

Cognitive & Behavioral Assessment

# A cognitive stress test for prodromal Alzheimer's disease: Multiethnic generalizability

Rosie E. Curiel Cid<sup>a,\*</sup>, David A. Loewenstein<sup>a</sup>, Monica Rosselli<sup>b</sup>, Jordi A. Matias-Guiu<sup>c</sup>,  
Daema Piña<sup>a</sup>, Malek Adjouadi<sup>d</sup>, Mercedes Cabrerizo<sup>d</sup>, Russell M. Bauer<sup>e</sup>, Aldrich Chan<sup>a</sup>,  
Steven T. DeKosky<sup>e</sup>, Todd Golde<sup>e</sup>, Maria T. Greig-Custo<sup>f</sup>, Gabriel Lizarraga<sup>d</sup>, Ailyn Peñate<sup>f</sup>,  
Ranjan Duara<sup>f</sup>

<sup>a</sup>Department of Psychiatry and Behavioral Sciences, Center for Cognitive Neuroscience and Aging, University of Miami Miller School of Medicine, Miami, FL, USA

<sup>b</sup>Department of Psychology, Florida Atlantic University, Boca Raton, FL, USA

<sup>c</sup>Department of Neurology, San Carlos Research Health Institute (Hospital Clínico San Carlos, IdISSC), Universidad Complutense, Madrid, Spain

<sup>d</sup>Center for Advanced Technology and Education, Florida International University, Miami, FL, USA

<sup>e</sup>Department of Neurology and McKnight Brain Institute, University of Florida, Gainesville, FL, USA

<sup>f</sup>Wien Center for Alzheimer's Disease and Memory Disorders, Mount Sinai Medical Center, Miami Beach, FL, USA

## Abstract

**Introduction:** Culturally fair cognitive assessments sensitive to detecting changes associated with prodromal Alzheimer's disease are needed.

**Methods:** Performance of Hispanic and non-Hispanic older adults on the Loewenstein-Acevedo Scale of Semantic Interference and Learning (LASSI-L) was examined in persons with amnesic mild cognitive impairment (aMCI) or normal cognition. The association between a novel cognitive marker, the failure to recover from proactive semantic interference (frPSI), and cortical thinning was explored.

**Results:** English-speaking aMCI participants scored lower than cognitively normal participants on all LASSI-L indices, while Spanish-speaking aMCI participants scored lower in learning, frPSI, and delayed recall. Healthy controls obtained equivalent scores on all indices except retroactive semantic interference. English-speaking and Spanish-speaking aMCI participants had equivalent scores except English speaker's greater vulnerability to frPSI. Across aMCI groups, frPSI was associated with cortical thinning of the entorhinal cortex and precuneus ( $r = -0.45$  to  $r = 0.52$ ;  $P < .005$ ).

**Discussion:** In diverse populations, LASSI-L performance differentiated patients with aMCI from cognitively normal older adults and was associated with thinning in Alzheimer's disease-prone regions, suggesting its clinical utility.

© 2019 The Authors. Published by Elsevier Inc. on behalf of the Alzheimer's Association. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Keywords:

Prodromal Alzheimer's disease; Mild cognitive impairment; Semantic interference; Cognitive assessment; Diversity

## 1. Introduction

As the population of America's elders continues to grow rapidly, the prevalence of Alzheimer's disease (AD) is

expected to nearly double by 2050 [1] and may rise to epidemic proportions if no cure is found [2]. Prevalence of incident AD in the United States (US) has been found to be higher among ethnic minorities including Hispanics, which represent the largest and fastest growing ethnic group in the nation [3,4]; however, the manner in which AD presents and progresses among Hispanic individuals remains grossly understudied.

\*Corresponding author. Tel.: 305-355-9080; Fax: 305-355-9076.  
E-mail address: [RCuriel2@miami.edu](mailto:RCuriel2@miami.edu)

Many cognitive outcome measures have not been subjected to examination for cultural, language, and education-related bias [5] which can result in erroneous diagnoses and misinterpretation of behaviors that may deviate from their cultural norm [6,7]. While the field has attempted to address potential clinical diagnostic biases as it relates to educational variance [8–10], these methods were not derived from studying diverse individuals at risk for AD. Cognitive outcome measures with greater sensitivity and specificity to detect subtle changes earlier on the disease continuum are needed [11]. Measuring these changes have been challenging because ubiquitously employed outcome measures, while relatively successful at distinguishing between normal cognition and later stage mild cognitive impairment (MCI), or dementia, are insensitive to detect cognitive change in clinically asymptomatic persons who have positive AD biomarkers. Moreover, the use of biomarkers in the diagnosis of MCI due to AD is often limited to clinical research settings, academic centers, or through clinical trials. Thus, it is imperative to develop effective clinical tools and become widely accessible and broadly utilized in any setting.

To address these concerns, our laboratory has developed cross-culturally sensitive “cognitive stress tests” that employ assessment paradigms sensitive to AD during the preclinical and prodromal stages. The Loewenstein-Acevedo Scale of Semantic Interference and Learning (LASSI-L) is unique in its ability to measure the failure to recover from proactive semantic interference (frPSI), a novel cognitive marker of early brain pathology highly associated with incipient AD. PSI occurs when previous learning (List A) interferes with the ability to learn a new list of semantically competing words (List B). The LASSI-L also taps the failure to recover from the effects of PSI (frPSI) or continued difficulty in recalling the semantically competing target words (List B) despite a second exposure, which is measured during a second cued recall trial of the List B words. This breakdown in memory has been shown to be superior to traditional memory measurement in detecting prodromal and preclinical stages of AD [11] as has been referred to as a “cognitive stress test” [11,12] because it was designed to elicit PSI, challenging the inhibition of previously learned semantically related material and making considerable demands on source memory [13]. Loewenstein et al. [12] showed that frPSI on the LASSI-L is highly associated with increased amyloid load in cognitively normal elders and with volumetric loss and cortical thinning among those with early amnesic MCI (aMCI) [14]. Matias-Guiu et al. [15] led the translation of the LASSI-L for a Spaniard population. They generated age- and education-adjusted normative data using logistic regression and validated the LASSI-L for the diagnosis of aMCI and mild AD among 97 healthy participants: 34 individuals with aMCI and 33 with mild AD. They found high internal consistency (0.932) and moderate convergent validity with the Free and Cued Selective Reminding Test. The area under the

receiver-operating characteristic curve for discriminating between healthy controls and aMCI was 0.909, and between controls and mild AD was 0.986. LASSI-L subscales representing maximum encoding, frPSI, and delayed recall yielded the highest diagnostic accuracy, which deemed the LASSI-L a reliable and valid test that could be used for the diagnosis of aMCI and mild AD in a Spanish-speaking population. Subsequent work by this group aimed to compare the diagnostic accuracy of the Free and Cued Selective Reminding Test and the LASSI-L for the diagnosis of prodromal AD using  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography as a reference [16]. The results indicated that frPSI and delayed recall as measured by the LASSI-L allowed for better classification AD/non-AD in comparison to the Free and Cued Selective Reminding Test providing further evidence that frPSI might be a key cognitive marker of prodromal AD with early diagnostic utility. Recent preliminary work by Sanchez et al. [17] in Buenos Aires, Argentina, studied performance on the LASSI-L among Hispanic middle-aged asymptomatic children of patients with late-onset AD. Notably, frPSI deficits differentiated this at-risk group from age-equivalent controls without a family history of late-onset AD and were related to decreased brain connectivity on functional magnetic resonance imaging (MRI).

The present study evaluates comparative performance on the LASSI-L among older adults diagnosed with aMCI versus controls with normal cognition in two culture/language groups: predominantly Spanish-speaking older adults who identified as Hispanic from various countries in Latin America, and primarily English-speaking older adults, most of whom identified as European-American. We were particularly interested in performance as it relates to frPSI (measured by total correct scores on the second cued recall trial of List B). A second aim of the current investigation was to determine the extent to which scores on the LASSI-L B2 cued recall trial (sensitive to frPSI) was associated with cortical thinning on MRI in AD-prone brain regions in both Hispanic and non-Hispanic aMCI groups compared to controls. Performance across groups for other LASSI-L indices (maximum learning [cued A2], PSI [cued B1], retroactive semantic interference [cued A3] and delayed recall) were also studied, given that these indices have previously demonstrated the ability to differentiate between older adults with and without cognitive impairment [11–16].

## 2. Methods

### 2.1. Participants

For the purposes of the current investigation, we studied 247 participants, aged 60 to 98 (114 predominant Spanish speakers and 133 predominant English speakers), from a National Institute of Health funded longitudinal study at the University of Miami Miller School of Medicine as well as from the 1Florida Alzheimer's Disease Research Center

Table 1  
Demographic characteristics of 247 English- and Spanish-speaking aMCI and cognitively normal (CN) older adults

	English-speaking CN n = 62	Spanish-speaking CN n = 51	English-speaking aMCI n = 71	Spanish-speaking aMCI n = 63	F-value or X <sup>2</sup> value	P value
Age (range 60–98 years)	73.89 <sup>ab</sup> SD = 8.3	70.74 <sup>a</sup> SD = 6.2	75.18 <sup>b</sup> SD = 8.5	74.00 <sup>ab</sup> SD = 7.4	3.33	<b>.02</b>
Years of education (range 4–21)	15.83 <sup>b</sup> SD = 2.6	13.22 <sup>a</sup> SD = 3.6	15.78 <sup>ab</sup> SD = 2.9	13.76 <sup>a</sup> SD = 3.4	10.89	<b>&lt;.001</b>
Sex (% female)	69.4	78.4	46.5	60.3	14.64	<b>.002</b>
MMSE (range 23–30)	29.03 <sup>b</sup> SD = 1.2	28.59 <sup>b</sup> SD = 1.5	27.39 <sup>a</sup> SD = 2.1	26.98 <sup>a</sup> SD = 1.8	20.14	<b>&lt;.001</b>

NOTE. Means with different alphabetic superscripts are statistically significant at  $P \leq .05$  by the Tukey's honestly significant difference (HSD) procedure. For example: for age, the only means that are statistically significant after the Tukey's HSD adjustment was Spanish-speaking CN and English-speaking aMCI. P-values that were statistically significant at  $P < .05$  are indicated in bold.

Abbreviations: aMCI, amnesic mild cognitive impairment; MMSE, Mini-Mental State Examination; SD, standard deviation.

(ADRC) for this institutional review board–approved study. In both settings, common assessment protocols were employed with identical diagnostic criteria. At each site, an experienced clinician administered a standard clinical assessment protocol, which included the Clinical Dementia Rating (CDR) scale [18] and the Mini-Mental State Examination (MMSE) [19]. 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 amnesic MCI (aMCI), pending the results of formal neuropsychological testing. Next, a standard neuropsychological battery was administered uniformly across sites independent of the clinical examination.

On the basis of the independent clinical interview and performance on the neuropsychological test battery, diagnostic groups were classified using the following criteria:

### 2.2. Amnesic MCI group

Participants were diagnosed to have aMCI if there were (1) subjective cognitive complaints by the participant and/or collateral informant; (2) evidence by clinical evaluation or a history of memory or other cognitive decline; (3) Global CDR scale of 0.5; (4) below expected performance on delayed recall of the Hopkins Verbal Learning Test, Revised or delayed paragraph recall from the National Alzheimer's Coordinating Center, Uniform Data Set as measured by a score that is 1.5 standard deviation or higher, below the mean using age-, education-, and language-related norms.

### 2.3. Cognitively normal group

Participants were deemed cognitively normal if there were (1) no subjective cognitive complaints made by the participant and/or a collateral informant; (2) no evidence by clinical evaluation or history of memory or other cognitive decline after an extensive interview with the

participant and an informant; (3) Global CDR scale of 0; (4) all memory and nonmemory measures described previously were no lower than 1.0 standard deviation below normal limits for age, education, and language group.

The vast majority of the predominantly English-speaking sample included U.S. born Americans of European descent who were native English speakers and identified as non-Hispanic. The predominantly Spanish-speaking sample included all native Spanish speakers who had immigrated to the United States from a Latin American country and self-identified as Hispanic. Some of the predominantly Spanish-speaking participants were bilinguals, proficient in both languages. We administered the entire test battery in the participants' dominant and preferred language by highly trained and fluent Spanish/English bilingual psychometricians. There were no predominantly Spanish-speaking individuals who had the tests administered in English in the present study. There was careful determination of what the appropriate test language should be to test our bilingual individuals that included a questionnaire to determine language proficiency, consideration of the language that they were educated in, as well as their subjectively preferred language. This resulted in 62 cognitively normal participants who were tested in English and 51 cognitively normal participants who were tested in Spanish (Table 1). In addition, 71 aMCI participants were tested in English, while 63 Hispanic aMCI participants were tested in Spanish, their dominant and preferred language.

## 3. Materials and methods

### 3.1. Neuropsychological measures

The neuropsychological battery included the Hopkins Verbal Learning Test, Revised [20], delayed paragraph recall from the Uniform Data Set of the National Alzheimer's Coordinating Center [21], Category Fluency [22], Block Design of the Wechsler Adult Intelligence Scale, Fourth Edition [23], and the Trail Making Test (Parts A and B)

Table 2  
LASSL-L subscale performance among 247 English- and Spanish-speaking cognitively normal (CN) and aMCI older adults

LASSL-L subscales	English-speaking CN, n = 62	Spanish-speaking CN, n = 51	English-speaking aMCI, n = 71	Spanish-speaking aMCI, n = 63	F-value adjusted for age, sex, and education	P value	Eta-squared uncorrected effect size
Maximum storage (A2 cued recall)	13.50 <sup>a</sup> SD = 1.5 (range 9–15)	13.06 <sup>a</sup> SD = 1.5 (range 8–15)	11.27 <sup>b</sup> SD = 2.3 (range 5–15)	11.24 <sup>b</sup> SD = 2.0 (range 6–14)	19.52	<b>&lt;.001</b>	23.56%
Proactive semantic interference (B1 cued recall)	7.68 <sup>a</sup> SD = 2.8 (range 3–14)	7.43 <sup>ab</sup> SD = 2.7 (range 2–12)	5.54 <sup>c</sup> SD = 2.4 (range 3–14)	6.06 <sup>bc</sup> SD = 2.2 (range 1–11)	8.44	<b>&lt;.001</b>	11.97%
Failure to recover from proactive semantic interference (B2 cued recall)	11.44 <sup>a</sup> SD = 2.3 (range 5–15)	11.02 <sup>a</sup> SD = 2.2 (range 6–15)	8.30 <sup>c</sup> SD = 2.5 (range 2–14)	9.37 <sup>b</sup> SD = 2.2 (range 5–14)	21.54	<b>&lt;.001</b>	24.32%
Retroactive semantic interference (A3 cued recall)	8.79 <sup>a</sup> SD = 2.4 (range 3–14)	7.2 <sup>b</sup> SD = 2.1 (range 3–12)	6.47 <sup>b</sup> SD = 2.0 (range 1–10)	6.37 <sup>b</sup> SD = 2.0 (range 1–11)	16.10	<b>&lt;.001</b>	16.65%
Delayed free recall (both Lists A and B)	19.50 <sup>a</sup> SD = 4.7 (range 0–28)	18.0 <sup>a</sup> SD = 3.8 (range 10–26)	13.30 <sup>b</sup> SD = 5.9 (range 0–24)	13.64 <sup>b</sup> SD = 5.5 (range 0–24)	20.55	<b>&lt;.001</b>	22.91%

NOTE. Unadjusted means are presented. Means with different alphabetic superscripts are statistically significant at  $P < .05$  by the Sidak procedure after statistical adjustment for age, education, and sex.  $P$ -values that were statistically significant at  $P < .05$  are indicated in bold.

Abbreviations: aMCI, amnesic mild cognitive impairment; LASSL-L, Loewenstein-Acevedo Scale of Semantic Interference and Learning; SD, standard deviation.

[24]. For Spanish speakers, previously validated Spanish language versions of tests and test instructions were used. When these were not available, translations were conducted using the Brislin method for cross-cultural research [25]. The LASSL-L was not used for diagnostic determination.

### 3.2. Loewenstein-Acevedo Scale of Semantic Interference and Learning

The LASSL-L employs controlled learning and cued recall to maximize storage of a list of to-be-remembered target words representing three semantic categories [11].

Test-retest reliabilities of the LASSL-L have been shown to be high in previous studies ( $r = 0.60$  to  $r = 0.89$ ) among aMCI and early dementia, and the accuracy of classification of older adults with MCI versus cognitively normal has exceeded 90% [26,27]. The LASSL-L has demonstrated adequate test-retest reliabilities, and high discriminative and concurrent validity [15–17,26,27].

During the administration of the LASSL-L, the examinee is instructed to remember a list of 15 common words that belong to one of the three semantic categories. The first presentation is followed by free recall and then a cued recall trial. Then, the same list is presented for a second time,

Table 3  
Comparison of average proportion of intrusion errors on LASSL-L as a function of total responses on measures of maximum learning on subscales susceptible to proactive and retroactive semantic interference across different groups (N = 247)

LASSL-L indices	English-speaking CN, n = 62	Spanish-speaking CN, n = 51	English-speaking aMCI, n = 71	Spanish-speaking aMCI, n = 63	F-value adjusted for age, education, and sex	P value	Uncorrected effect size eta-squared
Mean % List A2 semantic intrusions (maximum storage)	2.6% <sup>a</sup> SD = 4.5% (range 0.0–.19)	4.1% <sup>a</sup> SD = 6.0% (range 0.0–.24)	6.5% <sup>ab</sup> SD = 9.2% (range 0.0–.31)	9.9% <sup>bc</sup> SD = 13.0% (range 0.0–.33)	7.02	<b>&lt;.001</b>	10.98 %
Mean % List B1 semantic intrusions (PSI)	28.0% <sup>a</sup> SD = 21% (range = 0.00–.71)	27.3% <sup>a</sup> SD = 20% (range = 0.00–.82)	41.9% <sup>b</sup> SD = 23% (range = 0.00–.92)	41.6% <sup>b</sup> SD = 19.2% (range = 0.00–.78)	6.79	<b>&lt;.001</b>	10.17 %
Mean % List B2 semantic intrusions (frPSI)	13.9% <sup>a</sup> SD = 12% (range = 0.00–.58)	14.2% <sup>a</sup> SD = 12% (range = 0.00–.42)	27.60% <sup>b</sup> SD = 18% (range = 0.00–.70)	26.5% <sup>b</sup> SD = 14% (range = 0.00–.58)	12.96	<b>&lt;.001</b>	16.62%
Mean % List A3 semantic intrusions (RSI)	24.5% <sup>a</sup> SD = 16% (range = 0.00–.63)	32.3% <sup>ab</sup> SD = 19% (range = 0.00–.73)	38.5% <sup>b</sup> SD = 20% (range = 0.00–.80)	43.9% <sup>bc</sup> SD = 17% (range = 0.00–.78)	10.36	<b>&lt;.001</b>	14.22%

NOTE. Means with different alphabetic superscripts are statistically significant at  $P < .05$  by the Tukey's honestly significant difference (HSD) test.  $P$ -values that were statistically significant at  $P < .05$  are indicated in bold.

Abbreviations: aMCI, amnesic mild cognitive impairment; CN, cognitively normal; frPSI, failure to recover from proactive semantic interference; LASSL-L, Loewenstein-Acevedo Scale of Semantic Interference and Learning; RSI, retroactive semantic interference.

Table 4  
Cortical thickness among different diagnostic groups (n = 149)

Brain regions of interest	English-speaking CN (n = 42)	Spanish-speaking CN (n = 25)	English-speaking aMCI (n = 46)	Spanish-speaking aMCI (n = 36)	F-value adjusted for age	P value	Effect size
Entorhinal cortex	6.62 <sup>b</sup> SD = .74 (range 4.7–7.9)	6.9 <sup>b</sup> SD = .7 (range 4.9–8.2)	5.97 <sup>a</sup> SD = .98 (range 3.9–8.0)	6.13 <sup>ab</sup> SD = .78 (range 4.4–7.3)	7.19	<.001	12.13%
Parahippocampal	5.29 <sup>abc</sup> SD = .52 (range 3.9–6.3)	5.60 <sup>c</sup> SD = .58 (range 3.9–6.6)	5.11 <sup>b</sup> SD = .60 (range 3.8–6.2)	5.09 <sup>ab</sup> SD = .68 (range 3.6–6.6)	4.11	.008	9.67%
Precuneus	4.46 SD = .32 (range 3.4–5.1)	4.59 SD = .19 (range 4.2–5.0)	4.44 SD = .31 (range 3.9–5.2)	4.42 SD = .3 (range 3.6–5.0)	1.39	.25	3.90%
Posterior cingulate	4.82 <sup>b</sup> SD = .32 (range 4.1–5.4)	4.86 <sup>b</sup> SD = .31 (range 4.3–5.6)	4.73 <sup>ab</sup> SD = .24 (range 4.3–7.9)	4.62 <sup>a</sup> SD = .38 (range 4.7–5.3)	3.89	.01	6.33%
Superior frontal	5.12 SD = .29 (range 4.4–5.9)	5.20 SD = .24 (range 4.7–5.6)	5.05 SD = .27 (range 4.4–5.8)	5.10 SD = .31 (range 4.5–5.9)	1.57	.20	3.00%
Rostral middle frontal	4.44 SD = .26 (range 3.8–5.0)	4.58 SD = .25 (range 4.2–5.2)	4.45 SD = .27 (range 3.8–5.0)	4.53 SD = .32 (range 3.8–5.4)	1.92	.13	4.40%
Superior temporal	5.13 SD = .31 (range 4.5–5.9)	5.22 SD = .23 (range 4.8–5.8)	5.03 SD = .37 (range 4.2–5.8)	5.03 SD = .31 (range 4.0–5.5)	2.47	.06	6.24%
Inferior temporal	5.25 <sup>ab</sup> SD = .35 (range 4.4–5.9)	5.42 <sup>b</sup> SD = .28 (range 4.9–5.9)	5.16 <sup>a</sup> SD = .40 (range 3.8–6.0)	5.33 <sup>ab</sup> SD = .34 (range 4.5–5.9)	3.48	.02	7.08%
Superior parietal	4.09 <sup>a</sup> SD = .25 (range 4.0–5.1)	4.26 <sup>ab</sup> SD = .2 (range 4.3–5.2)	4.17 <sup>ab</sup> SD = .26 (range 3.9–5.3)	4.27 <sup>b</sup> SD = .3 (range 3.8–5.1)	4.01	.01	4.74%
Inferior parietal	4.54 SD = .28 (range 4.3–5.9)	4.72 SD = .21 (range 4.9–5.9)	4.55 SD = .26 (range 4.5–6.1)	4.58 SD = .30 (range 4.8–6.1)	2.36	.06	6.63%

NOTE. Means with different alphabetic superscripts are statistically significant at  $P < .05$  by the Sidak procedure. Abbreviations: aMCI, amnesic mild cognitive impairment; CN, cognitively normal; SD, standard deviation.

followed by a second cued recall trial which measures maximum encoding (Trial A2). Immediately following, a second competing list of to-be-remembered semantically similar words (List B) is presented in the same manner as the first list. Shared semantic categories across both Lists A and B elicits a considerable amount of PSI (measured on Trial B1). Unlike other memory measurement paradigms, the second presentation and subsequent cued recall of this second list of words measures an individual's ability to recover from the effects of PSI (cued B2 recall). Previously published work describes the specific elements of the test in more detail [11,26,27]. The frPSI has been conceptualized in different ways; however, in the current investigation, since this is the first direct comparison between a large number of Hispanics versus non-Hispanic older adults, we opted to define frPSI, our primary outcome measure, in the most straightforward manner consistent with our previous studies of preclinical and prodromal at-risk populations: the total number of correct responses on the LASSI-L cued B2 recall trial. Other indices of interest based on previous findings included maximum learning (cued A2), PSI (cued B1), retroactive semantic interference (cued A3), and delayed recall.

### 3.3. MRI measurements

A subsample of 82 aMCI participants (36 Spanish speakers and 46 English speakers) underwent brain imaging using a Siemens Skyra 3T MRI scanner at either the University of Miami or Mount Sinai Medical Center, given that both hospitals have the identical scanner and imaging protocol. Brain parcellation was obtained using a 3D T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo sequence with 1.0-mm isotropic resolution using FreeSurfer version 5.3 software (<http://surfer.nmr.mgh.harvard.edu>). We examined mean cortical thickness in AD-prone signature regions [28–30], including the medial temporal regions (parahippocampal gyrus, entorhinal cortex), the precuneus, inferior and superior parietal lobules, rostral middle and superior frontal lobules, inferior and superior temporal lobules, and posterior cingulate.

### 3.4. Statistical analyses

A major goal of the study was to determine the extent to which older adults from different ethnicities diagnosed with

Table 5

Relationship between LASSI-L measures and cortical thickness in AD-prone brain regions in 36 Spanish speakers (SS) and 46 English speakers (ES) diagnosed with aMCI

Brain regions of interest	LASSI-B2 frPSI, Spanish (n = 36); English (n = 46)	LASSI-A2 maximum storage, Spanish (n = 36); English (n = 46)	LASSI-B1 proactive semantic interference, Spanish (n = 36); English (n = 46)	LASSI-A3 retroactive semantic interference, Spanish (n = 36); English (n = 46)
ERC	SS: $r = 0.48, P = .003$ ES: $r = 0.48, P < .001$	SS: $r = 0.24, P = .151$ ES: $r = 0.53, P < .001$	SS: $r = 0.13, P = .465$ ES: $r = 0.45, P = .002$	SS: $r = -0.12, P = 0.489$ ES: $r = 0.14, P = 0.35$
Parahippocampal	SS: $r = 0.19, P = .266$ ES: $r = 0.25, P = .096$	SS: $r = 0.08, P = .664$ ES: $r = 0.32, P = .029$	SS: $r = -0.20, P = .251$ ES: $r = 0.17, P = .271$	SS: $r = -0.09, P = .586$ ES: $r = 0.03, P = .863$
Precuneus	SS: $r = 0.45, P = .006$ ES: $r = 0.52, P < .001$	SS: $r = 0.16, P = .351$ ES: $r = 0.34, P = .022$	SS: $r = 0.10, P = .569$ ES: $r = 0.28, P = .060$	SS: $r = -0.06, P = .752$ ES: $r = 0.03, P = .870$
Posterior cingulate	SS: $r = -0.14, P = .425$ ES: $r = 0.48, P < .001$	SS: $r = -0.04, P = .821$ ES: $r = 0.42, P = .004$	SS: $r = 0.28, P = .060$ ES: $r = 0.21, P = .164$	SS: $r = 0.03, P = .266$ ES: $r = 0.16, P = .300$
Inferior parietal thickness	SS: $r = 0.13, P = .466$ ES: $r = 0.26, P = .078$	SS: $r = 0.09, P = .585$ ES: $r = 0.18, P = .246$	SS: $r = -0.13, P = .467$ ES: $r = 0.11, P = .489$	SS: $r = -0.13, P = .460$ ES: $r = 0.01, P = .952$
Superior parietal	SS: $r = 0.22, P = .197$ ES: $r = 0.36, P = .015$	SS: $r = 0.07, P = .703$ ES: $r = 0.23, P = .128$	SS: $r = 0.17, P = .327$ ES: $r = 0.34, P = .021$	SS: $r = -0.08, P = .636$ ES: $r = -0.03, P = .828$
Rostral middle frontal	SS: $r = -0.04, P = .798$ ES: $r = 0.10, P = .503$	SS: $r = .16, P = .338$ ES: $r = 0.04, P = .770$	SS: $r = -0.02, P = .893$ ES: $r = 0.15, P = .446$	SS: $r = 0.06, P = .726$ ES: $r = 0.06, P = .679$
Superior frontal	SS: $r = 0.07, P = .694$ ES: $r = 0.22, P = .147$	SS: $r = 0.24, P = .155$ ES: $r = 0.04, P = .770$	SS: $r = -0.17, P = .322$ ES: $r = 0.12, P = .446$	SS: $r = -0.11, P = .535$ ES: $r = 0.03, P = .890$
Inferior temporal	SS: $r = 0.30, P = .080$ ES: $r = 0.47, P < .001$	SS: $r = 0.19, P = .280$ ES: $r = 0.46, P < .001$	SS: $r = 0.17, P = .313$ ES: $r = 0.49, P < .001$	SS: $r = -0.17, P = .325$ ES: $r = 0.11, P = .455$
Superior temporal	SS: $r = 0.19, P = .272$ ES: $r = 0.49, P < .001$	SS: $r = 0.03, P = .847$ ES: $r = 0.51, P < .001$	SS: $r = -0.08, P = .665$ ES: $r = 0.27, P = .072$	SS: $r = -0.15, P = .398$ ES: $r = 0.30, P = .045$

NOTE.  $P$  values represent an uncorrected two-tailed test of statistical significance. Bolded correlations are statistically significant at  $P \leq .05$  for each language group for different measures after adjusting for false discovery rate (FDR) for each.

Abbreviations: aMCI, amnesic mild cognitive impairment; frPSI, failure to recover from proactive semantic interference; LASSI-L, Loewenstein-Acevedo Scale of Semantic Interference and Learning.

aMCI could be differentiated from their cognitively normal counterparts on LASSI-L indices, particularly the one that measures frPSI. A second goal was to determine the extent to which cognitive performance on the measure is associated with cortical thinning in AD-prone brain regions. We examined demographic variables using a series of one-way analyses of variance models and chi-square analyses. To compare English-speaking and Spanish-speaking aMCI with cognitively normal groups on various LASSI-L measures, we employed analyses of covariance (ANCOVA) models using age, sex, and level of education as covariates. Conservative post hoc tests on adjusted means were conducted with the Sidak procedure, to control for multiple comparisons, at  $P \leq .05$ . We conducted a series of Pearson analyses adjusting  $P$  values to account for the false discovery rate [31] associated with each LASSI-L index that correlated with 10 MRI regional cortical thickness measures for each ethnic/language group. While unadjusted  $P$  values were presented (see Table 5) for each correlation coefficient, only corrected  $P$  values of  $P \leq .05$  after correction for false discovery rate were considered statistically significant, and this was denoted by using bolded font.

#### 4. Results

There were significant group differences in age, educational attainment, sex, and MMSE scores (Table 1). Post hoc tests employing the Tukey's honestly significant

difference procedure showed that cognitively normal Spanish speakers were younger than Spanish-speaking participants diagnosed with aMCI. English-speaking cognitively normal participants were also older than the Spanish-speaking cognitively normal group. The aMCI English-speaking cohort had more males than females, while the other groups consisted of predominantly females. There were no significant differences in male-to-female ratios. There were group differences in educational attainment, where English-speaking cognitively normal participants were more educated than Spanish-speaking groups. English-speaking and Spanish-speaking aMCI groups evidenced equivalent MMSE scores, but as expected, these were lower than the two cognitively normal groups, which did not differ in their MMSE total score.

##### 4.1. Comparative performance on different LASSI-L measures

To examine the comparative performance of English-speaking cognitively normal, Spanish-speaking cognitively normal, English-speaking aMCI, and Spanish-speaking aMCI groups on different LASSI-L indices, we conducted a series of one-way ANCOVAs with age, education, and sex as covariates in all models. Since all ANCOVA analyses yielded statistically significant results at  $P \leq .001$ , we conducted a series of conservative post hoc tests employing the Sidak procedure at  $P \leq .05$ .

All cognitively normal participants obtained equivalent scores on the LASSI-L measure tapping maximum learning of List A targets (cued A2), PSI (cued recall of List B1), frPSI (cued recall of List B2), and delayed recall (Table 2). Spanish-speaking cognitively normal participants obtained lower scores on a measure susceptible to retroactive semantic interference (cued Recall A3) as compared to their English-speaking counterparts. Retroactive semantic interference occurs when newly learned material interferes with the recall of previously learned material.

English-speaking aMCI participants scored lower than English-speaking cognitively normal participants on all LASSI-L measures. Spanish-speaking aMCI participants scored lower than Spanish-speaking cognitively normal participants on measures of maximum learning, frPSI, and delayed recall but evidenced equivalent scores on cued B1 (measuring PSI) and cued A3 (retroactive semantic interference). Finally, despite frPSI differentiating cognitively normal participants from aMCI participants across culture/language groups, this cognitive marker was more impaired in the non-Hispanic cohort (English-speaking aMCI participants).

Another indicator of semantic interference is the number of semantic intrusion errors on each list. These errors are calculated as a percentage of total responses exhibited on cued A2 recall (maximum learning), cued B1 recall (PSI), cued B2 recall (frPSI), and cued A3 recall (retroactive semantic interference) (Table 3). Across culture/language groups, aMCI made more errors on indices sensitive to PSI and frPSI than their cognitively normal counterparts. English-speaking aMCI exhibited a higher percentage of semantic intrusions on A3 cued recall (a measure of retroactive semantic interference) than individuals in the English-speaking cognitively normal group. In contrast, Spanish-speaking aMCI persons exhibited a higher percentage of semantic intrusions than their Spanish-speaking cognitively normal counterparts on cued A2 (maximum learning of List A).

#### 4.2. Cortical thickness in Hispanic and non-Hispanic diagnostic groups

There were statistically significant group differences in cortical thickness in the entorhinal cortex, parahippocampal gyrus, posterior cingulate, and superior parietal regions at  $P \leq .01$  among the four diagnostic groups (Table 4). Post hoc tests of means indicated that cognitively normal Spanish-speaking and English-speaking individuals evidenced similar nonstatistically significant values in these regions. Similarly, Spanish-speaking and English-speaking MCI participants also achieved comparable and nonstatistically significant values. English-speaking aMCI participants evidenced less cortical thickness in the entorhinal cortex than cognitively normal counterparts of

both cultures/languages. Conversely, Spanish-speaking cognitively normal older adults had greater cortical thickness than both aMCI groups in the parahippocampus. Finally, Spanish-speaking cognitively normal participants had greater cortical thickness than Spanish-speaking aMCI participants in the posterior cingulate.

#### 4.3. Associations between LASSI-L subscales and cortical thickness in aMCI

We examined the associations between cortical thickness in AD-prone regions and different LASSI-L measures among 36 Spanish-speaking and 46 English-speaking participants diagnosed as aMCI.

All Spanish-speaking and English-speaking aMCI participants exhibited moderately strong associations between frPSI and cortical thickness in the entorhinal cortex ( $r = 0.48$ ;  $P = .003$  and  $r = 0.48$ ;  $P = .001$ , respectively) and precuneus ( $r = 0.45$ ;  $P = .006$  and  $r = 0.52$ ;  $P < .001$ , respectively) (Table 5). English-speaking aMCI participants demonstrated additional associations between frPSI and cortical thickness in the posterior cingulate ( $r = 0.48$ ;  $P = .001$ ); inferior temporal ( $r = 0.47$ ;  $P = .001$ ), superior temporal ( $r = 0.49$ ;  $P = .001$ ), and superior parietal regions ( $r = 0.46$ ;  $P = .015$ ). Further, for these participants, maximum encoding of List A2 also showed statistically significant associations with the entorhinal cortex, parahippocampus, precuneus, posterior cingulate, and inferior and superior temporal regions (range of  $r$  values from 0.32 to 0.53). For English-speaking participants diagnosed with aMCI, the only statistically significant association was between B1 cued recall (PSI) and cortical thickness in the inferior temporal regions ( $r = 0.49$ ;  $P = .001$ ). All of the aforementioned correlations remained statistically significant after correction for false discovery rate.

## 5. Discussion

This is the first investigation to directly compare the performance of predominantly Spanish-speaking older adults who identify as Hispanic with predominantly English-speaking counterparts who identify as non-Hispanic on the LASSI-L, a cognitive stress test that assesses memory using a semantic interference paradigm. We sought to expand upon previous investigations of the LASSI-L that demonstrated the instrument's efficacy in detecting preclinical and prodromal AD and its association with early biological markers brain pathology [12–14]. In the present study, we specifically examined the relationship between frPSI and cortical thickness in AD-prone brain regions.

Even after statistical adjustment for demographic factors, all cognitively normal participants obtained equivalent scores on all LASSI-L subscales with the exception of

performance on a subscale that taps retroactive semantic interference. Cognitively normal individuals outperformed participants with aMCI on subscales measuring maximum encoding (A2 cued recall), recovery from PSI (B2 cued recall), and delayed recall. These findings support the ability of the LASSI-L to discriminate individuals with normal cognition from older adults diagnosed with aMCI across two ethnic groups. Notably, the deficits noted in this heterogeneous population of predominantly Spanish-speaking Hispanics in the U.S. were similar to a recent study conducted in Spain showing that the LASSI-L effectively discriminated between patients diagnosed with aMCI or probable AD from healthy elderly Spanish controls [16]. As noted by Loewenstein et al. [11], both PSI and the failure to recover from the effects of PSI (frPSI) can be observed in normal aging, MCI, and dementia. The value of measuring frPSI, in particular, is that the vast majority of individuals with normal cognition are able to recover from the semantic interference effect when given another opportunity to learn to the competing list, while a significant number of older adults diagnosed with MCI (particularly those with underlying AD brain pathology) do not recover from the performance deficit observed as a result of PSI. Therefore, it is not that frPSI is absent in normal aging, but rather, that these effects are accentuated among persons with amyloid load and other manifestations of neurodegeneration in the brain [12–14]. The inability to accurately recollect target exemplars in the semantic network and difficulties with source memory have long been associated with AD pathology [11].

In the present study, after correction for false discovery rate, cortical thinning in AD-vulnerable brain regions among aMCI participants such as the entorhinal cortex and the precuneus, two of the earliest affected brain regions in AD revealed moderately strong relationships with frPSI deficits, regardless of the culture/language group. In addition, for predominantly English-speaking aMCI participants specifically, frPSI deficits were also associated with cortical thinning in the posterior cingulate, superior and inferior temporal, and superior parietal regions. Given less propensity to exhibit frPSI than their English-speaking counterparts, it is possible that Hispanic individuals had an attenuated relationship with other AD-prone clinical regions. Another possibility is that English-speaking aMCI participants may have had a predominant neocortical subtype of AD as opposed to Spanish speakers who may have had more of a limbic predominant subtype. Although beyond the scope of the present study, this is an interesting finding which may be worthy of further research. Cortical thinning in both the entorhinal cortex and precuneus suggests that frPSI deficits are associated with brain pathology in prodromal AD states. It should be noted that even though the association between the cortical thickness measures,

such as the entorhinal cortices and LASSI-L indices, yielded total explained variance that was relatively modest (<30%), these correlations in fact represent relatively robust relationships in the neuroimaging literature. This likely reflects the fact that LASSI-L performance is not only related to the structural integrity of the brain region but may also be related to unmeasured factors, such as the presence of amyloid load, tau burden, synaptic dysfunction, neuroinflammation, and so forth. This is always an issue when comparing a cognitive test, which measures more functional parameters, to brain volume or cortical thickness tap structure rather than function. Future studies should include multimodal imaging including fMRI, tau, and amyloid positron emission tomography/computed tomography.

The current investigation represents the first direct comparison of Hispanic and non-Hispanic elders in the U.S. using a cognitive stress test and adds to the literature regarding the clinical characterization of aging Hispanics with MCI [32]. Strengths of the current investigation include a large sample size, carefully diagnosed participants, and the use of MRI cortical thickness measures. We also included statistical adjustments for demographic variables (i.e., education, and so forth) and controlled for the large number of MRI and LASSI-L comparisons using adjustments to account for false discovery rate, which increases confidence in our findings.

Potential weaknesses included the lack of cerebrospinal fluid or neuroimaging measures of amyloid and tau burden, as well as functional biomarkers such as fMRI. It was also not possible to compare the LASSI-L to other commonly used neuropsychological measures, which unlike the LASSI-L, were used to diagnose as doing so would lead to circularity in argument.

The current findings indicate that performance on various LASSI-L subscales have clinical diagnostic utility in Hispanics older adults at risk for developing AD. Particularly important is the relationship between the cognitive marker, frPSI, and cortical thinning in hallmark brain regions affected in AD. Longitudinal follow-up of these and additional ethnically diverse participants should provide further clarity regarding the ability of the LASSI-L to predict progression of cognitive decline over time.

### Acknowledgments

This research was funded by the National Institute on Aging Grant 1 R01 AG047649-01A1 (David Loewenstein, PI), 5 P50 AG047726602 (Florida Alzheimer's Disease Research Center (Todd Golde, PI), and National Science Foundation awarded to Malek Adjouadi under NSF grants CNS-1532061, CNS-0959985, CNS-1551221, and HRD- 0833093.



## RESEARCH IN CONTEXT

1. Systematic review: Hispanics represent the fastest growing minority group in the nation. As the population ages, the field needs culturally fair cognitive outcome measures sensitive enough to detect prodromal Alzheimer's disease. The current investigation represents the first direct comparison of Hispanic and non-Hispanic elders using the Loewenstein-Acevedo Scale of Semantic Interference and Learning (LASSI-L), a cognitive stress test, sensitive to memory changes that occur in the mild cognitive impairment (MCI) stage or before.
2. Interpretation: Performance deficits on various LASSI-L indices differentiated persons with normal cognition from those with amnesic MCI, across both culture/language groups and LASSI-L performance was associated with cortical thinning in Alzheimer's disease-prone regions.
3. Future directions: This large sample included Hispanics from diverse Latin American countries who performed similar to Spanish-speaking elderly in Spain, which suggests that the findings may be generalizable to heterogeneous groups of Hispanics throughout the U.S. and adds to the existing literature about the clinical characterization of aging Hispanics with MCI.

## References

- [1] West LA, Cole S, Goodkind D, He W. 65+ in the United States: 2010. US Census Bureau; 2014. p. 23–212.
- [2] Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. *J Alzheimer's Dement* 2007;3:186–91.
- [3] Hebert LE, Scherr PA, L Bienias J, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Arch Neurol* 2003;60:1119–22.
- [4] US Alzheimer's Association. Alzheimer's disease facts and figures. *J Alzheimer's Dement* 2010;6:158–94.
- [5] Manly JJ. Advantages and disadvantages of separate norms for African Americans. *Clin Neuropsychologist* 2005;19:270–5.
- [6] Ardila A. Impact of culture in neuropsychological assessment. In: Uzzell B, Pontón M, Ardila A, eds. *International Handbook of Cross-Cultural Neuropsychology*. 2nd ed. New Jersey: Lawrence; 2013.
- [7] Rogler LH, Malgady RG, Rodriguez O. *Hispanics and Mental Health: A Framework for Research*. Florida: Krieger; 1989.
- [8] Cherner M, Suarez P, Lazzaretto D, Fortuny LAI, Mindt MR, Dawes S, et al. Demographically corrected norms for the brief visuospatial memory test-revised and Hopkins verbal learning test-revised in monolingual Spanish speakers from the US–Mexico border region. *Arch Clin Neuropsychol* 2007;22:343–53.
- [9] Dotson VM, Kitner-Triolo M, Evans MK, Zonderman AB. Literacy-based normative data for low socioeconomic status African Americans. *Clin Neuropsychologist* 2008;22:989–1017.
- [10] Steinberg BA, Bieliauskas LA, Smith GE, Ivnik RJ, Malec JF. Mayo's Older Americans normative studies: Age-and IQ-adjusted norms for the auditory verbal learning test and the visual spatial learning test. *Clin Neuropsychologist* 2005;19:464–523.
- [11] Loewenstein DA, Curiel RE, Duara R, Buschke H. Novel cognitive paradigms for the detection of memory impairment in preclinical Alzheimer's disease. *J Assess* 2018;25:348–59.
- [12] Loewenstein DA, Curiel RE, Greig MT, Bauer RM, Rosado M, Bowers D, et al. A novel cognitive stress test for the detection of preclinical Alzheimer disease: discriminative properties and relation to amyloid load. *J Geriatr Psychiatry* 2016;24:804–13.
- [13] Loewenstein DA, Curiel RE, DeKosky S, Bauer RM, Rosselli M, Guinjoan SM, et al. Utilizing semantic intrusions to identify amyloid positivity in mild cognitive impairment. *J Neurol* 2018;91:e976–84.
- [14] Loewenstein DA, Curiel RE, Wright C, Sun X, Alperin N, Crocco E, et al. Recovery from proactive semantic interference in mild cognitive impairment and normal aging: relationship to atrophy in brain regions vulnerable to Alzheimer's disease. *J Alzheimer's Dis* 2017;56:1119–26.
- [15] Matias-Guiu JA, Cabrera-Martín MN, Curiel RE, Valles-Salgado M, Rognoni T, Moreno-Ramos T, et al. Comparison between FCSRT and LASSI-L to detect early stage Alzheimer's disease. *J Alzheimer's Dis* 2018;61:103–11.
- [16] Matías-Guiu JA, Curiel RE, Rognoni T, Valles-Salgado M, Fernandez-Matarrubia M, Hariramani R, et al. Validation of the Spanish version of the LASSI-L for diagnosing mild cognitive impairment and Alzheimer's disease. *J Alzheimer's Dis* 2017;56:733–42.
- [17] Sánchez SM, Abulafia C, Duarte-Abritta B, de Guevara M, Castro MN, Drucaroff L, et al. Failure to recover from proactive semantic interference and abnormal limbic connectivity in asymptomatic, middle-aged offspring of patients with late-onset Alzheimer's disease. *J Alzheimer's Dis* 2017;60:1183–93.
- [18] Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *J Neurol* 1993;43:2412–4.
- [19] 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;12:189–98.
- [20] Benedict RH, Schretlen D, Groninger L, Brandt J. Hopkins verbal learning test—revised: normative data and analysis of inter-form and test-retest reliability. *Clin Neuropsychologist* 1998;12:43–55.
- [21] Beekly DL, Ramos EM, Lee WW, Deitrich WD, Jacka ME, Wu J, et al. The National Alzheimer's Coordinating Center (NACC) database: the uniform data set. *Alzheimer Dis Assoc* 2007;21:249–58.
- [22] Binetti G, Magni E, Cappa SF, Padovani A, Bianchetti A, Trabucchi M. Semantic memory in Alzheimer's disease: an analysis of category fluency. *J Clin Exp Neuropsychol* 1995;17:82–9.
- [23] Wechsler D. *Wechsler Adult Intelligence Scale—4th ed.* Texas: NCS Pearson; 2008 (WAIS-IV).
- [24] Brislin RW. Back-translation for cross-cultural research. *J Cross-cultural Psychology* 1970;1:185–216.
- [25] Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills* 1958;8:271–6.
- [26] 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* 2013;1:1000102.
- [27] Crocco E, Curiel RE, Acevedo A, Czaja S, Loewenstein DA. An evaluation of deficits in semantic cueing and proactive and retroactive interference as early features of Alzheimer's disease. *J Geriatr Psychiatry* 2014;22:889–97.
- [28] Dickerson BC, Bakkour A, Salat DH, Feczko E, Pacheco J, Greve DN, et al. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cereb Cortex* 2009;19:497–510.

- [29] Sperling RA, Johnson KA, Doraiswamy PM, Reiman EM, Fleisher AS, Sabbagh MN, et al. Amyloid deposition detected with florbetapir F 18 ((18) F-AV-45) is related to lower episodic memory performance in clinically normal older individuals. *Neurobiol Aging* 2013;34:822–31.
- [30] Joshi AD, Pontecorvo MJ, Lu M, Skovronsky DM, Mintun MA, Devous MD. A semiautomated method for quantification of F 18 florbetapir PET images. *J Nucl Med* 2015;56:1736–41.
- [31] Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Statistical Society Ser B (Methodological)* 1995;289:300.
- [32] O'Bryant SE, Johnson L, Balldin V, Edwards M, Barber R, Williams B, et al. Characterization of Mexican Americans with mild cognitive impairment and Alzheimer's disease. *J Alzheimers Dis* 2013;33:373–9.