HHS Public Access

Author manuscript

*Am J Geriatr Psychiatry*. Author manuscript; available in PMC 2017 October 01.

Published in final edited form as:

*Am J Geriatr Psychiatry*. 2016 October ; 24(10): 804–813. doi:10.1016/j.jagp.2016.02.056.

# A Novel Cognitive Stress Test for the Detection of Preclinical Alzheimer's Disease: Discriminative Properties and Relation to Amyloid Load

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## Abstract

**OBJECTIVE—**To examine the utility of a novel “cognitive stress test” to detect subtle cognitive impairments and amyloid load within the brains of neuropsychologically normal community-dwelling elders.

**DESIGN—**Participants diagnosed as cognitively normal (CN), subjective memory impairment (SMI), mild cognitive impairment (MCI) and pre-clinical mild cognitive impairment (PreMCI) were administered the LASSI-L, a sensitive test of proactive semantic interference (PSI), retroactive semantic interference and uniquely, the ability to recover from the effects of PSI.

**SETTING—**Ninety-three subjects (31 males and 62 females) were recruited from three academic institutions in a research consortium. A subset of these individuals underwent F-18 Florbetapir PET scanning.

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Conflicts: Michael Pontecorvo and Abhinay Joshi are employees of Avid Radiopharmaceuticals, a wholly owned subsidiary of Eli Lilly and Company. None of the other authors have any conflicts of interest related to this investigation.

**MEASURES—**Relative percentages of impairment for each diagnostic group on the LASSI-L were calculated by chi-square and Fisher's Exact Test. Spearman's rho was employed to examine associations between amyloid load, and different cognitive measures.

**RESULTS—**LASSI-L deficits were identified among 89% of those with MCI, 47% with PreMCI, 33% with SMI and 13% of those classified as CN. CN subjects had no difficulties with recovery from PSI while SMI, preMCI and MCI participants evidenced deficits in recovery from PSI effects. Among a subgroup of participants with normal scores on traditional neuropsychological tests, the strong associations were between the failure to recover from theeffects of PSI and amyloid load in the brain.

**CONCLUSIONS—**Failure to recover or compensate for the effects of PSI on the LASSI-L distinguishes the LASSI-L from other widely used neuropsychological tests and appears to be sensitive to subtle cognitive impairments and increasing amyloid load.

### Keywords

Proactive Interference Recovery; Amyloid; PreMCI; MCI; LASSI-L

## INTRODUCTION

There is increasing recognition that cognitive measures originally designed for the assessment of early dementia may not be optimal for identifying older adults with subtle cognitive impairments in preclinical stages of Alzheimer's disease (AD).[1] Traditional memory measures are subject to individual differences in learning strategies, cognitive reserve and other sources of variability that may effectively lower the signal-to-noise ratio, hampering the assessment of the earliest stages of cognitive deficits in AD, and the ability to track changes over time.[2]

It is essential to optimize the sensitivity of cognitive tests intended to be used to assess cognitive deficits associated with very early biological changes in AD, that are now measurable by positron emission tomography and CSF biomarkers.[3] Akin to exercise electrocardiograms, used to detect early coronary artery disease, we have developed “cognitive stress tests” with enhanced sensitivity, as compared to traditional cognitive measures. Customarily, cognition is assessed in relatively less stressed conditions, which enables the use of compensatory strategies and subsequently results in greater intra-individual variance in initial learning. Thus, applying more cognitively challenging test paradigms may enhance their sensitivity to detecting early brain pathology.[2,4,5].

We previously developed a novel cognitive stress paradigm called the Loewenstein- Acevedo Scale for Semantic Interference and Learning (LASSI-L), which uses controlled learning and cued recall over two trials to *maximize storage* of to-be-remembered semantic information. This is followed by the administration of a semantically similar list of targets, so as to produce proactive semantic interference (old learning inhibits new learning of semantically similar targets).

Thereafter, a repeated learning trial of the new list can determine the ability to *recover* from the initial proactive semantic interference (PSI) effects. Retroactive interference is assessed

by determining the effect of new learning on the retrieval of original list of semantically related targets. Maximum storage as defined the second cued recall of List A targets on the LASSI-L combined with the first cued recall for List B targets (most vulnerable to proactive interference) could optimally distinguish between participants with mild amnestic cognitive impairment (aMCI) from cognitively normal elders (sensitivity= 87.9% and specificity=91.5%), demonstrating superior classification relative to traditional memory measures.[6,7] In addition, among subjects with aMCI, measures of medial temporal atrophy on MRI scans were strongly associated with both measures of proactive interference and failure to recover from the effects of PSI on the LASSI-L[6]. A unique and novel aspect of the LASSI-L which distinguishes it from all other memory measures is that the List B targets are presented twice so as to assess the recovery from PSI.

In the current investigation, we examined the ability of the LASSI-L to distinguish between different at-risk pre-clinical AD groups and examined the association of LASSI-L maximal storage of to-be-remembered List A targets derived by cued recall, initial cued recall for List B targets (vulnerable to proactive interference) and second cued recall for List B targets (ability to recover from proactive interference) which have been shown to be predictors of MCI in previous studies[6,7] as well as other LASSI-L subtests to biological changes in the brain at potentially very early stages of disease. We examined carefully worked up cognitively normal (CN) subjects, those with Subjective Memory Impairment (SMI) only, those with mild cognitive impairment (MCI) and subjects diagnosed with PreMCI (an intermediary state between SMI and MCI) which has been shown to confer an elevated risk for the progression of memory deficits.[8, 9] We used PET measures of regional brain amyloid load in a subset of patients to assess very early biological changes associated with AD so as to relate amyloid load to LASSI-L subtest scores.

## METHODS

We recruited 93 subjects (31 males and 62 females) from three academic institutions in a research consortium [University of Miami School of Medicine (UM); Mount Sinai Medical Center (MSMC) and the University of Florida (UF)]. Dr. Loewenstein was the Principal Investigator of this Consortium and clinicians and neuropsychologists from all three-study sites engaged in several group consensus conferences in which they reviewed common protocols and achieved high diagnostic agreement. All participants were administered a common clinical assessment protocol, the Clinical Dementia Rating Scale (CDR) and MMSE. Memory and other cognitive complaints were assessed by an experienced geriatric psychiatrist (MG), neurologist (MW) or a clinical psychologist (DL) who were blind to the neuropsychological test results. All of these individuals had formal training in administering the Clinical Dementia Rating Scale (CDR) and considerable research experience as investigators of a federally funded Alzheimer's Disease Research Center and/or clinical trials experience conducting extensive interview including the CDR. The 93 participants were all 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, Patients and their informants were asked “Does the individual have any difficulties with their memory and/or thinking?” This was followed by an extensive interview with both the participant and a

collateral informant and administration of the full CDR. Based on this extensive clinical interview and CDR, the experienced clinician concluded whether they thought complaints were subjective if they could find no cognitive deficit on examination and there no clinical and CDR evidence of cognitive decline. In cases where there was evidence of cognitive decline by history and/or clinical examination, the clinician scored the Global CDR as .5 and considered a diagnosis of MCI based on their examination, pending the results of formal neuropsychological testing. Subsequently, a standard neuropsychological battery was administered at each site and was conducted independently of the Clinical examination and included a list learning test [either the Hopkins Verbal Learning Test-Revised (HVLT-R; 63% of sample) or Fuld Object Memory Evaluation (FOME; 37% of sample)], National Alzheimer's Coordinating Center (NACC) delayed paragraph recall, Category Fluency, Letter Fluency, Block Design of the WAIS-IV, and the Trail Making Test (Parts A and B).

Based on a consensus diagnosis panel including the extensive interview by an experienced psychiatrist) and/or neurologist) and separate input from the neuropsychologist (DL, RC, RB) at each site, participants were assigned to one of four groups.

### Criteria for Cognitively Normal (CN) subjects (N=31)

**a)** After an extensive clinical interview with the patient and the informant, there were no subjective memory or other cognitive complaints by the participant or collateral informant (e.g., has there been any difficulties with memory or thinking?); b) no evidence by extensive clinical evaluation or history of memory or other cognitive decline; c) Global Clinical Dementia Rating Scale of 0 rated by the Clinician; d) all memory and non-memory neuropsychological measures scored within normal limits relative to age and education related norms as determined by an experienced (this was typically less than 1.0 SD below normative values for all tests).

### Criteria for Subjective Memory Impairment (SMI) (N=18)

a) subjective memory complaints by the participant and/or or collateral informant after an extensive clinical interview with the patient and the informant in which a subjective memory or other cognitive complaints was established by the participant or collateral informant (e.g., has there been any difficulties with memory or thinking?); b) no further evidence by extensive clinical evaluation or history of memory or other cognitive decline; c) even with the subjective memory complaint, the experienced clinician judged that the overall Clinical Dementia Rating scale was 0 and did not suggest any indication of actual memory/cognitive difficulties or decline; d) all memory and non-memory neuropsychological measures scored within normal limits relative to age and education related norms as determined by an experienced neuropsychologist (this was typically less than 1.0 SD below normative values for all tests).

### Criteria for Pre Mild Cognitive Impairment (PreMCI-Clinical) (N=15)

a) subjective memory complaints by the participant and/or or collateral informant; b) evidence by clinical evaluation or history of memory or other cognitive decline; c) Global Clinical Dementia Scale was 0.5; d) all other neuropsychological criteria fell completely within normal limits using the criteria specified for CN and SMI groups as outlined above.

While both SMI and PreMCI- Clinical subjects both evidenced memory complaints in the absence of neuropsychological impairment, PreMCI-Clinical subjects had evidence of decline in cognition by clinical history of cognitive decline whereas SMI participants did not evidence such deficits upon clinical evaluation. The PreMCI-Clinical classification has been previously been found in a significant number of persons with neuropsychological impairment and has been shown to be a risk factor for progression to a formal diagnosis of MCI or dementia over a 2-3 year period (See Loewenstein et al., 2012).[9]

### Criteria for Mild Cognitive Impairment (MCI) (n=29) was as follows

a) subjective memory complaints by the participant and/or or collateral informant; b) evidence by clinical evaluation or history of memory or other cognitive decline; c) Global Clinical Dementia Scale of .5; d) one or more memory or non-memory measures 1.5 SD or below normal limits relative to age and education related norms.

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

This is a novel measure that uses controlled learning and cued recall to maximize storage of an initial list of to-be- remembered targets representing three semantic categories. What is unique about the measure is the presentation of another list-of to-be-remembered targets sharing the same semantic categories are in the first list, eliciting a considerable amount of proactive interference. Unlike other memory paradigms, the individual is again administered this second list of targets to measure recovery from proactive semantic interference effects. Retroactive interference is also assessed. The specific elements of the test are described below:

The participant is instructed to remember a list of 15 common words that are fruits, musical instruments or articles of clothing (five words per category). The person is asked to read the words from the target list aloud, as each word is presented individually at 4-second intervals. In the unlikely event that the person cannot correctly read the word, the word is read by the examiner and the person is asked to repeat the word. If a person does not know one of the words (also unlikely), the examiner tells the person what category the word belongs to (e.g., “Lime is a fruit.”) and the person is asked to repeat the word. After the person has read all 15 words, they are asked to recall the words. After free recall has ended, the subject is presented with each category cue (e.g., clothing) and asked to recall the words that belonged to that category (LASSI-L A1).

The participant is then presented with the target stimuli for a second learning trial with subsequent cued recall to strengthen the acquisition and recall of the List A targets, providing maximum storage of the to-be-remembered information (LASSI-L A2]. Following this trial, the participant is exposed to a semantically related list (i.e., List B) which is then presented in the same manner as exposure to List A. List B consists of 15 words which are different from List A, five of which 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 interference effects (LASSI-L B1). Then, each category cue is given and they are asked to recall each of the List B words that belonged to each of the categories. List B words are

presented again, followed by a second category-cued recall trial. This second learning trial for the new list allows the assessment of the ability to recover from the initial semantic interference effects (LASSI-L B2). This recovery from proactive interference is a feature of the LASSI-L that is not assessed by any existing list-learning measure. Finally, to assess retroactive interference, the participant is asked to provide cued recall the original List A words (LASSI-L A3). Test-retest reliabilities of the LASSI-L have been shown to be high in previous studies and the accuracy of classification of aMCI patients versus elderly subjects exceeded 90%. [6,7]

### Amyloid PET Scans

Thirty-one of the aforementioned participants at the MSMC site received Amyloid PET Scans, including CN (n=7), SMI (n=11), PreMCI (n=3), MCI (n=10) Eight of the ten amnestic MCI cases were diagnosed with aMCI while two were diagnosed with non-amnestic MCI. PET scans were acquired 50 minutes following administration of 370 MBq (10 mCi) bolus injection of 18F-AV45 (Florbetapir), over a 20-minute scanning period and images were reconstructed immediately thereafter. A standard uptake value ratio (SUVR) was computed, relative to the cerebellum, for the following composite of cortical regions: frontal, lateral temporal, parietal, anterior cingulate, posterior cingulate and precuneus. The choice of regions was based on the neocortical regions where amyloid deposition occurs early and which are particularly vulnerable to neurodegeneration associated with AD.[10,22] The regions were chosen to be sensitive to amyloid accumulation in AD. Previous studies have demonstrated that the regional composite produces a high sensitivity and specificity for detecting patients with moderate to frequent amyloid plaques[23] that can be detected in some elderly clinically normal subjects[10]. SUVR values ranged from .82 to 1.54. None of CN subjects met the traditional 1.11 threshold for Total SUVR amyloid positivity, 3 of the SMI subjects meet amyloid positivity, 2 of the PreMCI were amyloid positive and 4 of the MCI participants were amyloid positive. However, it should be noted that these traditional thresholds were largely derived for optimal separation between clinically diagnosed AD and healthy controls and it is increasingly recognized that MCI and PreMCI patients may have values below established amyloid thresholds[24,25.] and this fact prompted the use of measures of association as described in the results below.

## STATISTICAL METHODS

For demographic information, a series of ANOVAs were employed. Following a statistically significant F at $p \leq .05$, we employed the Tukey HSD procedure. Chi-square analyses were employed for ordinal data. On neuropsychological measures, we determined impairments among subjects in each diagnostic group, using three different scores representing impairment (based on a conservative 2 SD cut-off) from a previous study[6]. It should be noted that there was absolutely no overlap between subjects in the previous study and participants in the current investigation.

The proportion of subjects with impairment on neuropsychological tests in different diagnostic groups was compared, using overall chi-square analyses. Because subject numbers in some cells were modest, the Fisher's Exact Test was employed. For primary

analyses of the correlation between amyloid load and neuropsychological test performance, presented in Tables 3-5, the criterion for significance was set at p≤ .01, to correct for multiple comparisons. Because modest subject numbers raised concerns about normality assumptions in some analyses, we employed a non-parametric (distribution-free) Spearman test of ranks with the criterion for statistical significance set at p≤.01.

## RESULTS

As depicted in Table 1, participants in CN, SMI, PreMCI and MCI groups did not differ with regards to age, gender and level of educational attainment. The MCI group had MMSE scores that were slightly lower than in the other study groups. MCI subjects also evidenced lower scores than all other study groups on LASSI-L Cued A1, LASSI-L Cued A2, LASSI-L Cued BI and LASSI-L Cued B2 scales. MCI participants also scored lower on the LASSI-L Cued A3 scale than participants in the CN group. CN subjects also evidenced higher LASSI-B2 scores than participants in the PreMCI but not the SMI group.

A clinically relevant analytic approach was to compare the frequency of impairment among CN, SMI, PreMCI and MCI groups, by identifying “impairment” as a subject's score on any measure as being at least 2.0 SD below that of cognitively normal subjects.[6] We focused on the A2 cued recall that emphasizes maximum storage, cued B1 recall (producing initial proactive interference) and B2 cued recall (assessing recovery from proactive interference) in that they showed the most discriminative ability in previous studies with other samples MCI and cognitively normal subjects[6,7]. As indicated in Table 2, on the LASSI-L A2 cued recall, a measure of maximum storage, none of the CN, PreMCI and a limited number of SMI persons failed to achieve maximal storage compared to almost a third of MCI patients. On LASSI-L B1 cued recall, a measure indicating initial susceptibility to proactive interference, almost 80% of MCI participants were impaired compared to approximately 47% of participants with PreMCI, approximately a third of participants with SMI, and 12.9% for CN subjects. Post -hoc chi-square analyses revealed that a greater percentage of participants in the MCI and PreMCI groups evidenced greater impairments relative to participants in the CN group. On LASSI-L B2, a measure indicating susceptibility to impairment in release from proactive interference, 61% of MCI participants were impaired compared to 27% for PreMCI, 17% for SMI and 0% for CN subjects. Post-hoc tests revealed that a greater percentage of participants in the SMI, PreMCI and MCI diagnostic groups had LASSI-L B2 impairments than the CN group. In sum, approximately 90% of MCI subjects have one or more LASSI-L deficits, as compared to almost half of PreMCI participants, approximately 39% for SMI and 12.9 % of CN subjects Post- hoc chi-square analyses revealed that a greater percentage of participants in the MCI and PreMCI groups evidenced impairments relative to those participants in the CN group. It should be noted that all the errors made by CN subjects were on LASSI-L B1 subtest and no CN subjects evidenced deficits on maximum storage (LASSI-L-A2) or release from proactive interference measures (LASSI-L-B2).

As depicted in Table 3, the strongest and most consistent statistically significant index of association between amyloid load and a neuropsychological measure using Spearman Rank Order correlation coefficients was for LASSI B2 cued recall (measuring degree to which the

person was able to recover from PSI effects) and amyloid load in the precuneus, posterior cingulate region and whole brain. When eight subjects with amnestic MCI were removed, so that only those with normal neuropsychological scores (n=23) were included in the analyses, these correlations were stronger for the precuneus (r=−.62; p<.001), posterior cingulate (r=−.50; p<.001), and whole brain (r=−.60; p<.001 (See Table 4). Increased amyloid load in the anterior cingulate and precuneus was also associated with reduced LASSI-L A1 cued recall in both analyses with and without MCI subjects (See Table 3 and 4). There was no statistically significant relationship between any LASSI-L measure and amyloid load in the temporal and parietal regions.

As depicted in Table 5, among traditional memory and non-memory measures there was no association with total and most regional SUVRs for amyloid load. The only exception was Trails A in which decreased performance was related to increased amyloid load in the precuneus (r=.44) and posterior cingulate regions (r=.47).

## DISCUSSION

This study is one of the first to investigate a novel measure of vulnerability to proactive and retroactive semantic interference among elderly individuals diagnosed with PreMCI and subjective memory impairments (SMI). This is important in that many studies previously focusing on subjective memory complaints include subjects who actually may have PreMCI and have not distinguished between the two conditions. More importantly, the LASSI-L is unique from other memory measures in that it allows for an evaluation of recovery from the effects of proactive interference.

In fact, the current findings indicate that deficits in the ability to successfully recover or compensate for PSI (Recall B2) were significantly greater among MCI, PreMCI, and SMI subjects, as compared to demographically similar cognitively normal participants. This represents the first such result reported in the literature. Additionally, in a subset of persons undergoing amyloid PET, recovery from PSI as assessed by LASSI-L Cued Recall B2 was by far, the most highly associated with total amyloid load and regional amyloid values among participants who had no evidence of cognitive on a traditional battery of neuropsychological measures. The fact that these associations were higher in magnitude when subjects with MCI were excluded in the analyses is consistent with the notion of Chételat and associates[11] that amyloid may exert its effects in the earliest stages of disease and other pathological downstream features may drive processes such as atrophy and cognitive decline as AD progresses.

Amyloid load in the neocortex has been found to be a prominent risk factor for AD among cognitively normal individuals and those with memory disorders.[12, 13, 23] In fact, persons who perform normally on appropriate cognitive tests (such as those classified in this study as CN, SMI and PreMCI) and are found to be amyloid positive, are classified as having “Preclinical Alzheimer's Disease[3]. PreMCI and SMI individuals are at increased risk, as compared to completely normal individuals, for progression of cognitive deficits and/or elevation of AD biomarkers over time.[14, 15, 9]

Although amyloid status may be a sensitive marker of early disease or risk of progression, it is not practical to use amyloid PET imaging, CSF amyloid assays and newly developed tau imaging in primary screening. Thus, there is a need to develop more challenging cognitive measures that are sensitive to early disease. To that end, the strong association of failure to recover from proactive semantic interference with amyloid load observed in this study is potentially important. Although beyond the scope of the current investigation, continued follow-up of our sample be key to determine differences in individual rates of progression among these individuals. It would also be useful to explore other modalities such as tau imaging.

Current findings that the LASSI-L differentiates between MCI and normal elderly are consistent with our previous research. Susceptibility to proactive interference is a feature of MCI patients and is a risk factor for progression to AD.[16-18] There have also been recent findings relating PSI to amyloid load[5]. However, the current findings suggest that it may not merely be proactive interference but the ability to *recover* from proactive interference effects that may be one of the earliest indicators of cognitive deficits in those at risk for AD. To investigate this possibility, we performed post-hoc analyses and calculated the percentage decrement in Cued B1 recall from Cued A1 Recall for cognitively normal elders (30%) versus participants with MCI Cued B2 (41%), which indicates comparative percentages of initial PSI (p=ns). Similarly, we calculated the percentage decrement in Cued B2 recall from Cued A2 Recall for cognitively normal elders (13%) versus participants with MCI (30%) which suggested much less recovery from PSI for the MCI group (p<.001). Coupled with the finding that amyloid load was much more strongly associated with B2 than B1 performance lends further support to the notion that the failure to recover proactive semantic interference rather than the initial effects of proactive interference may be more pronounced in those at greater biological risk for AD. Indeed, findings that based on previously established cut-offs, indicated that that our cognitively normal elderly control subjects had no difficulties in recovery from proactive semantic interference, whereas these were evident in SMI and PreMCI indicates that the LASSI-L B2 may potentially be a sensitive indicator for early cerebral dysfunction.

An interesting finding in this study was that the only traditional neuropsychological measure which was associated with amyloid load was Trails A, a measure of simple visual scanning / processing speed and the regional correlations were specific to the precuneus and posterior cingulate gyrus (regions which are found have high amyloid deposition in Alzheimer's disease[20]). In a previous investigation, with a mixed sample of aMCI and normal elderly subjects, Trails A performance was associated with high overall amyloid burden[19] among community-dwelling elders. Further, among 137 healthy normal subjects, a composite measure of processing speed measure was highly related to total amyloid load[20].

Although, this study indicates the potential efficacy of a test measuring recovery from semantic interference, limitations of this investigation include modest sample sizes for the amyloid PET studies and the lack of other biomarkers such as tau imaging and medial temporal volumetric analysis on MRI. Results from larger numbers of subjects with multimodal neuroimaging modalities and additional comparison groups are awaited. Nonetheless, the obtained results, although preliminary, suggest that failure to recover from

proactive interference, as measured by the LASSI-L distinguished different older groups at higher risk for preclinical AD. Further the failure to recover from proactive semantic interference was particularly sensitive to amyloid disposition in a number of areas of the brain among non-demented individuals.

Novel semantic interference paradigms such as the LASSI-L[6, 7] and newly developed Buschke Memory Binding Tests in response to semantic cues, reported in recent studies[4,21] are tests that capitalize on controlled learning with active encoding and maximum depth of processing of to-be-remembered material and explicit identification of the semantic categories around which learning should be organized, encouraging encoding specificity. We further believe that the LASSI-L is unique in that it provides valuable data on PSI, RSI and particularly, recovery from PSI. While these results are preliminary, research on the role of these and other novel cognitive paradigms in early diagnosis and monitoring of Preclinical AD is important and worthy of further research.

## Acknowledgments

This research was supported by 1 R01 AG047649-01A1, David Loewenstein, PI, the Ed and Ethel Moore Research Program, ALZ002- David Loewenstein, PI and (Avid) –A-14 award (PI: Ranjan Duara)

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**Table 1**

Demographic Information and Initial LASSI-L Performance Among Different Diagnostic Groups

| | Cognitively Normal (n=31) | Subjective Memory Disorder (n=18) | PreMCI Clinical (n=15) | MCI (n=29) | F (df=3,89) or $X^2$ (df=3) | p-value |
|---|---|---|---|---|---|---|
| Age Range (61-91) | 74.6 (8.1) | 75.4 (6.6) | 77.4 (6.2) | 78.7 (6.3) | 1.89 | .14 |
| Education Range (7-20) | 15.7 (2.9) | 15.2 (3.2) | 15.8 (3.2) | 14.2 (3.6) | .82 | .490 |
| Gender % female | 74% | 81% | 60% | 60.7% | 2.97 | .40 (df=3) |
| MMSE Range (24-39) | 29.1[a] (.8) | 28.9[a] (1.1) | 29.2[a] (.8) | 27.0 [b] (2.0) | 16.27 | <.001 |
| Cued A1 | 11.45[b] (2.1) | 10.33[b] (2.1) | 10.20[b] (1.9) | 7.9[a] (2.5) | 12.94 | <.001 |
| Cued A2 | 13.84 [b] (1.3) | 13.22[b] (1.7) | 13.33[b] (1.5) | 11.14[a] (2.4) | 12.25 | <.001 |
| Cued B1 | 7.8[b] (2.3) | 7.1[b] (2.5) | 7.4[b] (2.4) | 4.5[a] (2.2) | 11.87 | <.001 |
| Cued B2 | 12.0[a] (1.9) | 10.7[ab] (2.3) | 10.1[b] (2.4) | 7.8 [c] (2.3) | 19.02 | <.001 |
| Cued A3 | 8.9 [a] (2.6) | 7.8 [ab] (2.8) | 7.5[ab] (2.8) | 6.6[b] (2.3) | 4.05 | ≤.01 |

Note: Following a statistically significant F-value, post-hoc tests of means with different alphabetic superscripts for each measure are statistically different at p< .05 by the Tukey's Honestly Significant Difference (HSD) Test.

**Table 2**

Percentage of Cognitively Normal, Subjective Memory Complaints, PreMCI and MCI community dwelling elders with LASSI-L Impairment (N=93)

| | **Normal Cognition (n=31)** | **Subjective Memory Complaint (n=18)** | **Pre-MCI Clinical (n=15)** | **MCI (n=29)** | **$X^2$ Fisher's Exact Test (df=3)** |
|---|---|---|---|---|---|
| Impaired Cued A2 LASSI-L Performance (Maximal Storage) Cut-off ≤ 10 | 0% | 5.6% | 0% | 31.1%# | 15.68 (p<.001) |
| Impaired Cued B1 LASSI-L Performance (Proactive Interference) Cut-off ≤ 4 | 12.9 % | 33.3% | 46.7%# | 78.6%# | 27.73 (p<.001) |
| Impaired Cued B2 LASSI-L Performance (Release from Proactive Interference) Cut-off ≤ 8 | 0% | 16.7%# | 26.7%# | 60.7%# | 30.86 (p<.001) |
| Impaired Any LASSI-L Measure | 12.9 % | 38.9 % | 46.7%# | 89.3%# | 37.81 (p=.001) |

Note: Values demoted with # across a horizontal line are significantly significant from values of the normal cognition group.

**Table 3**

Association Between LASSI-L Indices and Total Amyloid Load on Florbetapir (18 F) Amyloid Brain Scans for MCI and Non-Demented Community-Dwelling Subjects (N=31)

| | SUVR TOTAL | ANTERIOR CINGULATE | POSTERIOR CINGULATE | PRECUNEUS | FRONTAL LOBE |
|---|---|---|---|---|---|
| LASSI Cued B1 (Vulnerable to Proactive Interference) | $r_s$=−.35* | $r_s$=−.39* | $r_s$=−.34* | $r_s$=−.35* | $r_s$=−.30* |
| LASSI Cued B2 (Susceptible to Release from Proactive Interference) | ***$r_s$=−.47*** ** | **$r_s$=−.40** ** | **$r_s$=−.43** ** | **$r_s$=−.53*** ** | $r_s$=−.36* |
| LASSI Cued A1 (Initial Learning) | **$r_s$=−.41** ** | **$r_s$=−.42** ** | $r_s$=−.37* | **$r_s$=−.47** ** | $r_s$=−.37* |
| LASSI Cued A2 (Maximum Storage) | $r_s$= −.30* | $r_s$=−.32* | $r_s$=−.29 | $r_s$=−.36* | $r_s$=−.23 |
| LASSI Cued A3 (Susceptible to Retroactive Interference | $r_s$=−.34* | **$r_s$=−.40** ** | $r_s$=−.35* | $r_s$=−.38* | $r_s$=−.30* |

Note:

With modest sample sizes it is difficult to ascertain whether data approximates a normal distribution. As a result, we applied Spearman Rank order correlation coefficients that not require normality and are much less sensitive to outliers. The degrees of freedom (df) for the correlation coefficients above are 29. Given the large number of contrasts, and to reduce family-wise only p values ≤ .01 are bolded.

* p≤.05 and

** p≤.

**Table 4**

Association Between LASSI-L Indices and Total Amyloid Load on Florbetapir (18 F) Amyloid Brain Scans for Non-Demented Community-Dwelling Subjects (N=23) with Normal Standard Neuropsychological Evaluation

| | SUVR TOTAL | ANTERIOR CINGULATE | POSTERIOR CINGULATE | PRECUNEUS | FRONTAL LOBE |
|---|---|---|---|---|---|
| LASSI Cued B1 (Vulnerable to Proactive Interference) | $r_s$=−.42* | $r_s$=−.42* | $r_s$=−.41* | $r_s$=−.40 | $r_s$=−.31 |
| LASSI Cued B2 (Susceptible to Release from Proactive Interference) | ***$r_s$=−.60*** | **$r_s$=−.48** | **$r_s$=−.50** | **$r_s$=−.62** | $r_s$=−.43* |
| LASSI Cued A1 (Initial Learning) | $r_s$=−.44* | **$r_s$=−.49** | $r_s$=−.35* | **$r_s$=−.47** | $r_s$=−.44* |
| LASSI Cued A2 (Maximum Storage) | $r_s$= −.26 | $r_s$=−.31 | $r_s$=−.19 | $r_s$=−.32 | $r_s$=−.20 |
| LASSI Cued A3 (Susceptible to Retroactive Interference | $r_s$ = **−.37** | $r_s$=−.42* | $r_s$=−.41* | $r_s$=−.42* | $r_s$=−.30 |

Note: With modest sample sizes it is difficult to ascertain whether data approximates a normal distribution. As a result, we applied Spearman Rank order correlation coefficients that not require normality and are much less sensitive to outliers. The degrees of freedom (df) for the correlation coefficients above are 21. Given the large number of contrasts, and to reduce family-wise only p values ≤ .01 are bolded.

**Table 5**

Association Between Traditional Neuropsychological Indices and Total Amyloid Load on Florbetapir (18 F) Amyloid Brain Scans for Non-Demented Community-Dwelling Subjects (N=23) with Normal Standard Neuropsychological Evaluation

| | SUVR TOTAL | ANTERIOR CINGULATE | POSTERIOR CINGULATE | PRECUNEUS | FRONTAL LOBE |
|---|---|---|---|---|---|
| NAC Delayed Memory for Passage | $r_s$=−.29 | $r_s$ =−.35* | $r_s$ =−.08 | $r_s$ =−.17 | $r_s$ =−.36* |
| Fuld Object Memory Evaluation Three-Trial Recall | $r_s$ =−.16 | $r_s$ =−.17 | $r_s$ =−.10 | $r_s$ =−.16 | $r_s$ =−.16 |
| Category Fluency | $r_s$ =−.42* | $r_s$ =−.36* | $r_s$ =−.17 | $r_s$ =−.29 | $r_s$ =−.30 |
| Trails A | $r_s$ =.37* | $r_s$ =.37* | **$r_s$ =.47****| **$r_s$=.44**** | $r_s$ =.25 |
| Trails B | $r_s$ =.31 | $r_s$ =.25 | $r_s$ =.38* | $r_s$ =.40* | $r_s$ =.14 |
| WAIS-IV Block Design | $r_s$ = −.15 | $r_s$ =−.15 | $r_s$ =−.19 | $r_s$ =−.20 | $r_s$ =.02 |

Note: With modest sample sizes it is difficult to ascertain whether data approximates a normal distribution. As a result, we applied Spearman Rank order correlation coefficients that not require normality and are much less sensitive to outliers. The degrees of freedom (df) for the correlation coefficients above are 21. Given the large number of contrasts, and to reduce family-wise only p values ≤ .01 are bolded.