The relationship of semantic intrusions to different etiological subtypes of MCI and cognitively healthy older adults

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Abstract
Introduction: There is increasing evidence that susceptibility to proactive semantic interference (PSI) and the failure to recover from PSI (frPSI) as evidenced by intrusion errors may be early cognitive markers of both preclinical and prodromal Alzheimer’s disease (AD).

Methods: One hundred forty-five participants were administered extensive clinical and neuropsychological evaluations including the Loewenstein-Acevedo Scales for Semantic Interference and Learning (LASSI-L), a sensitive cognitive stress test measuring PSI and frPSI. Participants also underwent structural magnetic resonance imaging (MRI) and amyloid positron emission tomography/computed tomography (PET/CT) imaging.

Results: PSI and frPSI errors were much more prevalent in the mild cognitive impairment (MCI)-AD (amyloid positive) group than the other diagnostic groups. The number of intrusion errors observed across the other MCI groups without amyloid pathology and those with normal cognition were comparable.

Discussion: Semantic intrusion errors on the LASSI-L occur much less frequently in persons who have different types of non–AD-related MCI and may be used as an early cognitive marker of prodromal AD.

KEYWORDS
Alzheimer’s disease, amyloid, biomarkers, cognitive assessment, etiological subtypes of MCI, Intrusion errors, memory, mild cognitive impairment, neuropsychological tests, semantic interference

1 | INTRODUCTION

Alzheimer’s disease (AD) is a devastating condition affecting nearly 6 million Americans. By 2060, this number is expected to more than double to 14 million due to the growing aging population.1,2 As such, there is an urgent need to develop therapeutic treatments that can prevent, slow, or stop the progression of AD.3 The failure of clinical trials has been largely attributed to the fact that therapeutic interventions were administered too late in the disease process.4-8 Moreover, due to the high costs associated with diagnostic imaging such as amyloid positron emission tomography (PET) and its limited access, many studies ended up enrolling participants who did not have underlying AD pathology.9
The ability to accurately and inexpensively identify individuals with amyloid positivity earlier on the AD continuum is essential for the success of future clinical trials.

Identifying reliable and sensitive clinical markers that measure early cognitive change associated with the presence of brain amyloid would improve the identification of individual at-risk for neurodegeneration who are in the preclinical or prodromal stages of illness, when intervention is likely to yield the highest efficacy. Preclinical states of AD have been defined as a period with the absence of clinical signs and symptoms of AD, but with the presence of at least one biomarker of AD pathology. The prodromal stage of AD, also referred as mild cognitive impairment (MCI) due to AD, is a period where there are obvious symptoms of brain dysfunction with the primary underlying pathophysiology of AD.

Using traditional neuropsychological assessments to identify early cognitive changes associated with AD presents significant limitations. Specifically, most traditional neuropsychological measurements fail to detect the earliest neurocognitive deficits present during the prodromal or preclinical stages of AD and have had relatively modest correlations with the hallmark biomarkers of AD. A novel yet widely studied cognitive stress test, the Loewenstein-Acevedo Scales for Semantic Interference (LASSI-L), has shown to be sensitive to early cognitive changes associated with AD and has outperformed other widely used traditional memory tests in detecting prodromal AD.

The LASSI-L measures cognitive performance that includes the susceptibility to proactive semantic interference (PSI: old semantic learning interfering with new learning); the failure to successfully recover from the effects of PSI, despite being given an additional learning trial (frPSI: the inability to recover from PSI effects); and semantic intrusion errors. Studies conducted by our group and others have shown that the LASSI-L has excellent psychometric properties and is useful to effectively differentiate community-dwelling older adults with MCI from those who are cognitively unimpaired. The failure to recover from PSI in particular has been strongly associated with volumetric reductions in areas prone to AD neurodegeneration (hippocampus, precuneus, inferior temporal lobules, superior parietal areas, and temporal pole), among persons with amnestic MCI (aMCI), whereas traditional neuropsychological tests have shown no or only weak associations.

Recently, it was found that intrusion errors produced on the LASSI-L scales tapping into PSI and frPSI were able to successfully differentiate individuals with aMCI who were amyloid positive (presumably prodromal AD) from other aMCI groups who were amyloid negative; however, the limitation of this previous work was that amyloid-negative MCI individuals were not classified according to the underlying etiology (neurological vs non-neurological impairment) and no cognitively normal group was included for comparison purposes.

In the current investigation, the amount of intrusion errors on the LASSI-L subscales that measure both PSI and frPSI was compared among cognitively normal participants, MCI participants who were non-neurologically impaired and amyloid negative, MCI participants who were neurologically impaired and amyloid negative, and MCI participants who were amyloid positive with presumptive underlying AD pathology (amyloid positive).

### RESEARCH IN CONTEXT: THE RELATIONSHIP OF SEMANTIC INTRUSIONS TO DIFFERENT ETIOLOGICAL SUBTYPES OF MCI AND COGNITIVELY HEALTHY OLDER ADULTS

1. **Systematic review**: Pertinent literature was reviewed utilizing online databases (e.g., PubMed). The Loewenstein-Acevedo Scales for Semantic Interference (LASSI-L), a cognitive stress test, has previously shown sensitivity for detection of early cognitive changes associated with Alzheimer’s disease (AD) neuropathology in presymptomatic older adults. Reliable/sensitive cognitive markers related to biological markers of AD neuropathology are needed.

2. **Interpretation**: Semantic intrusion errors on the LASSI-L were more prevalent among persons with mild cognitive impairment (MCI) who were amyloid positive in comparison to other diagnostic groups, suggesting that semantic intrusions represent a cognitive marker associated with presumptive underlying AD.

3. **Future directions**: Future studies should focus on the replication/extension of these preliminary findings. Obtaining tau scans, examining functional magnetic resonance imaging (fMRI) connectivity, and employing larger subgroups of MCI participants with within-group heterogeneity could further elucidate specific mechanisms underlying semantic intrusions.

### METHODS

In the current investigation, we recruited 145 community-dwelling older adults ages 54 to 98, who were functionally independent (56% who were predominant Spanish speakers and 44% who were predominant English speakers), from the 1Florida Alzheimer’s Disease Research Center (ADRC), Clinical Core site (Dr. Duara, Principal Investigator) at Mount Sinai Medical Center, Miami Beach, Florida. All human subjects provided informed consent. The 1Florida ADRC baseline evaluation included extensive clinical and neuropsychological evaluations, magnetic resonance imaging (MRI), and amyloid positron emission tomography/computed tomography (PET/CT) imaging to assess fibrillar amyloid plaques. A common clinical assessment was administered to all participants, which included the Clinical Dementia Rating (CDR) scale and the Mini Mental State Examination (MMSE) (range 24-31). The neuropsychological evaluation included the Hopkins Verbal Learning Test-Revised (HVLT-R), Delayed Recall from the Logical Memory subtest of the National Alzheimer’s Coordinating Center
Uniform Data Set (NACC UDS), the Block Design subtest of the Wechsler Adult Intelligence Scales-Fourth Edition, and parts A and B of the Trail Making Test. As part of the testing protocol, all participants were administered the LASSI-L, which was not used for diagnostic classification. Diagnostic groups were classified using the following criteria.

2.1  |  Cognitively normal group (CN; n = 31)

Participants were classified as cognitively normal (CN) if there were (1) no subjective cognitive complaints made by the participant and/or a collateral informant; (2) no indication of memory/cognitive decline after an extensive clinical interview with the participant and their informant; (3) Global Clinical Dementia Rating (CDR; 42) scale score of 0; (4) all memory (e.g., HVLT-R or delayed paragraph recall from the NACC UDS) and non-memory measures (e.g., Category Fluency, Trails A & B, and the Block Design subtest [WAIS-IV]) were less than 1.0 SD below normal limits for age, education, and language group; and (5) a negative amyloid scan as read by an experienced rater (RD). Notably, high inter-rater reliability has been established previously between RD and other expert readers.

2.2  |  Mild cognitive impairment with presumptive AD (MCI-AD; n = 44)

Participants in this group presented with the following: (1) fulfilled Petersen’s criteria for MCI (45–47); (2) subjective cognitive complaints reported by the participant and/or collateral informant; (3) Global CDR scale score of 0.5; (4) impaired delayed recall (ie, scored 1.5 SD or greater, below the mean, accounting for age, education, and language of testing) for either the HVLT-R or the delayed paragraph recall from the NACC UDS and/or scored 1.5 SD below expected levels on non-memory measures as described for the CN group; (5) clinical course, history, and brain imaging not consistent with AD but with another specific neurological condition; and (6) amyloid scans read by an experienced rater as amyloid negative. Specifically, four cases were diagnosed with diffuse Lewy body disease, three cases were diagnosed with cognitive impairment attributed to frontal temporal lobar degeneration, three cases with cerebrovascular disease, one case with cancer-related cognitive dysfunction, and four were unspecified but presented as neurodegenerative in nature.

2.3  |  Mild cognitive impairment with suspected non-AD pathology (MCI-SNAP; n = 38)

These participants presented with the following: (1) fulfilled Petersen’s criteria for MCI (45–47); (2) subjective cognitive complaints were reported by the participant and/or collateral informant; (3) Global CDR scale score of 0.5; (4) impaired delayed recall (ie, scored 1.5 SD or more below the mean, accounting for age, education, and language of testing) for either the HVLT-R or the delayed paragraph recall from the NACC UDS and/or scored 1.5 SD below expected levels on non-memory measures as described for the CN group; (5) clinical course and history consistent with AD with evidence of AD-related neurodegeneration on brain imaging; and (e) amyloid scans read by an experienced rater as amyloid negative.

2.4  |  Mild cognitive impairment non-AD neurological pathology (MCI non-AD neuro; n = 15)

These participants presented with the following: (1) fulfilled Petersen’s criteria for MCI (45–47); (2) subjective cognitive complaints were reported by the participant and/or collateral informant; (3) Global CDR scale score of 0.5; (4) impaired delayed recall (ie, scored 1.5 SD or greater, below the mean, accounting for age, education, and language of testing) for either the HVLT-R or the delayed paragraph recall from the NACC UDS and/or scored 1.5 SD below expected levels on non-memory measures as described for the CN group; (5) clinical course, history, and brain imaging not consistent with AD but with another specific neurological condition; and (6) amyloid scans read by an experienced rater as amyloid negative. Specifically, four cases were diagnosed with major depressive disorder, three cases were diagnosed with anxiety, one with Posttraumatic Stress Disorder, two with Sleep Apnea and one with Unspecified Neurocognitive Disorder.

2.5  |  Mild cognitive impairment non-neurological pathology (MCI non-neuro; n = 17)

These participants presented with the following: (1) fulfilled Petersen’s criteria for MCI (45–47); (2) subjective cognitive complaints were reported by the participant and/or collateral informant; (3) Global CDR scale score of 0.5; (4) impaired delayed recall (ie, scored 1.5 SD or greater, below the mean, accounting for age, education, and language of testing) for either the HVLT-R or the delayed paragraph recall from the NACC UDS and/or scored 1.5 SD below expected levels on non-memory measures as described for the CN group; (5) clinical course, history, and brain imaging consistent with a non-neurological condition; and (6) amyloid scans read by an experienced rater as amyloid negative. Specifically, 10 cases were diagnosed with Major Depressive Disorder, three were diagnosed with anxiety, one with Posttraumatic Stress Disorder, two with Sleep Apnea and one with Unspecified Neurocognitive Disorder.

2.6  |  MRI assessment

All participants described above underwent structural MRI using a Siemens Skyra 3T MRI scanner at Mount Sinai Medical Center, Miami Beach Florida. Brain parcellation was obtained using a three-dimensional (3D) T1-weighted sequence (MPRAGE) with 1.0 mm isotropic resolution using FreeSurfer Version 5.3 software (http://surfer.nmr.mgh.harvard.edu). The images were evaluated by visual inspection to help with determination regarding the etiology of cases and quantitatively to obtain volumetric data for brain regions. We
examined mean volume in the hippocampus (HPC) and entorhinal cortex (ERC), which are two critical medial temporal lobe structures that have been previously associated with AD neurodegeneration. Total HPC and ERC volumes were examined by normalization to whole brain intracranial volume.

### 2.7 Amyloid imaging

PET/CT imaging was obtained using a 3D Hoffmann brain phantom to establish a standardized acquisition and reconstruction method. Participants were infused with [18-F] florbetaben 300 MBQ over a 3-minute period. Scanning commenced 70–90 minutes after the infusion for a duration of 20 minutes. We scanned all participants on a Siemens Biograph 16 PET/CT scanner operating in 3D mode (55 slices/frame, 3 mm slice thickness 128 × 128 matrix). The PET data were reconstructed into a 128 × 128 × 63 (axial) matrix with voxel dimensions of 0.21 × 0.21 × 0.24 cm. A small number of participants had florbetapir as their amyloid tracer. Reconstruction was performed using manufacturer-supplied software and included corrections for attenuation, scatter, random coincidences, and dead time. Images for regional analyses were processed using Fourier analysis followed by direct Fourier reconstruction. Images were smoothed with a 3 mm Hann filter. Following reconstruction, image sets were inspected and, if necessary, corrected for inter-frame motion. Images were obtained from the top of the head to the top of the neck and CT data were employed for initial attenuation correction and image reconstruction in the sagittal, axial, and coronal planes. Nineteen percent of our sample received florbetaben PET scans, whereas 81% received florbetaben scans. The centiloid method is a means of placing different tracers on the same scale of measurement.

### 2.8 Visual ratings of amyloid PET scans

All amyloid beta (Aβ) PET scans were interpreted by an experienced reader (RD) who was blind to the cognitive and clinical diagnosis, using a methodology similar to that described by Seibyl et al. Tracer uptake was assessed in six cortical regions (orbitofrontal, frontal, parietal, lateral temporal, occipital, and precuneus/posterior cingulate cortex, combining values from the left and right hemispheres) using the regional cortical tracer uptake (RCTU) system. A final dichotomous (A+ vs A−) diagnosis was rendered. Loewenstein and colleagues found extremely high agreement between RD and an independent rater in reading these scans.

### 2.9 Loewenstein-Acevedo Scales for Semantic Interference and Learning (LASSI-L)

The LASSI-L was not used for diagnostic determination in this study. This cognitive stress test represents 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. Participants were tested in their preferred language (English vs Spanish) and the LASSI-L has been shown previously to be culturally fair and valid in either language.

During the administration of the LASSI-L, 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). There are two presentations of the first list. The first presentation is followed by a free recall and then a cued recall trial. The second presentation is followed by a cued recall trial only. The cued recall after the second presentation is a measure of maximum storage capacity (Trial A2). A unique aspect of this paradigm is the presentation of a second competing list of to-be-remembered words that is presented in the same manner as the first list. That is, immediately following the second cued recall trial of List A, List B is presented. As in List A, there are two presentations of List B. The first presentation is followed by a free recall and then by a cued recall trial (Trial B1). The second presentation is followed by a cued recall trial only (Trial B2). The second list introduces different words, but shares the same previously presented semantic categories in order to elicit a considerable amount of PSI (PSI as measured on Trial B1).

Unlike other traditional memory paradigms, the re-administration and subsequent recall of this second list of words measures the individual’s ability to recover from the effects of PSI (frPSI Trial B2). The number of intrusion errors on PSI and frPSI have been thought to reflect deficits in source memory and inhibitory control. For the current study, we focused on the most sensitive subscales of the LASSI-L that have been sensitive to amyloid load, presumably underlying AD (eg, number of intrusion errors on the Cued B1 and Cued B2 subscales). These intrusion errors are usually either words that were presented on the first semantically related list of words, or less commonly they are unrelated words that share a similar semantic category.

### 2.10 Statistical analyses

For initial comparisons between diagnostic groups (illustrated in Table 1) we employed a series of one-way analyses of variance for interval-level variables. Both parametric and non-parametric analyses (eg, Kruskal-Wallis) yielded similar results; therefore, only parametric findings are presented. Following a statistically significant f-value of \( P < .05 \), we utilized the Tukey Honestly Significant Difference Test for mean comparisons. Adjusting for covariates such as age did not influence the obtained results. Chi-square analyses with Fisher exact test were used to analyze categorical variables and this procedure is optimal in analyses where certain cells have a modest count relative to other cells. For this study, we utilized cutoff points for high intrusion error input on Cued B1 and Cued B2 that were previously employed in other studies and chi-square analyses with Fisher exact test (illustrated in Table 2).

### 3 RESULTS

As depicted in Table 1, the MCI-SNAP participants were older than the MCI Non-AD Neuro group and the MCI Non-Neuro participants.
4 | DISCUSSION

This study represents the first investigation to examine the occurrence of semantic intrusion errors among a group of Non-Neurologically impaired participants diagnosed with MCI. The results indicate that participants with MCI who were amyloid positive, presumptive AD (MCI-AD) had a higher number of intrusion errors on Cued Recall B1 (74.4%) and Cued Recall B2 (75.0%), which was substantially higher than the errors made by other individuals in the MCI-AD group (40.0%). When previously derived cut-offs for high number of intrusion errors on Cued Recall B1 (3.3%) and Cued Recall B2 (4.4%) were used,29 23.3% of the MCI group had a higher number of errors relative to all other groups. Notably, MCI-AD participants had higher number of errors relative to the other MCI-AD group. The total explained variance in the model (R² = 0.32) was higher among MCI-AD, MCI-AD SNAP, and MCI-AD Neuro individuals. This was confirmed in individuals in the MCI-AD group (40%).

Although participants with MCI who had presumptive AD and amyloid positivity could not be differentiated with regard to mean hippocampal or entorhinal cortex volume, the number of total correct responses did differ from each other, with regard to the group with higher number of errors on Cued Recall B1 (74.4%) and Cued Recall B2 (75.0%). The total explained variance in the model (R² = 0.32) was higher among MCI-AD, MCI-AD SNAP, and MCI-AD Neuro individuals. This was confirmed in individuals in the MCI-AD group (40%).

As indicated in Table 1, CN participants had higher total hippocampal volumes relative to MCI-AD SNAP and MCI-AD Neuro. The total explained variance in the model (R² = 0.32) was higher among MCI-AD, MCI-AD SNAP, and MCI-AD Neuro individuals. This was confirmed in individuals in the MCI-AD group (40%).

The MCI patients evidenced lower mean Mini Mental Status Examination (MMSE) score than all other groups except the MCI-Non Neuro group. The MMSE scores in Table 1 indicated that none of the other non-AD amyloid-negative groups had significantly different scores compared to the MCI-AD group. As a result, the MCI-AD group was used as a reference group. The total explained variance in the model (R² = 0.32) was higher among MCI-AD, MCI-AD SNAP, and MCI-AD Neuro individuals.
TABLE 2  Percentage of intrusion errors on Cued B1 (proactive semantic interference) and Cued B2 (failure to recover from proactive semantic interference)

|                          | Percentage Positive Intrusions Cued B1 | Percentage Positive Intrusions Cued B2 |
|--------------------------|----------------------------------------|----------------------------------------|
| Cognitively Normal: Amyloid Negative (N = 31) | 12.9%                                  | 6.5%                                   |
| MCI - Non-Neurological: Amyloid Negative (N = 17) | 23.5%                                  | 5.9%                                   |
| MCI – Neurological: Amyloid Negative (N = 15)    | 33.3%                                  | 40.0%                                  |
| MCI – SNAP: Amyloid Negative                      | 21.1%                                  | 23.7%                                  |
| MCI – AD: Amyloid Positive                        | 74.4%                                  | 75.0%                                  |
| Fisher exact test                                  | 38.57; P < .001                        | 51.54; P < .001                        |

Note: Five or more intrusion errors is the established threshold for impairment on Cued B1 and four or more intrusion errors is the established threshold for impairment on Cued B2.

entorhinal volumes, there was clear evidence that LASSI-L intrusion errors sensitive to PSI and the failure to recover from proactive interference (frPSI) occurred more frequently (74.4-75.0%) in persons with prodromal AD as compared to cognitively healthy controls (6.5-12.9%). As noted in the Results section, the mean number of PSI and frPSI intrusions cannot be explained on the basis of other demographic variables or other covariates.

In general, the percentage of PSI intrusion errors made by CN and MCI Non-Neuro participants did not differ from other MCI participants who were amyloid negative but with specific neurological diagnoses. The above results provided further support for the notion that semantic intrusion errors could likely represent a cognitive marker that is sufficiently sensitive and perhaps specific to detect MCI patients who are amyloid positive, with presumptive underlying AD pathology. This needs to be further explored by assessing a large group of individuals who share a similar diagnosis (homogenous group) that is not AD.

There is increasing evidence that semantic intrusion errors are likely the result of incomplete or faulty storage and consolidation of initial to-be-remembered information. When a semantically related list of competing information is presented, deficits in inhibitory systems and elective impairments in source memory occur. We are aware that correlation does not necessarily imply causation and that the current results should not be taken to imply that amyloid in and of itself is responsible for increased PSI and frPSI errors. In fact, even in early AD, synaptic dysconnectivity, tau deposition, and other brain-related processes may underlie PSI and frPSI errors. Notable in the present data is the fact that even when provided a second chance to remember the second target list, 75% individuals with amyloid-positive MCI (MCI-AD Group, presumptive AD) exhibited what would be considered a pathological level of intrusion error responses. This was observed only in less than 7% of CN participants. It is important to note that Sanchez and colleagues demonstrated that these types of intrusive errors occurred (although to a lesser degree) in 50% of middle-aged offspring of a parent diagnosed with late-onset AD compared to 0% of controls. Most interesting is that the number of intrusion errors was highly related to cortico-limbic dysfunction on functional MRI (fMRI).

A strength of the current study is the inclusion of under-represented groups, such as the Spanish-speaking individuals, who are at increased risk for AD. Moreover, the current study is unique in its use of carefully clinically defined MCI neurological and non-neurological groups, with structural neuroimaging and amyloid scans rated by an expert reader. An amyloid-negative CN group was also valuable for comparative purposes. Our sample size, although modest, represents the first preliminary data in this area. We are in the process of further assessing additional neurological and non-neurological amyloid negative cases as well as conducting longitudinal follow-up studies. This will allow for the replication and extension of the current preliminary findings. Future studies employing larger subgroups of MCI participants with within-group homogeneity ("pure" non-AD pathologies) could provide further evidence for the findings observed in this study. In addition, obtaining tau scans and examining fMRI connectivity may further elucidate specific mechanisms that may underlie semantic intrusion errors.

Regardless of the mechanisms involved, it has become increasingly clear that semantic intrusion errors have significant clinical diagnostic and prognostic potential and should be the subject of further research and evaluation of its potential clinical applications.

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CONFLICTS OF INTEREST

Dr. Loewenstein is a co-inventor of intellectual property used in this study. Dr. Curiel is a co-inventor of intellectual property used in this study. The other authors have no potential conflicts of interest.

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