

Vulnerability to Proactive Semantic Interference and Progression to Dementia among Older Adults with Mild Cognitive Impairment

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Key Words

Semantic interference · Mild cognitive impairment ·
Semantic Interference Test · Alzheimer's disease

Abstract

There is evidence that vulnerability to proactive semantic interference may be an early manifestation of early Alzheimer's disease and other neurodegenerative disorders. At present, there is a paucity of data regarding the extent to which such deficits relate to the progression of cognitive deficits and to clinically significant endpoints such as dementia. In this study, we followed 76 older adults, initially diagnosed with mild cognitive impairment, for a period of up to 3 years. Twenty-seven of these individuals (35.5%) progressed from mild cognitive impairment to dementia. An examination of baseline neuropsychological performance indicated lower baseline scores for object memory among those progressing to dementia. However, baseline Mini-Mental State Examination scores, delayed memory for passages, delayed visual memory, letter fluency, category fluency, Trails B and Block Design did not differ among study groups. In contrast, the Semantic Interference Test, a measure susceptible to vulnerability to proactive semantic interference showed the greatest baseline differentiation between those who progressed and those who did not pro-

gress to dementia. Further, scores on this measure predicted future progression to dementia with high accuracy. Vulnerability to proactive interference may be an early manifestation of an early dementing process and may have utility in predicting future progression to dementia.

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Introduction

There has been an increasing emphasis on the detection of early manifestations of mild cognitive impairment (MCI) in the elderly. Since some persons with MCI may progress to greater degrees of impairment while others do not, it is important to determine predictors of important endpoints such as dementia. Performance on list learning and semantic memory tests assessing immediate and delayed recall has been the most predictive of progression to dementia among older adults who do not meet criteria for dementia upon initial evaluation [1–4] and among initially normal community-dwelling elders [5]. However, nonmemory tests such as information and animal fluency [6], attention and executive function [7] and psychomotor speed [8] have also been found to be predictive of progression to dementia. This raises the issue that the earliest cognitive symptoms of an underlying degen-

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erative process may be variable and that it may correspond to specific areas of the brain that may be initially affected.

With the promise of newer pharmacological agents on the horizon, investigators have turned to other paradigms in an attempt to identify the earliest cognitive manifestations of MCI and neurodegenerative disease. In an attempt to elucidate these early mechanisms, our group has found that increased vulnerability to semantic interference may be an early manifestation of cognitive impairment among elderly patients with early Alzheimer's disease (AD). After learning an initial list of items over several trials, susceptibility to proactive interference for other semantically related targets had a high degree of sensitivity and specificity in distinguishing mildly impaired AD patients, patients with prodromal AD who did not meet criteria for dementia, and normal elderly controls [9, 10]. The fact that mean group differences persisted after controlling for overall memory performance suggests that susceptibility to proactive interference may reflect impaired inhibitory processes and potential dysfunction that extends beyond memory impairment [9].

More recent work suggests that susceptibility to semantic interference may not be limited to AD but may be observed among patients with other neurological conditions such as multiple cerebral infarctions, which commonly affect executive function [11]. While vulnerability to semantic interference may be an effective marker of early cognitive impairment, little is known about the utility of such measures to predict those persons who might be more susceptible to cognitive decline and progression to dementia. In this study, we followed 76 subjects with MCI for up to 3 years. The primary goal of the study was to assess the extent to which baseline vulnerability to semantic interference and performance on other neuropsychological measures could differentiate persons who would progress to dementia from those who would not progress to dementia.

Methods

Subjects

The initial pool of subjects consisted of 435 community-dwelling subjects who were participants in a longitudinal study of aging. Subjects were recruited from a community memory disorders screening program, via newspaper advertisement, or were patients of an outpatient memory disorders clinic or their spouses. All subjects had extensive clinical and neuropsychological assessment at baseline by board-certified neuropsychologists or post-doctoral fellows under their supervision. Approximately 56% of the sample were judged to have normal cognition at baseline, 26%

were classified as having cognitive impairment without dementia, 9% were classified as having questionable cognitive impairment, and 9% were classified as having dementia. Since this study was designed to examine cognitive predictors of progression from MCI to dementia, we focused on the 115 subjects in the cohort who were judged to have cognitive impairment without dementia at baseline.

Cognitively Impaired Individuals at Baseline

A total of 96 of the 115 cognitively impaired subjects met Petersen's criteria [12] for MCI adapted for this study which included: (a) reported cognitive impairment and/or the clinician judged that there was cognitive impairment during an extensive clinical interview; (b) there was verified objective cognitive impairment which was quantified at 1.5 SD or below on one or more measures of cognition tapping memory, language, visuospatial skills or executive function as described below; (c) score on the Mini-Mental State Examination (MMSE) [13] was no less than 23, and (d) there was no evidence of deterioration in social and/or occupational function required by the DSM-IV criteria for a dementia syndrome. Follow-up longitudinal data were available on 76 of these 96 MCI subjects. There were no differences in level of educational attainment between the MCI subgroup that was followed longitudinally versus the subgroup that was lost to follow-up. However, the group that remained in the study was slightly younger (mean age = 77.34 ± 5.5 years) than the group lost to follow-up (mean age = 80.45 ± 6.6 years) [$F(1, 95) = 4.62; p < 0.04$]. In addition, the 20 MCI patients lost to follow-up did not differ from the 76 patients who were followed longitudinally with regards to scores on any of the neuropsychological measures at baseline as described below.

Progression to Dementia

Subjects were classified as having progressed to dementia if during their annual follow-up they met the following DSM-IV criteria for dementia: (a) impairment in memory and at least one additional cognitive domain confirmed by neuropsychological tests at 1.5 SD or below expected levels; (b) deterioration in social and/or occupational function required by DSM-IV criteria for dementia, and (c) no fluctuation of consciousness indicative of delirium.

Neuropsychological Measures

Neuropsychological measures tapped memory (3-Trial Fuld Object Memory Evaluation [14, 15]; Delayed Logical Memory [16]; Delayed Visual Reproduction [17]); language (Category Fluency [18]); visuospatial function (Block Design [19]) and executive function (Trails B [20]; COWAT Letter Fluency [21]). Impairment within a cognitive domain was confirmed if performance in one or more tests within that domain was 1.5 SD below age- and education-related data derived from a large local normative database of English- and Spanish-speaking cognitively normal subjects collected by our group over the past 10 years.

Semantic Interference Test

In addition to the neuropsychological measures listed above, we administered the Semantic Interference Test (SIT) [9, 10]. The SIT adds an additional set of ten items (i.e. Bag B) that are semantically related to items on the Fuld OME and that is administered to subjects after the three recall trials of the modified Fuld OME. Subjects are required to recall this new set of objects, a recall that

Table 1. Demographic characteristics of MCI subjects who progressed to dementia (n = 27) versus subjects who did not progress to dementia (n = 49)

	Progression to dementia	Nonprogression to dementia	F	χ^2	p value
Age	77.19 \pm 6.2	77.43 \pm 5.2	0.03		0.856
Years of education	14.00 \pm 3.3	12.16 \pm 4.5	3.43		0.068
MMSE score	26.37 \pm 1.9	26.20 \pm 2.1	0.12		0.729
Females	33.3%	51.0%		1.55	0.214
English language	74.1%	51.0%		2.94	0.097

Values for age, years of education and MMSE score are expressed as mean \pm SD.

is susceptible to proactive interference (i.e. old learning of the previous OME items interferes with learning of the new set). This is followed by recall of the original list of OME objects (Bag A), a recall that is vulnerable to retroactive interference (i.e. new learning of Bag B items interferes with retrieval of previously learned information).

Although scores on other neuropsychological measures were employed to provide confirmation of cognitive impairment that was noted in the clinical evaluation, it should be noted that in the present study, performance on the SIT was not utilized in the initial or the follow-up diagnostic classification of subjects.

Statistical Analyses

Group differences in baseline demographic and neuropsychological measures were analyzed using one-way analyses of variance (ANOVAs). Because contrasts on multiple dependent neuropsychological measures increases the probability of family-wise α -error, and there were 9 neuropsychological measures examined, a Bonferroni correction was applied and the test-wise criterion for each individual contrast was $p < 0.006$. For each measure, η^2 was calculated by taking the derived sum of squares for the group effect and then dividing this by the total sum of squares in an ANOVA model. This corresponds to the degree of variability in the dependent measure that could be attributed to the group effect (those who progressed to dementia versus those who did not progress to dementia) and is equivalent to an R^2 obtained in regression models. The ability of baseline neuropsychological measures to predict progression was examined by discriminant function analysis (DFA) which allowed classification of each case by a discriminant function derived on all other cases except the case being classified. We also examined comparative predictive values of the different neuropsychological measures under the receiver operating characteristic (ROC) curve.

Results

Subjects were followed from 11 to 39 months with a mean follow-up time of 21.49 months (SD = 8.5). Of the 76 subjects that had MCI at baseline and were available

for follow-up, 27 (35.5%) progressed to dementia. The average time of follow-up for those who progressed to dementia was 19.7 months (SD = 9.0) and was not significantly different from those who did not progress to dementia (22.5 months, SD = 8.2). As depicted in table 1, those individuals who progressed to dementia did not differ with regards to age, education, language of evaluation or global cognitive impairment on the Folstein MMSE. Fifty-six percent of those who progressed to dementia were diagnosed with probable AD, 16% were diagnosed with multiple cerebral infarctions and 13% were diagnosed with Diffuse Lewy Body Disease. The remaining subjects had cognitive signs consistent with AD but did not have an MRI of the brain that would allow ruling out other possible causes of cognitive impairment and, in addition, did not seek neurological follow-up.

We examined potential baseline neuropsychological differences between those individuals who progressed to dementia versus those who did not. As shown in table 2, the results of ANOVAs indicated that those individuals that progressed to dementia evidenced lower baseline Fuld OME scores [F (1, 74) = 10.62; $p < 0.002$]; Bag B, and proactive interference score on the SIT [F (1, 74) = 22.35; $p < 0.001$]. There were no statistically significant differences between groups with regards to performance on other neuropsychological measures. The magnitude of effect between those individuals who progressed versus those who did not progress to dementia was calculated by dividing the explained sum of squares attributed to the group effect divided by the total sum of squares in the ANOVA model (η^2). The greatest η^2 was observed for Bag B recall, where group membership explained 23.2% of variability on this measure.

To determine the extent to which low Bag B scores represented proactive interference as opposed to merely im-

Table 2. Baseline neuropsychological performance of subjects who progressed to dementia (n = 27) versus subjects who did not progress to dementia (n = 49)

	Progression to dementia (mean ± SD)	Nonprogression to dementia (mean ± SD)	F value	p value	η^2 , %
3-Trial Fuld OME	17.22 ± 4.3	20.22 ± 3.6	10.62	0.002	12.6
SIT Bag B Proactive Interference	3.44 ± 2.1	5.53 ± 1.7	22.35	<0.001	23.2
SIT Bag A Retroactive Interference	3.11 ± 2.0	2.92 ± 1.9	0.17	0.684	0.2
WMS III Delayed Recall for Passages	13.70 ± 7.8	14.84 ± 7.5	0.39	0.534	0.5
WMS-R Delayed Visual Reproduction	7.81 ± 6.5	11.10 ± 6.6	4.32	0.041	5.6
Trails B (time), s	189.81 ± 77.1	194.02 ± 88.7	0.04	0.840	0.1
Block Design WAIS-III	23.26 ± 6.8	20.59 ± 6.2	2.93	0.092	4.0
FAS Letter Fluency	30.41 ± 13.3	29.14 ± 12.2	0.18	0.667	0.2
Category Fluency	29.93 ± 7.8	33.20 ± 8.7	2.67	0.107	3.5

Due to multiple contrasts and enhanced probability of family-wise α -error, the criterion for significance for each individual test-wise comparison was set at $p \leq 0.006$ by the Bonferroni procedure.

paired memory, we employed both the Total Recall of the Fuld OME and Delayed Visual Reproduction in group comparisons for which Bag B was an outcome measure. Even after these covariates were entered into the model, the Bag B proactive score was significantly different between those subjects who progressed to dementia and those subjects who did not progress to dementia [$F(1, 73) = 10.18$; $p \leq 0.002$].

Another method of separating the effects of overall memory impairment from the effects of proactive interference is to calculate a proactive interference ratio using the formula used in a previous SIT study [9] (i.e. Bag SIT B recall/(Sum of Fuld OME Recall Trials 1–3)/3). This effectively controls for the overall strength of learning and memory for the original set of items when trying to learn an equivalent list of semantically related items. A lower proactive interference ratio indicates a greater degree of semantic interference. In this study, those persons who progressed to dementia had a lower proactive interference ratio (mean = 0.587; SD = 0.32) than those individuals who did not progress to dementia (mean = 0.823; SD = 0.25) [$F(1, 74) = 12.88$; $p \leq 0.001$].

We entered neuropsychological variables into a stepwise DFA. The only significant variable in the model was the SIT Bag B recall with Wilk's $\lambda = 0.768$; $\chi^2 = 19.40$; $p < 0.001$. We employed a cross-validation technique so that each case was classified by all cases in the model except that case. Among those who progressed to dementia (cut-off score = 4), the correct classification rate was 70.4% while the correct classification rate of those who

did not progress to dementia was 73.5%. The overall correct classification rate was 72.4%.

A series of ROC analyses indicated that the area under the ROC curve (AUC) was the greatest for Bag B recall (AUC = 0.775), followed by the total score of the Fuld Object Memory Evaluation (AUC = 0.707), Delayed Visual Reproduction (AUC = 0.662), Category Fluency (AUC = 0.619), Block Design (AUC = 0.584), Trails B (AUC = 0.573), Logical Memory Delayed (AUC = 0.550) and FAS (AUC = 0.522). There was a statistically significant greater AUC for SIT Bag B than for Delayed Logical Memory and for every neuropsychological measure except the Fuld OME score and Visual Reproduction Delayed (approaching significance at $p = 0.08$).

Discussion

The results of the present investigation indicated that after an average follow-up of about 2 years, 35.5% of patients initially diagnosed with MCI progressed to dementia. This is consistent with our previous research indicating a 44% conversion rate among MCI patients presenting to a memory disorders clinic over a 2.5-year period [22] and is consistent with rates of progression of 32% observed in previous population-based studies of similar duration of follow-up [8].

Consistent with previous work [22], the sum of the three learning trials of the Fuld OME differentiated between those who progressed and those who did not prog-

ress to dementia. A unique finding in this study was that a measure susceptible to proactive interference on the SIT demonstrated the largest effect size and was only one of two measures that differentiated between subjects who progressed and those who did not progress to dementia. Bag B performance on the SIT resulted in the highest η^2 , the highest AUC, and was the only measure that was predictive of progression to dementia in DFA (72.4% accuracy). Further, the AUC was greater for the SIT Bag B measure than for delayed memory for passages, category fluency and other widely employed neuropsychological measures.

After controlling for performance on the learning trials of the 3-trial Fuld OME, the measure of proactive interference (i.e. Bag B recall) continued to demonstrate statistically significant differences between study groups. By accounting for strength of recall on these measures, it is apparent that performance on Bag B recall on the SIT is tapping cognitive processes beyond the effects of initial learning and memory alone [9].

There are a number of explanations for poor performance on Bag B of the SIT. First, the difficulties in recalling a new list of semantically related items may reflect a general inhibitory effect that may be particularly pronounced due to competing semantic information. Alternatively, these deficits may reflect poor source memory or confusion in distinguishing between competing elements that have been poorly encoded. Although somewhat speculative, it is possible that deficits on proactive interference measures of the SIT reflect a deficit between elements of memory function and its interface with executive processes in the anterior cingulate region or oth-

er frontal systems of the brain. It should be noted that deficits in executive function have been previously related to subsequent functional decline in at-risk populations [23].

The follow-up period in the current study averaged just over 21 months. It is possible that with longer follow-up periods, those persons who did not have low Bag B scores on the SIT may have progressed to dementia. The answer to this question awaits further follow-up. Further, we had a heterogeneous sample of subjects which included a nonclinic sample as well as a clinic sample from a memory disorders clinic, with individuals having different etiologies for their cognitive impairment. Future work will be required to determine if the predictive utility of measures such as the SIT is equally effective for different diagnostic entities.

The SIT employs commonly employed household objects and can be easily administered to individuals with low educational attainment and from varied cultural/language backgrounds. Given the sensitivity to early cognitive impairment in MCI and its association with progression to dementia, the role of proactive semantic interference is worthy of further research.

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