Published in final edited form as:

J Alzheimers Dis. 2017 ; 59(1): 131–139. doi:10.3233/JAD-170276.

Recovery from Proactive Semantic Interference and MRI Volume: A Replication and Extension Study

David A. Loewenstein^{a,b,*}, Rosie E. Curiel^{a,b}, Steven DeKosky^e, Monica Rosselli^c, Russell Bauer^{d,e}, Maria Grieg-Custo^b, Ailyn Penate^{a,b}, Chunfei Li^f, Gabriel Lizagarra^f, Todd Golde^e, Malek Adjouadi^f, and Ranjan Duara^{b,e,g,h}

^aCenter on Aging and Department of Psychiatry and Behavioral Sciences, Miller School of Medicine, University of Miami, Miami, FL, USA

^bWien Center for Alzheimer's Disease and Memory Disorders Mount Sinai Medical Center, Miami Beach, FL, USA

^cDepartment of Psychology, Florida Atlantic University, Boca Raton, FL, USA

^dDepartment of Clinical and Health Psychology, University of Florida, Gainesville, FL, USA

^eDepartment of Neurology, University of Florida, Gainesville, FL, USA

^fDepartment of Electrical and Computer Engineering, Center for Advanced Technology and Education, College of Engineering and Computing, Florida International University, Miami, FL, USA

^gCenter for Translational Research In Neurodegenerative Diseases, University of Florida, Gainesville, FL, USA

^hHerbert Wertheim College of Medicine, Florida International University, Miami, FL, USA

Abstract

Background—The rise in incidence of Alzheimer's disease (AD) has led to efforts to advance early detection of the disease during its preclinical stages. To achieve this, the field needs to develop more sensitive cognitive tests that relate to biological markers of disease pathology. Failure to recover from proactive interference (frPSI) is one such cognitive marker that is associated with volumetric reductions in the hippocampus, precuneus, and other AD-prone regions, and to amyloid load in the brain.

Objective—The current study attempted to replicate and extend our previous findings that frPSI is a sensitive marker of early AD, and related to a unique pattern of volumetric loss in AD prone areas.

*Correspondence to: David A. Loewenstein, PhD, Professor of Psychiatry and Behavioral Sciences, Miller School of Medicine, University of Miami, 1695 NW 9th Avenue, Behavioral Health Hospital Building, Suite 3208G, Miami, Florida 33136, USA. Tel.: +1 305 355 9068; Fax: +1 305 355 9076; DLoewenstein@med.miami.edu.

Authors' disclosures available online (<http://j-alz.com/manuscript-disclosures/17-0276r2>).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <http://dx.doi.org/10.3233/JAD-170276>.

Methods—Three different memory measures were examined relative to volumetric loss and cortical thickness among 45 participants with amnesic mild cognitive impairment.

Results—frPSI was uniquely associated with reduced volumes in the hippocampus ($r = 0.50$) precuneus ($r = 0.41$), and other AD prone regions, replicating previous findings. Strong associations between frPSI and lower entorhinal cortex volumes and cortical thickness ($r = 0.60$) and precuneus ($r = 0.50$) were also observed.

Conclusion—Unique and strong associations between volumetric reductions and frPSI as observed by Loewenstein and colleagues were replicated. Together with cortical thickness findings, these results indicate that frPSI is worthy of further study as a sensitive and early cognitive marker of AD.

Keywords

Cortical thickness; LASSI-L; mild cognitive impairment; MRI volume; proactive semantic interference

INTRODUCTION

Cognitive stress tests may be more sensitive to the early manifestations of Alzheimer's disease (AD) than traditional neuropsychological measures [1–3]. Akin to an exercise electrocardiogram which may reveal deficits not observed in the resting state, challenging the memory system with cognitive stress paradigms may reveal deficits which otherwise might be obscured by cognitive reserve and individual compensatory strategies.

The aging of the population and related rise in incidence of AD has resulted in increased interest in the development of more sensitive neuropsychological tests for the early detection of cognitive impairment. One novel test, the Loewenstein-Acevedo Scales for Semantic Interference and Learning (LASSI-L) [3, 4], is a cognitive stress paradigm that employs controlled learning and cued recall to maximize the storage and retrieval of 15 target words belonging to three semantic categories (fruits, articles of clothing, and musical instruments). A unique aspect of the LASSI-L is the instrument's ability to measure proactive semantic interference (PSI: old semantic learning interfering with new learning) and recovery from proactive semantic interference (the ability to recover from PSI effects, by effectively learning a competing list of targets when offered an additional learning trial). Maximum storage of the original targets, PSI, and recovery from PSI have been shown to be very sensitive in discriminating between older adults with mild cognitive impairment (MCI) and those who are cognitively normal and to have good test-retest reliabilities [3, 4]. Equally important, among community-dwelling older adults who scored normally on traditional neuropsychological measures, failure to recover from PSI (frPSI) demonstrated strong associations with amyloid load in the precuneus, posterior cingulate, and whole brain [2]. These strong associations between amyloid load in regions vulnerable to AD pathology and sensitive indices of the LASSI-L (PSI and frPSI) suggest that the LASSI-L may be sensitive enough to detect early cognitive changes associated with amyloid-related neurodegeneration in pre-symptomatic AD. The previous study [2] also explored the association of brain

amyloid load with other standard neuropsychological measures, where only weak or no associations were found.

While brain amyloid load represents an early risk factor for subsequent clinical AD, reductions in regional brain volumes, measured by MRI, may provide a better measure of the actual neurodegeneration associated with the AD cascade. Holland et al. [5] and Dickerson et al. [6] identified several brain regions (discernable on MRI) which may represent a signature of the neurodegeneration that presents early in the course of the illness. In the current investigation, we assessed participants diagnosed with amnesic MCI (aMCI) and correlated the volumes of AD signature brain regions to performance on the LASSI-L and other commonly used memory measures. We wanted to determine the extent to which we could replicate previous findings and hypothesized that frPSI was related to volumetric reductions in the hippocampus and precuneus as well as other AD-prone regions [1]. We also attempted to investigate the relationship between frPSI and cortical thickness (CoTH) in those regions susceptible to AD neurodegeneration.

MATERIALS AND METHODS

Participants

Forty-five older adult participants from the NIH-funded 1Florida Alzheimer's Disease Research Center were recruited into this IRB approved investigation at Mount Sinai Medical Center, Miami Beach, Florida. Participants were evaluated using a standard clinical assessment protocol, which included the Clinical Dementia Rating Scale (CDR) [7], and the Mini-Mental State Examination (MMSE) [8]. An experienced geriatric psychiatrist (MG) who was blind to the neuropsychological test results and had formal training in administering the CDR and MMSE, assessed memory and other cognitive complaints. All participants were community-dwellers, independent in their activities of daily living, had knowledgeable collateral informants, and did not meet DSM-V criteria for Major Neurocognitive Disorder, active Major Depression, or any other neuropsychiatric disorder. In cases where there was evidence of cognitive decline by history and/or clinical examination, the clinician scored the Global CDR as 0.5 and a probable diagnosis of aMCI, pending the results of formal neuropsychological testing. Next, we administered a standard neuropsychological battery uniformly across groups independent of the clinical examination. The neuropsychological battery included delayed recall of the Revised Hopkins Verbal Learning Test (HVLT-R) [9], the National Alzheimer's Coordinating Center (NACC) delayed paragraph recall [10], Category Fluency [11], Block Design of the Wechsler Adult Intelligence Scale–Fourth Edition [12], and the Trail Making Test (Parts A and B) [13]. The LASSI-L was not used for diagnostic determination.

On the basis of the independent clinical interview and performance on the neuropsychological tests, an individual was considered to have aMCI if there were: a) subjective memory complaints by the participant and/or collateral informant; b) evidence by clinical evaluation or history of memory or other cognitive decline; c) Global CDR scale of 0.5; d) one or more memory measures fell below normal limits at 1.5 SD or more relative to age and education related normative data.

The mean age of the aMCI sample was 73.6 (SD = 8.2 years) and the average level of education was 14.57 (SD = 3.3 years). There were 55.6% female participants and 51.1% of participants spoke English as their primary language. The mean MMSE score was 27.00 (SD = 2.1). The LASSI-L has been validated in both English and Spanish [3, 14] and we administered the test battery in the participants' primary and/or preferred language by fluent Spanish/English bilingual psychometricians.

Neuropsychological measures

Loewenstein-Acevedo Scales for Semantic Interference and Learning—The LASSI-L is a novel paradigm that employs controlled learning and cued recall to maximize storage of a list of to-be-remembered target words representing three semantic categories [4]. Test-retest reliabilities of the LASSI-L have been shown to be high in previous studies, and the accuracy of classification of MCI patients versus cognitively normal elderly participants has exceeded 90% [1, 4]. A unique aspect of this paradigm is the presentation of a second list of to-be-remembered words, which share the same semantic categories in the first list, eliciting a considerable amount of proactive semantic interference. Unlike other memory measurement paradigms, the individual is again administered this second list of words to measure recovery from proactive semantic interference. We describe the specific elements of the test below.

The examinee is instructed to remember a list of 15 common words that are fruits, musical instruments, or articles of clothing (five words per category). After being presented all 15 words, the examinee is asked to recall them. After free recall has ended, the examinee is presented with each category cue (e.g., clothing) and asked to recall the words that belonged to that category (LASSI-L A1). The examinee is again presented with the target stimuli for a second learning trial of List A 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 different, but semantically related word list (i.e., List B), which is 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 person is asked to freely recall the List B words; this assesses proactive semantic interference effects (LASSI-L B1). Then, participants are asked to recall the List B words that belonged to each of the three categories. List B words are presented again, followed by a second category-cued recall trial. This second learning trial for the new list measures the participant's ability to recover from the proactive semantic interference effects (LASSI-L B2). Difficulties with LASSI-L B2 recall is thought to represent frPSI. The LASSI-L has been determined to have adequate test-retest reliabilities ($r = 0.60$ to $r = 0.89$) among aMCI and early dementia. High discriminative and concurrent validity have also been reported [15].

Hopkins Verbal Learning Test—The HVLT-R [9] a short test of verbal memory, consists of 12 words belonging to three distinct semantic categories. Psychometrists read the word-list to participants, who were asked to immediately recall as many words as they could remember. This procedure was repeated for a total of 3 trials. After a delay of 20–25 min,

another free recall occurred. The HVLTL has been found to have good sensitivity and specificity in differentiating among normal patients and those with possible MCI [16].

NACC delayed paragraph recall—This is a widely-used measure that is employed by the National Alzheimer's Coordinating Center and involves a 20-min delayed recall for a story passage consisting of 25 elements [10].

MRI measurements—The 45 aMCI participants underwent MRI scanning using a Siemens Skyra 3T MRI scanner at the Mount Sinai Medical Center. Brain parcellation 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 AD signature regions [5, 6, 17], including the hippocampus, entorhinal cortex (ERC), precuneus, posterior cingulate gyrus, inferior temporal gyrus, temporal pole, superior parietal lobule, superior frontal gyrus, and posterior cingulate gyrus. 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 is indicative of greater ventricular dilatation and is inversely correlated with measures such as the hippocampus and other brain regions.

We employed visual inspection of the segmentation as outlined in the Alzheimer's Disease Neuroimaging Initiative protocol. There were no segmentation issues with any of the scans and none of the patients required manual adjustments. Given the high degree of association between corresponding structures in the right and left hemispheres, homologous structures (e.g., precuneus, inferior temporal lobules) were combined and normalized using intracranial volume [1]. We also calculated absolute mean CoTH in both hemispheres in those regions in which AD volumes had been calculated and combined them with these hemispheric values to obtain total CoTH for specific brain regions.

Statistical analyses—A major goal of the study was to determine the extent to which we could replicate previous findings showing that frPSI was strongly and/or uniquely related to reduced MRI volumes. We chose those vulnerable regions in the Loewenstein et al. study [1] including the hippocampi, ERC, rostral frontal regions, inferior lateral ventricle, precuneus, inferior temporal lobules, temporal poles, superior parietal lobules, and posterior cingulate. We conducted a series of Pearson Analyses adjusting p -values to account for the false discovery rate (FDR: Benjamini and Hochberg) [18, 19] associated with each individual cognitive measure which correlated with ten MRI regional volumes. Only corrected p -values of $p < 0.05$ were considered. Analyses were also conducted controlling for FDR, which evaluated the associations between specific cognitive variables and CoTH measures.

RESULTS

After adjusting p -values for FDR, frPSI (captured by LASSI-L B-2 Cued Recall) was associated with lower volumes in the hippocampus ($r = 0.50$; $p = 0.005$), ERC ($r = 0.61$; $p = 0.005$), precuneus ($r = 0.41$; $p = 0.015$), temporal pole ($r = 0.39$; $p = 0.016$), superior parietal lobule ($r = 0.37$; $p = 0.020$), and inferior temporal lobule ($r = 0.35$; $p = 0.026$), and with increased inferior lateral ventricle dilatation ($r = -0.46$; $p = 0.006$) (Table 1). Following

correction for FDR, no other cognitive measures evidenced statistically significant associations with MRI volumetric indices.

Following adjustment for FDR, frPSI was correlated with cortical thinning in the ERC ($r = 0.60$; $p = 0.004$), precuneus ($r = 0.50$; $p = 0.004$), and temporal pole ($r = 0.43$; $p = 0.011$) (Table 2). However, statistically significant associations between HVLt-R total free recall scores and ERC CoTH was observed for the ERC ($r = 0.42$; $p = 0.008$) and pre-cuneus ($r = 0.47$; $p = 0.008$). Further, HVLt-R total free recall scores were associated with lower CoTH in the superior parietal lobules. NACC delayed passage recall was also associated with reduced CoTH in the precuneus and superior parietal lobules.

We were able to compare the strength of directional association between the LASSI-L B2 Cued Recall (measuring frPSI) ($r = 0.60$) with the HVLt-R total recall score ($r = 0.42$) in the ERC. Using Steiger's (1980) Equations 3 and 10 [19], we computed the asymptotic covariance of the estimates; this enabled us to calculate these quantities employing an asymptotic z-test converted into a z-score using Fisher's r-to-z transformation. This calculation resulted in a z score of 1.828 ($p = 0.034$ for a one-tailed test of differential magnitude of association).

In Supplementary Table 1, as part of exploratory analyses, we compared the LASSI-L B2 Cued recall measure with 43 additional Freesurfer MRI volumetric regions available including but not limited to lateral orbital frontal, caudal middle frontal, medial orbital, frontal pole, caudal and rostral anterior cingulate, isthmus cingulate, lingual, pericalcrine, cuneus, fusiform, lateral occipital, brain stem, caudate, putamen, paladium, thalamus, supramarginal, paracentral, precentral, transverse temporal, middle temporal, cerebellar gray matter as well as cerebellar white matter, different aspects of the corpus callosum (anterior, central, posterior), 3rd, 4th, and 5th ventricles, banks of the superior temporal sulcus, superior temporal lobes, inferior parietal, acumbens, choroid plexus, amygdala, parsorbitalis, parsopercularis, and parstriangularis.

After correction for FDR, statistically significant associations were found for the fusiform, supramarginal gyrus, middle temporal, superior temporal, and amygdala regions, all areas that have been associated with neurodegeneration associated with AD [1, 5, 6, 20] (although not preselected as the ten targeted AD regions that were a focus of this replication study). The associations between the thalamus and accumbens regions also remained statistically significant after controlling for FDR.

The scatterplots representing the association between frPSI, delayed paragraph recall and hippocampal volumes as are presented in Figs. 1–3 indicating that there was a wide range of cognitive scores on each measure associated with hippocampal volumes.

DISCUSSION

In an independent sample of older adults diagnosed with aMCI, we were able to largely replicate our previous work [1] demonstrating that frPSI as measured by the LASSI-L is uniquely and significantly associated with volumetric loss in AD prone areas such as the hippocampus, precuneus, inferior temporal lobules, superior parietal areas, and temporal

pole. In addition, we replicated our earlier finding that inferior lateral ventricular enlargement is also associated with frPSI. This is an important observation since ventricular dilatation is an early neuroimaging feature in those with preclinical AD [21].

In the current investigation, we also found strong correlations between the ERC and frPSI, which was not observed in our previous study. We were unable to replicate previous findings of a relationship between frPSI and volumetric reductions in the rostral middle frontal regions in the present study, however. Indeed, Supplementary Table 1 indicates that additional prefrontal and other frontal regions similarly were not related to frPSI. This may be related to differences between samples in the current versus the previous study. While age and average MMSE scores were equivalent in both investigations, it is likely that reductions in ERC volumes and measures of CoTH in the current investigation stems from differences in the admixture of etiological diagnoses in the two distinct aMCI cohorts. In our previous 2017 study [1], the aMCI sample was predominantly community-based, whereas in the present investigation, many of our aMCI participants were recruited from a specialty outpatient memory disorders clinic. It is well established that the base rate of underlying AD is much higher in those seeking evaluation for memory disorders than in the general community [20]. Presumably, the present sample had a greater admixture of participants with underlying AD and this may account for the strong associations between frPSI and volumetric loss in the ERC. This conclusion is further supported by the fact that frPSI was also highly associated with reduced CoTH measures in the ERC, was more strongly associated than immediate recall on the HVLT-R, and was not found with other memory measures. These associations with the ERC are particularly important in that this is an area of neurofibrillary tangle deposition in the early stages of AD [17].

In addition to ERC and hippocampus findings, frPSI was strongly associated with both volume reduction and cortical thinning in the precuneus. This is important given our previous findings that amyloid load in whole brain, and particularly the precuneus was related to frPSI in neuropsychologically normal, but elderly (and therefore, at-risk) community-dwelling elders [2]. Minors, Palmer, and Love [22] found that decreased perfusion in the precuneus is an early finding in AD. Indeed, Lundstrom, Ingvar, and Peterson [23] have emphasized the precuneus in source memory and its relationship and connectivity to a number of brain regions involved in efficient cognitive processing.

Strengths of the current study include the replication of many of our 2017 [1] findings on a larger sample size of aMCI participants using similar diagnostic criteria as our previous cohort of aMCI participants. We also employed methods to control for false discovery rates and to minimize the possibility of family-wise Type 1 errors. Our examination of CoTH and volumetric reductions in aMCI participants demonstrated convergence between volumetric loss and CoTH with regards to performance on the LASSI-L measure most sensitive to frPSI. While frPSI on the LASSI-L were associated with volumetric reductions across a wide range of AD prone brain regions, reduced volumes did not correlate with other memory measures. Although the associations between frPSI and CoTH were stronger for the ERC, other cognitive measures tapping learning, particularly HVLT-R total recall, were related to CoTH in the ERC. Interestingly, HVLT-R total recall and NACC delayed recall for a passage were uniquely related to decreased CoTH in the superior parietal regions. There is

increasing recognition that volumetric measures may differ from measures of CoTH in relationship to cognitive processes [24, 25], and our findings indicate that this is an area worthy of further research.

A potential weakness of the current investigation was that some of the memory measures such as HVL-R delay and delayed NACC passage were used as part of the diagnostic process and it is possible that there was a lower potential range of scores than for the LASSI-L. However, this is unlikely for a number of reasons. First, an inspection of scatterplots in Figs. 1–3 showed a wide distribution of scores on delayed passage recall as well as the HVL-R total score. Secondly, the HVL-R total recall score was not used in diagnostic determination and had a much broader range of scores than the frPSI score of the LASSI-L. Finally, other LASSI-L scores not associated with MRI findings were within equal range as the LASSI-L frPSI measure.

It might also be argued that List B2 cued recall is assessing a process other than putative frPSI effects. Since subjects were only asked to recall targets from List B, it is difficult to evoke deficient supraspan the mechanism that we believe is contributing to the observed frPSI effects. Moreover, a defective supraspan would not explain the high associations between B2 frPSI measures and MRI indices, while no such associations exist for B1 measures vulnerable to PSI. In fact, even after expressing frPSI as a ratio of B2 cued recall to A2 cued recall there were continued statistically significant associations with MRI volumes in the hippocampus, ERC, and inferior lateral ventricles. As we have noted elsewhere, some of the frPSI effects may be related to deficits in source memory which may have some executive components [3] which may reflect disconnection between regions that may not be readily observed with structural MRI. Finally, although a proactive semantic interference (PSI effect) in and of itself was not related to MRI measures, future studies should address traditional memory measures that have a proactive interference component (although existing measures do not address frPSI).

As attention is focused on identification of cognitive deficits in pre-clinical stages of neurodegenerative disorders such as AD, it is important to employ 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 other cognitive measures, is that it has a second cued recall trial which measures the ability to recover from the initial effects of PSI. Proactive semantic interference results in individuals being unable to dismiss information that is no longer relevant and it has been interpreted as an inability to control information coming from memory content [26, 27]. This inhibitory process appears to diminish with repeated administrations of the new target, but not among those with aMCI [2, 3]. It is this frPSI that appears to be related to brain biomarkers associated with AD.

This replication study indicates that frPSI is associated with volumetric measures across a wider spectrum of AD signature regions and more specifically, it is the most highly associated with both volume and CoTH of the ERC. Subsequent longitudinal studies including diverse ethnic/cultural groups, are required to determine the universality of this

finding and whether measures susceptible to frPSI are predictive of longitudinal changes in cognition and specific biomarkers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by the National Institute of Aging Grant number 5 P50 AG047726602 1Florida Alzheimer's Disease Research Center (Todd Golde, PI) and 1 R01 AG047649-01A1 (David Loewenstein, PI).

References

- Loewenstein DA, Curiel RE, Wright C, Sun X, Alperin N, Crocco E, Czaja SJ, Raffo A, Penate A, Melo J, Capp K, Gamez M, Duara R. Recovery from proactive semantic interference in mild cognitive impairment and normal aging: Relationship to atrophy in brain regions vulnerable to Alzheimer's disease. *J Alzheimers Dis.* 2017; 56:1119–1126. [PubMed: 28106554]
- Loewenstein DA, Curiel RE, Greig MT, Bauer RM, Rosado M, Bowers D, Wicklund M, Crocco EA, Pontecorvo M, Joshi AD, Rodriguez R, Barker WW, Hidalgo J, Duara R. A novel cognitive stress test for the detection of preclinical Alzheimer disease: Discriminative properties and relation to amyloid load. *Am J Geriatr Psychiatry.* 2016; 24:804–813. [PubMed: 27160985]
- Loewenstein DA, Curiel R, Buschke H, Duara R. Novel cognitive paradigms for the detection of memory impairment in preclinical Alzheimer's disease. Assessment. 2017; First published date: February-12-2017. doi: 10.1177/1073191117691608
- Crocco E, Curiel RE, Acevedo A, Czaja SJ, Loewenstein DA. An evaluation of deficits in semantic cueing and proactive and retroactive interference as early features of Alzheimer's disease. *Am J Geriatr Psychiatry.* 2014; 22:889–897. [PubMed: 23768680]
- Holland D, Brewer JB, Hagler DJ, Fennema-Notestine C, Dale AM. Subregional neuroanatomical change as a biomarker for Alzheimer's disease. *Proc Natl Acad Sci U S A.* 2009; 106:20954–20959. [PubMed: 19996185]
- Dickerson BC, Stoub TR, Shah RC, Sperling RA, Killiany RJ, Albert MS, Hyman BT, Blacker D, Detoleto-Morrell L. Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults. *J Neurol.* 2011; 76:1395–1402.
- Morris JC. The Clinical Dementia Rating (CDR): Current version and scoring rules. *J Neurol.* 1993; 43:2412–2414.
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975; 12:189–198. [PubMed: 1202204]
- Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test - Revised: Normative data and analysis of inter-form and test-retest reliability. *Clin Neuropsychol.* 1998; 12:43–55.
- Beekly DL, Ramos EM, Lee WW, Deitrich WD, Jacka ME, Wu J, Hubbard JL, Koepsell TD, Morris JC, Kukull WA. The National Alzheimer's Coordinating Center (NACC) database: The Uniform Data Set. *Alzheimer Dis Assoc Disord.* 2007; 21:249–258. [PubMed: 17804958]
- Lucas JA, Ivnik RJ, Smith GE, Bohac DL, Tangalos EG, Graff-Radford NR, Petersen RC. Mayo's older Americans normative studies: Category fluency norms. *J Clin Exp Neuropsychol.* 1998; 20:194–200. [PubMed: 9777473]
- Wechsler, D. Wechsler Adult Intelligence Scale. Fourth. Pearson; San Antonio, TX: 2008.
- Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills.* 1958; 8:271–276.
- Matías-Guiu JA, Curiel RE, Rognoni T, Valles-Salgado M, Fernández-Matarrubia M, Hariramani R, Fernández-Castro A, Moreno-Ramos T, Loewenstein DA, Matías-Guiu J. Validation of the

Spanish version of the LASSI-L for diagnosing mild cognitive impairment and Alzheimer's disease. *J Alzheimers Dis.* 2017; 56:733–742. [PubMed: 27983554]

15. Curiel RE, Crocco E, Acevedo A, Duara R, Agron J, Loewenstein DA. A new scale for the evaluation of proactive and retroactive interference in mild cognitive impairment and early Alzheimer's disease. *J Aging Sci.* 2013; 1:102.
16. De Jager CA, Schrijnemaekers ACM, Honey TEM, Budge MM. Detection of MCI in the clinic: Evaluation of the sensitivity and specificity of a computerized test battery, the Hopkins Verbal Learning Test and the MMSE. *Age Ageing.* 2009; 38:455–460. [PubMed: 19454402]
17. Shen Q, Loewenstein DA, Potter E, Zhao W, Appel J, Greig MT, Raj A, Acevedo A, Schofield E, Barker W, Wu Y, Potter H, Duara R. Volumetric and visual rating of magnetic resonance imaging scans in the diagnosis of amnesic mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement.* 2011; 7:e101–e108. [PubMed: 21784342]
18. Glickman ME, Rao SR, Schultz MR. False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. *J Clin Epidemiol.* 2014; 67:850–857. [PubMed: 24831050]
19. Steiger JH. Tests for comparing elements of a correlation matrix. *Psychol Bull.* 1980; 87:245.
20. Brooks LG, Loewenstein DA. Assessing the progression of mild cognitive impairment to Alzheimer's disease: Current trends and future directions. *Alzheimers Res Ther.* 2010; 2:28. [PubMed: 20920147]
21. Apostolova LG, Thompson PM. Mapping progressive brain structural changes in early Alzheimer's disease and mild cognitive impairment. *Neuropsychologia.* 2008; 46:1597–1612. [PubMed: 18395760]
22. Miners JS, Palmer JC, Love S. Pathophysiology of hypoperfusion of the precuneus in early Alzheimer's disease. *Brain Pathol.* 2016; 26:533–541. [PubMed: 26452729]
23. Lundstrom BN, Ingvar M, Petersson KM. The role of precuneus and left inferior frontal cortex during source memory episodic retrieval. *Neuroimage.* 2005; 27:824–834. [PubMed: 15982902]
24. Gerrits NJ, van Loenhoud AC, van den Berg SF, Berendse HW, Foncke EM, Klein M, Stoffers D, van der Werf YD, van den Heuvel OA. Cortical thickness, surface area and subcortical volume differentially contribute to cognitive heterogeneity in Parkinson's disease. *PLoS One.* 2016; 11:e0148852. [PubMed: 26919667]
25. Sørensen L, Igel C, Pai A, Balas I, Anker C, Lillholm M, Nielsen M. Differential diagnosis of mild cognitive impairment and Alzheimer's disease using structural MRI cortical thickness, hippocampal shape, hippocampal texture, and volumetry. *Neuroimage Clin.* 2016; 13:470–482. [PubMed: 28119818]
26. Friedman NP, Miyake A. The relations among inhibition and interference control functions: A latent-variable analysis. *J Exp Psychol Gen.* 2004; 133:101–135. [PubMed: 14979754]
27. Borella E, Carretti B, Mitolo M, Zavagnin M, Caffarra P, Mammarella N, Fairfield B, Gamboz B, Pira F. Characterizing cognitive inhibitory deficits in mild cognitive impairment. *Psychiatry Res.* 2017; 251:342–348. [PubMed: 28254625]

Fig. 1.
Association between Hippocampal Volume and frPSI.

Fig. 2.
Association between Hippocampal Volume and Delay Passage Recall.

Fig. 3.
Association between Hippocampal Volume and HVL-T-R Total Recall.

Table 1

Associations between MRI volumes and LASSI-L and other memory measures for 45 amnesic MCI participants

	LASSI-L A2 Max. Storage	LASSI-B1 PSI	LASSI-B2 frPSI	HVLT-R Total Recall	HVLT-R Delayed Recall	NACC Delayed Passage Memory
Hippocampal Volume	$r = 0.24$ ($p = 0.292$)	$r = 0.37$ ($p = 0.121$)	$r = 0.50^{**}$ ($p = 0.005$)	$r = 0.30$ ($p = 0.113$)	$r = 0.20$ ($p = 0.663$)	$r = 0.15$ ($p = 0.557$)
Inferior Lateral Ventricle	$r = -0.27$ ($p = 0.227$)	$r = -0.25$ ($p = 0.240$)	$r = -0.46^{**}$ ($p = 0.006$)	$r = -0.36$ ($p = 0.100$)	$r = -0.24$ ($p = 0.575$)	$r = -0.09$ ($p = 0.652$)
Precuneus Volume	$r = 0.15$ ($p = 0.400$)	$r = 0.03$ ($p = 0.865$)	$r = 0.41^{*}$ ($p = 0.015$)	$r = 0.24$ ($p = 0.176$)	$r = -0.12$ ($p = 0.862$)	$r = 0.19$ ($p = 0.557$)
Inferior Temporal Volume	$r = 0.14$ ($p = 0.400$)	$r = 0.24$ ($p = 0.240$)	$r = 0.35^{*}$ ($p = 0.026$)	$r = 0.14$ ($p = 0.372$)	$r = -0.08$ ($p = 0.862$)	$r = 0.09$ ($p = 0.652$)
Superior Parietal Lobe Volume	$r = 0.05$ ($p = 0.358$)	$r = -0.04$ ($p = 0.865$)	$r = 0.37^{*}$ ($p = 0.020$)	$r = 0.25$ ($p = 0.176$)	$r = -0.04$ ($p = 0.862$)	$r = -0.02$ ($p = 0.917$)
Rostral Middle Frontal Volume	$r = 0.13$ ($p = 0.736$)	$r = -0.12$ ($p = 0.437$)	$r = -0.08$ ($p = 0.601$)	$r = 0.35$ ($p = 0.100$)	$r = -0.02$ ($p = 0.862$)	$r = -0.13$ ($p = 0.557$)
Superior Frontal Volume	$r = 0.22$ ($p = 0.300$)	$r = 0.04$ ($p = 0.865$)	$r = 0.15$ ($p = 0.366$)	$r = 0.18$ ($p = 0.305$)	$r = -0.06$ ($p = 0.862$)	$r = 0.22$ ($p = 0.557$)
ERC Volume	$r = 0.36$ ($p = 0.160$)	$r = 0.30$ ($p = 0.215$)	$r = 0.61^{**}$ ($p = 0.005$)	$r = 0.24$ ($p = 0.176$)	$r = 0.30$ ($p = 0.460$)	$r = 0.08$ ($p = 0.652$)
Posterior Cingulate Volume	$r = 0.17$ ($p = 0.400$)	$r = 0.19$ ($p = 0.437$)	$r = 0.26$ ($p = 0.259$)	$r = 0.15$ ($p = 0.372$)	$r = 0.18$ ($p = 0.780$)	$r = 0.24$ ($p = 0.557$)
Temporal Pole Volume	$r = 0.30$ ($p = 0.227$)	$r = 0.28$ ($p = 0.234$)	$r = 0.39^{*}$ ($p = 0.016$)	$r = 0.30$ ($p = 0.123$)	$r = -0.04$ ($p = 0.862$)	$r = 0.18$ ($p = 0.557$)

* $p < 0.05$;** $p < 0.01$. p values for each of the other cognitive indices were corrected for their comparison against 10 MRI measures using corrected p -values considering False Discovery Rate.

Table 2

Associations between MRI cortical thickness (CoTH) and LASSI-L and other memory measures for 45 amnesic MCI participants

	LASSI-L A2 Max. Storage	LASSI-B1 PSI	LASSI-B2 fPSI	HVLT-R Total Recall	HVLT-R Delayed Recall	NACC Delayed Passage Memory
ERC CoTH	$r = 0.37$ ($p = 0.074$)	$r = 0.40$ ($p = 0.056$)	$r = 0.60^{**}$ ($p = 0.004$)	$r = 0.42^{**}$ ($p = 0.008$)	$r = 0.25$ ($p = 0.781$)	$r = 0.20$ ($p = 0.307$)
Precuneus CoTH	$r = 0.32$ ($p = 0.074$)	$r = 0.23$ ($p = 0.276$)	$r = 0.50^{**}$ ($p = 0.004$)	$r = 0.47^{**}$ ($p = 0.008$)	$r = 0.05$ ($p = 0.781$)	$r = 0.38^{*}$ ($p = 0.040$)
Inferior Temporal CoTH	$r = 0.15$ ($p = 0.445$)	$r = 0.18$ ($p = 0.316$)	$r = 0.24$ ($p = 0.176$)	$r = 0.13$ ($p = 0.442$)	$r = 0.12$ ($p = 0.781$)	$r = 0.11$ ($p = 0.456$)
Superior Parietal Lobe CoTH	$r = 0.33$ ($p = 0.074$)	$r = 0.24$ ($p = 0.276$)	$r = 0.27$ ($p = 0.138$)	$r = 0.38^{*}$ ($p = 0.027$)	$r = -0.04$ ($p = 0.781$)	$r = 0.43^{*}$ ($p = 0.032$)
Rostral Middle Frontal CoTH	$r = -0.08$ ($p = 0.681$)	$r = -0.21$ ($p = 0.280$)	$r = -0.08$ ($p = 0.593$)	$r = 0.23$ ($p = 0.223$)	$r = 0.13$ ($p = 0.781$)	$r = -0.12$ ($p = 0.456$)
Superior Frontal CoTH	$r = 0.26$ ($p = 0.131$)	$r = 0.04$ ($p = 0.791$)	$r = 0.19$ ($p = 0.277$)	$r = 0.18$ ($p = 0.335$)	$r = -0.09$ ($p = 0.781$)	$r = 0.26$ ($p = 0.221$)
Posterior Cingulate CoTH	$r = -0.01$ ($p = 0.715$)	$r = -0.07$ ($p = 0.761$)	$r = -0.13$ ($p = 0.445$)	$r = 0.00$ ($p = 0.994$)	$r = 0.07$ ($p = 0.781$)	$r = 0.20$ ($p = 0.307$)
Temporal Pole CoTH	$r = 0.31$ ($p = 0.074$)	$r = 0.29$ ($p = 0.200$)	$r = 0.43^{**}$ ($p = 0.011$)	$r = 0.33^{*}$ ($p = 0.054$)	$r = -0.16$ ($p = 0.781$)	$r = 0.16$ ($p = 0.384$)

** $p < 0.05$;* $p < 0.01$. d' -values for each of the other cognitive indices were adjusted for their comparison against 8 MRI measures using corrected p -values considering False Discovery Rate.