Associations of Stages of Objective Memory Impairment With Amyloid PET and Structural MRI

The A4 Study

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Abstract

Background and Objectives

The goal of this work was to investigate the neuroimaging correlates of the Stages of Objective Memory Impairment (SOMI) system operationalized with the Free and Cued Selective Reminding Test (FCSRT), a widely used episodic memory measure.

Methods

The FCSRT begins with a study phase in which items (e.g., grapes) are identified in response to unique semantic cues (e.g., fruit) that are used in the test phase to prompt recall of items not retrieved by free recall. There are 3 test trials of the 16 items (maximum 48). Data from 4,484 cognitively unimpaired participants from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study were used. All participants had amyloid PET imaging, and a subset of 1,262 β-amyloid (Aβ)–positive had structural MRIs. We compared the Aβ mean cortical standardized uptake value ratio (SUVR) and volumetric measures of hippocampus, parahippocampal gyrus, entorhinal cortex, and inferior temporal cortex between the 5 SOMI stages.

Results

Participants had a mean age of 71.3 (SD 4.6) years; 40.6% were male; and 34.6% were APOE ε4 positive. Half had no memory impairment; the other half had retrieval deficits, storage limitations, or both. Analysis of covariance in the entire sample while controlling for age, sex, education, and APOE ε4 showed that individuals in higher SOMI stages had higher global amyloid SUVR ($p < 0.001$). Both SOMI-4 and -3 subgroups had higher amyloid SUVR than SOMI-0 and SOMI-1 subgroups. Individuals in higher SOMI stages had smaller hippocampal volume ($p = 0.003$), entorhinal cortex ($p < 0.05$), and inferior temporal lobes ($p < 0.05$), but there was no difference between parahippocampal gyrus volume of different SOMI stages. Pairwise comparison of SOMI subgroups showed that the SOMI-4, -3, and -2 subgroups had smaller hippocampal volume than the SOMI-0 and -1 subgroup. The SOMI-4 subgroup had significantly smaller entorhinal cortex and smaller inferior temporal lobe compared to all other groups.

Discussion

Presence of Alzheimer disease pathology is closely related to memory impairment according to SOMI stages in the cognitively unimpaired sample of A4. Results from structural MRIs suggest that memory storage impairment (SOMI-3 and -4) is present when there is widespread medial temporal lobe atrophy.

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Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **A4** = Anti-Amyloid Treatment in Asymptomatic Alzheimer's; **BLSA** = Baltimore Longitudinal Study of Aging; **EAS** = Einstein Aging Study; **FCSRT** = Free and Cued Selective Reminding; **FR** = free recall; **HABS** = Harvard Aging Brain Study; **LEARN** = Longitudinal Evaluation of Amyloid Risk and Neurodegeneration; **LMDR-IIa** = Logical Memory Delayed Recall; **MCI** = mild cognitive impairment; **PACC** = Preclinical Alzheimer Cognitive Composite; **pFCSRT + IR** = picture version of the FCSRT that includes Immediate Recall; **SOMI** = Stages of Objective Memory Impairment; **SUVR** = standardized uptake value ratio; **TR** = total recall.

Classification of Evidence
This study provides Class I evidence that, in normal older individuals, higher stages of memory impairment assessed with FCSRT were associated with higher amyloid imaging burden and lower volume of hippocampus, entorhinal cortex, and inferior temporal lobes.

Performance on the Free and Cued Selective Reminding (FCSRT) defines what is sometimes called the core clinical phenotype of Alzheimer disease (AD), a memory disorder that cannot be remediated by effective encoding and retrieval processes.[1,2] This phenotype is also called the amnestic syndrome of the hippocampal type because of its association with structural changes in medial temporal lobe, especially in the hippocampus and its subfields.[3] Many studies have reported strong associations among AD biomarkers, including neuroimaging and CSF biomarkers of amyloid, tau, and neurodegeneration, and the 2 main FCSRT measures: free recall (FR) and total recall (TR), the sum of FR and cued recall.[4-11]

The FCSRT is effective in identifying prevalent dementia; predicting incident mild cognitive impairment (MCI), dementia, and AD; and distinguishing between AD and non-AD dementias in various longitudinal aging cohorts[12-18] because the test controls the conditions of learning. In the study phase, participants are asked to identify items (e.g., grapes) in response to unique semantic cues (fruit); these cues are used in the test phase to prompt recall of items not retrieved by FR.[19] In contrast to passively listening as items are presented in conventional word list learning tests, the FCSRT requires active cognitive engagement and deep semantic processing. By coordinating the conditions of encoding and retrieval with category cues, the FCSRT optimizes encoding specificity and maximizes recall.[20]

While impaired FR has predicted incident AD in several longitudinal aging cohorts,[12,15,18,21] it is not optimized to identify β-amyloid (Aβ) status in cognitively normal individuals.[22] To overcome this limitation and to identify participants at an earlier point in the preclinical AD trajectory, we developed the Stages of Objective Memory Impairment (SOMI) system, which provides practical cutoffs for classification of participants into 1 of 5 stages by both FR and TR scores (Table 1).[23] Using Einstein Aging Study (EAS) data, we investigated whether the SOMI system is effective in identifying individuals at higher risk of incident AD. We showed that the first 3 SOMI stages (SOMI 0–2) typically precede clinical dementia by 5 to 8 years and reflect increasing retrieval difficulty, shown by declining FR in the context of intact TR. The next 2 SOMI stages (SOMI−3 and −4) precede clinical dementia by ≈1 to 3 years; in these stages, cuing fails to recover all of the items missed on FR. The advantage of SOMI over individual FR and TR scores is that it separates the measurement of retrieval impairment from memory storage impairment. Because these processes break down at different points in the predementia phase, the ability to distinguish between them allows an estimate of the participant's stage of illness along the AD continuum.

We have recently shown that participants whose picture version of the FCSRT that includes Immediate Recall (pFCSRT + IR) performance classified them as SOMI-2 (moderate retrieval impairment) were at higher risk of incident AD (personal communication, Drs. Lynn Kuo and Qi Qi, November 31, 2021). Of 1,508 participants from the Baltimore Longitudinal Study of Aging (BLSA) who were free of dementia at baseline, 85 individuals developed AD over an average of >8 years of follow-up. Using bayesian joint modeling and all observed assessments, we found that the diagnostic accuracy of SOMI (83%-86%) was superior to that of FR alone (72%) or the sum of FR + TR (71%) in identifying incident AD after 3, 5, and 7 years of follow-up, demonstrating the advantage of SOMI over individual FR and TR scores.

The SOMI system could be useful for screening in clinical trials if performance was associated with the antemortem biomarkers of amyloid, tau, and neurodegeneration used in the National Institute on Aging–Alzheimer's Association Research Framework.[24] Because the pFCSRT + IR is currently used in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study[25] and prerandomization data are publicly available, we were able to classify participants into SOMI stages. This

Table 1 SOMI Defined by FR and TR Score Ranges and Years to Diagnosis on the pFCSRT + IR

SOMI		FR scores	TR scores	Class of memory impairment
0	No memory impairment	>30	>46	None detected by pFCSRT + IR
1	Subtle retrieval impairment	25–30	>46	Free recall declines at a constant rate; storage is preserved
2	Moderate retrieval impairment	20–24	>46	Rate of FR decline doubles; executive dysfunction accelerates; storage is preserved
3	Subtle storage impairment	Any	45–46	Cuing fails to normalize TR
4	Significant storage impairment compatible with dementia	Any	33–44	Intellectual decline accelerates, heralding ADL impairment

Abbreviations: ADL = activities of daily living; FR = free recall; pFCSRT+IR = picture version of the Free and Cued Selective Reminding Test With Immediate Recall; SOMI = Stages of Objective Memory Impairment; TR = total recall.
A subset of participants do not meet the SOMI criteria as summarized in the table (FR < 20 and TR > 46). Their retrieval is impaired but storage is unimpaired.

allowed us to examine the association of SOMI with PET amyloid imaging and neurodegeneration using volumetric MRI. We predicted that participants in higher stages (SOMI-3 and -4) will have both higher global amyloid deposition and greater atrophy of hippocampal subregions than participants with no or mild impairment (SOMI-0 and -1).

Methods

Participants

A4 is a multicenter clinical trial being conducted in the United States, Canada, Australia, and Japan. Details of the screening process have been described previously.[18] In brief, participants eligible for screening were 65 to 85 years of age, were assessed to be cognitively normal, were living independently, and had a study partner who would be able to provide information on daily life cognitive function on an annual basis. Participants with very low (≤1.5 SD below norms) Logical Memory Delayed Recall (LMDR-IIa) scores were excluded to eliminate individuals with MCI. Participant with very high (>1.5 SD above norms) LMDR-IIa scores were excluded after screening visit 1 to enhance enrollment of participants at higher risk of imminent cognitive decline associated with AD pathology. Participants with a Clinical Dementia Rating score of 0, Mini-Mental State Examination score of 25 to 30, and LMDR-IIa score of 6 to 18 were eligible to proceed to florbetapir PET imaging.

FCSRT Assessment

In the study phase of pFCSRT + IR, participants were asked to search a card containing 4 line drawings (e.g., grapes) for an item that goes with a unique category cue (e.g., fruit). A stimulus card is included in the supplemental material (eFigure 1, links.lww.com/WNL/B804). After all 4 items were identified, immediate cued recall of just those 4 items was tested. The study phase was repeated for all 16 drawings. The test phase consisted of 3 trials of FR each followed by cued recall for items not retrieved by FR (maximum score 48). Participants were stratified into different SOMI subgroups with the use of the score ranges of FR and TR (sum of FR and cued recall) as shown in Table 1.

Amyloid PET Imaging

At screening, participants underwent amyloid PET imaging acquired with florbetapir F-18 and measured with a mean cortical standardized uptake value ratio (SUVR) with a whole cerebellar reference region.[26] We used a quantitative SUVR threshold of ≥1.10 to define amyloid positivity (Aβ+).[27]

Volumetric MRI

Only a subset of participants who were Aβ+ underwent structural MRI at baseline visit. Therefore, volumetric MRI measures were available for 1,262 Aβ+ participants. Volumetric measures of different cortical and subcortical regions were calculated automatically for all participants with Free-Surfer 6.0.[28] For the purpose of this study, volumetric measures were collapsed across hemispheres and adjusted for estimated total intracranial volume.

Statistical Analyses

Statistical analyses were completed with SPSS version 25 (SPSS Inc, Chicago, IL) and Python version 3.9 (Python Software Foundation, Fredericksburg, VA). Sample characteristic differences among SOMI groups were examined with χ^2 tests for categorical variables and analyses of variance for continuous variables (2 sided, $p < 0.05$). We used analysis of covariance to compare biomarker values of SOMI groups accounting for age, sex, education, and APOE ε4 status. Post hoc pairwise comparisons with Sidak correction were performed to assess differences between groups defined by SOMI, and values of $p > 0.005$ were considered significant (α = 0.05, 10 group comparisons).

Data Availability

Anonymized data are publicly available to any qualified investigator through the LONI website (ida.loni.usc.edu/login.jsp?project=ADNI).

Results

Sample Characteristics

A total of 4,484 cognitively unimpaired adults were included in this study, and volumetric MRI was available for 1,262 Aβ+

Table 2 Sample Characteristics

	SOMI stage						
	All (n = 4,484)	0 (n = 2,194)	1 (n = 1,210)	2 (n = 407)	3 (n = 463)	4 (n = 48)	RISU (n = 162)
Female, %	40.6	30.6	44.5	55.3	54.2	62.5	71.6
APOE ε4 positive, %	34.6	34.7	35.1	35.3	34.1	31.2	38.6
Aβ+, %	32.3	30.0	31.0	34.9	40.0	43.8	42.5
Age, mean (SD), y	71.3 (4.6)	70.4 (4.2)	71.5 (4.5)	72.9 (4.9)	72.3 (5.1)	74.1 (6.2)	73.5 (5.4)
Education (SD), y	16.5 (2.8)	16.6 (2.8)	16.5 (2.9)	16.5 (2.8)	16.3 (2.8)	15.9 (2.6)	16.8 (2.6)
PACC score, mean (SD)	0 (2.5)	1.2 (2.1)	−0.4 (1.9)	−2.1 (2.0)	−1.6 (2.4)	−3.9 (3.2)	−3.1 (1.9)
MMSE score, mean (SD)	28.7 (1.2)	28.9 (1.1)	28.7 (1.9)	28.4 (1.3)	28.4 (1.3)	27.9 (1.5)	28.5 (1.2)
LMIR score, mean (SD)	12.9 (3.1)	13.4 (3.1)	12.9 (3.1)	12.3 (3.0)	12.1 (3.0)	10.5 (2.7)	11.6 (2.9)
LMDR score, mean (SD)	11.7 (3.2)	12.2 (3.1)	11.6 (3.2)	10.8 (3.0)	10.6 (3.2)	8.9 (2.5)	10.3 (2.7)
Digit symbol score, mean (SD)	43.7 (8.9)	45.6 (8.7)	43.2 (8.6)	40.4 (8.5)	41.4 (9.0)	39.7 (9.3)	38.6 (8.4)
GDS score, mean (SD)	1.5 (0.5)	1.0 (1.4)	1.03 (1.4)	1.12 (1.3)	1.01 (1.4)	1.2 (1.6)	1.36 (1.7)

Abbreviations: Aβ = β-amyloid; GDS = Geriatric Depression Scale; LRDR = Logical Memory Delayed Recall; LRIR = Logical Memory Immediate Recall; MMSE = Mini-Mental State Examination; PACC = Preclinical Alzheimer Cognitive Composite; RISU = retrieval impaired storage unimpaired; SOMI = Stages of Objective Memory Impairment.

participants. Participants had a mean age of 71.3 (SD 4.6) years, were 40.6% male, and had 16.6 years of education; 34.6% were _APOE_ ε4 positive. The mean FR was 29.0 (SD 5.59) and TR was 47.4 (SD 0.9).

Table 2 summarizes sample characteristics and classification of participants into SOMI stages. Participants in higher SOMI stages were older ($F = 44.7$, $p < 0.001$) and more likely to be female ($F = 54.0$, $p < 0.001$). SOMI groups did not differ in education or relative frequency of _APOE_ ε4 status. A total of 162 (3.6%) individuals could not be classified by the SOMI system because retrieval was impaired but storage was unimpaired. Compared with Aβ− individuals classified as in SOMI-0 or SOMI-1, those categorized as in SOMI-3 or SOMI-4 were older ($p < 0.001$ for all comparisons) and more likely to be female ($p < 0.001$ for all), but they did not differ in education. Table 3 summarizes the characteristics of Aβ− and Aβ+ individuals according to SOMI stages.

Differences in Amyloid Levels

Analysis of covariance in the entire sample showed that individuals in higher SOMI stages had higher global amyloid SUVR ($F = 8.4$, $p < 0.001$). Specifically, those in SOMI-4 had higher amyloid SUVR than those in SOMI-0, -1, and -2 ($p < 0.001$ for all) Individuals in SOMI-3 had higher amyloid SUVR than those in SOMI-0 ($p < 0.001$) and SOMI-1 ($p = 0.003$). There was no difference between amyloid SUVR of individuals in SOMI-0 and SOMI-1. (Figure 1A). We stratified the sample into Aβ− and Aβ+ subgroups to evaluate subthreshold and suprathreshold amyloid SUVR differences between the SOMI stages. At subthreshold levels (Aβ−), amyloid SUVR was not significantly different between SOMI stages. At suprathreshold levels (Aβ+), those in SOMI-4 had higher amyloid SUVR than individuals in SOMI-0 ($p < 0.001$) and SOMI-1 ($p = 0.002$), and those in SOMI-2 and SOMI-3 stage had higher amyloid SUVR than those in SOMI-0 ($p = 0.002$ for both) (Figure 1B).

Differences in Volumetric MRI Measures

Univariate analysis accounting for age, sex, education, and _APOE_ ε4 showed that individuals in higher SOMI stages had smaller hippocampal volume ($F = 3.66$, $p = 0.003$) (Figure 2). Pairwise comparison showed that those in SOMI-0 had the largest hippocampal volume compared to all other groups (SOMI-1 $p = 0.002$; SOMI-2, -3, and -4 $p < 0.001$ for all). Individuals in SOMI-1 also had larger hippocampal volume than those in SOMI-3 ($p < .001$), and SOMI-4 ($p < 0.001$). There was no difference in hippocampal volume between individuals in SOMI-2 and SOMI-3 ($p = 0.202$), SOMI-2 and SOMI-4 ($p = 0.026$), or SOMI-3 and SOMI-4 ($p = 0.102$). Addition of amyloid SUVR to the univariate analysis as a covariate attenuated the differences;

Table 3 Characteristics of Sample Stratified by Amyloid Status and SOMI

SOMI stage	0		1		2		3		4		RISU	
Amyloid status	−	+	−	+	−	+	−	+	−	+	−	+
No. (%)	1,538 (70.0)	658 (30.0)	835 (69.0)	376 (31.0)	265 (65.2)	142 (34.9)	279 (60.0)	186 (40.0)	27 (56.3)	21 (43.8)	93 (57.4)	69 (42.6)
Female, %	29.2	32.1	45.4	42.6	61.1	44.4	55.9	51.6	74.1	47.6	64	52
APOE ε4 positive, %	25.1	56.4	22.4	62.5	24.5	54.2	19.7	54.3	11.1	57.1	23.7	56.5
Age, mean (SD), y	70.0 (4.0)	71.1 (4.4)	71.2 (4.5)	72.0 (4.7)	72.8 (5.0)	73.2 (5.0)	71.5 (4.9)	73.6 (5.2)	73.9 (6.1)	74.4 (6.5)	74.5 (5.0)	72.9 (5.8)
Education, y	16.6 (2.8)	16.6 (2.7)	16.6 (2.8)	16.5 (3.0)	16.6 (2.9)	16.6 (2.5)	16.2 (2.8)	16.6 (2.8)	16.3 (2.8)	16.6 (2.5)	17.1 (2.7)	16.6 (2.3)
PACC score, mean (SD)	1.4 (2.1)	1.0 (2.1)	−0.3 (1.9)	−0.5 (2.0)	−2.00 (2.0)	−2.3 (2.1)	−1.4 (2.3)	−1.9 (2.5)	−3.1 (3.3)	−3.0 (2.7)	−3.4 (2.2)	−2.9 (2.2)

Abbreviations: Aβ = β-amyloid; PACC = Preclinical Alzheimer Cognitive Composite; RISU = retrieval impaired storage unimpaired; SOMI = Stages of Objective Memory Impairment.

however, the difference between SOMI subgroups remained significant ($F = 3.24$, $p = 0.007$).

There was no significant difference between parahippocampal gyrus volume between SOMI subgroups. Those in higher SOMI stages had smaller entorhinal cortex ($F = 2.25$, $p = 0.047$) and inferior temporal lobes ($F = 2.39$, $p = 0.036$). Post hoc analysis showed that those in SOMI-4 had smaller entorhinal cortex than individuals in SOMI-0 ($p < 0.001$), SOMI-1 ($p = 0.002$), and SOMI-2 ($p = 0.005$), but there was no difference in entorhinal cortex volume among other subgroups. In addition, post hoc analysis showed that participants in SOMI-3 had smaller inferior temporal lobes than participants in SOMI-0 ($p < 0.001$) and SOMI-1 ($p = 0.004$). Addition of amyloid SUVR to the univariate analysis as a covariate did not affect significant differences observed between subgroups.

Classification of Evidence

This study provides Class I evidence that, in normal older individuals, higher stages of memory impairment assessed with FCSRT were associated with higher amyloid imaging burden and lower volume of hippocampus, entorhinal cortex, and inferior temporal lobes.

Discussion

The SOMI system distinguishes retrieval impairment observed in preclinical AD in the context of intact memory storage from memory storage impairment that occurs later in the AD continuum. We used FR and TR scores on pFCSRT + IR to classify participants from the A4 study into SOMI stages. The sample was screened to have a Clinical Dementia Rating global score of 0, a Mini-Mental State Examination score of 25 to 30, and an LMDR-IIa score of 6 to 18. Even in this sample, extensively screened to identify and eliminate participants with cognitive impairment, including memory impairment based on delayed story recall, 511

of 4,484 (11.4%) were in SOMI-3 or -4, indicating that they had both memory retrieval and storage impairment based on the FCSRT. This indicates that the FCSRT detects memory impairment in an ostensibly cognitively normal group.

We examined the association of SOMI stage with global amyloid levels. In the entire cohort, as SOMI stage increased, the proportion of participants who were Aβ+ also increased. Among Aβ+ individuals, those in higher SOMI stages had higher global amyloid levels. Individuals in SOMI-3 and -4 (those with storage and retrieval deficits) had significantly higher amyloid levels compared to individuals in earlier SOMI stages (those with unimpaired memory or mildly impaired retrieval). These findings suggest that individuals with memory impairment detected by SOMI in this "cognitively normal" group have a biological substrate for cognitive impairment; higher levels of amyloid are associated with concurrent storage and retrieval deficits.

The relationship between SOMI stage and atrophy of medial temporal lobe subregions complements the relationship between SOMI and global amyloid levels. Only Aβ+ individuals underwent structural MRI at baseline, providing volumetric measures of the hippocampus, parahippocampal gyrus, entorhinal cortex, and inferior temporal cortex. The relationship of volumetric measure to SOMI stage differed among measures: (1) progressing from 1 SOMI stage to the next was associated with increasing levels of hippocampal atrophy; (2) individuals with impairment of memory storage (SOMI-3 and -4) displayed greater atrophy of the inferior temporal cortex compared to those with no storage impairment; and (3) atrophy of the entorhinal cortex was present only in individuals in SOMI-4 compared to those in all other stages who did not differ.

Our results indicate that even among individuals screened for cognitive impairment, hippocampal atrophy is evident in Aβ+
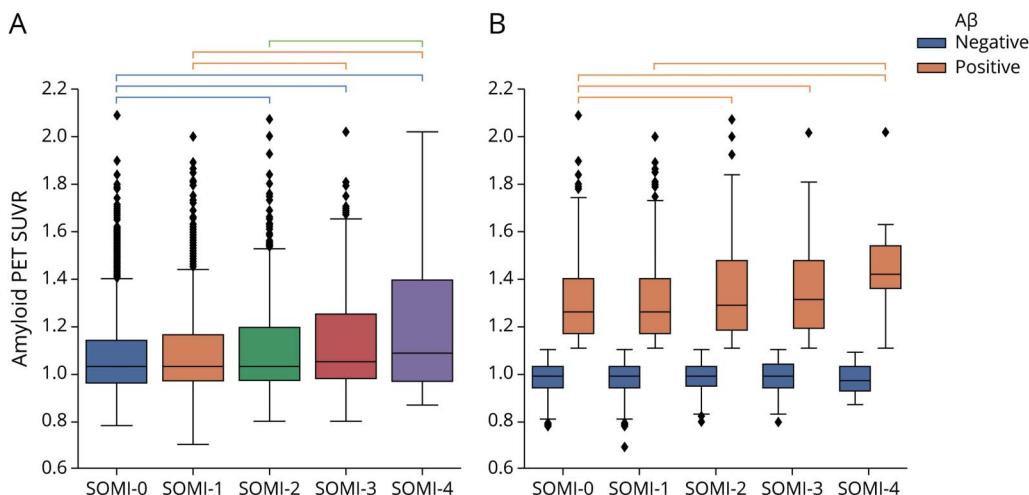
Groups significantly different from each other are connected to each other with brackets ($p < 0.005$). Aβ = β-amyloid; SOMI = Stages of Objective Memory Impairment; SUVR = standardized uptake value ratio.

subgroups with retrieval but not storage impairment. Prior studies suggest that hippocampal volume atrophy might be the earliest sign of neurodegeneration due to AD.[29,30] The development of memory storage impairment was associated with atrophy of inferior temporal cortex, but volume loss in entorhinal cortex occurred only with advanced storage issues in SOMI-4.

We expect that the relationship between SOMI stage and MRI volumetrics would likely be weaker in a sample not screened for amyloid positivity. This is a limitation on generalizability of our results imposed by the design of A4 study. Volumetric data are currently available only for the amyloid-positive individuals in the A4 study, but a parallel study (Longitudinal Evaluation of Amyloid Risk and Neurodegeneration [LEARN] cohort) is following up a smaller sample (N = 600) of amyloid-negative individuals from the A4 study, and we are hoping to conduct a follow-up study using data from that sample.

SOMI stages displayed a similar relationship to hippocampal volume and tau PET imaging of the entorhinal and inferior temporal cortices among participants in the Harvard Aging Brain Study (HABS).[31] Mean hippocampal volume for individuals in SOMI-3 and -4 combined was smaller than for individuals in SOMI-0, -1, and -2. Mean inferior temporal tau in SOMI-3 and -4 was higher compared to SOMI-0 and 1, and mean entorhinal tau in SOMI-3 and -4 was higher compared to SOMI-0. Together, these results indicate that memory storage impairment is present when there is widespread medial temporal lobe pathology.

In this study, the base rate of amyloid positivity among all participants was 32%. Rates of amyloid positivity were 30% for

stage 0, 31% for stage 1, 35% for stage 2, 40% for stage 3, and 44% for stage 4. A sensitivity analysis indicated that the SOMI system can add incremental value to using a single FR and TR cutoff for identifying amyloid-positive individuals. The optimal Youden index–based cutoff point for prediction of Aβ positivity for FR was 30 (Aβ+ = 35.2% for FR ≤ 30 vs Aβ+ = 28.2 for FR > 30) and for TR was 47 (Aβ+ = 35.7 for TR ≤ 47 and Aβ+ = 29.5 for TR = 48). Individuals in SOMI-3 and SOMI-4 stages have higher rates of amyloid positivity (40.0% and 43.8%, respectively). While SOMI stage does not eliminate the need for amyloid screening, it provides a strategy for increasing the yield of amyloid positivity among those receiving biomarker assessment.

These data pertain to a study of an amyloid-targeted therapy. For trials that target other pathologic mechanisms (e.g., tau), when data become available, we would assess rates of tau positivity by SOMI stage to optimize a sampling design. However, as indicated by the many failed trials of AD, presence of target pathology (i.e., amyloid) and even the successful removal of it from brain (e.g., aducanumab trials) do not guarantee trial success. Using sensitive clinical tests such as SOMI and Preclinical Alzheimer Cognitive Composite (PACC), which are proven to be effective tests for detecting early and late cognitive decline during the preclinical stages of AD, in combination with biomarkers can lead to improved trial design.

A recent study from the HABS showed that Aβ+ cognitively normal individuals demonstrated longitudinal decline on all individual PACC components and all PACC variations.[32] Differences between the Aβ+ and Aβ− groups emerged earlier when FCSRT FR was included in the PACC. FR alone or combined with TR was the only individual component of the

Figure 2 Volume of Different Regions by SOMI Stage

Figure 2 Volume of Different Regions by SOMI Stage
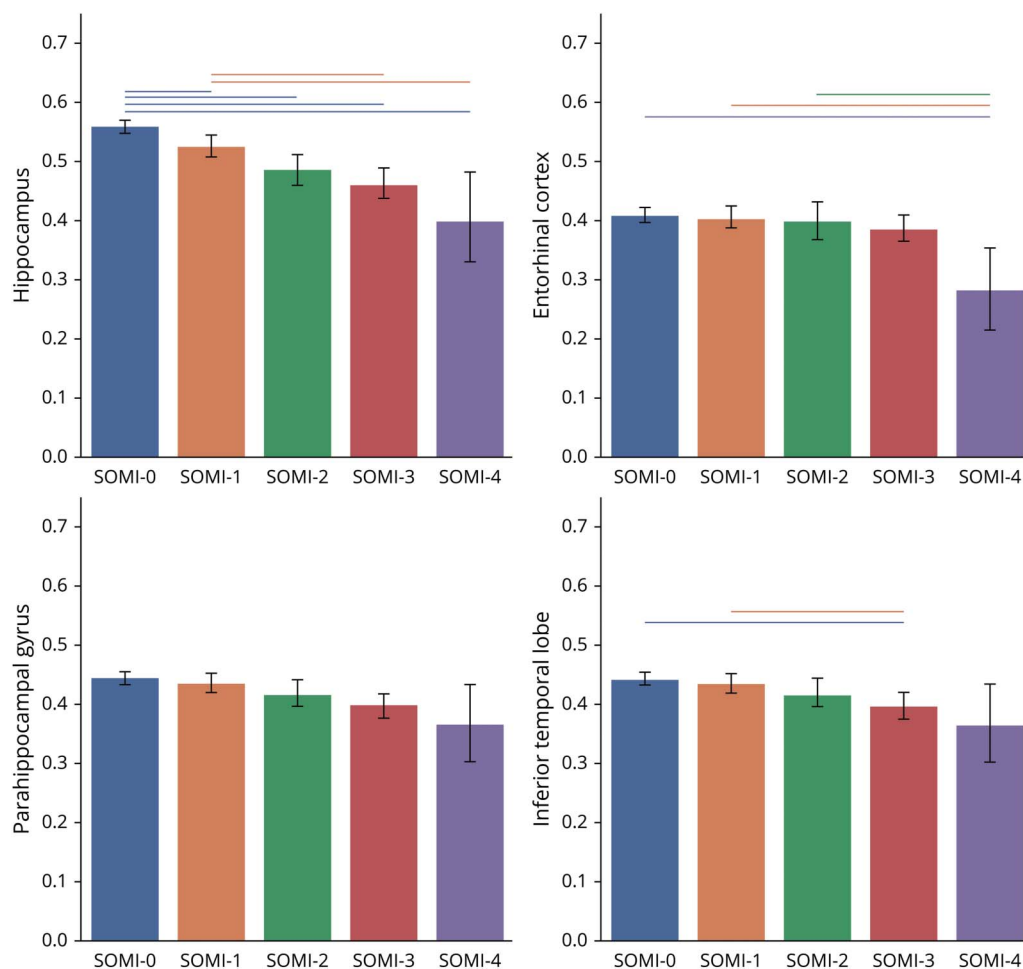
Volumetric measures are normalized and rescaled to 0 to 1 to improve comparability. Groups significantly different from each other (*p* < 0.005) are connected to each other with lines. SOMI = Stages of Objective Memory Impairment.

PACC to show differences between the Aβ+ group who progressed to Clinical Dementia Rating score of 0.5 and those that remained stable. These findings support the notion that using the FSCRT-derived SOMI system can improve our ability to detect early and late cognitive decline during the preclinical stages of AD, which may prove advantageous in the design of prevention trials.

In the context of clinical trials, we envision that SOMI could be used as a criterion for prioritizing enrollment of participants. The optimal criterion for sample enrichment based on SOMI depends on the design of trial, its duration, and its objectives. One approach could be using SOMI staging for selecting participants who are more likely to be amyloid positive before evaluation with expensive or invasive biomarkers such as PET scans or CSF-based biomarkers. SOMI-3 and -4 groups are more likely to be amyloid positive; However, selecting individuals in SOMI-3 and -4 for biomarker evaluation has its own drawbacks. While this approach would increase biomarker positivity rate and decrease the cost

of biomarker assessment before enrollment, it would also require cognitive screening of far more individuals with the FCSRT, which could potentially slow down recruitment and limit the generalizability of findings to those who are in SOMI-3 and -4 at the time of enrollment.

An alternative approach might be to enroll individuals who are in SOMI-1 or greater. While this approach has minimal value in the enrichment of a sample with amyloid-positive individuals before obtaining amyloid PET, from our previous studies, this group is expected to show faster cognitive decline and incident dementia in a shorter time frame, which is more appropriate for trials.[21,23] In the EAS, we showed that among 142 participants who developed AD over 10 years, average time to diagnosis was 7 years if FR was intact >30 (SOMI-0), 5 years if SOMI-1, 4 years if SOMI-2, and 2 years if SOMI-3 and -4.[23] The trajectory of FR decline in the preclinical AD continuum of the BLSA participants was consistent with the SOMI prediction. FR declined gradually, beginning at 7 years, until there was a doubling of the rate of FR decline ≈4 years

later.[21] From these results, we expect that in a trial in which time to dementia is the endpoint, the SOMI system would add important information that could be used to match the characteristics of the eligible sample to the design and duration of the study. Given the long duration of progression to dementia in the SOMI-0 group, the expected rate of memory decline is likely too slow to demonstrate treatment benefits in any of the current clinical trials.

The SOMI system could also inform clinical trial design as an outcome measure. SOMI-3 is highly associated with AD neuropathology defined by current guidelines[33] and neurofibrillary tangle pathology defined by Braak and Braak.[34] Compared to participants with no memory impairment (SOMI-0), participants classified into SOMI-3 and -4 stages were 4 times more likely to have positive AD neuropathology and were nearly 6 times as likely to have more advanced Braak neurofibrillary tangle pathology. Using conversion from earlier stages to SOMI-3 as an outcome in conjunction with biomarkers could be an effective method to reduce the duration of active treatment in the trials.

It should be noted that we do not believe that the FCSRT is capturing something unique. Other memory tests are also effective at predicting incident MCI and dementia.[35,36] However, the ability to distinguish measures of storage and retrieval and the control of cognitive processes may provide particular benefits. Many studies by our group and others indicate that FCSRT is a sensitive cognitive test for detecting signs of memory impairment in both storage and retrieval in prodromal stages of AD and other dementia.[15-18] SOMI staging provides a practical system (and cutoffs for classification) that can be used as part of the design of future interventional studies.

Another approach to identifying persons in the earliest stages of AD includes using at least 2 tests of a single domain or single tests of multiple domains in addition to specific memory parameters (e.g., learning slope).[37,38] This approach has theoretical advantages and disadvantages over our approach, which relies on a single cognitive test. We expect there to be overlap between early and late MCI and SOMI stages. These approaches have not been compared head to head in terms of simplicity, ease of use, and predictive validity for biomarkers or cognitive decline.

There are limitations of this study worth noting. Of the participants, 3.4% could not be classified into a SOMI stage because their retrieval was impaired but memory storage was unimpaired. We plan to study characteristics of this unique group in our future studies. 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 clinical memory AD phenotype. The A4 study is a prevention trial; therefore, all participants who had PET scans were cognitively normal at baseline. Excluding participants with very high LMDR-IIa criteria (>1.SD) from the A4 trial slightly affects the generalizability of our study. However, even after the exclusion of these participants, the sample includes a large range of cognitive abilities among individuals considered normal according to the current gold standard diagnostic criteria. Another limitation is the high educational level of the cohort. We are hoping to follow up this study in a more diverse cohort in the future to confirm its generalizability to other samples.

In this study, we used data from a very large sample of older adults. While using large datasets is generally considered an advantage in epidemiologic studies, it also poses a statistical challenge. In large samples, analysis power is substantially increased. This might lead to an exaggerated tendency to reject the null hypotheses while differences are not clinically or biologically meaningful. However, our results could be considered robust because they are hypothesis driven and consistent with literature and prior studies in other samples with diverse populations and different sample sizes.[4,6-8,10,17] Last, the relationship between SOMI stage and MRI volumetrics would likely be weaker in a sample not screened for amyloid positivity.

Even in highly selected cognitively normal older adults, the presence of AD pathology is closely related to memory impairment based on SOMI stages. We envision that SOMI could be used for enrichment of future clinical trials.

Acknowledgment

Appendix Authors

Name	Location	Contribution
Ellen Grober, PhD	Department of Neurology, Albert Einstein College of Medicine, Bronx, NY	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Richard B. Lipton, MD	Department of Neurology, Albert Einstein College of Medicine, Bronx, NY	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Reisa A. Sperling, MD	Harvard Aging Brain Study, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston; Center for Alzheimer Research and Treatment, Department of Neurology, Brigham and Women's Hospital, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Kathryn V. Papp, PhD	Harvard Aging Brain Study, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston; Center for Alzheimer Research and Treatment, Department of Neurology, Brigham and Women's Hospital, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Keith A. Johnson, MD	Harvard Aging Brain Study, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston; Center for Alzheimer Research and Treatment, Department of Neurology, Brigham and Women's Hospital, Boston, MA	Major role in the acquisition of data

Continued

Appendix *(continued)*

Name	Location	Contribution
Dorene M. Rentz, PhD	Harvard Aging Brain Study, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston; Center for Alzheimer Research and Treatment, Department of Neurology, Brigham and Women's Hospital, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Amy E. Veroff, PhD	Department of Neurology, Albert Einstein College of Medicine, Bronx, NY	Drafting/revision of the manuscript for content, including medical writing for content
Paul S. Aisen, MD	Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego	Major role in the acquisition of data
Ali Ezzati, MD	Department of Neurology, Albert Einstein College of Medicine, Bronx, NY	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

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