75.8 years) may have affected the lower rate of amyloid positivity [22]. Regardless of these disparities, the APOE ϵ 4 rate and

age of our cohort were still at comparable levels to J-ADNI's APOE ϵ 4 rate (24%) and CN individuals' ages (mean, 67.9) [18].

Our major finding was that the A β + CN individuals presented a lower performance in verbal memory, visual memory, and executive functions compared to A β - CN, which was generally consistent with the findings of previous meta-analyses. In terms of memory, there has been a consensus that episodic memory has a strong association with A β burden [23–25]. Unlike episodic memory, the results regarding executive functions in the previous studies are not entirely consistent. A recent meta-analysis suggested a significant difference in executive function [24], while two others showed either a small effect size or a weak association with A β burden [23, 25]. This may be because the previous studies did not consider the effects of measurement errors that could impact the individual test scores. However, applying a factor analysis with the latent variables, we controlled for the measurement errors from each test score for more precise measurement of the corresponding cognitive function.

In the present study, we developed the PASC to predict amyloid positivity using the SVLT-E delayed recall, the RCFT delayed recall, the COWAT animal, and the CWST color reading from the three cognitive domains, and the K-MMSE. We included the K-MMSE in the PASC because the Mini-Mental State Exam (MMSE) is a practical neuropsychological test to examine individual cognitive function holistically [26]. The PASC seems similar to the Preclinical Alzheimer Cognitive Composite (PACC) [27]. However, the PACC was not developed for differentiation of preclinical AD, but rather has been used in prevention trials for preclinical AD [1, 27].

There are a few reasons why we tried to observe cognitive differences in CN individuals with a unidimensional outcome. First, there is a need to create a novel and reliable measure to holistically assess cognitive domains specific to preclinical AD. AD pathology progression involves the deterioration of multiple cognitive domains instead of a single cognitive function. Currently, the MMSE [26] and the Clinical Dementia Rating (CDR) [28] are commonly used to assess individual cognitive function holistically. However, they often display ceiling effects in CN individuals [29, 30]. Therefore, they are not sensitive measures for CN individuals. Furthermore, the ratings of the CDR primarily rely on clinicians' judgments following patient and caregiver interviews. Thus, bias is rarely avoidable. Another advantage of obtaining a composite model is that a single factor model allows for a more precise differentiation of distinct groups. Compared to multi-outcomes, a primary outcome usually yields lower background noise in the measurement, which derives a lower risk of Type-I error [8, 31]. Therefore, a primary outcome has better reliability and sensitivity in terms of detecting subtle cognitive differences.

The strength of our study is the large sample size of the CN cohort who underwent amyloid PET. In spite of this strength, there are a few limitations to our study, as well. First, our composite model was not cross-validated. Future studies are needed to cross-validate this composite model in different patient groups and data sets. Second, the participants went through different types of PET ligands. The variety of the tracers may have affected the visual reads of amyloid deposition. However, this limitation can be somewhat alleviated by the high correlations among the different ligands [32, 33]. Moreover, we did not

explore the clinical effects of the PASC. Future studies with clinical impacts of the PASC on other biomarkers like tau or cortical atrophy may be recommended. Lastly, our study was a single-center study with the cohort recruited from a hospital. Since we did not recruit the participants from the general population, the generalizability of our study may be challenging.

Conclusions

Our study created the PASC that is a sensitive cognitive composite model for A β + in CN elderly individuals, since we also investigated some distinctive cognitive features of A β + in CN elderly individuals. The PASC, which employed significant tests in episodic memory and executive functions, along with the global cognitive measure of the K-MMSE, can be used to develop a sensitive composite score to identify A β + in CN individuals. Therefore, the PASC may contribute to the early detection of AD and, eventually, early intervention.

List Of Abbreviations

A β : Amyloid- β

AD: Alzheimer's disease

APOE ϵ 4: Apolipoprotein E

CAA: cerebral amyloid angiopathy

CDR: the Clinical Dementia Rating

CDT: the Clock Drawing Test

CFA: confirmatory factor analysis

CN: cognitively normal

COWAT: the Controlled Oral Word Association Test

DSC: Digit Symbol Coding

DST: Digit Span Test

KBASE: the Korean Brain Aging Study for the Elderly Diagnosis and Prediction of Alzheimer's disease

K-BNT: the Korean version of the Boston Naming Test

K-CWST: the Korean-Color Word Stroop test

K-MMSE: the Korean Mini-Mental State Examination

K-TMTE: the Korean Trail Making Test-Elderly's version

MANCOVA: multivariate analysis of covariance

MIMIC: the multiple-indicator multiple-cause

MMSE: the Mini-Mental State Exam

PACC: the Preclinical Alzheimer Cognitive Composite

PASC: the Preclinical Amyloid Sensitive Composite

PET: positron emission tomography

RCFT: the Rey-Osterrieth Complex Figure Test

SD: standard deviation

SE: standard error

SEM: structural equation modeling

SNSB-II: the Seoul Neuropsychological Screening Battery

SVLTE: the Seoul Verbal Learning Test-Elderly's version

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board at the Samsung Medical Center. All methods were implemented in accordance with the approved guidelines.

Consent for publication

None to report.

Competing interests

None to report.

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Potential Conflicts of Interest

None to report.

Author Contributions

Conception and design of the study: Alice Hahn, Young Ju Kim, Juhee Chin, and Sang Won Seo

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Final approval of the manuscript: Juhee Chin and Sang Won Seo

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

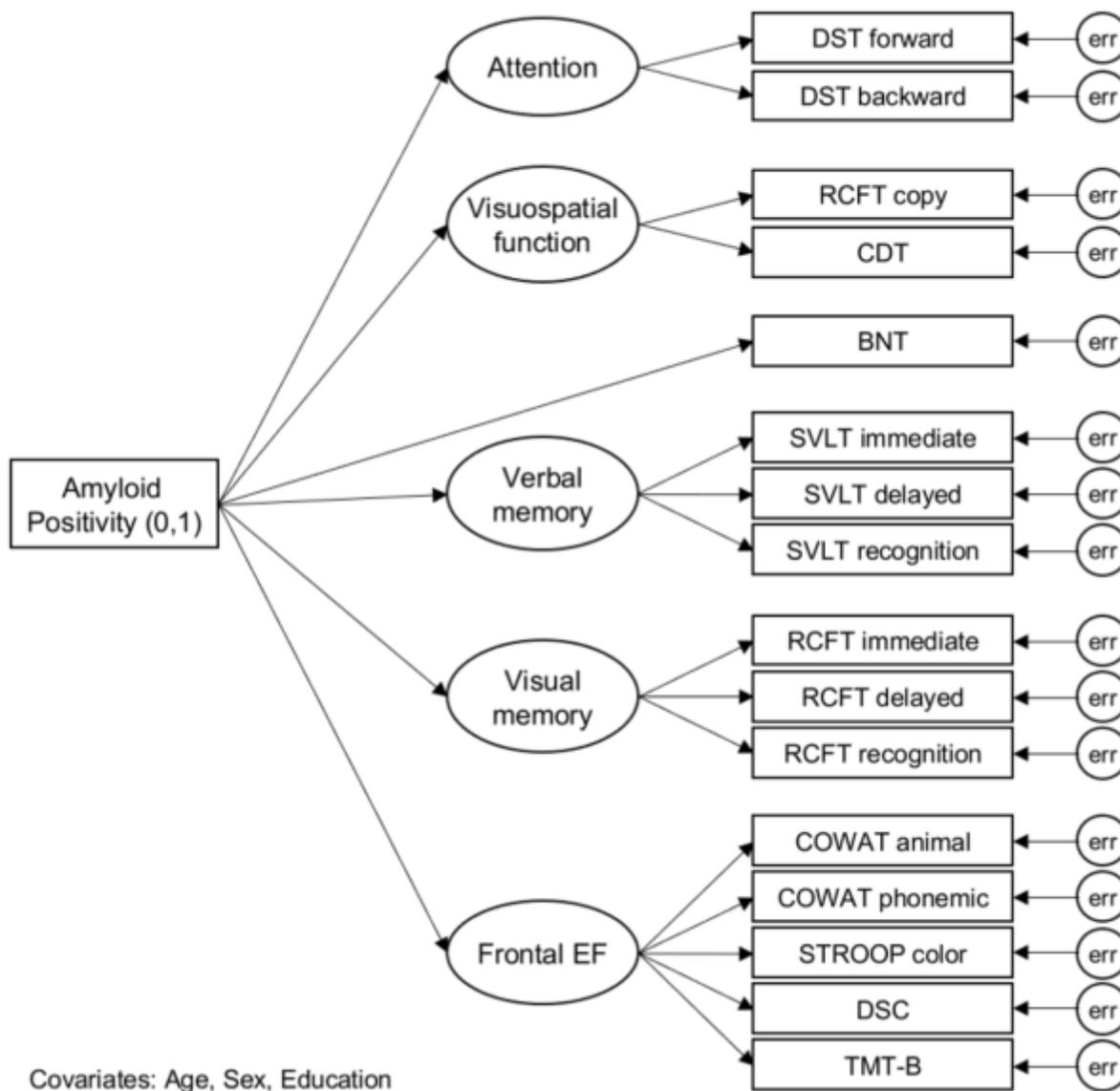


Figure 1

The MIMIC model of the SNSB-II. The model was created for latent mean comparisons in the cognitive domains between A β + and A β -.

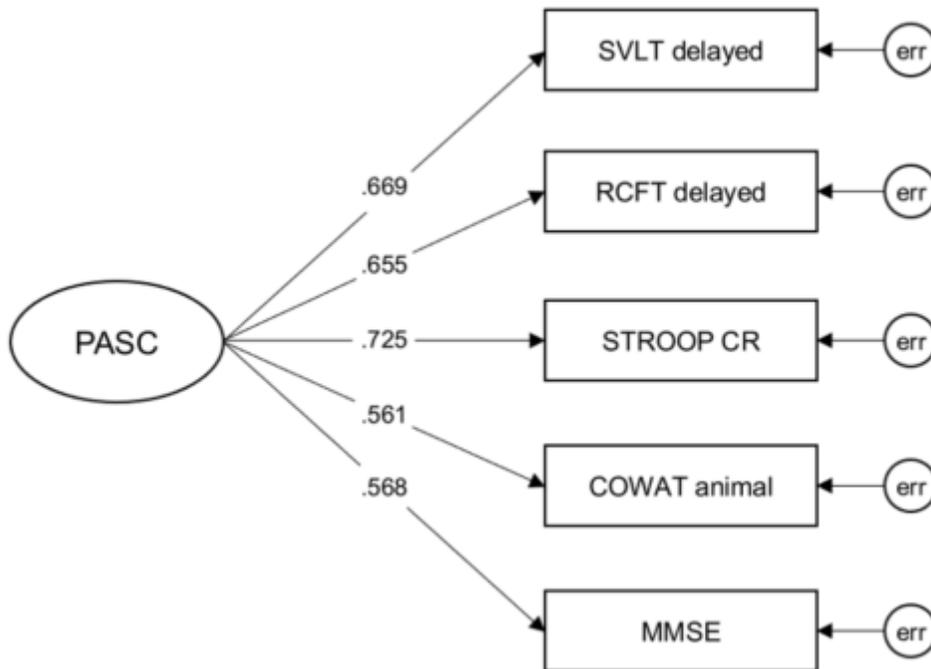


Figure 2

The CFA model of the PASC

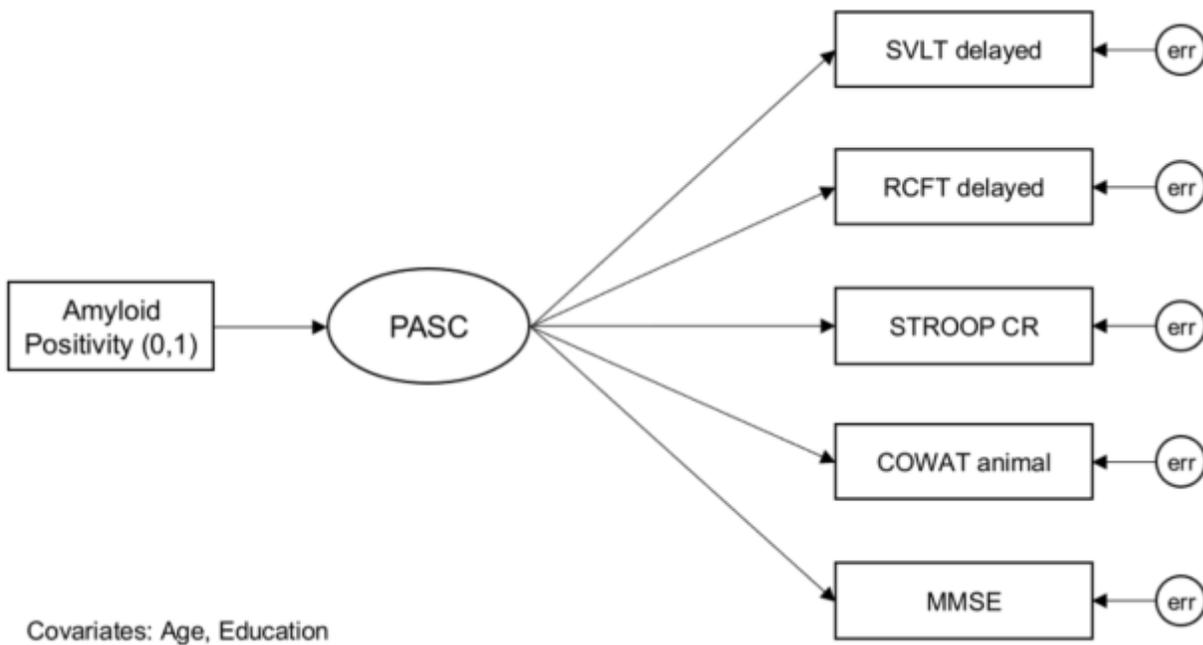


Figure 3

The MIMIC model of the PASC for latent mean comparison between $A\beta^+$ and $A\beta^-$