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Associations of Stages of Objective Memory Impairment with Cerebrospinal Fluid and Neuroimaging Biomarkers of Alzheimer's Disease

K.K. Petersen[1], **A. Ezzati**[1], **R.B. Lipton**[1], **B.A. Gordon**[2], **J. Hassenstab**[2], **J.C. Morris**[2], **E. Grober**[1]

1. Saul R. Korey Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA

2. Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA

Abstract

OBJECTIVE: To investigate cerebrospinal fluid (CSF) and neuroimaging correlates of Stages of Objective Memory Impairment (SOMI) based on Free and Cued Selective Reminding Test (FCSRT) performance, and to evaluate the effect of APOE ε4 status on this relationship.

METHODS: Data from 586 cognitively unimpaired individuals who had FCSRT, CSF, and volumetric magnetic resonance imaging (MRI) measures available was used. We compared CSF measures of β-amyloid (Aβ42/Aβ40 ratio), phosphorylated tau (p-Tau181), total tau (t-Tau), hippocampal volume, and PIB-PET mean cortical binding potential with partial volume correction (MCBP) among SOMI groups in the whole sample and in subsamples stratified by APOE ε4 status.

RESULTS: Participants had a mean age of 67.4 (SD=9.1) years, had 16.1 (SD=2.6) years of education, 57.0% were female, and 33.8% were APOE ε4 positive. In the entire sample, there was no significant difference between SOMI stages in Aβ42/Aβ40 ratio, p-Tau181, t-Tau, or PIB-PET MCBP when adjusted for age, sex, and education. However, higher SOMI stages had smaller hippocampal volume (F=3.29, p=0.020). In the stratified sample based on APOE ε4 status, in APOE ε4 positive individuals, higher SOMI stages had higher p-Tau181 (F=2.94, p=0.034) higher t-Tau (F=3.41, p=0.019), and smaller hippocampal volume (F=5.78, p<0.001). There were

Corresponding Author: Kellen K. Petersen, Albert Einstein College of Medicine, 1225 Morris Park Avenue, Bronx, NY 10461, USA, kellen.petersen@einsteinmed.edu.

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no significant differences in CSF or imaging biomarkers between SOMI groups in the APOE ε4 negative subsample.

CONCLUSION: Cognitively normal older individuals with higher SOMI stages have higher in-vivo tau and neurodegenerative pathology only in APOE ε4 carriers. These original results indicate the potential usefulness of the SOMI staging system in assessing of tau and neurodegenerative pathology.

Keywords

APOE ε4; cerebrospinal fluid; cognition; SOMI; biomarkers

Introduction

In an effort to identify cognitive impairment as early as possible in the Alzheimer's Disease (AD) continuum and chart its progression to clinical dementia, a staging model named the Stages of Objective Memory Impairment (SOMI) system was previously proposed by us that describes the breakdown of episodic memory (1). SOMI consists of five sequential stages defined by free recall (FR) and total recall (TR) scores on the picture version of the Free and Cued Selective Reminding Test with immediate recall (pFCSRT+IR) as summarized in Table 1. SOMI was based on extensive literature mapping of FCSRT performance to clinical outcomes and biological markers (2–10). SOMI-1 and SOMI-2 are defined by reductions in FR that are remediable with cuing. Storage remains unimpaired until SOMI-3 when cuing is no longer effective, defining the core clinical memory phenotype of AD (11). By SOMI-4, storage impairment is consistent with incipient dementia.

The structural and molecular neuroimaging correlates of SOMI are promising in terms of their potential to facilitate secondary prevention trials and as a low-cost alternative to expensive methods of obtaining biomarker information (12). Cognitively normal (CN) participants from the Harvard Aging Brain Study (HABS) with both memory storage and retrieval deficits (SOMI-3/4) had smaller hippocampal volumes and higher entorhinal and inferior temporal tau burden than participants with no memory impairment (SOMI-0) or mild retrieval difficulty (SOMI-1). Amyloid deposition did not differ among SOMI stages. Among the β-amyloid positive (Aβ+) subgroup in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study, participants with both storage and retrieval impairments had higher amyloid deposition and smaller structural MRI volumes in the hippocampus, entorhinal cortex, and inferior temporal cortex in comparison with participants with only retrieval impairment (13).

The ε4 allele of the apolipoprotein E gene (APOE ε4) is the strongest known genetic risk factor for late onset AD. APOE ε4 genotype is associated with increased Aβ burden and may be associated across biomarkers (14–18). Recent studies evaluating the relationship between APOE ε4, neuroimaging, and episodic memory in cognitively normal (CN) individuals have identified important interactions between AD-biomarkers and memory function as a function of APOE ε4 status (19–21). In APOE ε4 carriers but not non-carriers, higher Aβ levels as measured by PET imaging were associated with lower memory scores (19, 20). Another study showed that APOE ε4 carriers had significantly more entorhinal and

hippocampal tau pathology as measured by PET in comparison with non-carriers, and was also independent of cortical Aβ and clinical status (21, 22). Few studies have investigated APOE ε4-related effects on biomarkers of amyloid, tau, and neurodegeneration (ATN) and their interactive effects on memory function in the same sample.

The Knight Alzheimer Disease Research Center (ADRC) has a large sample of CN older adults, with complete neuropsychological evaluations, structural imaging, CSF collection, and APOE ε4 genotyping, which allows us to compare the effect of APOE ε4 genotype on biomarkers among individuals with different levels of memory function as measured by SOMI stages. In this study, we aimed to examine the association of SOMI stages with cerebrospinal fluid (CSF) biomarkers and hippocampal atrophy with a focus on APOE ε4 status. We hypothesized that SOMI stage would be associated with CSF markers and hippocampal atrophy, primarily in APOE ε4 carriers.

Methods

Participants

We used data from participants enrolled in longitudinal studies of normal aging and dementia from the Charles F. and Joanne Knight Alzheimer Disease Research Center (ADRC) at Washington University in St. Louis, Missouri. Details about recruitment procedures have been reported previously (23). Study protocols were approved by the Washington University institutional review board, and written informed consent was obtained from all participants or their caregivers at the time of participation. This current study is approved by the institutional review board at Albert Einstein College of Medicine and uses a subset of individuals from the Knight ADRC participants that meet the eligibility criteria (see Subsection 2.2). No new data was collected as part of this study.

Eligibility criteria

A total of 586 participants met eligibility criteria for this study. Participants had normal cognition, defined by global CDR score of 0, at their visit nearest to when CSF was obtained. For each participant, we selected the cognitive scores closest to when CSF was collected. Additional inclusion criteria were having structural MRIs within 2 years of CSF measurement. A subset of 295 participants had PIB performed within 2 years of the CSF measurement. Supplementary Figure 1 provides a flow chart of study participants.

Clinical assessment

All participants are followed annually and undergo annual clinical and neuropsychological assessments. Participant are assessed by experienced clinicians, who assign Clinical Dementia Rating (CDR®) to individuals based on neurological examinations, interviews with participant, and separately with an informant who knows the patient (24). A CDR ≥ 0.5 indicates clinically significant cognitive impairment (24). Participants who had CDR = 0 were used for this study.

The picture version of the FCSRT with Immediate Recall (pFCSRT+IR) was administered as part of the standard Knight ADRC cognitive assessment. In the encoding phase, participants

identify pictured items (e.g., grapes) in response to category cues (e.g., fruit) that are used in the test phase to prompt recall of items not retrieved by free recall (25). Scores includes free recall (FR) alone (range 0–48) and total recall (TR), the sum of FR and cued recall. Participants were stratified into different SOMI subgroups using the score ranges of FR and TR as shown in Table 1. A total of 16 individuals (2.7% of total population) could not be classified by the SOMI system because their retrieval was impaired but their storage was unimpaired (RISU).

Cerebrospinal fluid biomarkers

CSF sampling procedures are described previously (26). In brief, lumbar puncture was done by experienced neurologists at 8 AM after an overnight fast. CSF levels of Aβ40, Aβ42, phosphorylated tau (p-Tau181), and total tau (t-Tau) were measured using ELISA (INNOTEST, Fujirebio (formerly Innogenetics)). CSF levels of Aβ42 and the Aβ42/Aβ40 ratio (indicative of amyloid deposition) are reduced in AD, whereas biomarkers of tauopathy (p-Tau181) and neurodegeneration (t-Tau) are elevated (27).

Following the traditional ATN framework, amyloid status (Aβ negative = Aβ− or Aβ positive = Aβ+) was defined using a cutoff value of 0.0673pg/ml for Aβ42/Aβ40 ratio (28, 29). Whether tau pathology was abnormal (T+) or normal (T−) was determined by a cutoff value of 44.3 pg/ml for CSF p-Tau181 level. Presence or absence of global neurodegeneration (N+ or N−, respectively) was defined using a cutoff value of 335 pg/ml for CSF t-Tau level. All cutoff values were obtained using receiver operating characteristic (ROC) and concordance analysis for PET imaging (28–31).

Imaging Biomarkers

Volumetric MRI. FreeSurfer 5.3 (freesurfer.net) was used for automated volumetric segmentation to identify regions of interest for further analysis. Hippocampal volumes were adjusted for head size with a regression approach and summed across hemispheres. A cut-off value of 6.723 cm^3 was used to define hippocampal atrophy and AD-related neurodegeneration (32).

Pittsburgh compound B uptake (PIB) measurement. PET fibrillar Aβ imaging was performed for a subset of participants and processed as previously described.33 In brief, a 60-minute dynamic scan was acquired after injection of about 10 mCI of [11C] Pittsburgh compound B (PIB) (34). Reconstructed PET frames were corrected for motion, summed, and coregistered to an anatomical MRI performed in a separate imaging session. Three-dimensional regions of interest (ROIs) were created yielding regional time-activity curves. Using the cerebellum ROI data as the reference tissue input function, a time activity curve for each ROI is analyzed for specific PiB binding. The slope of each curve reflects the tracer distribution volume in the tissue of interest relative to the input function. A binding potential (BP) value reflecting the ROI binding value proportional to the number of binding sites for each ROI is calculated using the following equation:

$$\mathrm{BP} = \text{distribution volume} - 1.$$

The mean cortical BP with partial volume correction (MCBP) is obtained by taking the mean of the BPs from brain regions known to have high uptake among participants with AD dementia: the prefrontal cortex, gyrus rectus, lateral temporal cortex, and precuneus (33). To correct for partial volume effects a regional spread function-based technique was used (35, 36).

Statistical analyses

Statistical analyses were completed with MATLAB (version 2021a). Sample characteristic differences among SOMI groups were examined with $\chi 2$ tests for categorical variables and analyses of variance for continuous variables (ANOVA, 2-sided, $p<0.05$). We implemented multiple regression models with and without SOMI* APOE ε4 interaction terms to test for interactions between SOMI stages and APOE ε4 status. We used analysis of covariance (ANCOVA) to compare biomarker values of SOMI groups, stratified by APOE ε4 status, with age, sex, education, and APOE ε4 status as covariates. Finally, we performed additional analysis as previously described on Aβ− and Aβ+ subgroups. As the sample size was small for higher SOMI stages, and to increase our power to detect differences between groups, we combined SOMI-3/4 groups (groups with storage impairment) for the purpose of analyses.

Results

Sample Characteristic

Participants had a mean age of 67.4 years (SD=9.1, range 43–91), had 16.1 years of education (SD=2.6), 57.0% were women, and 33.8% were APOE ε4 positive. Mean FR was 30.5 (SD=5.9) and mean TR was 47.8 (SD=1.0). The median difference between CSF collection and administration of cognitive tests was 0.21 years (range: −1.16 – 1.19 years). Table 2 summarizes characteristics of the entire sample and characteristics of participants based on their SOMI stages.

Participants in higher SOMI stages were older ($F=11.7$, $p<0.001$) and more likely to be female ($\chi^2=35.2$, $p<0.001$). SOMI groups did not differ in education, race, or relative frequency of APOE ε4 alleles.

Supplementary Table 1 summarized characteristics of the sample stratified by APOE ε4 status and SOMI stages. There was no difference in any of the demographic or neuropsychological variables between APOE ε4 carriers and non-carriers; however, in comparison with APOE ε4 carriers, non-carriers had significantly higher Aβ42/Aβ40 levels ($p<0.001$) as well as significantly lower levels of p-Tau181 ($p<0.001$) and t-Tau ($p<0.001$). Supplementary Table 2 summarizes ATN biomarker status of study participants based on CSF measures.

SOMI and CSF biomarkers

Analysis of covariance (with age, sex, education, and APOE ε4 status as covariates) in the entire sample showed there was no significant difference between SOMI stages in Aβ42/Aβ40 ratio, p-Tau181, or t-Tau (Figure 1).

To investigate the interaction between APOE ε4 status and SOMI, multiple regression was performed where the dependent variables were CSF measures and the independent variables were SOMI, age, sex, education, and APOE ε4 status. Models were run with and without an interaction term between SOMI and APOE ε4 status and results can be seen in Table 3. For Aβ42/Aβ40 ratio as the outcome the APOE ε4*SOMI-2 interaction was marginally significant (p=0.062), for p-Tau181 the APOE ε4*SOMI-3/4 interaction was significant (p=0.007), and for t-Tau both APOE ε4*SOMI-1 (p=0.024) and APOE ε4*SOMI-3/4 (p=0.039) interactions were significant.

When stratified by APOE ε4 status, analysis of covariance in the APOE ε4 negative subsample showed there was no significant difference between SOMI stages in the Aβ42/Aβ40 ratio, p-Tau181, or t-Tau. However, in APOE ε4 positive individuals, there were significant differences in p-Tau181 between SOMI stages (F=2.94, p=0.034) such that post-hoc analysis found SOMI-0 and SOMI-1 had significantly lower levels of p-Tau181 than SOMI-3/4 (p=0.005 and p=0.026, respectively). Similarly, for APOE ε4 positive individuals, ANCOVA found differences in t-Tau between SOMI stages (F=3.41, p=0.019). SOMI-1 and SOMI-3/4 had significantly higher levels of t-Tau than SOMI-0 (p=0.016 and p=0.018, respectively). Figure 2 shows plots, stratified by APOE ε4 status, of the mean of Aβ42/Aβ40, p-Tau181, t-Tau, and hippocampal atrophy for each SOMI group.

SOMI and neuroimaging biomarkers

Analysis of covariance in the entire sample was indicative of hippocampal atrophy in higher SOMI stages (F=3.29, p=0.020). Pairwise comparison showed that SOMI-3/4 had smaller hippocampal volume than both SOMI-0 (p=0.045) and SOMI-1 (p=0.014), and that SOMI-2 had smaller hippocampal volume compared to SOMI-1 (p=0.022). There were no significant differences between other groups.

As was done with CSF measures, multiple regression models were run with and without an interaction term between SOMI and APOE ε4 status. The interaction term APOE ε4*SOMI-3/4 was found to be significantly associated with hippocampal atrophy (p = 0.001).

When stratified by APOE ε4 status, ANCOVA found no significant difference in hippocampal volume between SOMI stages for the APOE ε4 negative subsample (F=1.21, p=0.306), but there were significant differences in the APOE ε4 positive subsample (F=5.78, p<0.001). Post-hoc analysis found that SOMI-3/4 had smaller hippocampal volume than SOMI-0 (p<0.001), SOMI-1 (p<0.001), and SOMI-2 (p=0.028), and SOMI-2 had smaller hippocampal volume in comparison with SOMI-1 (p=0.022). SOMI-2 marginally missed significance in comparison with SOMI-0 (p=0.077) and SOMI-1 (p=0.075). There were no significant differences between other groups.

Next, we looked at differences in PIB-PET MCBP among SOMI subgroups in the subsample of participants who completed PIB-PET (N=295). Multiple regression models with and without interaction terms between SOMI and APOE ε4 were performed (Table 3) and the interaction term APOE ε4*SOMI-2 was found to be marginally significant (p=0.053). ANCOVA analysis indicated that there was no significant difference between

these groups in PIB-PET MCBP (F=0.52, p=0.667). Characteristics of this sample are summarized in Supplementary Table 3. Box plots and mean plots comparing values across SOMI stage for PIB-PET MCBP can be found in Supplementary Figure 2.

APOE ε4 status, SOMI stage, and biomarkers

We evaluated biomarker differences between APOE ε4 negative and positive groups in the entire sample as well as SOMI subsamples. ANCOVA analysis in the entire sample indicated that in comparison with APOE ε4 negative group, APOE ε4 positive group had lower CSF Aβ42/Aβ40 ratio (F=137.2, p<0.001) and higher p-Tau181 (F=17.3, p<0.001), t-Tau (F=8.7, p=0.003), and PIB-PET MCBP (F=25.8, p<0.001) but there was no difference between their hippocampal volume. Summary of results for differences in biomarkers based on APOE ε4 status in the sample stratified based on SOMI stage is presented in Table 4 and Supplementary Figures 3.

Multiple regression models were on APOE ε4-stratified subsamples (Supplementary Table 4). In the APOE ε4 negative group, SOMI was not found to be significantly associated with any CSF or neuroimaging biomarkers. In the APOE ε4 positive group, SOMI-3/4 was associated with p-Tau181 (p = 0.010), SOMI-1 (p = 0.012) and SOMI-3/4 (p = 0.035) were associated with t-Tau, and SOMI-3/4 was associated with HVa (p<0.001).

Amyloid status, SOMI stage, and biomarkers

Finally, we evaluated biomarker differences between Aβ− and Aβ+ groups, defined using the cutoff for the Aβ42/Aβ40 ratio (Supplementary Figure 4). Analysis of covariance (ANCOVA with age, sex, education, and APOE ε4 status as covariates) showed there was no significant difference between SOMI stages in Aβ42/Aβ40 ratio, p-Tau181, t-Tau, or HVa in both the Aβ− and Aβ+ groups (Supplementary Figure 5). Similarly, in the subsample of individuals with PIB-PET MCBP data, there was no significant difference in PIB-PET MCBP between SOMI stages.

Additionally, stratification by APOE ε4 status was done in both the Aβ− and Aβ+ groups to assess differences across SOMI stage (Supplementary Figures 6 and 7). ANCOVA found no differences in biomarkers across SOMI stage in the Aβ−, APOE ε4 negative subsample. In the Aβ+, APOE ε4 negative subsample the only significant difference was determined in Aβ42/Aβ40 ratio (F = 3.0, p = 0.039).

In the Aβ−, APOE ε4 positive group, only marginally significant differences were found across SOMI stage for t-Tau (F = 2.7, p =0.050) and HVa (F = 2.6, p = 0.055). In the Aβ+, APOE ε4 positive group, significant differences for HVa were found across SOMI stage (F = 5.92, p = 0.001) and marginally significant differences were found across SOMI stage for Aβ42/Aβ40 (F = 2.7, p = 0.053) and p-Tau181 (F = 2.2, p = 0.093).

Multiple regression models were on Aβ-stratified subsamples (Supplementary Table 5). In models without APOE ε4*SOMI interaction terms for Aβ− group, SOMI stages were not found to be significantly associated with any biomarkers. In models with interaction terms of the Aβ− group, APOE ε4*SOMI-1 was associated with t-Tau (p = 0.045) and APOE ε4*SOMI-3/4 was associated with HVa (p = 0.019). In the Aβ+ group, for models without

interactions terms SOMI-2 was associated with Aβ42/Aβ40 (p = 0.003), HVa (p = 0.034), and PIB-PET (p = 0.042). In the same group, for models with interaction terms, SOMI-2 was associated with Aβ42/Aβ40 (p = 0.006) and APOE ε4*SOMI-3/4 was associated with p-Tau181 (p = 0.020), t-Tau (p = 0.038), and HVa (p = 0.004).

Discussion

The present study provides evidence that the association of episodic memory impairment measured by SOMI with hippocampal atrophy and CSF measures of amyloid, tau, and neurodegeneration depends on APOE ε4 status. APOE ε4 non-carriers had significantly higher Aβ42/Aβ40 levels and lower levels of p-Tau181 and t-Tau compared to APOE ε4 carriers. Controlling for age, sex, education, and APOE ε4 status in the entire sample, no significant differences were found between SOMI stages in CSF biomarkers, but lower hippocampal volume was associated with higher SOMI stages. When stratified by APOE ε4 status, there were no significant differences between CSF biomarkers or hippocampal volume among SOMI stages in APOE ε4 non-carriers. In APOE ε4 carriers, there were significant differences between SOMI stages in p-Tau181, t-Tau, and hippocampal volume.

Our hypothesis that APOE ε4 carriers will have worse biomarker profiles and worse memory performance, was supported by the results in part. APOE ε4 carriers had moderately decreased Aβ42/Aβ40 levels, and increased p-Tau181 and t-Tau, smaller hippocampal volume, and worse memory performance when compared to APOE ε4 non-carriers (Figure 3). These results are largely consistent with other studies that evaluated association of APOE ε4 genotype with biomarkers and evaluated the effect of APOE ε4 on the relationship between AD-biomarkers and memory performance (37–40).

A recent study in two independent large cohorts showed that APOE ε4 genotype was associated with increased tau-PET uptake in the entorhinal cortex and hippocampus independently of Aβ (41). In another study in non-demented older adults from the Alzheimer's Disease Neuroimaging Initiative, Weigand et al. (38), showed that adjusting for tau levels, Aβ was not associated with memory performance and had no interaction with APOE ε4 status, but adjusting for Aβ levels, tau was associated with all cognitive domains. Furthermore, they showed that there was a stronger moderating effect of APOE ε4 on MTL tau and memory associations in APOE ε4 carriers regardless of Aβ status. Our results support the results of these studies. We found that amyloid levels measured by CSF or PIB-PET are not associated with SOMI stage regardless of APOE ε4 status, while CSF measures of p-Tau181 and t-Tau as well as hippocampal volume were different among SOMI stages in APOE ε4 carriers.

Based on one of the hypothetical models that Jack, et al. proposed for dynamic biomarkers of the Alzheimer's pathological cascade, an independently arising Aβ pathophysiology can accelerate an antecedent tauopathy (42). Since this model was proposed, substantial evidence is accumulated which supports that tau pathology accumulates in the brainstem and entorhinal cortex independently and, importantly, prior to Aβ (43–45). Furthermore, while effects of tau accumulation on neurodegeneration and cognitive dysfunction is accelerated by the presence of Aβ, its effect on cognition remain persistent even in the absence of Aβ

(46). Our results indicate that in cognitively normal APOE ε4 carriers, memory performance as measured by the SOMI system is not affected by Aβ levels, however it is affected by tau accumulation and neurodegeneration. Due to the cross-sectional nature of this study, we cannot make any causal conclusion about the relationship of memory performance and underlying neuropathology, however these findings warrant follow up research on Aβ-independent mechanisms of pathologic tau accumulation and neurodegeneration, including potential role of APOE ε4 in the pathological cascade.

In both the whole sample as well as SOMI stages stratifications, our analysis indicated that having an APOE ε4 allele is strongly associated with having higher amyloid. These findings are largely consistent with previous cross-sectional findings (26, 40). We found significant differences in CSF p-Tau181 and t-Tau between APOE ε4 negative and positive for the whole sample. While studies by Roe et al and Morris et al, did not report similar findings (26, 40) others have reported APOE ε4 positive individuals showing a trend toward increased tau accumulation over time (47). This might be partially explained by differences in sample selection, eligibility criteria for each study, and previous studies being underpowered.

The primary strength of this study was that we were able to evaluate biomarker differences based on the SOMI system using data from a large study at a single site, which benefits from a large collection of CSF, MRI, and PIB-PET biomarkers in a cognitively normal sample. However, there were some limitations. We used a convenience sample of older adults who were willing to be followed longitudinally and were able to tolerate MRI, PET-BIP, and lumbar punctures, which reduces the generalizability of the findings to the larger population. Considering small sample size in some subgroups (e.g., SOMI-3/4), there should be caution in over-interpreting the results. Furthermore, we focused only on global measures of PIB-PET, one volumetric MRI measure (hippocampus) and CSF biomarkers, which by nature lack spatial information about the underlying pathology. Extending analysis to include measures of amyloid, tau, and neurodegeneration from different regions of brain will provide more insight into a mechanistic understanding of disease and influence of APOE ε4 genotype on disease expression and progression.

In conclusion, our results indicate that CN older individuals with higher SOMI stages have higher tau pathology and neurodegeneration though this effect of AD-related pathology was limited to APOE ε4 carriers. These original results indicate the potential usefulness of the SOMI staging system in assessing of tau and neurodegenerative pathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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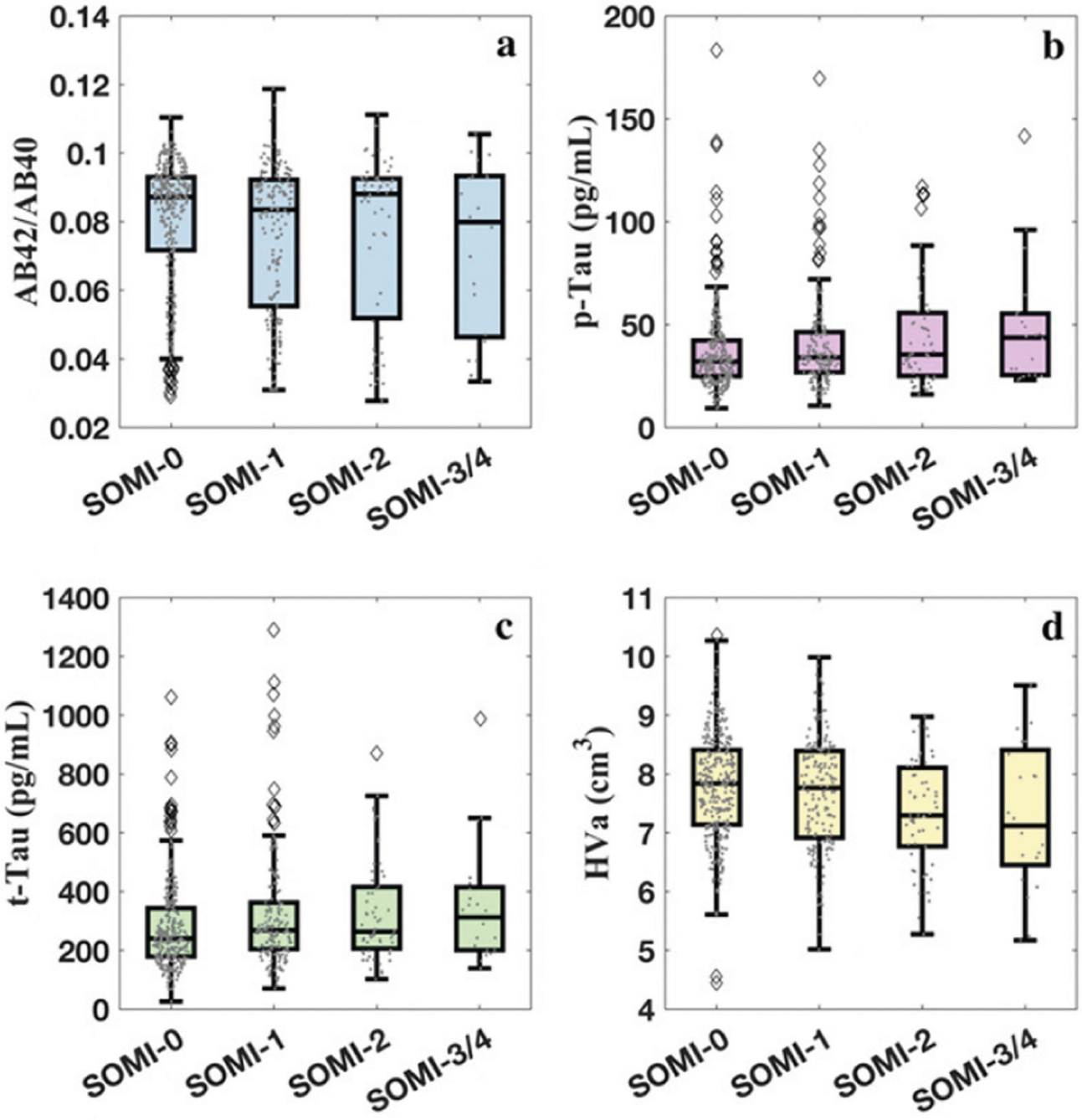

Figure 1.

Box plots comparing Aβ42/Aβ40 (a), p-Tau181 (b), t-Tau (c), and hippocampal atrophy (d) across different SOMI groups

Outliers depicted by diamond markers.

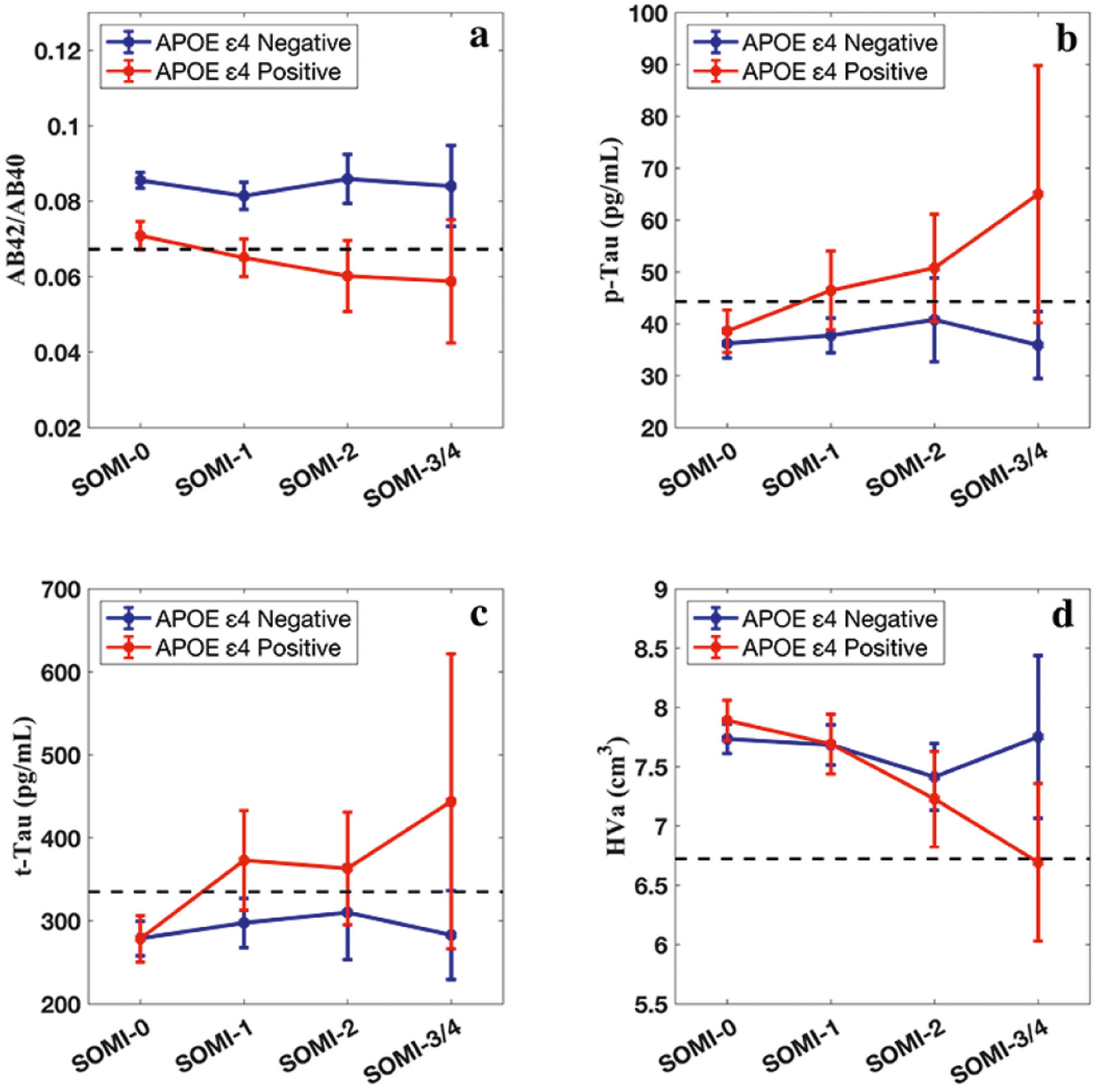

Figure 2.

Plots, stratified by APOE ε4 status, of the mean of Aβ42/Aβ40 (a), p-Tau181 (b), t-Tau (c), and hippocampal atrophy (d) for each SOMI group with standard mean error bars Dashed lines represent proposed diagnostic cut-offs for each biomarker.

Table 1.

Sample characteristics by SOMI stage.

	Entire	SOMI-0	SOMI-1	SOMI-2	SOMI-3/4	RISU
N	586	311	179	59	21	16
Age	67.4 (9.1)	65.2 (9.3)	69.3 (8.1)	70.4 (7.4)	67.7 (9.0)	76.4 (8.7)
Education	16.1 (2.6)	16.1 (2.5)	16.2 (2.6)	15.4 (2.8)	15.2 (2.9)	16.4 (2.8)
Female, N (%)	334 (57.0%)	214 (68.8%)	77 (43.0%)	27 (45.8%)	11 (52.4%)	5 (31.3%)
***APOE4*+, N (%)**	198 (33.8%)	104 (33.4%)	60 (33.5%)	22 (37.3%)	9 (42.9%)	3 (18.6%)
White, N (%)	525 (89.6%)	280 (90.0%)	160 (89.4%)	50 (84.8%)	19 (90.5%)	16 (100.0%)
MMSE	29.2 (1.2)	29.4 (0.9)	29.0 (1.4)	29.1 (1.1)	28.4 (1.4)	28.1 (2.2)
FSCRT-FR	30.5 (5.9)	35.0 (3.1)	27.8 (1.8)	22.3 (1.4)	21.9 (6.1)	17.0 (1.6)
FSCRT-TR	47.8 (1.0)	48.0 (0.2)	47.9 (0.3)	47.8 (0.4)	44.1 (3.2)	47.6 (0.5)
TMT-B	77.7 (31.8)	72.0 (30.1)	80.4 (31.1)	89.7 (33.2)	96.3 (40.3)	91.9 (28.45)
CSF Aβ42/Aβ40	0.078 (0.020)	0.081 (0.018)	0.076 (0.021)	0.076 (0.024)	0.073 (0.025)	0.074 (0.023)
CSF p-Tau, pg/mL	39.7 (22.8)	37.0 (20.8)	40.7 (23.3)	44.5 (25.2)	48.4 (29.4)	52.6 (27.9)
CSF t-Tau, pg/mL	304.1 (174.5)	278.7 (149.8)	322.8 (194.9)	329.9 (171.6)	352.0 (203.0)	430.4 (251.3)
HVa, cm ^{3}	7.67 (0.96)	7.79 (0.90)	7.69 (0.95)	7.34 (0.90)	7.30 (1.23)	6.79 (1.02)

Note. [1]Values are mean (SD) unless otherwise noted. *Abbreviations*: Aβ= β-amyloid; RISU= retrieval impaired storage unimpaired; *APOE4*= apolipoprotein E ε4 allele; FSCRT= free and cued selective reminding test, FCSRT-FR: Free-recall part of FCSRT; FCSRT-TR=total recall part of the FCSRT; MMSE= mini-mental state Exam; TMT-B=Part B of the Trail Making Test (higher scores = worse performance); HVa=adjusted hippocampal volume; RISU=retrieval impaired storage unimpaired; t-tau=total Tau; p-Tau=phosphorylated tau

Table 2.

Multiple regression models for five using SOMI, *APOE4* status, age, sex, and education as dependent variables and biomarker outcomes as dependent variables. Each outcome has a model with and without interaction terms between SOMI and *APOE4* where SOMI-0 is the reference stage for SOMI.

		Predictors																			
Outcome	**Interaction Term**	***APOE4***		**SOMI-1**		**SOMI-2**		**SOMI-3/4**		**APOE4*SOMI-1**		**APOE4*SOMI-2**		**APOE4*SOMI-3/4**		**Age**		**Sex**		**Education**	
		β	**p**	**β**	**p**	**β**	**p**	**β**	**p**	**β**	**p**	**β**	**p**	**β**	**p**	**β**	**p**	**β**	**p**	**β**	**p**
CSF Aβ42/Aβ40	**N**	−0.87	<0.001	−0.11	0.205	−0.01	0.929	−0.20	0.295							−0.32	<0.001	−0.08	0.327	0.01	0.694
	Y	−0.78	<0.001	−0.09	0.404	0.16	0.299	0.00	0.999	−0.06	0.716	−0.47	0.062	−0.50	0.207	−0.31	<0.001	−0.07	0.373	0.01	0.758
CSF p Tau	**N**	0.32	<0.001	0.04	0.668	0.15	0.282	0.39	0.065							0.32	<0.001	0.10	0.234	−0.03	0.524
	Y	0.17	0.137	−0.05	0.642	0.05	0.763	−0.09	0.748	0.25	0.167	0.26	0.337	1.14	0.007	0.32	<0.001	0.08	0.350	−0.02	0.565
CSF t Tau	**N**	0.24	0.003	0.15	0.092	0.14	0.318	0.32	0.126							0.28	<0.001	0.10	0.237	−0.04	0.291
	Y	0.05	0.637	0.01	0.922	0.05	0.765	−0.04	0.891	0.42	0.024	0.24	0.378	0.88	0.039	0.28	<0.001	0.08	0.335	−0.04	0.295
HVa	**N**	−0.04	0.559	0.10	0.228	−0.18	0.137	−0.38	0.051							−0.51	<0.001	−0.09	0.252	0.02	0.572
	Y	0.07	0.479	0.15	0.144	−0.09	0.543	0.15	0.541	−0.12	0.472	−0.25	0.320	−1.26	0.001	−0.51	<0.001	−0.07	0.391	0.02	0.643
PIB-PET MCBP	**N**	0.57	<0.001	0.15	0.244	0.11	0.593	0.17	0.654							0.34	<0.001	−0.09	0.440	−0.02	0.771
	Y	0.52	0.001	0.18	0.240	−0.15	0.542	0.10	0.829	−0.08	0.749	0.81	0.053	0.21	0.789	0.34	<0.001	−0.09	0.422	−0.01	0.920

β = standardized regression coefficient; CSF = cerebrospinal fluid; HVa = adjusted hippocampal volume; PIB-PET MCBP = Pittsburgh compound B uptake positron emission tomography of the mean cortical binding potential with partial volume correction.

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Table 3.

Results from performing ANCOVA on the entire sample, as well as stratified by SOMI stage, showing differences based on *APOE4* status (with age, sex, and education as covariates).

	CSF Aβ42/Aβ40		CSF p-Tau		CSF t-Tau		HVa		PIB-PET MCBP	
	F	p	F	p	F	p	F	p	F	p
Entire	137.22	<0.001	17.30	<0.001	8.70	0.003	0.55	0.458	25.87	<0.001
SOMI-0	68.33	<0.001	2.37	0.124	0.02	0.588	0.61	0.435	13.32	<0.001
SOMI-1	31.71	<0.001	7.24	0.007	6.96	0.009	0.20	0.653	4.02	0.048
SOMI-2	23.16	<0.001	2.25	0.138	1.25	0.266	0.50	0.479	6.41	0.019
SOMI-3/4	7.43	0.014	4.27	0.055	2.53	0.131	3.49	0.079	0.72	0.551

Table 4.

Results from performing ANCOVA on the entire sample, as well as stratified by SOMI stage, showing differences based on APOE ε4 status (with age, sex, and education as covariates)

	CSF Aβ42/Aβ40		CSF p-Tau181		CSF t-Tau		HVa		PIB-PET MCBP	
	F	p	F	p	F	p	F	p	F	p
Entire	137.22	<0.001	17.30	<0.001	8.70	0.003	0.55	0.458	25.87	<0.001
SOMI-0	68.33	<0.001	2.37	0.124	0.02	0.588	0.61	0.435	13.32	<0.001
SOMI-1	31.71	<0.001	7.24	0.007	6.96	0.009	0.20	0.653	4.02	0.048
SOMI-2	23.16	<0.001	2.25	0.138	1.25	0.266	0.50	0.479	6.41	0.019
SOMI-3/4	7.43	0.014	4.27	0.055	2.53	0.131	3.49	0.079	0.72	0.551