

SHORT REPORT

Neuroimaging correlates of Stages of Objective Memory Impairment (SOMI) system

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Abstract

Introduction: To assess the relationship between memory performance defined by the Stages of Objective Memory Impairment (SOMI) system and the Alzheimer's disease (AD) ATN (amyloid beta [A], pathologic tau [T], and neurodegeneration [N]) biomarker system.

Methods: We used data from the Harvard Aging Brain Study cohort to estimate the level of ATN biomarkers: amyloid beta (C-Pittsburgh compound B-positron emission tomography [PET]), tau (F-18-flortaucipir [FTP] PET), and neurodegeneration (magnetic resonance imaging volumetrics). We assessed the cross-sectional relationship of SOMI classification with global amyloid levels, entorhinal and inferior temporal tau deposition, and hippocampal atrophy.

Results: Participants 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 burden did not differ among SOMI stages.

Discussion: This pilot supports the close relationship between tau pathology and memory impairment across the AD continuum. SOMI may be useful to determine eligibility for randomized controlled trials prior to the assessment of biomarker status.

KEYWORDS

Alzheimer's disease, ATN biomarker system, Cued Selective Reminding Test, memory, preclinical Alzheimer's disease

1 | INTRODUCTION

We have proposed a staging model to describe the breakdown of episodic memory across the Alzheimer's disease (AD) continuum, named the Stages of Objective Memory Impairment (SOMI) system.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 S1](#) in supporting information. It 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

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Research in Context

- 1. Overarching goal:** To determine the relationship between memory performance defined by the Stages of Objective Memory Impairment (SOMI) system and Alzheimer's disease ATN (amyloid beta [A], pathologic tau [T], and neurodegeneration [N]) biomarker system.
- 2. Systematic review:** We did PubMed searches using the terms "Stages of Memory Impairment," SOMI, and Free and Cued Selective Reminding Test and reviewed those papers. As SOMI is a relatively new concept the literature focused on this staging system is limited. We also searched PubMed for biomarkers of ATN and memory using the following search terms: memory storage and retrieval, Alzheimer's disease biomarkers, amyloid, tau, neurodegeneration.
- 3. Interpretation:** Participants 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 burden did not differ among SOMI. The results support the close relationship between tau pathology and memory impairment across the AD continuum.
- 4. Future directions:** Based on these findings we believe that SOMI can be used as an initial screen to determine eligibility for randomized controlled trials (RCTs) prior to the assessment of biomarker status. This approach could increase the efficiency and decrease the cost of selecting samples for RCTs. SOMI may also provide an operational categorical cognitive outcome measure for clinical trials, which may be an alternative to mild cognitive impairment and/or dementia.

impairment is consistent with incipient dementia. Compared to participants with no memory impairment, participants classified into SOMI-3 and -4 stages were four times more likely to have positive AD neuropathology and nearly six times as likely to have more advanced Braak neurofibrillary tangle (NFT) pathology.¹²

In this brief report, we describe a pilot study exploring the association of the SOMI system with the *ante mortem* biomarkers in the current research Framework for AD: amyloid beta ($A\beta$) deposition, tau, and neurodegeneration (ATN).¹³ We used data from the Harvard Aging Brain Study (HABS) cohort to estimate the level of ATN biomarkers including $A\beta$ (C Pittsburgh compound B positron emission tomography [C-PiB-PET]), tau (F-18-flortaucipir [FTP] PET), and neurodegeneration (structural magnetic resonance imaging [MRI] volumetrics). We assessed the cross-sectional relationship of SOMI classification with global amyloid levels, entorhinal and inferior temporal tau deposition, and hippocampal atrophy. We hypothesized that higher SOMI stages

are associated with higher AD pathology. Based on prior pathologic correlations¹² we predicted that persons with impairment in memory storage (SOMI-3, -4) would have greater atrophy and more tau deposition compared to persons free of memory storage impairment (SOMI-1, -2).

2 | METHODS

2.1 | Participants

We used HABS data release 2.0 obtained in November 2020 (habs.mgh.harvard.edu). HABS is a longitudinal study of aging conducted at the Massachusetts General Hospital.¹⁴ The study was conducted using procedures approved by the Partners Human Research Committee. Participants provided written informed consent before undergoing any procedures.

A total of 191 participants met eligibility criteria for this study. Participants had normal cognition at the time of enrollment in the study, defined by global Clinical Dementia Rating (CDR) score of 0, scores above education-adjusted cutoffs on Logical Memory-II story A, and Mini-Mental State Examination (MMSE) > 25. Exclusion criteria included a history of alcohol/drug abuse, head trauma, or current serious medical/psychiatric illness. Because Tau-PET was introduced later to HABS, we used pFCSRT+IR data from the first year that Tau-PET data was available for each person. Additional inclusion criteria were having PiB-PET, and structural MRIs within 2 years of Tau-PET.

2.2 | Neuropsychological evaluation

Participants underwent comprehensive annual neuropsychological testing. Our primary focus was on the pFCSRT+IR.¹⁵ FR and TR scores from the pFCSRT+IR closest to the Tau-PET were used to classify participants into different SOMI subgroups (Table 1).

2.3 | Neuroimaging biomarkers

For PiB-PET, we used a composite PiB-PET distribution volume ratio (DVR) measure of cortical $A\beta$ burden, which consisted of frontal, lateral, and retrosplenial tracer (FLR) uptake determined for each participant by calculating the median PiB uptake value across voxels in the precuneus, rostral anterior cingulate, medial orbitofrontal, superior frontal, rostral middle frontal, inferior parietal, inferior temporal, and middle temporal regions of interest from both hemispheres divided by the median PiB-PET DVR from cerebellar gray matter. The regions constituting the FLR are known to show elevated PiB binding in patients with AD dementia.¹⁶

For FTP-PET, we focused our analyses on two regions of interest, the entorhinal and inferior temporal cortices defined individually on each participant's MRI data. The entorhinal cortex is among the first regions to develop tau pathologic changes, even in the absence of $A\beta$. The

TABLE 1 Sample characteristics based on SOMI status

	Study Group							P-value
	ALL (n = 192)	SOMI-0 (n = 112)	SOMI-1 (n = 47)	SOMI-2 (n = 13)	SOMI-3 (n = 10)	SOMI-4 (n = 5)	RISU (n = 5)	
Age (years)	76.56 (6.22)	75.05 (5.52)	77.86 (6.91)	79.78 (5.21)	79.07 (7.05)	83.1 (2.04)	78.35 (8.05)	.001
Education (years)	16.14 (3.04)	16.46 (2.87)	15.62 (3.33)	15.31 (3.04)	16.00 (2.49)	17.60 (1.67)	14.80 (5.02)	.306
Female, no. (%)	115 (59.9)	70 (62.5)	28 (59.6)	4 (30.8)	6 (60.0)	3 (60)	4 (80)	.336
APOE ϵ 4, %	28.9	27.9	32.6	7.7	30.0	40.0	60.0	.325
MMSE	29.10 (1.19)	29.29 (1.09)	29.02 (1.26)	28.69 (1.25)	28.7 (1.06)	27.00 (1.00)	29.80 (10.97)	<.001
Digit symbol	46.93 (10.9)	49.3 (10.47)	45.21 (10.84)	43.69 (11.28)	38.2 (9.37)	38.40 (9.01)	45.00 (10.9)	.003
A β FLR DVR (PVC)	1.21 (0.21)	1.19 (0.20)	1.21 (0.21)	1.27 (0.32)	1.32 (0.27)	1.32 (0.21)	1.36 (0.24)	.124
EC FTP-PET SUVR (PVC)	1.12 (0.12)	1.10 (0.11)	1.12 (0.12)	1.15 (0.13)	1.18 (0.15)	1.24 (0.12)	1.25 (0.12)	.007
IT FTP-PET SUVR (PVC)	1.20 (0.10)	1.18 (0.08)	1.21 (0.08)	1.22 (0.11)	1.26 (0.14)	1.39 (0.25)	1.30 (0.13)	<.001
aHV (cm ³)	7.17 (0.80)	7.35 (0.71)	7.13 (0.74)	7.01 (0.85)	6.38 (0.74)	5.76 (0.47)	7.02 (1.09)	<.001

Abbreviations: A β , amyloid beta; aHV, adjusted hippocampal volume; APOE, apolipoprotein E; DVR, distribution volume ratio; EC, entorhinal cortex; FLR, frontal, lateral, and retrosplenial tracer; FTP, flortaucipir F 18; IT, inferior temporal cortex; MMSE, Mini-Mental State Examination; PVC, partial volume correction; RISU, retrieval impaired storage unimpaired; SD, standard deviation; SOMI, Stages of Objective Memory Impairment; SUVR, standardized uptake value ratio.

^a Unless otherwise indicated, data are expressed as mean (SD). Retrieval impaired, storage unimpaired (RISU) individuals were not included in significance testing.

inferior temporal cortex is an established surrogate marker for neocortical hyperphosphorylated tau deposition; inferior temporal cortex FTP-PET shows the largest effect size between impaired and nonimpaired individuals as reported in previous studies.¹⁷

Structural MRI analysis was performed using FreeSurfer v5.1.¹⁸ We used hippocampal volume (HV) as a surrogate for neurodegeneration. HV was collapsed across hemispheres and adjusted for estimated total intracranial volume.

2.4 | Statistical analyses

Statistical analyses were completed with SPSS version 25. Sample characteristic differences among SOMI groups were examined with χ^2 tests for categorical variables and analyses of variance for continuous variables (2-sided, $P < .05$). We used analysis of covariance (ANCOVA) to compare biomarker values of SOMI groups with age, sex, and education. Post hoc uncorrected pairwise comparisons were performed to assess differences between groups defined by SOMI. Because 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 differentiated by the severity of memory storage impairment) for the purpose of analysis but present them separately in the tables.

3 | RESULTS

3.1 | Sample characteristics

Among 192 participants included in this study, 58.9% were women, with a mean age of 76.5 (standard deviation [SD] = 6.2) years, had

16.1 (SD = 3.0) years of education, and 28.9% were APOE ϵ 4-positive. In the whole population, mean pFCSRT-FR was 32.5 (SD = 6.7) and mean pFCSRT-TR was 47.6 (1.1). Table 1 summarizes sample characteristics and classification of participants into SOMI stages. Participants in higher SOMI stages had older age ($F = 5.3, P < .001$); however, SOMI groups did not differ on sex, education, or APOE ϵ 4 status. We identified five individuals who could not be classified by the SOMI system because their retrieval was impaired, but their storage was unimpaired (retrieval impaired storage unimpaired [RISU]).

3.2 | Imaging biomarkers

In ANCOVA, there was no significant difference in global amyloid SUVR between SOMI groups. Mean HV significantly differed by SOMI group ($F_{1,183} = 4.43, P = <.001$). Specifically, mean aHV for SOMI-3/4 was smaller than SOMI-0 ($t = -4.64, P <.001$) and SOMI-1 ($t = -3.95, P <.001$) and SOMI-2 ($t = -3.95, P = .003$). Mean inferior temporal tau SUVR was significantly different between SOMI groups ($F_{1,183} = 5.99, P <.001$), with SOMI-3/4 group having higher tau SUVR compared to SOMI-0 ($t = 4.06, P <.001$) and SOMI-1 ($t = 2.84, P = .005$). Mean entorhinal tau SUVR was significantly different between SOMI groups ($F_{1,183} = 3.67, P = .010$), with SOMI-3/4 having significantly higher tau SUVR compared to SOMI-0 ($t = 2.21, P = .028$) (Figure 1).

4 | DISCUSSION

Compared to participants without memory impairment (SOMI-0), HABS participants in SOMI-3/4 (the groups with storage impairment) had smaller HVs and greater entorhinal and inferior temporal tau

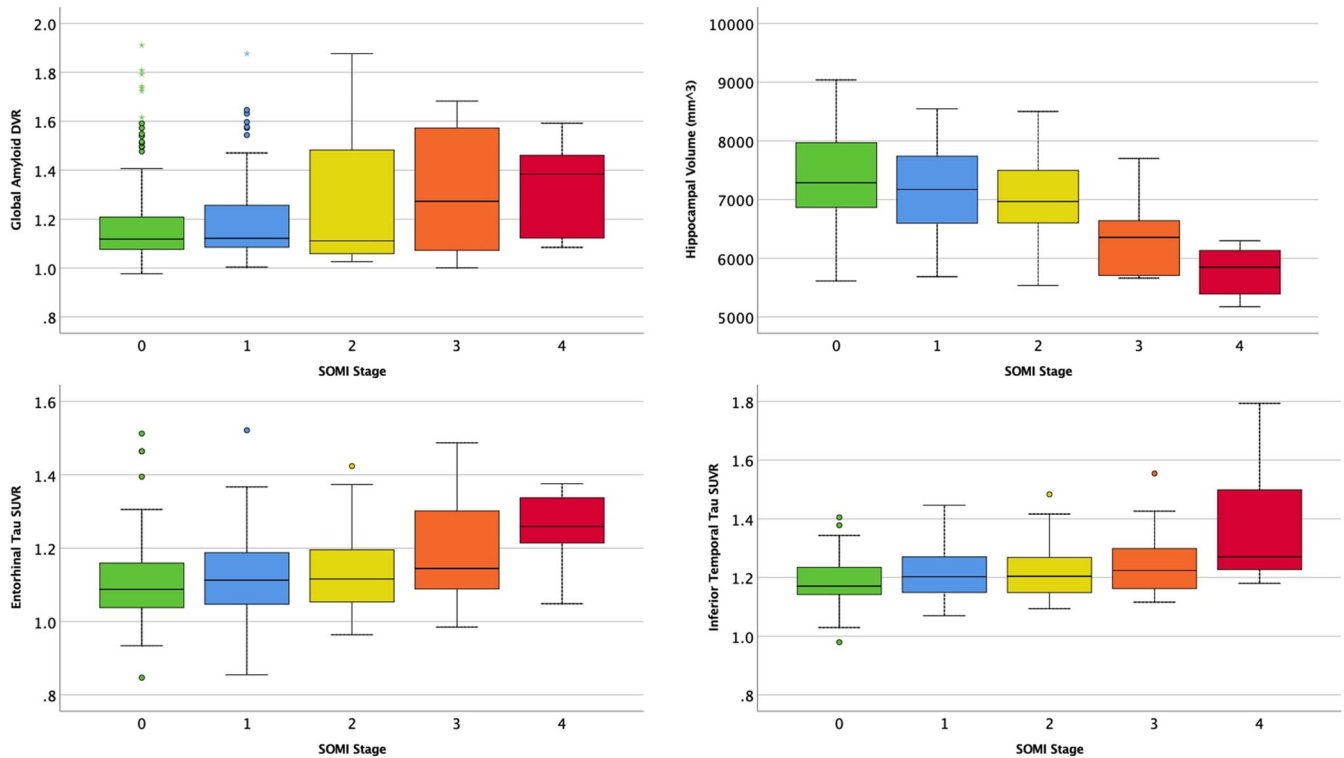


FIGURE 1 Biomarker levels by Stages of Objective Memory Impairment stage

deposition, surrogates for early AD-related tauopathy. The association of SOMI stage with amyloid did not reach statistical significance. These findings extend the previous report of associations of SOMI stages with AD neuropathology.¹² Neuropathological studies suggest that tau pathology and cognitive impairment across the AD continuum are weakly dependent on amyloid burden but is affected by region-specific tau pathology and neurodegeneration.¹⁹

SOMI-2 has high accuracy in identifying incident AD participants over 8 years of follow-up among participants from the Baltimore Longitudinal Aging Study free of dementia at baseline (personal communication). Eighty-five of the 1508 participants developed clinical AD over an average of more than 8 years of follow-up. Using Bayesian joint modeling and all observed assessments, the diagnostic accuracy of SOMI (82%) was superior to FR (74%) and FR+TR (71%) in identifying incident AD at 3, 5, and 7 years from baseline. Identifying participants at SOMI-2 had better sensitivity and specificity for predicting AD at all prediction windows over FR alone or the simple sum of FR and TR. SOMI's advantage is that it separates the measurement of impairment in retrieval from impairment in memory storage, facilitating the location of participants along the AD continuum.

The SOMI system could facilitate the execution of secondary prevention trials. SOMI could be used as an initial low-cost eligibility criterion to be followed with biomarkers of amyloid, tau, and neurodegeneration. Because SOMI-3 is highly associated with AD pathology, progression to SOMI-3 could provide a useful clinical outcome, potentially reducing the duration of active treatment in clinical trials. Categorical outcome measures based on SOMI could complement traditional con-

tinuously distributed change scores in cognitive measures or activities of daily living. SOMI-3 is better operationalized and may occur earlier than the endpoint of clinical diagnosis of AD dementia.

This pilot study is under-powered to provide reliable results because of the modest sample size among individuals classified into SOMI-3 and -4 stages. Because participants enrolled into HABS were all cognitively unimpaired at baseline, this was not surprising. The small sample size might be the reason for observing only trends in global amyloid deposition. A second limitation was that 5 of the 191 participants could not be classified into a SOMI stage because their retrieval was impaired but memory storage was unimpaired (RISU). This group showed relative preservation of hippocampal volume in the setting of amyloid and tau deposition and is deserving of further study. In the setting of clinical trials, in which screening with the FCSRT precedes biomarker assessment, excluding unclassified participants until we better understand them may improve outcomes by decreasing the number of participants who do not display the core memory AD phenotype.

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CONFLICTS OF INTEREST

E.G. receives a small royalty for commercial use of the Free and Cued Selective Reminding Test with Immediate Recall (FCSRT+IR). The test is available at no cost to researchers and clinicians. The Albert Einstein College of Medicines holds the copyright for the test.

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AUTHOR CONTRIBUTIONS

Ellen Grober, study concept and design; drafted manuscript. Ali Ezzati, study design and analysis; drafted manuscript. Aaron Schultz, contributed data. Kathryn V. Papp, collected data, edited manuscript. Dorene M. Rentz, collected data, edited manuscript. Reisa A. Sperling, PI HABS, edited paper. Keith A. Johnson, PI HABS, contributed data. Rebecca E. Amariglio, collected data, edited manuscript. Richard B. Lipton, edited paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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