HHS Public Access

Author manuscript

J Psychiatr Res. Author manuscript; available in PMC 2018 September 11.

Published in final edited form as:

J Psychiatr Res. 2018 January ; 96: 33–38. doi:10.1016/j.jpsychires.2017.08.015.

A novel cognitive assessment paradigm to detect *Pre-mild cognitive impairment (PreMCI)* and the relationship to biological markers of Alzheimer's disease

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Abstract

Objective: A number of older adults obtain normal scores on formal cognitive tests, but p resent clinical concerns that raise suspicion of cognitive decline. Despite not meeting full criteria for Mild Cognitive Impairment (MCI), these PreMCI states confer risk for progression to Alzheimer's disease (AD). This investigation addressed a pressing need to identify cognitive measures that are sensitive to PreMCI and are associated with brain biomarkers of neurodegeneration.

Method—Participants included 4 9 older adults with a clinical history suggestive of cognitive decline but norm al scores on an array of neuropsychological measures, thus not meeting formal criteria for MCI. The performance of these PreMCI participants were compared to 117 cognitively normal (CN) elders on the LASSI-L, a cognitive stress test that uniquely assesses the failure to recover from proactive semantic interference effects (frPSI). Finally, a subset of these individuals had volumetric analyses based on MRI scans.

Results: PreMCI participants evidenced greater LASSI- L deficits, particularly with regards to frPSI and delayed recall, relative to the CN group. No differences on MRI measures were observed. Controlling for false discovery rate (FDR), frPSI was uniquely related to increased dilatation of the inferior lateral ventricle and decreased MRI volumes in the hippocampus,

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Author disclosures and conflicts of interest

The authors have no disclosures or relevant conflicts of interest.

precuneus, superior parietal region, and other AD prone areas. In contrast, other LASSI-L indices and standard memory tests were not related to volumetric findings.

Conclusions: Despite equivalent performance on traditional memory measures, the frPSI distinguished between PreMCI and CN elders and was associated with reductions in brain volume in numerous AD-relevant brain regions.

Keywords

Preclinical Alzheimer's; MCI; LASSI-L; MRI; Semantic interference

1. Introduction

In 2011, the National Institutes on Aging and Alzheimer's Association (NIA-AA) established broad research criteria for the diagnosis of preclinical Alzheimer's disease (AD). The focus of these guidelines was to address the to define AD in terms of its underlying pathophysiological disease process rather than NIA-AA guidelines for clinical stages of the disease relative to individuals with mild cognitive impairment (MCI) who had MRI or amyloid PET evidence of AD pathology (Albert et 2011) or dementia related to Alzheimer's Disease (McKhann et al., 2011).

From a cognitive standpoint, accurately identifying individuals on the Alzheimer's disease (AD) continuum during the preclinical stages is challenging given that there are older adults who may have suspected cognitive deficits, score within normal limits on neuropsychological evaluation and do not meet formal criteria for mild cognitive impairment (MCI). These individuals, classified as PreMCl, *experienced a much greater likelihood* of experiencing a decline to formal MCI or dementia *longitudinally than cognitively normal older adults* (Loewenstein et al., 2012). In fact, the neuropsychological test performance of persons with PreMCl has also been associated with biomarkers of AD pathology (Duara et al., 2011; Loewenstein et al., 2016; Loewenstein, Curiel, Buschke and Duara 2017a.

The ability to identify individuals with PreMCI is important since many persons evaluated may not have access to advanced neuroimaging such as *amyloid PET scans and that* emerging therapies, *both* now and in the future, are likely to be more efficacious before multisystem brain deterioration has occurred.

Recent findings have suggested that cognitive "stress tests" may be sensitive to the earliest changes in AD (Loewenstein et al., 2016). These measures are analogous to an exercise EKG that may reveal cardiac deficits that simply cannot be identified in a resting state. One such test, the LASSl-L, requires learning of 15 words belonging to three semantic categories and taps vulnerability to semantic proactive interference by presenting a competing semantically similar set of targets. A unique feature of the LASSl-L is a second presentation of the second target list that taps failure to recover from proactive semantic interference (frPSl). The LASSl-L frPSl measure has been found to be: highly related to total and regional amyloid load in neuropsychologically normal community-dwelling elders (Loewenstein et al., 2016); has differentiated between aMCl patients with suspected AD from cognitively unimpaired elderly controls (CN) (Curiel et al., 2013; Crocco et al., 2014;

Matías-Guiu et al., 2016); and has been associated with volumetric loss in AD prone areas among elders with amnestic MCl (Loewenstein et al., 2017b).

The current investigation is unique in that it represents a first attempt to determine whether failure to recover from proactive semantic interference (frPSl) differentiates between older adults with PreMCl and those who are cognitively normal (CN). A further goal was to determine the extent to which frPSl was associated with volumetric structural MRl changes in AD related brain regions (Dickerson et al., 2011; Holland et al., 2009; Loewenstein et al., 2017b) among our participants.

2. Methods

2.1. Participants

The sample included 166 older adult participants from an NlH funded and lRB approved DETECT-pAD study at the University of Miami School of Medicine designed to measure the longitudinal trajectories of decline in PreMCl participants, *A major focus of the longitudinal investigation was to determine the extent to which novel cognitive stress tests versus traditional neuropsychological measures could predict different trajectories of decline among persons who were cognitively normal, those diagnosed with MCI other diagnosed with PreMCl.*

All participants were independent community-dwellers, with the vast majority having knowledgeable collateral informants. None of these individuals met DSM-V criteria for Major Neuro-cognitive Disorder, active Major Depression or any other neuropsychiatric disorder *after an extensive clinical interview which included the Neuropsychiatric Inventory (NP:).* Participants were evaluated using a standard clinical assessment protocol consisting of the Mini-mental State Examination (MMSE) (Folstein et al., 1975) and Clinical Dementia Rating Scale (CDR) (Morris, 1993). Neuropsychologists or post-doctoral fellows, who had formal training in the administration of the CDR, assessed the memory and the presence of other cognitive complaints among the participants and also conducted the CDR interview with a collateral informant that knew the patient well. *Over 95% of participants had collateral informants such* as *a spouse, children, sibling or close friend who could rate any changes in the individuals cognitive status in the previous year and years prior as well as a structured interview about the ability to perform different cognitive and functional tasks.* A standard neuropsychological battery was subsequently administered after the clinical examination. The neuropsychological battery included the Hopkins Verbal Learning Test-Revised (HLVT-R: Benedict et al., 1998), National Alzheimer's Coordinating Center (NACC) delayed paragraph recall (Beekly et al., 2007), Category Fluency (Lucas et al., 1998), Block Design of the WAlS-lV (Wechsler, 2008), and the Trail Making Test (Parts A and B) (Reitan, 1958). *The LASSI-L was not used for diagnostic determination. All tests including the LASSI-L had been translated and back-translated into Spanish using methods that we have previously reported and those persons who reported Spanish as their primary language were tested in Spanish (*Acevedo et al, 2007, 2009*). We have an extensive normative database for English and Spanish-speaking subjects in all the neuropsychological tests administered.*

On the basis of the independent clinical interview and performance on the neuropsychological tests, an individual was considered to have PreMCl if all of the following conditions were met: a) subjective memory complaints by the participant and/or or collateral informant; b) evidence by clinical evaluation or history of memory or other cognitive decline *determined after the extensive CDR interview);* c) Global CDR scale of 0.5; d) the neuropsychological battery was deemed normal (DL) and generally, no measures in the neuropsychological battery fell 1.0 SD or more below normal limits relative to age and education related normative data. PreMCl represents more than a mere subjective memory complaint. lt requires a careful interview with both the participant and a collateral informant and the determination by the clinician is that there has been cognitive decline beyond that expected for age. For example, a participant might not notice any changes in their memory or other cognitive functions, yet a knowledgeable informant provides concrete examples of decline in recent memory during the previous year. This decline is not sufficient to interfere with social/occupational functioning and independent traditional neuropsychological testing is within normal limits for age, education and primary language (perhaps due to cognitive reserve). Because the clinician judges that there has been cognitive decline in spite of normal neuropsychological testing, this participant is classified as having PreMCl.

Participants were diagnosed as cognitively normal (CN) if: a) there was no subjective memory complaints by the participant and/or or collateral informant; b) no evidence by clinical evaluation or history of memory or other cognitive decline; c) Global Clinical Dementia Rating scale of 0; d) Global CDR scale of 0.5; d) the neuropsychological battery was deemed normal (DL) and generally, no measures in the neuropsychological battery fell 1.0 SD or more below normal limits relative to age and education related normative data.

As indicated in Table 1, there were no differences between PreMCl and CN participants with regards to age, educational attainment, average MMSE scores or performance on the HVLT-R *immediate or delayed recall.* lndividuals with PreMCl were more likely to be Hispanic and thus, this factor was employed in covariate analyses when evaluating potential differences between study groups and the gender distribution was predominantly female but there were no statistically significant differences in gender between study groups.

3. Materials

3.1. Neuropsychological measures

3.1.1. Loewenstein- acevedo scales for semantic interference and learning (LASSI-L)—

The LASSI-L is a novel cognitive stress paradigm that employs controlled learning and cued recall to maximize storage of a list of to-be-remembered target words representing three semantic categories. The accuracy of classification of MCI patients *versus* cognitively normal elderly participants has exceeded 90% (Crocco et al., 2014; Loewenstein et al., 2017b). A unique aspect of this paradigm is the presentation of a second list of to-be-remembered words, which share the same semantic categories as in the first list, eliciting considerable proactive interference. Unlike other memory paradigms, the individual is again administered this second list of words to measure recovery from proactive semantic interference. The specific elements of the test are described below:

The examinee is instructed to remember a list of 15 common words that are musical instruments, fruits, or articles of clothing (five words per semantic category) which they are asked to immediately recall after exposure. After the initial free recall trial, the examinee is presented with each category cue (e.g., clothing) and asked to recall the words that belonged to that category (LASSIL A1). The examinee is then presented with the target stimuli for a second learning trial with subsequent cued recall to strengthen the acquisition and recall of the List A targets, providing maximum storage of the to-be-remembered information (LASSI-L A2). Following this trial, the participant is introduced to a semantically related list (i.e., List B) which is then presented in the same manner as List A targets. List B consists of 15 words which are different from List A, five that belong to each of the three categories used in List A (i.e., fruits, musical instruments, and articles of clothing). Following the presentation of the List B words, the examiner asks the person to freely recall the List B words; this assesses proactive semantic interference effects (LASSI-L B1). Then, the participants are asked to recall each of the List B words that belonged to each of the categories. List B words are presented again, followed by a second category-cued recall trial. Performance on this second learning trial for the new list measures the examinee's ability to recover from the effects of proactive semantic interference (LASSI-L B2). Finally, the participant is required to use free and cued recall to recall remember the original target list which is sensitive to vulnerabilities in retroactive interference effects (RSI). The LASSI-L has been found to have adequate test-retest reliabilities ($r = 0.60$ to $r = 0.89$) among persons with aMCI and early dementia, in addition to high discriminative and concurrent validity (Crocco et al., 2014).

3.1.2. Hopkins verbal learning test (HVLT-R)—

The HVLT-R (Benedict et al., 1998) consists of 12 words. The words are read to participants, who are then asked to freely recall as many words as they can remember. This procedure is repeated for three trials. After a delay of 20–25 min, another free recall takes place. The HVLT has been found to have adequate sensitivity and specificity in differentiating among normal patients and those with possible MCI (Carmichael et al., 2007).

3.2. MRI measures

Seventy-six of the participants described above (23 PreMCI and 53 CN) underwent MRI scanning using a Siemens Skyra 3 T MRI scanner at the University of Miami. Since PreMCI and CN groups achieved equivalent scores on all MRI measures, the groups were combined for purposes of correlation with LASSI-L and other cognitive measures. Brain parcelation was obtained using a 3D T1-weighted sequence (MPRAGE) with 1.0 mm isotropic resolution. FreeSurfer Version 5.3 software (http://surfer.nmr.mgh.harvard.edu) was employed to assess atrophy in Alzheimer's signature regions (Dickerson et al., 2011; Holland et al., 2009; Loewenstein et al., 2017a), including the hippocampus, entorhinal cortex (ERC), precuneus, posterior cingulate, superior temporal lobule, inferior temporal lobule, temporal pole, superior parietal lobule, inferior parietal lobule, supramarginal gyrus, superior frontal lobule and rostral middle frontal lobule under the supervision of one of our investigators (NA). We also included the volume of the inferior lateral ventricles, a sensitive index of atrophy in surrounding brain regions, which are affected early in AD. Larger

inferior ventricle volume size is indicative of greater ventricular dilatation and is inversely correlated with measures of the hippocampus and other brain regions.

Given the high degree of association between corresponding structures in the right and left hemispheres of the brain, homologous structures (e.g., precuneus, inferior temporal lobules) were combined and normalized using intracranial volume (Shen et al., 2011).

We specifically focused on the LASSI-L frPSI measure since that index has been previously shown to be extremely sensitive to both amyloid load in neuropsychologically normal elders (Loewenstein et al., 2016) as well as volumetric loss in AD prone areas among older adults with aMCI (Loewenstein et al., 2017b) as well as LASSIL measures sensitive to retroactive semantic interference (RSI).

3.3. Statistical analyses

Comparisons between diagnostic groups were conducted utilizing a series of one-way analyses of variance (ANOVA). When appropriate, ANCOVA analyses were employed to correct for baseline differences due to primary *language*. *We also evaluated scores on the Geriatric Depression Scale as an interval level covariate which had no influence on obtained findings.* We conducted a series of Pearson Analyses adjusting p-values to account for the false discovery rate (FDR: Benjamini and Hochberg, 1995) associated with each individual cognitive measure (e.g., frPSI which was correlated with thirteen MRI regional volumes. Only FDR corrected p-values of <0.05 were considered).

4. Results

As indicated in Table 1, despite equivalent ages, MMSE and HVLT-R scores, and after statistically controlling for primary language, PreMCI participants evidenced lower scores on LASSI-L A1 Free Recall [F (1,163) = 3.93; p = 0.049], LASSI-L A2 Cued Recall [F (1,163) = 5.78; p = 0.017], LASSI-B2 Cued Recall [F (1,163) = 5.93; p = 0.016], LASSI-A3 Free Recall [F (1,163) = 4.88; p = 0.029], and LASSI-L Delayed Recall [F (1,163) = 9.46; p = 0.002] relative to CN participants [Table 2]. All of these measures except LASSI-L A1 Free Recall remained statistically significant at $p < 0.05$ after adjusting for the False Discovery Rate (FDR).

Seventy-six of our participants had volumetric MRI (23 PreMCI and 53 CN). There were no statistically significant differences between MRI volumes in any of the brain regions investigated. We calculated the correlations between cognitive tests and volumetric measures in the entire sample of participants for which MRI was available. As depicted in Table 3, after controlling for the false discovery rate, there were statistically significant associations between LASSI-L frPSI and inferior lateral ventricular dilatation (r = −0.46), as well as reduced volumes in the following regions: hippocampal (r = 0.33), superior parietal (r = 0.33), precuneus (r = 0.31), superior frontal (r = 0.31), superior temporal (r = 0.29), entorhinal cortex (ERC) (r = 0.28), rostral middle frontal (r = 0.28), posterior cingulate (r = 0.27), and supramarginal (r = 0.25). In contrast, there were no statistically significant associations between any of these MRI volumes *on initial learning of the first LASSI-L target list, RSI indices* or traditional memory tests such as HVLT-R total and delayed recall.

5. Discussion

This investigation represents the first attempt to determine the extent to which ailure to recover from proactive semantic interference (frPSI) on a novel *cognitive stress test, could differentiate between PreMCI and cognitively normal (CN) older adults. Despite equivalent MMSE scores and equivalent scores on traditional memory measures such immediate and delayed recall of the HVLT-R, PreMCI patients obtained significantly lower scores than CN participants on LASSI-L measures tapping maximum learning, frPSI, retroactive semantic interference (rSI) and delayed recall as compared to CN participants.* We observed similar results when primary language (Spanish or English) or *GDS.*

Despite the lack of differences in volumetric loss in between PreMCI and CN groups, we were able to determine the extent performance on the LASSI-L and the HVLT-R were related to volumetric reductions on MRI in AD prone regions. An important finding was that LASSI-B2 cued recall, which is vulnerable to frPSI was *uniquely found to be associated with volumetric reductions on MR within medial temporal lobes (eg., entorhinal cortex), other AD prone regions (e.g., precuneus, superior frontal and superior parietal regions)* and dilatation of the inferior lateral ventricle. These associations were not observed on HVLT-R, nor were they evidenced on LASSI-L RSI or LASSI-L List A learning measures or LASSI-L delayed recall measures.

Thus, among older community-dwelling older adults, all which scored within normal limits on formal neuropsychological measures, increased frPSI was distinctly related to reduced volumes in AD prone regions on MRI.

The finding that the strongest associations observed were between frPSI and enlargement of the inferior lateral ventricle are particularly interesting. There is an increasing body of evidence that ventricular dilatation is an early neuroimaging feature in those with preclinical AD and may precede the formal clinical diagnosis of MCI by several years (Apostolova and Thompson, 2007; Carmichael et al., 2007).] The associations between the frPSI, hippocampus, precuneus, posterior cingulate and AD prone regions in the frontal temporal and parietal lobules (Dickerson et al., 2011; Holland et al., 2009) are particularly relevant since no such associations were observed for other traditional memory measures. This provides further evidence that frPSI may be a *unique* marker of early cognitive deficits and preclinical neurodegenerative disease.

Recovery from PSI has been shown to be very sensitive in discriminating between older adults with mild cognitive impairment (MCI) and those who are cognitively normal (CN) (Loewenstein et al., 2016). Equally important, among community-dwelling older adults who scored normally on traditional neuropsychological measures, frPSI has been strongly associated with amyloid load in the precuneus, posterior cingulate and whole brain (Loewenstein et al., 2016). Moreover, participants with aMCI have shown the same pattern of associations between frPSI and volumetric loss in similar AD prone areas (Loewenstein et al., 2017b), although these associations have been stronger in aMCI samples than our current sample of neuropsychologically normal older adults. This is likely due to a greater range of

volumetric loss among aMCI patients as well as a greater range of scores on LASSI-L measures than our PreMCI and MCI groups.

The unique ability of the LASSI-L measures to differentiate between carefully diagnosed AD versus CN as well as the unique relation between LASSI-LfrPSI and volumetric reductions in AD prone areas on MRI have important clinical as well as research implications. While PreMCI can be readily diagnosed in specialty memory disorders clinics using trained clinical raters and comprehensive neuropsychological test batteries, there are often situations in real world clinical and research settings. First, it is often difficult to obtain a collateral informant in situations in which a person is widowed and his/her family lives out of town. In addition, in many settings there are not extensive neuroimaging resources such as amyloid PET or MRI to help aid in diagnostic determination. In such cases, an objective measure, the LASSI-L provides an efficient and objective way of capturing early cognitive deficits that have not been identified using traditional neuropsychological measures and importantly relates to reduction of volume in AD prone regions.

Strengths of the current study include stringent diagnostic criteria for PreMCI and CN participants (Loewenstein et al., 2012). We also employed methods to control for false discovery rates to minimize the possibility of family-wise Type 1 errors. In comparative analyses between PreMCI and CN groups, we also accounted for potential confounding factors such as a greater percentage of Spanish-speakers in the PreMCI group relative to the CN group. It will be important to follow these participants over time to determine the relationship between frPSI and cognitive decline over time as well as further volumetric loss on MRI measures.

As attention is focused on the identification of cognitive deficits in preclinical stages of neurodegenerative disorders such as AD, it is important to consider the potential value of cognitive stress tests to detect subtle deficits among older adults who may have little or no cognitive impairment on traditional neuropsychological measures. A unique aspect of the LASSI-L, relative to existing cognitive measures, is that it employs a second cued recall trial, which provides a means to examine the ability to recover from the initial effects of PSI. Proactive semantic interference results in individuals being unable to s*uppress* information that is no longer relevant and it has been interpreted as an inability to control information coming from memory content (Borella et al., 2016; Friedman and Miyake, 2004). Although this inhibitory process appears to diminish with repeated administrations of the new target in cognitively normal individuals, this is not the case among those with *classified* as PreMCI.

The biological subtrates of frPSI remain unclear. While this study and previous investigations have shown that frPSI to vulnerability to AD pathology, this does not address the neurocognitive mechanisms underlying the inability to recover from inhibitory failures and its biological substrates in the brain. We believe that brain circuits underlying this phenomenon are likely related to circuits involving the medial temporal lobe structures (entorhinal cortex, hippocampus) and frontal lobe circuits that are related to inhibitory failures and source memory. Our ongoing work with other collaborators using FDG-PET and fMRI studies should help elucidate this particular issue.

Despite using a comprehensive clinical interview with the NPI, there is a possibility that some persons not meeting criteria for a Major Axis 1 disorder many have experienced some sub-syndromal mood disorders that could have affected cognitive performance and MRI findings. This is highly unlikely for several reasons. First, in our experience with the LASSI-L there has been no evidence that mild mood symptoms are associated with frPSI on the LASSI-L. Indeed, scores on the Geriatric Depression Scale showed no relationship with frPSI in the current sample. Secondly, it has been increasingly recognized that depressed mood, apathy and other neurobehavioral syndromes may be some of the earliest symptoms for neurodegenerative disease (Crocco, Castro and Loewenstein, 2010).

Finally, the fact that frPSI but not the HVLT-R was associated with volumetric loss on AD prone regions such as the entorhinal cortex precuneus and superior parietal regions typically related to neurode-generative changes in AD suggests that further suggests that our findings are more reflective of underlying neurodegenerative disease.

The present findings also provide support for an increasing body of research, which indicates that PreMCI states are associated with early biological changes within the brain and is a risk factor for future cognitive decline (Brooks and Loewenstein, 2010; Loewenstein et al., 2012). The failure to recover from PSI (frPSI) seems to be a sensitive cognitive marker of early cognitive impairment and is worthy of further research.

Acknowledgements/funding source

The National Institute of Aging grant number supported this research: 1 R01 AG047649–01A1 (David A. Loewenstein, Principal Investigator).

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Table 1

Comparison of PreMCI subtype and cognitively normal elders on demographic measures.

	CN (n = 117)	PreMCI- Clinical (n = 49)	F-Value or X^2 After Yates Correction
Age	72.10 (SD = 7.9)	73.29 (SD = 6.5)	0.85 (p = 0.358)
Education	14.57 (SD = 3.4)	14.35 (SD = 3.8)	0.14 (p = 0.711)
Gender(% F)	77.5%	75.5%	0.01 (p = 0.938)
Hispanic %	37.5%	57.1%	4.70 (p = 0.030)
MMSE	28.71 (SD = 1.7)	28.51 (SD = 1.7)	0.50 (p = 0.490)
HVLT-R Total Recall	24.48 (SD = 4.3)	23.14 (SD = 4.4)	1.73 (p = 0.190)
HVLT-R Delayed Recall	8.82 (SD = 2.0)	8.25 (SD = 1.9)	1.98 (p = 0.162)

Note: F-values for HVLT-R Subtests were adjusted for primary language.

CN= Cognitively Normal; PreMCI = Preclinical Mild Cognitive Impairment.

Table 2

Comparison of Different PreMCI Subtypes and Cognitively Normal Elders on LASSI-L Measures tapping frPSI and other Cognitive Processes.

	CN (n = 117)	PreMCI- Clinical (n = 49)	F-Value
LASSI-LFree Recall A-1	9.01 (SD = 2.4)	8.00 (2.4)	3.93 (p = 0.049)
LASSI-L Cued Recall A-1	9.97 (SD = 2.2)	9.22 (SD = 2.2)	1.80 (p = 0.181)
LASSI-L Cued A-2 Initial Learning Capacity	13.20 (SD = 1.5)	12.43 (SD = 1.7)	5.78 (p = 0.017)
LASSI-L B1 Free Recall	7.01 (SD = 2.4)	6.20 (SD = 2.3)	3.15 (p = 0.078)
LASSI-B1 Cued Recall (Measures Proactive Semantic Interference)	7.39 (SD = 2.7)	6.88 (SD = 2.3)	1.03 (p = 0.311)
LASSI-L Cued B2 (Measures frPSI)	11.12 (SD = 2.3)	10.16 (SD = 2.1)	5.93 (p = 0.016)
LASSI-A3 Free Recall (Measures Retroactive Interference)	5.67 (SD = 2.7)	4.45 (SD = 2.5)	4.88 (p = 0.029)
LASSI-L A-3 Cued Recall	7.90 (SD = 2.3)	7.47 (SD = 2.4)	0.43 (p = 0.512)
LASSI-L Delayed Recall	18.62 (SD = 4.4)	15.82 (SD = 5.6)	9.46 (p = 0.002)

Note: F-values for HVLT-R and LASSI-L subtests adjusted for primary language.

Table 3

Associations between MRI volumes among 13 regions of interest and memory measures for 76 participants adjusted for false discovery rate.

	LASSI-L B2 frPSI	LASSI-L A3 RSI	HVLT- R Total Recall	HVLT-R Delay Recall
Inferior Lateral Ventricle	r = −0.46	r = 0.24	r-0.19	r = −0.27
	(p = 0.013)	p = 0.179	p = 0.637	p = 0.189
Hippocampus	r = 0.33	r = 0.11	r = 0.07	r = 0.25
	(p = 0.017)	p = 0.474	p = 0.756	p = 0.189
ERC	r = 0.28	r = −0.22	r = 0.09	r = 0.16
	(p = 0.028)	p = 0.342	p = 0.756	p = 0.247
Precuneus	r = 0.31	r = 0.16	r = 0.25	r = 0.14
	(p = 0.018)	p = 0.179	p = 0.402	p = 0.247
Posterior Cingulate	r = 0.27	r= 0.23	r = 0.03	r = 0.17
	(p = 0.036)	p = 0.371	p = 0.778	p = 0.247
Inferior Temporal	r = 0.21	r= 0.13	r = 0.04	r= 0.06
	(p = 0.075)	p = 0.431	p = 0.778	p = 0.623
Superior Temporal	r = 0.29	r= 0.16	r = 0.06	r= 0.15
	(p = 0.034)	p = 0.361	p = 0.756	p = 0.247
Temporal Pole	r = 0.16	r= 0.00	r = 0.07	r= 0.16
	(p = 0.161)	p = 0.991	p = 0.756	p = 0.247
Inferior Parietal	r = 0.23	r= 0.02	r = 0.13	r= 0.13
	(p = 0.056)	p = 0.574	p = 0.637	p = 0.295
Superior Parietal	r = 0.33	r= 0.32	r = 0.17	r= 0.19
	(p = 0.017)	p = 0.065	p = 0.637	p = 0.247
Surpamarginal	r = 0.25	r= 0.03	r = 0.05	r= 0.15
	(p = 0.036)	p = 0.847	p = 0.756	p = 0.247
Superior Frontal	r = 0.31	r= 0.14	r = 0.12	r= 0.17
	(p = 0.018)	p = 0.431	p = 0.637	p = 0.247
Rostral Middle Frontal	r = 0.28	r= 0.09	r = 0.14	r= 0.15
	(p = 0.028)	p = 0.574	p = 0.637	p = 0.247

Note: Adjusted p-values for each memory measure for 13 MRI Regions of Interest frPSI = failure to recover from Proactive Semantic Interference, RSI = Retroactive Semantic Interference.