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

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Abstract

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—Twenty-seven 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.

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No Disclosures to Report

CONCLUSION—In non-demented individuals, vulnerability to PSI highly associated with total and regional beta-amyloid load and may be an early cognitive marker of brain pathology.

Keywords

Amyloid Scanning; Florbetapir; Proactive interference; Semantic interference; MCI; Subjective memory complaints; Semantic Interference Test; SIT

INTRODUCTION

Buschke and colleagues (1) emphasized that deficits in using semantic cues to learn new information was characteristic of early Alzheimer's 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 was developed [SIT (3)]. The SIT uses semantically related items on two competing lists to elicit proactive semantic interference (PSI) and retroactive interference (RSI) effects. The PSI measure of the SIT was able to distinguish amnesic MCI (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).

Beta-amyloid protein, which can be quantified regionally in the brain using PET amyloid imaging, is a preclinical biomarker of AD pathology, that have 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 global Clinical Dementia Rating (CDR) score of 0 or .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), amnesic mild cognitive impairment (aMCI:n=4) and non-amnesic 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 ten-item (from Bag A) Fuld Object Memory Evaluation (FOME; 9) by administering a new set of ten

objects (from Bag B), each item semantically corresponded to one of the ten 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 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 while subsequent recall of the 10 targets on List A are susceptible to RSI (3).

Each subject received an Amyloid PET Brain Scan, using 18-F labeled PET ligand flobetapir. Standard uptake value ratios (SUVR) 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.

STATISTICAL METHODS

Primary analyses of the association of amyloid load to neuropsychological test performance, presented in Table 1, employed multiple Pearson Correlation Coefficients. The individual criterion for significance was adjusted to $p = .01$ for multiple comparisons, to reduce the possibility of family-wise alpha error although absolute p-values are listed in Table 1. These analyses were repeated using Spearman Rank Order Correlation Coefficients and similar results were obtained. Comparative proportions of subjects in different diagnostic groups with proactive and retroactive interference deficits were by Chi-square analyses at $p < .05$.

RESULTS

Total SUVR amyloid levels ranged from .80 to 1.65 (Median= .98). Seven individuals achieved an SUVR cut-off of 1.11, which is the cut-off point for an overall positive amyloid scan (1 cognitively normal participant, 3 subjective memory complaint participants; 3 amnesic MCI participants). Using cut-offs for *recall susceptible to PSI* of 1.0 SD or lower than previous normative values (Bag B recall = 5) and *recall susceptible to RSI* (Short Delay Bag A recall = 3), PSI impairment on the SIT was 0% for normals, 18.2 % for those with subjective memory and 62.5% for subjects with MCI [χ^2 (df=2)= 8.72 $p < .02$]. Impairment on the RSI measure was 12.5% for normals, 36.4% for subjective memory disorder, and 62.5% for MCI participants [χ^2 (df=2)= 4.29; $p = .12$]. The total number of subjects having either type of semantic interference (PSI or RSI) deficits was as follows: normal (12.5%), subjective memory disorder (44.5 %), and MCI (75.0%) [χ^2 (df=2)=6.34; $p < .05$].

As depicted in Table 1, examining the relationship between amyloid load and cognitive test performance among 27 participants, the strongest and most consistent association was between SIT Bag B recall (i.e., susceptibility to PSI) and SUVR reflecting total mean brain amyloid and amyloid load in the anterior cingulate, posterior cingulate, precuneus, frontal lobe, temporal lobe and parietal lobe with statistically significant correlation coefficients ranging from $r = -.50$; (df=25) $p < .01$ to $r = -.72$; (df=25) $p = .001$. Immediate recall on Bag A was related to total mean brain amyloid load and amyloid load in the anterior cingulate, posterior cingulate and frontal lobe. Finally, performance for delayed memory for passages

was associated with total mean brain amyloid load and amyloid deposition in the anterior cingulate. Performance on the FOME itself and on all non-memory tests was not related to brain amyloid load.

When post-hoc parametric analyses were conducted with only those persons with subjective memory complaints and those who were cognitively normal, strong Bag B associations were also found for SUVR total ($r = -.63$; ($df=25$) $p < .01$), anterior cingulate ($r = -.62$; ($df=25$) $p < .01$), precuneus ($r = -.65$; ($df=25$) $p < .01$) and frontal regions ($r = -.61$; ($df=25$) $p < .01$). While Short Delay Recall SIT A was modestly correlated with *anterior cingulate* ($r = -.47$; ($df=25$) $p < .05$) and frontal regions ($r = -.49$; ($df=25$) $p < .05$). No other memory or non-memory measures were associated with amyloid load.

DISCUSSION

This study is the first to investigate the association between vulnerability to proactive and retroactive interference and amyloid deposition, in a wide array of brain regions among non-demented community-dwelling elders who were either cognitively normal, with or without subjective complaints and those with MCI. Bag B recall, a measure of proactive semantic interference (PSI) *accounted for over 51%* of the observed variability within the anterior cingulate region and was also substantial in several other brain regions such as the precuneus, frontal regions and posterior cingulate. These associations persisted when examining only subjects without MCI and at much higher level found with episodic memory measures in our study and in previous investigations (10). Previous studies have shown that susceptibility to PSI has distinguished aMCI patients from cognitively normal elderly with high levels of sensitivity and specificity (3) and was a strong predictor of progression from MCI to dementia (6). The significance of the current findings is that PSI may be an early cognitive marker of Alzheimer's disease, because elevated amyloid load on PET scans is representative of meaningful beta-amyloid plaque and PSI and RSI occurs in the very early stages of amyloid deposition, even before a diagnosis of MCI is clinically warranted. As such, continued follow-up of our sample will be important. Indeed over 45% of participants with subjective or no reported memory complaints had SIT deficits but had no impairment on standard neuropsychological tests. Further, these results demonstrate that the correlations between PSI and RSI measures of the SIT and beta-amyloid load are present across a range of SUVRs, which are both above and well below the threshold considered to be "amyloid positive" (i.e., $SUVR = 1.11$). It is possible, that by studying larger numbers of subjects who are either normal or in the very mildly impaired range, that these associations between neuropsychological measures and amyloid load may provide future insights as to the amount of beta amyloid deposition that is biologically significant.

In conclusion, the obtained results, although preliminary, were not due to the results of outliers and similar results were found when non-parametric Spearman Rank order correlation coefficients were employed. This suggests that A β pathology in persons with normal or preclinical disease states can correlate with cognitive test performance given that vulnerability to PSI as measured by the SIT, is particularly sensitive to amyloid deposition in many brain regions among non-demented individuals. The strong associations between SIT Bag B performance and abnormal beta amyloid deposition occurred in subjects before a

diagnosis of MCI and with amyloid load concentrations both above and below the threshold of amyloid positivity, further illustrates the utility of semantic interference paradigms in research with individuals at risk for prodromal Alzheimer's disease and may confer an advantage over traditional cognitive measures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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 OME	$r=-.23$ $p=.225$	$r=-.28$ $p=.161$	$r=-.23$ $p=.248$	$r=-.19$ $p=.346$	$r=-.25$ $p=.210$	$r=-.21$ $p=.301$	$r=-.09$ $p=.668$
Delayed Passage Recall	$r=-.47^*$ $p=.013$	$r=-.53^*$ $p=.005$	$r=-.45$ $p=.020$	$r=-.44$ $p=.022$	$r=-.43$ $p=.025$	$r=-.44$ $p=.023$	$r=-.33$ $p=-.091$
SIT BAG B (Susceptible to Proactive Interference)	$r=-.67$ $p<.001$	$r=-.72$ $p<.001$	$r=-.59$ $p=.001$	$r=-.62$ $p=.001$	$r=-.67$ $p<.001$	$r=-.63$ $p<.001$	$r=-.50$ $p=.008$
SIT BAG A (Susceptible to Retroactive Interference)	$r=-.48$ $p=.011$	$r=.55$ $p=.003$	$r=-.50$ $p=.008$	$r=-.45$ $p=-.018$	$r=-.51$ $p=.006$	$r=-.34$ $p=.08$	$r=-.29$ $p=.15$
Category Fluency	$r=-.36$ $p=.067$	$r=-.41$ $p=.033$	$r=-.36$ $p=.066$	$r=-.32$ $p=.100$	$r=-.32$ $p=.109$	$r=-.32$ $p=.101$	$r=-.22$ $p=.264$
Trails A	$r=.29$ $p=.138$	$r=.31$ $p=.111$	$r=.41$ $p=.035$	$r=.37$ $p=.058$	$r=.24$ $p=.227$	$r=.16$	$r=.11$ $p=.597$
Trails B	$r=.03$ $p=.885$	$r=.03$ $p=.877$	$r=.21$ $p=.295$	$r=.18$ $p=.370$	$r=-.08$ $p=.681$	$r=-.11$ $p=.570$	$r=-.09$ $p=.664$
WAIS-R Block Design	$r=-.20$ $p=.329$	$r=-.19$ $p=.348$	$r=-.26$ $p=.197$	$r=-.25$ $p=.203$	$r=-.13$ $p=.515$	$r=-.09$ $p=.672$	$r=-.17$ $p=.407$

Note: Because of multiple comparisons, the two-tailed criterion for significance was set at $p=.01$ 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.*