Proactive Semantic Interference Is Associated With Total and Regional Abnormal Amyloid Load in Non-Demented Community-Dwelling Elders: A Preliminary Study

David A. Loewenstein, Ph.D.,
Maria T. Greig, M.D.,
Rosie Curiel, Psy.D.,
Rosemarie Rodriguez, Ph.D.,
Meredith Wicklund, M.D.,
Warren W. Barker, M.S.,
Jacqueline Hidalgo, M.S.,
Marian Rosado, Psy.D.,
Ranjan Duara, M.D.

Objective: *To evaluate the relationship between susceptibility to proactive semantic interference (PSI) and retroactive semantic interference (RSI) and brain amyloid load in non-demented elders.* **Methods:** *27 participants (11 cognitively normal [CN] with subjective memory complaints, 8 CN without memory complaints, and 8 with mild cognitive impairment [MCI]) underwent complete neurological and neuropsychological evaluations. Participants also received the Semantic Interference Test (SIT) and AV-45 amyloid PET imaging.* **Results:** *High levels of association were present between total amyloid load, regional amyloid levels, and the PSI measure (in the entire sample and a subsample excluding MCI subjects). RSI and other memory measures showed much weaker associations or no associations with total and regional amyloid load. No associations between amyloid levels and non-memory performance were observed.* **Conclusions:** *In non-demented individuals, vulnerability to PSI was highly associated with total and regional beta-amyloid load and may be an early cognitive marker of brain pathology.* (Am J Geriatr Psychiatry 2015; ■:■−■)

Key Words: Amyloid, proactive interference, semantic interference, MCI

Buschke and colleagues[1] emphasized that deficits in using semantic cues to learn new information was characteristic of early Alzheimer disease (AD). Subsequently, Loewenstein et al.[2] proposed that semantic intrusions on list-learning tasks reflected vulnerability in the ability of those with early AD to inhibit interference from competing semantic exemplars within a specific semantic category. To explore these concepts further, the Semantic Interference Test[3] (SIT) was developed. The SIT uses semantically related items on two competing lists to elicit proactive semantic interference (PSI) and retroactive semantic interference (RSI) effects. The PSI measure of the SIT was able to distinguish amnestic mild cognitive impairment (aMCI) from cognitively normal individuals, with a sensitivity/specificity of 83.1%/83.1%, which increased to 84.6%/96.2% when RSI measures of were included. Subsequent studies have also suggested that vulnerability to PSI is an early feature of AD[4,5] and PSI indices better predicted progression from aMCI to dementia than traditional neuropsychological measures.[6]

Received June 11, 2015; revised July 17, 2015; accepted July 17, 2015. From the Department of Psychiatry and Behavioral Sciences, Miller School of Medicine (DAL, RCMR), University of Miami and Center on Aging, Miami, FL; the Wien Center for Alzheimer's Disease and Memory Disorders, Mount Sinai Medical Center (DAL, MTG, RR, WWB, JH, RD), Miami Beach, FL; the Department of Neurology (MW), University of Florida, Gainesville, FL; the Department of Medicine, Miller School of Medicine (RD), University of Miami, Miami, FL; and the Department of Neurology, Herbert Wertheim College of Medicine (RD), Florida International University, Miami, FL. Send correspondence and reprint requests to David A. Loewenstein, Ph.D., Professor of Psychiatry and Behavioral Sciences, Miller School of Medicine, 1695 NW 9th Avenue, Behavioral Health Hospital Building, Suite 3208G, Miami, Florida 33136. e-mail: DLoewenstein@med.miami.edu

Supplemental digital content is available for this article in the HTML and PDF versions of this article on the journal's Web site (www.ajgponline.org).

http://dx.doi.org/10.1016/j.jagp.2015.07.009

TABLE 1. Associations Between the Semantic Interference Test (SIT) and Amyloid Load on Florbetapir (18-F) Amyloid Brain Scans for Non-Demented Community-Dwelling Subjects (N = 27)

	SUVR Total	Anterior Cingulate	Posterior Cingulate	Precuneus	Frontal	Temporal	Parietal
Fuld Object Memory Evaluation	r = −0.23 (p = 0.225)	r = −0.28 (p = 0.161)	r = −0.23 (p = 248)	r = −0.19 (p = 0.346)	r = −0.25 (p = 0.210)	r = −0.21 (p = 0.301)	r = −0.09 (p = 0.668)
Delayed Passage Recall	**r = −0.47** (p = 0.013)	**r = −0.53** (p = 0.005)	r = −0.45 (p = 0.020)	r = −0.44 (p = 0.022)	r = −0.43 (p = 0.025)	r = −0.44 (p = 0.023)	r = −0.33 (p = −0.091)
SIT BAG B (Susceptible to Proactive Interference)	**r = −0.67** (p <0.001)	**r = −0.72** (p <0.001)	**r = −0.59** (p = 0.001)	**r = −0.62** (p = 0.001)	**r = − 0.67** (p <0.001)	**r = −0.63** (p <0.001)	**r = −0.50** (p = 0.008)
SIT BAG A (Susceptible to Retroactive Interference)	**r = −0.48** (p = 0.011)	**r = −0.55** (p = 0.003)	**r = −0.50** (p = 0.008)	r = −0.45 (p = −0.018)	**r = −0.51** (p = 0.006)	r = −0.34 (p = 0.08)	r = −0.29 (p = 0.15)
Category Fluency	r = −0.36 (p = 0.067)	r = −0.41 (p = 0.033)	r = −0.36 (p = 0.066)	r = −0.32 (p = 0.100)	r = −0.32 (p = 0.109)	r = −0.32 (p = 0.101)	r = −0.22 (p = 0.264)
Trails A	r = 0.29 (p = 0.138)	r = 0.31 (p = 0.111)	r = 0.41 (p = 0.035)	r = 0.37 (p = 0.058)	r = 0.24 (p = 0.227)	r = 0.16 (p = 0.008)	r = 0.11 (p = 0.597)
Trails B	r = 0.03 (p = 0.885)	r = 0.03 (p = 0.877)	r = 0.21 (p = 0.295)	r = 0.18 (p = 0.370)	r = −0.08 (p = 0.681)	r = −0.11 (p = 0.570)	r = −0.09 (p = 0.664)
WAIS-R Block Design	r = −0.20 (p = 0.329)	r = −0.19 (p = 0.348)	r = −0.26 (p = 0.197)	r = −0.25 (p = 0.203)	r = −0.13 (p = 0.515)	r = −0.09 (p = 0.672)	r = −0.17 (p = 0.407)

Notes: Because of multiple comparisons, the two-tailed criterion for significance was set at p ≤0.01, which are **bolded** in the table. All brain regions analyzed for amyloid load were normalized to the cerebellum. The degrees of freedom (df) for the correlation coefficients above are 25.

Beta-amyloid protein, which can be quantified regionally in the brain using PET amyloid imaging, is a preclinical biomarker of AD pathology that has shown high correlation with AD plaques on autopsy.[7,8]

In this study, we examined the association of amyloid load in different brain regions to performance on the SIT and other neuropsychological measures among non-demented community-dwelling elderly.

METHODS

Elderly community-dwelling participants without significant functional deficits and with a global Clinical Dementia Rating score of 0 or 0.5 were evaluated with an extensive clinical interview including a neurological examination and a neuropsychological battery. The battery included the three-trial Fuld Object Memory Evaluation, delayed recall of the NACC story passage, WAIS-IV Block Design, Trail Making Test, and Category Fluency Test. Participants (mean age: 79.9 years; SD: 5.7 years; range: 67−88 years) were classified at a consensus conference as cognitively normal (N = 8), cognitively normal with subjective memory complaints (N = 11), amnestic mild cognitive impairment (aMCI; N = 4) and non-amnestic mild cognitive impairment (NaMCI; N = 4). The mean MMSE score for the entire sample was 28.0 (SD: 2.1, range: 23−30).

The Semantic Interference Test[3] was administered after three trials of the 10-item (from Bag A) Fuld Object Memory Evaluation[9] by administering a new set of 10 objects (from Bag B), each item semantically corresponded to one of the 10 objects presented from Bag A (e.g., "key" from Bag A was paired with semantically related "lock" from Bag B). When items from Bag A interfere with recall for semantically related items in Bag B, this is referred to as PSI. Impairment in the recall of items in Bag A, in a subsequent trial, because of semantic interference from items in Bag B, is referred to as RSI. Thus, recall on SIT B recall is susceptible to PSI whereas subsequent recall of the 10 targets on List A are susceptible to RSI.[3]

Each subject received an amyloid positron emission tomography (PET) brain scan, using 18-F-labeled PET ligand flobetapir. Standard uptake value ratios (SUVRs) were derived using the counts from frontal, temporal, parietal, anterior cingulate, posterior cingulate, and precuneus regions, normalized to counts from the cerebellum.[10] The mean normalized counts for all regions provided a composite SUVR.