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Learning and Retention in Preclinical and Early Alzheimer's Disease

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Accelerated forgetting has been proposed as the first sign in preclinical and early Alzheimer’s disease (AD). The authors investigated learning and retention in participants who later developed AD with free and cued selective reminding (FCSR; Buschke, 1984; Grober & H. Buschke, 1987), a test that maximizes learning by inducing deep semantic processing and by controlling study and test conditions. AD patients in the preclinical stage recalled significantly fewer words than did matched control participants, indicating an impairment of learning; nonetheless, patients’ retention was identical to that of control participants. A retention deficit was documented 3 years later for AD patients but not for control participants, whose retention was still perfect. Thus, a retention deficit is not present in preclinical AD when hallmark learning deficits can be documented. Detection of preclinical and very early AD may be best accomplished by using robust learning tests that control cognitive processing.

Memory impairment, specifically the inability to learn new information, is a hallmark deficit of Alzheimer’s disease (AD) and is regarded as essential for the diagnosis. Learning in this study refers to the acquisition of new information and not the rate at which new information is acquired. Recently, there has been interest in determining whether, in addition to the learning deficit in early AD, retention is impaired. Accelerated forgetting has been observed in some studies (Larrabee & Youngjohn, 1993; Moss, Albert, Butters, & Payne, 1986; Welsh, Butters, Hughes, Mohs, & Heyman, 1991) but not in others (Becker, Boller, Saxon, & McGonigle-Gibson, 1987; Kopelman, 1985; Robinson-Whelen & Storandt, 1991; Tuokko, Vernon-Wilkinson, Weis, & Beattie, 1991). The discrepant findings (reviewed by Larrabee & Youngjohn, 1993) usually have been explained by differences in the time between initial learning and retention testing, and whether or not the AD and control groups were matched for initial learning. Reanalysis of the discrepant findings supported the view that accelerated forgetting is another feature of the memory impairment in early AD (Larrabee & Youngjohn, 1993). Furthermore, the finding that delayed recall discriminated mild AD patients from normal older participants better than did initial learning (Welsh et al., 1991) raises the possibility that the retention deficit is present before the learning deficit.

The retention deficit in AD is best examined with memory tests that control initial processing in order to obtain maximum learning, which is the basis for subsequent retention. Free and cued selective reminding (FCSR; Buschke, 1984; Grober & Buschke, 1987) is a memory test that controls attention and cognitive processing by having participants search for items (e.g., grapes) in response to cues (fruit) that are later used to elicit recall of items not retrieved by free recall (Buschke, 1984; Grober & Buschke, 1987). Unlike most clinical tests, FCSR maximizes recall because the study procedure was designed to minimize attention, promote deep semantic processing, and control conditions during encoding that are reinstated at retrieval. Control of cognitive processing is especially important when testing memory in older adults because age-related reductions in attentional resources and impoverished information processing limit learning when the study conditions are not controlled (e.g., Craik & Byrd, 1982; Perlmutter & Mitchell, 1982; Rabinowicz, Craik, & Ackerman, 1982; Waugh & Barr, 1982; see review in Light, 1991). Measuring retention of inadequately learned material can lead to contradictory results as previous studies on forgetting have shown (e.g., Becker et al., 1987; Moss et al., 1986).

The Baltimore Longitudinal Study of Aging (BLSA; see Shock et al., 1984) is a multidisciplinary 38-year investigation of normal aging conducted by the National Institute on Aging at the Gerontology Research Center. Since 1985, study participants over age 65 have received biennial neurological examinations and neuropsychological procedures (including FCSR) as part of their routine BLSA visits. By following normal older participants, some of whom develop dementia, the BLSA provides a unique opportunity to determine whether the retention deficit in AD patients occurs before or after the learning deficit.

Method

Participants

Participants were selected from 537 initially nondemented participants in the BLSA who were followed with neurological examinations for up

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Table 1
Mean Age, Education, and Neuropsychological Scores for AD (With Standard Deviations) and Control Participants at Baseline and 3-Year Follow-Up

<table>
<thead>
<tr>
<th>Background information and scores</th>
<th>AD participants*</th>
<th>Control participants*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Age in years</td>
<td><strong>79.3</strong></td>
<td>5.6</td>
</tr>
<tr>
<td>Education in years</td>
<td>16.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Mini-Mental</td>
<td>26.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Blessed IMC</td>
<td>3.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Boston Naming</td>
<td>14.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Free recall Trial 1</td>
<td>8.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Free recall Trial 2</td>
<td>9.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Free recall Trial 3</td>
<td>10.1</td>
<td>2.6</td>
</tr>
<tr>
<td>Free recall delay</td>
<td>10.0</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Note: Participants were selected from the Baltimore Longitudinal Study of Aging (Shock et al., 1984). Dashes indicate that education and gender were the same at baseline and follow-up, AD = Alzheimer’s disease; Mini-Mental = Mini-Mental State Examination (Folstein et al., 1975); Blessed IMC = Blessed Information Memory and Concentration Test (Blessed et al., 1968); Boston Naming = 15-item Boston Naming Test (Mack et al., 1992).

* 55% women, n = 11. We were unable to match the oldest female AD participant on gender. ** 52% women, n = 31. 15-item version.

To 7 years. Each of 20 incident cases of AD was matched by age (±2.5 years) and gender to 3 control participants from the cohort. Mean education level was college graduate, similar for both groups of participants. Table 1 presents background information about the AD participants and control participants at baseline and follow-up evaluation (3.1 years later for AD participants and 2.9 years later for control participants, t = .45, p = .61, df = 78). With one exception, baseline evaluation was done at least 1 year before the diagnosis was made (M = 3.4 years).

Participants were diagnosed during the neurological examination, independently of the neuropsychological information. Five of the 20 participants had autopsy-confirmed AD and 11 more met the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association criteria for probable AD (McKann et al., 1994). Two of the remaining participants met criteria for probable AD but did not have CT (computed tomography) scans of the head and therefore carried a diagnosis of consistent with probable AD. The two remaining participants were diagnosed as having possible AD. One of them had a history of depression and the other had an atypical course consisting of a rapid decline after 2 years of progression that was gradual and insidious.

**FCSR Procedure**

The 16 items to be learned were line drawings of easily recognizable objects, each from a different semantic category (Battig & Montague, 1969). Dominant items in a category were avoided to minimize guessing. Immediately before the FCSR test was administered, each of the 16 items was presented 1 at a time for naming. Afterward, the 16 items to be learned were presented 4 at a time on an 8.5 in. (21.6 cm) × 11.0 in. (27.9 cm) card with 1 item pictured in each quadrant. Each card with 4 items was placed in front of the participant, one card at a time, in the same order for all participants. The participant was asked to search each card and point to and name aloud each item (e.g., grapes) when its cue (fruit) was given verbally. If the participant was unable to name the item, he or she was given a phonemic cue. After all 4 items were identified correctly, the card was removed, and immediate recall of just those 4 items was tested. Category cues were verbally provided for items not retrieved by free recall. Phonemic cues were provided if the participant failed to recall the item in response to its category cue. The participant was verbally reminded of any item they failed to retrieve by cue recall (e.g., the vehicle was a train). Once immediate recall for a group of 4 items was complete, the next set of items was presented for study. Immediate recall serves several functions: It provides an initial successful trial of recall that, in turn, may act as an orienting task that effectively guides retrieval (Rabinowitz & Craik, 1986); it provides retrieval practice before the test phase (Craik & Rabinowitz, 1984; Landauer & Bjork, 1978); and it adds semantic information to the memory trace (Rabinowitz & Craik, 1986; Whittemore, 1978). Successful completion of the search phase shows that deep semantic processing has been carried out and that the participant understands the task.

The study phase was followed by three trials of recall each preceded by 20 s of counting backwards in order to obtain recall from secondary memory. Each recall trial consisted of two parts. First, an extended period of time up to 2 min was provided for participants to free recall as many items as possible. Next, category cues were provided verbally for items not retrieved by free recall. If the participant failed to retrieve the item with the category cue, a phonemic cue was provided. Participants were reminded of items they failed to retrieve by cue recall. The sum of free recall and category recall is called total recall. Thirty minutes after the last recall trial, delayed free and cued recall were tested. Retention was measured by the savings score method, which is defined as the number of items retrieved by free recall at delay divided by the number of items retrieved by free recall on the final, third learning trial. During the 30-min delay period, other tests were administered, including a spatial location test for the 16 items from the FCSR test, (Grober, 1984), the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975), the Trail Making test (Reitan, 1958), and tests of verbal fluency, constructional ability, and calculations.

**Study Design**

Baseline performance on the FCSR test by AD and control participants matched on age and gender was compared with their performance 3 years later, when AD participants were in the early stage of AD, to
determine whether the retention deficit occurred before or after the learning deficit. Learning was measured by three trials of free recall and compared with retention tested 30 min later by a final trial of free recall.

Predictions

Predictions follow from the view that the impaired retention found in some studies of mild AD resulted from the failure to use robust learning procedures during acquisition. To the extent that uncontrolled memory tests result in the storage of less stable memory traces than do controlled memory tests, these traces would be more vulnerable to decay over time. With respect to mild AD, the effect is especially pronounced because of other cognitive deficits that undermine learning on uncontrolled tests. Thus, measures of retention may appear to discriminate mild AD from normal aging better than do measures of initial learning (cf. Welsh et al., 1991).

In the present study, we expected learning to be impaired at baseline despite controlled processing, indicating that there is a genuine impairment of learning in preclinical AD that is not due to other cognitive deficits. Retention at baseline was expected to be intact, indicating that when information is acquired under robust learning conditions, patients with preclinical AD are able to retain the material at normal levels. To assess changes in learning and retention as disease severity progresses, follow-up performance on the FCSR test was compared with performance at baseline. A retention deficit was expected to be present in early AD as well a decline in learning from baseline levels.

Results

Figure 1 presents the mean number of items in free recall for control and AD participants on each of the three learning trials and on the final trial of delayed recall 30 min later at baseline and follow-up. The left half shows that AD participants at baseline retrieved fewer items than did control participants on every trial, and that delayed recall was similar to third trial recall for all participants. At follow-up, shown in the right half, delayed recall declined significantly for AD participants but not for control participants.

Although all the AD participants were in the preclinical stages of the disease at baseline, presumably they were at different points in the preclinical period. When baseline Blessed Information Memory and Concentration Score (BIMC; Blessed, Tomlinson, & Rooh, 1968) was used as a covariate to adjust for these differences, it did not significantly influence learning or retention (ps > .10) and therefore was not included in the analyses of variance (ANOVA).

Learning

A mixed-model ANOVA was performed on the free-recall data with repeated measures on time (baseline vs. follow-up) and trials. AD participants recalled significantly fewer words than did control participants, F(1, 78) = 35.7, p < .0001, r² = .31, and significantly fewer words were recalled at follow-up than at baseline, F(1, 78) = 19.2, p < .0001, r² = .20. The interaction between group and time was significant, F(1, 78) = 24.3, p < .0001, r² = .24. Planned comparisons of the sum of free recall over trials indicated, first, that AD participants recalled fewer words than control participants at baseline (27.3 vs. 32.5), t(30) = 3.2, p = .003, demonstrating a genuine impairment of learning in preclinical AD and, second, that learning declined from baseline to follow-up for AD participants (27.3 vs. 20.5), t(19) = 3.8, p = .001, but not for control participants (32.5 vs. 32.9), t(59) = 0.67, p = .51. Free recall improved over trials for all participants, F(2, 156) = 40.2, p < .0001. The interaction between group and trials was not significant (F < 1), indicating a similar rate of learning in the two groups. No other interactions were significant.

Total recall, the other measure of learning, was summed across the three trials and compared at baseline and follow-up. Similar to the analysis of the free-recall data, AD participants retrieved significantly fewer words than did control participants overall, F(1, 78) = 38.5, p < .0001, r² = .33, and significantly fewer words were retrieved at follow-up than at baseline, F(1, 78) = 23.5, p < .0001, r² = .23. The interaction between group and time was significant, F(1, 78) = 24.1, p < .0001, r² = .24. Planned comparisons of these means indicated that learning declined from baseline to follow-up for AD participants (46.6 vs. 43.9), t(19) = 2.9, p = .01, but not for control participants (47.7 vs. 47.7), t(59) = 0.16, p = .87. Total recall of the AD participants as a group at follow-up was below the cut score of 45 that indicates dementia in older adults (Grober et al., 1988), whereas it was above the cut score at baseline.

Retention

At baseline, all participants displayed perfect retention of the previously learned information as shown by savings scores that were not significantly different from 1 for AD participants (.994), t(19) = 0.13, p = .90, or control participants (1.048), t(59) = 1.75, p = .08. A mixed-model ANOVA was performed on the savings scores, with time as the repeated measure. Retention was significantly worse for AD participants than for control participants overall, F(1, 78) = 7.5, p = .008, r² = .09. Retention at follow-up was not significantly worse than retention at baseline, F(1, 78) = 2.1, p = .15, r² = .03. The interaction between group and time did not reach acceptable levels of significance, F(1, 78) = 2.7, p = .10, r² = .03. Planned comparisons indicated that retention was the same for AD and control participants at baseline (0.99 vs. 1.05), t(31) = 0.96, p = .35, whereas it was poorer for AD participants than for control participants at follow-up (0.87 vs. 1.06), t(24) = 2.4, p = .02. Notably, although retention was impaired in AD participants at follow-up, 87% of the initially learned material was retained in comparison with much lower levels observed for patients with mild AD on uncontrolled learning tests (e.g., 37% in Welsh et al., 1991).

Discussion

Patients in the preclinical stage of AD who had demonstrable learning deficits at baseline shown by impaired free recall relative to matched control participants nonetheless displayed perfect retention 30 min later when the words to be remembered were studied under FCSR test conditions. These conditions provide maximum recall by circumventing inattention and inducing deep semantic processing (Grober et al., 1989). Total recall, the sum of free recall and category recall, was near ceiling levels in the patients who were in the the preclinical stage of AD, indicating that patients could retrieve words by cueing recall that they failed to recall on their own. Retesting 3 years later
disclosed a retention deficit for AD patients but not for control participants, whose retention was still perfect. Learning as measured by free recall declined from baseline levels for AD patients, whereas it was unchanged for control participants. Total recall, the other measure of learning, also declined at follow-up from the normal level displayed by patients at baseline when they were in the preclinical stage of AD.

The retention deficit was absent in patients who were in the preclinical stage of AD and developed sometime after the learning deficit. This suggests that for discriminating patients with preclinical and early AD from normal older adults, learning tests should be preferred over retention tests. Furthermore, we believe that controlling cognitive processing during learning maximizes the discrimination of age-associated memory deficits from dementia-associated memory deficits, especially in the preclinical or early clinical stage of disease (Grober & Buschke, 1987; Grober, Buschke, Crystal, Bang, & Dresner, 1988). Age-associated memory deficits are due to impaired attention, reduced processing capacity, use of inefficient strategies, or impairment of other cognitive processes that limit learning (Craik & Byrd, 1982; Light, 1991; Perlmutter, 1978; Perlmutter & Mitchell, 1982; Rabinowitz et al., 1982; Waugh & Barr, 1982). Age-associated memory deficits are reduced when cognitive processing is controlled (Craik & Byrd, 1982; Perlmutter & Mitchell, 1982; Grober, Merling, Heimlich, & Lipton, 1999). In contrast, dementia-associated memory deficits are observed even when appropriate processing has been carried out and are due to impairment of specific memory processes such as those that encode and retrieve memory traces.

Because impaired learning is one of the earliest manifestations of dementia and because other causes of amnesic syndromes in older adults appear to be relatively infrequent, identification of impaired learning that is not due to other cognitive deficits is highly predictive of a clinically recognizable dementia (Grober et al., 1988). Previous work has shown that FCSR testing discriminates mildly demented patients from nondemented control individuals with very high accuracy (Grober & Buschke, 1987; Grober et al., 1988; Petersen, Smith, Ivnik, Kokmen. & Tangalos, 1994; Tsubko & Crockett, 1989; Tsubko et al., 1991). In the Grober et al. study, total recall correctly classified 97% of 120 participants who were diagnosed independently of FCSR testing including 50 demented participants with an average BIMC score of 12 (SD = 5). But in the preclinical phase as we see from the present study, total recall is intact at a time when decrements in free recall are apparent. For example, in our study we found that patients in the preclinical stage of AD who were unable to recall the words on their own succeeded in retrieving them when they were prompted with the cues initially used. Thus, total recall was above the cut score for dementia for the group of incident cases at baseline, although it was below the cut score 3 years later when dementia in the group had progressed to the early stage.

Overall, the data suggest that learning deficits, as measured
by free recall, occur before retention deficits in individuals who later develop clinical AD. Therefore, measurement of learning deficits is likely to be more valuable for the early diagnosis of AD. In fact, free recall from FCSR is sensitive to the early neuropathological changes of AD in comparison to the BIMC, which is insensitive to early disease (Grob et al. 1996).

Norms for free recall from the FCSR test have been developed for an older adult sample free of individuals with preclinical dementia (Sliwinski, Grober, Buschke, Scarisbrick, & Lipton, 1996). Excluding patients with preclinical dementia is important because conventional norms that include them underestimate normal performance and dramatically reduce the sensitivity of the test for detecting impairment (Sliwinski, Lipton, Buschke, & Stewart, 1996). Finally, free-recall performance in a sample of normal older adults was not affected by race and was minimally associated with education, although these variables influenced verbal IQ (Grob et al., Lipton, Katz, & Sliwinski, 1997), suggesting that FCSR testing may be used in racially mixed groups to determine dementia status without adjusting for race or education.

The utility of FCSR testing for identifying patients with preclinical AD requires prospective investigation in populations of diverse educational, social, and ethnic backgrounds.

References


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