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Beneficial effect of minimal interference on item memory but not on source memory in Alzheimer's disease

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Abstract

Objectives: research suggests beneficial effects of minimal interference on item memory in mild Alzheimer's disease (AD). We conducted a study to test whether these beneficial effects extend to source memory, i.e., the ability to remember the episodic context in which an information was previously acquired.

Methods: twenty-six mild AD participants and 28 controls manipulated six objects or watched the experimenter manipulating six other objects. After immediate item recall ("what were the items?") and source recall ("by whom the items were previously manipulated?"), an interference or a minimal interference condition was administrated. In the interference condition, participants were assessed with neuropsychological tests for 10 min. In the minimal interference condition, they rested alone in a dark and quiet room for 10 minutes. Both interference and minimal interference conditions were followed by delayed recall, on which participants were asked to remember the previously-presented objects and their source.

Results: Higher item memory was observed following minimal interference than following interference in AD participants ($p < .01$) and controls ($p < .01$). Also, AD participants demonstrated higher item memory on immediate recall than following interference ($p < .001$) or minimal interference ($p < .001$); controls also demonstrated higher item memory on immediate recall than following interference ($p < .001$) or minimal interference ($p < .001$). Considering source memory, similar source memory was observed following interference and minimal interference in AD participants ($p > .1$) and controls ($p > .1$). Also, AD participants demonstrated higher source memory on immediate recall than following interference ($p < .001$) or minimal interference ($p < .001$); controls also demonstrated higher source memory on immediate recall than following interference ($p < .001$) or minimal interference ($p < .001$).

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Conflict of interests

The authors declare no conflict of interest

Conclusions: failures of hippocampus-dependent associative or consolidation processes in AD may preclude benefits of minimal interference for source memory. Nevertheless, AD patients may show some capacity to retain simple material, should the material presentation be followed by short delays that are free of further stimuli.

Keywords

Alzheimer's disease; hippocampus; memory; memory rehabilitation; minimal interference; source memory

1. Introduction

Alzheimer's disease (AD) is a progressive age-related neurodegenerative disease involving insidiously progressive episodic memory impairment [1]. The disease is characterized by the accumulation of amyloid-beta (Aβ) deposits extracellularly and development of neurofibrillary tangles containing tau intracellularly [1]. AD-related episodic memory decline is specifically associated with these neuropathological changes in entorhinal cortex and other medial temporal lobe structures. The medial temporal lobe also includes the hippocampus, a brain structure critical for all forms of declarative memory that shows prominent functional dysfunction and structural compromise by the disease [2].

One of the earliest features of episodic memory impairment in AD is anterograde amnesia (i.e., inability to form new memories), a difficulty that is usually followed by retrograde amnesia (i.e., inability to retrieve old memories) [1, 3]. The memory decline in AD also results in difficulties performing basic activities of daily living (e.g., problems in remembering to take medications or to turn off the oven), disorientation in time and space (e.g., difficulties to remember date-related information or the way back home), and, in the advanced stages of the disease, difficulties remembering basic information such as the subject's own name [1]. Considering the devastating effects of memory decline in AD, clinical research aims to assess the efficiency of rehabilitation interventions that may alleviate this decline, and one prominent candidate of an intervention is minimal interference.

Research on minimal interference suggests that a brief wakeful rest after new learning may enhance memory for the learned material, an observation that was reported even in patients with severe amnesia [4, 5]. The beneficial effect of minimal interference was also observed in patients with mild cognitive impairment [6], and patients with mild AD [7]. In a pioneering study on minimal interference [4], six patients with severe amnesia due to anoxia, head injury, limbic encephalitis, or stroke, were presented with lists of words, which they had to recall immediately afterwards, as well as following a 10 min delay. During this delay, participants either engaged in neuropsychological assessment (an "interference condition"), or rested alone in a dark and quiet testing room (a "minimal interference condition"). Although two of the six patients were unable to recall any of the words in either condition, four patients showed higher recall of the words following the minimal interference (49% of correct recall) than the interference condition (14% of correct recall). Benefits were also observed in healthy controls, whose mean percentage recall were 74%

and 46% in the minimal interference and interference conditions respectively. Considering these outcomes, the authors (Cowan et al., 2004) conducted a second study of potential benefits of minimal interference for longer delay. The same participants were presented with sentences, and the interference and minimal interference conditions were extended to one hour instead of 10 minutes. Similarly to the first experiment, four of the six patients benefited significantly from the minimal interference (79% of correct recall) than from the interference condition (7% of correct recall). Benefits were also observed in the healthy controls, whose mean percentage recall was 89% and 79% in the minimal interference and interference conditions respectively. Regarding AD, Dewar, Pesallaccia (7) presented mild AD participants with lists of words, which they had to recall immediately afterwards as well as following a 10 min delay, a delay during which participants either engaged in a picture naming task, or rested alone in a dark and quiet testing room. These procedures showed higher word recall following the minimal interference than following the interference condition.

If minimal interference improves item memory in AD [7], then it would be of interest to investigate whether such an effect is also seen for a memory facet that is particularly vulnerable in AD, namely, source memory. Source memory refers to the ability to remember the episodic context in which an information was previously acquired (e.g., “where I met that person before?”) [8]. Unlike item memory, source memory is compromised in normal aging [9–11], although less so. Studies have shown source memory decline when AD participants are asked to remember whether words were previously generated by themselves or by the experimenter [12], whether actions were previously enacted or imagined (Fairfield & Mammarella, 2009), or whether drawings of objects were previously imagined or perceived [13] ((for a review, see, [14]). In a study assessing source memory with several tasks, mild AD participants were asked to remember 1) whether objects were previously manipulated with a black or white glove, 2) whether objects were previously manipulated by the participants or by the experimenter, or 3) whether objects were previously imagined or manipulated by the participants [15]. Results showed poorer source memory in AD participants than in healthy controls across the three conditions. For both populations, poorer source memory was observed in the third than in the second condition, and in the second than in the first condition.

Potential beneficial effects of minimal interference on memory in AD may be attributable to its effects on consolidation processes. Memory consolidation refers to the progressive post-acquisition stabilization of long-term memories [16]. Findings from animal and human studies suggest that wakeful resting enhances recall by allowing for better memory consolidation. For instance, in animals, sequential neural activation associated with recent learning (e.g., exploring a new maze) was found to be replayed during wakeful resting [17, 18]. This consolidation process was found to be prone to interference during pharmacological manipulations, such as injection of toxins, drugs and seizures [16]. In particular, pronounced detrimental effects were observed when the interference occurred immediately after learning, an interval during which newly acquired memory traces may be still weak and in need of strengthening [16]. Further evidence for the beneficial effect of resting on memory consolidation comes from neuroimaging human studies suggesting that sleep supports the consolidation of newly acquired memories [19].

The present study was designed to address the hypothesis that source memory decline in mild AD may be alleviated by minimal interference, similar to its beneficial effect on item memory [7]. To distinguish between potential beneficial effect of minimal interference on item and source memory in AD, we administrated a source memory task on which AD patients have previously shown lesser decline [15]. Specifically, AD and control participants were asked to manipulate items or to watch the experimenter do so. After immediate item recall ("what were the items"?) and source recall ("by whom the items were previously manipulated?"), participants either engaged in 10 min of neuropsychological testing, or rested alone for the same amount of time, followed by testing of item and source recall. We hypothesized that similar beneficial effects of minimal interference for item memory would be seen in both groups, but that any effects for source memory would be less pronounced in AD compared to control participants, given its heavier dependence on hippocampal processes [20, 21].

2. Method

2.1. Participants

We tested 26 participants at the mild stage of AD and 28 healthy control participants. The AD participants were recruited from two local retirement homes and were diagnosed with probable AD dementia by an experienced neurologist or geriatrician based on the National Institute on Aging-Alzheimer's Association clinical criteria [1]. The control participants were spouses or relatives of the AD participants, or were members of a local association promoting activities in retirement homes. Controls were functionally independent and living in their own homes. As showed in Table 1, controls were matched with the AD participants according to age, sex, and educational level. Exclusion criteria for all participants were: significant psychiatric or neurological illness other than AD, and alcohol or drug abuse. All participants presented no major visual or auditory acuity difficulties that would have prevented completion of study tasks. All participants provided informed consent. Two AD participants withdrew from the study for health problems without providing any research data (original AD sample, $n = 28$ participants).

2.1.1. Cognitive and clinical assessment.—We administered tests assessing general cognitive functioning, episodic memory, working memory, verbal fluency, inhibition, and depression. All scores are shown in Table 1.

General cognitive functioning was assessed with the Mini Mental State Exam [22], and the maximum score was 30 points. Episodic memory was evaluated with the task of Grober and Buschke (23). The participants had to retain 16 words, and after immediate cued recall, they proceeded to a 20-seconds distraction phase during which they had to count numbers aloud. This phase was followed by two minutes of free recall and the score from this phase (out of a maximum of 16) was retained as episodic score. For working memory assessment, participants had to repeat a string of single digits in the same order (i.e., forward span) or in the inverse order (i.e., backward span) [24]. On the verbal fluency task, participants were given two minutes to generate as many words beginning with the letter P, proper names and variants of the same words were not taken into account. Inhibition was evaluated with the

Stroop task [25], and the score referred to the completion time (in seconds) for the interference condition minus the average completion time for word reading and color naming. Depression was assessed with the self-report Hospital Anxiety and Depression Scale [26] consisting of seven items scored on a four-point Likert scale from zero (not present) to three (considerable). The maximum score was 21 points and the cut-off for definite depression was set at > 10/21 points ((for more details on the cognitive and clinical assessment, see [27, 28]); in line with a large body of evidence, [29, 30], higher depressions scores were observed in AD patients than in controls.

2.2. Procedures

Controls and AD participants were tested individually in quiet testing rooms at two retirement homes. The experiments took place over two sessions, spaced one week apart on average. In the first session, participants were assessed with a source memory task on which they were exposed to a set of 12 everyday-life objects (e.g., clothespin, candle, shoelace, paintbrush, chisel, spoon). Objects corresponded to medium- to high-frequency words, they were carefully selected to be normal-sized and without distinctive features, and were taken from a large pool used by previous studies assessing source memory [11, 15, 31–33].

Prior to the source memory task, participants were clearly instructed that they had to remember whether the objects were manipulated by themselves or by the experimenter, and that they would be asked about this immediately afterwards. No mention of a delayed recall phase was made. The objects were successively presented on a table, and participants were asked to name each object. Afterward, participants were asked either to insert the object in a black bag placed on the table or to watch the experimenter do so. Half of the 12 objects were pre-randomized to be inserted in the bag by the experimenter, whereas the other half were pre-randomized to be inserted in the bag by the participants. This order was predetermined and displayed on a grid so that the experimenter could easily carry out the task. Next, participants were asked to remember the objects in any order (i.e., immediate item memory), and for each object, they were asked to remember whether it had been originally inserted in the bag by themselves or by the experimenter (i.e., immediate source memory).

The immediate item and source memory recall was followed by 10 min during which their spans, verbal fluency, and depression scores were assessed in the same order for all participants. When the assessment exceeded 10 min, the tasks were interrupted and were resumed later (after the delayed recall). After the 10-minute delay, participants were asked to remember the previously-presented objects in any order (i.e., delayed item memory), and for each object, they were asked to remember whether it had been originally inserted in the bag by themselves or by the experimenter (i.e., delayed source memory).

Procedures were replicated in the second session, with two exceptions. A second set of object was administrated in the source memory task, and more critically, during the 10 min delay, participants rested alone in the testing room. Following immediate item and source recall, participants were informed that the experimenter would be leaving the testing room for several minutes in order to prepare the next task, and that he would dim the lights. Participants were instructed to sit back and rest until the return of the experimenter who

subsequently left the room, returning 10 min later. When the experimenter returned, testing of delayed item and source memory took place.

It should be noted that the two sessions were counterbalanced across participants. Item memory performance refers to percentage of correctly recalled items. Source memory performance refers to percentage of correctly recalled sources of the correctly recalled items

2.3. Results

Results are depicted in Table 2. Prior to performing analyses, all variables were plotted and checked for normal distribution with the Shapiro-Wilk test that showed that the assumption of normality was not met. Thus, non-parametric tests were used; Wilcoxon signed rank-sum tests were used for within-group comparisons, and Mann–Whitney U tests were used for between-group comparisons. For all tests, the level of significance was set as $p \leq 0.05$, whereas p values between 0.051 and 0.10 were considered as trends. Results were provided with the observed power: $d = .2$ can be considered a small effect size, $d = .5$ represents a medium effect size and $d = .8$ refers to a large effect size [34]. Note that Cohen's d was calculated for non-parametric tests following the recommendations by Rosenthal and DiMatteo (35), and Ellis (36).

2.3.1. Higher item memory after minimal interference than after interference.

—For AD participants, item memory was higher on immediate recall than following interference (Z = −4.20, $p < .001$, Cohen's $d = 2.90$) or minimal interference (Z = −3.67, $p < .001$, Cohen's $d = 2.07$). Interestingly, item memory was higher following minimal interference than following interference (Z = −2.62, $p < .01$, Cohen's $d = 1.20$). The same outcomes were observed for controls. Item memory was higher on immediate recall than following interference (Z = −4.31, $p < .001$, Cohen's $d = 2.81$) or minimal interference (Z = −3.63, $p < .001$, Cohen's $d = 1.88$). Item memory was higher following minimal interference than following interference (Z = −2.58, $p < .01$, Cohen's $d = 2.07$).

2.3.2. Similar source memory after interference and minimal interference.—

For AD participants, source memory was higher on immediate recall than following interference (Z = −4.22, $p < .001$, Cohen's $d = 2.94$) or minimal interference (Z = −4.32, $p < .001$, Cohen's $d = 3.19$). However, similar source memory was observed following interference and minimal interference (Z = −1.01, $p > .1$, Cohen's $d = .40$). The same outcomes were observed for controls. Source memory was higher on immediate recall than following interference (Z = −4.17, $p < .001$, Cohen's $d = 2.56$) or minimal interference (Z = −3.96, $p < .001$, Cohen's $d = 2.25$). Similar source memory was observed following interference and minimal interference (Z = −.80, $p > .1$, Cohen's $d = .31$).

2.3.3. Low item and source memory in AD—

Lower item memory was observed in AD participants than in controls for immediate recall ($Z = -4.68$, $p < .001$, Cohen's $d = 1.65$), interference ($Z = -4.82$, $p < .001$, Cohen's $d = 1.72$), and minimal interference ($Z = -4.71$, $p < .001$, Cohen's $d = 1.67$). Lower source memory was also observed in AD participants than in controls for immediate recall ($Z = -3.97$, $p < .001$, Cohen's $d = 1.16$),

interference ($Z = -4.41$, $p < .001$, Cohen's $d = 1.43$), and minimal interference ($Z = -4.73$, $p < .001$, Cohen's $d = 1.68$).

Regarding AD participants, higher item than source memory was observed for immediate recall ($Z = -4.36$, $p < .001$, Cohen's $d = 4.33$), interference ($Z = -2.57$, $p < .01$, Cohen's $d = 1.17$), and minimal interference ($Z = -4.10$, $p < .001$, Cohen's $d = 2.70$). Regarding controls, higher item than source memory was observed for immediate recall ($Z = -4.49$, $p < .001$, Cohen's $d = 3.23$), interference ($Z = -4.33$, $p < .001$, Cohen's $d = 3.11$), and minimal interference ($Z = -4.35$, $p < .001$, Cohen's $d = 3.16$).

We examined the potential effects of the order of assessment (interference vs. minimal interference) and found no significant effects on delayed item and source memory in in AD patients ($p > .1$) or controls ($p > .1$).

3. Discussion

In light of research suggesting beneficial effects of minimal interference on item memory in AD, the present study investigated whether source memory may also benefit from this condition. By assessing item and source memory during immediate recall and following interference and minimal interference, we showed beneficial effects of minimal interference for item but nor for source memory in mild AD.

Replicating the findings of Dewar, Pesallaccia (7) our study showed beneficial effects of minimal interference for item memory in mild AD. Our findings are also in agreement with previous research in patients with severe amnesia [4, 5] and mild cognitive impairment [6]. Regarding control participants, beneficial effects of minimal interference were also observed, in agreement with a study in which healthy older adults were presented with two stories, and one was followed by interfering tasks for 10 min, while the other one was followed by a 10 min delay of wakeful resting [37]. Results showed that minimal interference led to significant enhancement of memory after minimal interference. Hence, a brief wakeful rest after item learning may enhance item memory in both AD and normal aging, at least for short delays.

Disappointingly, unlike item memory, source memory did not benefit from minimal interference in either AD or control participants. A possible explanation may be that the age-related source memory compromise that is shared by both groups may not be amenable to improvement by behavioral interventions. Indeed, we showed much poorer source memory than item memory in both populations, regardless the experimental condition. These outcomes also mirror previous research, suggesting source memory impairment in normal aging [10, 11, 33] and AD [12, 13, 15, 38, 39].

The associative nature of source memory may also account for the absence of a beneficial effect of minimal interference. Unlike item memory, source memory requires associative processes linking the targeted item (e.g., a given face) to its learning context (e.g., where I met this face before), and these associative processes are found to be compromised in normal aging [40] and AD [41]. These associative processes draw heavily on hippocampal resources. Hippocampal lesions in animals typically show preservation of short-term item

memory, but result in consistent and profound deficits in memory for relational representations [42]. In a related vein, amnesic patients with hippocampal damage show greater deficits in source than in item memory [43]. Associative processes in the hippocampus imply binding or linking of disparate elements, each of which are stored separately within the cortex, into coherent representations [20, 21]. The hippocampus is not only implied in the integration and formation of associative representations, but also in comparisons of these representations to current perceptual input and/or previously stored representations, a comparison that is found to be mediated by the CA1 [42]. According to Olsen, Moses (42), these associative and comparison processes are intimately intertwined; as soon as perceptual input reaches the hippocampus, the associative processes begin and the output of that binding is compared to the relevant representations stored in memory. Since these comparative and associative processes are required for source memory and these processes are profoundly impaired in both normal aging and AD, mild physiologic interventions, such as minimal interference, may be unable to exert any measurable benefits.

Considering source memory, we found lower source memory in AD participants than in controls for immediate recall, interference, and minimal interference. These findings demonstrate negative effects of AD on source memory. These negative effects can be associated with several cognitive and clinical symptoms of AD, such as false memories and confabulations. Past research has documented relationships between source memory distortions and false memories in AD. More specifically, previous studies have shown a relationship between source memory distortions in AD and false alarms, i.e., incorrect statements by patients that a novel context had been encountered previously [15, 44–46]. Source memory distortions have been also associated with difficulties in AD patients in distinguishing between enacted and imagined events [15, 47]. Also, source memory distortions have been associated with confabulations, false memories without the intent to deceive [48, 49]. A study reported a relationship between confabulations AD and difficulties in attribution of the origin of memories (i.e., source memory); according to this study, AD patients who confabulate misattribute features of an event that occurred at one time to another event that occurred at another time [50] (for a similar account, see [51–53]).

Studies on minimal interference suggest that wakeful resting after learning allows new memory traces to be consolidated better and hence to be retained for much longer [5–7, 37]. Animal studies suggest that firing sequences observed in hippocampal ensembles during learning are found to be replayed during subsequent sleep [17]. In human studies, hippocampal areas that are found to be activated during learning are likewise activated during subsequent slow wave sleep [54]. Hence, the hippocampus plays a pivotal role in memory consolidation during resting. The beneficial effects of minimal interference for item memory we and others found imply that some hippocampus-dependent consolidation processes may be preserved in AD, at least enough to enhance item memory and/or for short delays.

It is possible that the beneficial effect of minimal interference on item memory might result from conscious rehearsal than from unconscious consolidation processes. In other words, when were alone, our participants might have rehearsed the items, an opportunity they missed in the interference condition, and this might have produced the beneficial effect of

minimal interference on item memory. Even though this possibility cannon be entirely ruled out, we were careful not to mention any delayed recall, in order to minimize their motivation to engage in conscious rehearsal.

Our results suggest that mild AD patients demonstrate some capacity to consolidate new information. It would be of interest to investigate whether this effect can be observed for longer delays. A prominent venue for investigation is sleep. Consolidation is believed to mainly occur during slow wave sleep, which strengthens the newly-acquired memories and makes them more resistant to interference [54, 55]. It would be of interest to investigate whether sleep may enhance item memory, and even, source memory in mild AD. The same suggestion can be made for healthy older adults and patients with mild cognitive impairment, as past research has demonstrated that sleep disruption may contribute to memory impairment in normal aging [56–58] and mild cognitive impairment [59, 60].

In everyday life, learning is almost invariably followed by further information or activity that interfere with the learned material. The same applies to assessments in memory clinics, where AD patients deal with new materials as soon as they are presented with a set of stimuli. As demonstrated by the present study, whether delay between learning and recall is filled or not with activity may influence recall in AD patients. AD patients may show some capacity to retain new material, should the material presentation be followed by short delays that are free of further stimuli. While AD patients demonstrate some benefit of minimal interference for item memory, no such benefit is observed for source memory, which may be considered as a limitation to the usefulness of minimal interference in the disease. These findings are worth considering by clinicians, caregivers and care facilities who provide care to patients with AD who may allow for regular periods of minimal interference to enhance memory performance. In addition, these findings are also valuable for clinical researchers who typically assess memory in AD patients in the setting of multi-faceted clinical studies that include multiple tests and experimental procedures. Such settings may be compromising to the fragile memory of AD patients and lead researchers to underestimate the patients' true cognitive performance.

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Table 1.

Demographic, cognitive, and clinical characteristics of Alzheimer's disease (AD) and control participants

		AD *n* = 26	Controls *n* = 28
Women/Men		18/8 *n/s*	20/8
Age in years		72.92 (6.85) *n/s*	71.75 (8.56)
Education in years		8.88 (3.05) *n/s*	9.25 (2.30)
General cognitive functioning	Mini-Mental State Examination	22.50 (1.69) ***	28.21 (1.50)
Episodic memory	Grober and Buschke	5.96 (2.32) ***	10.82 (3.33)
Working memory	Forward span	4.81 (1.16) **	6.21 (1.71)
	Backward span	3.58 (1.14) **	4.89 (1.37)
Verbal Fluency	Fluency task (letter P)	17.77 (5.56) **	23.67 (5.22)
Inhibition	Stroop	64.23 (6.94) ***	34.79 (9.76)
Depression	Hospital Anxiety and Depression Scale	8.85 (1.08) ***	7.04 (1.89)

Note. Standard deviations are given between brackets; performance on the Mini-Mental State Examination referred to correct responses/30; performance on the Grober and Buschkle's task referred to correct responses/16; performance on the forward and backward spans referred to number of correctly repeated digits; performance on verbal fluency referred to the number of correctly generated words; inhibition score referred to completion time in sec; the maximum score on depression scale was 21 points;

n/s differences between groups were non-significant; differences between groups were significant at *

** $p < .001$,

*** $p < .001$; gender differences was compared with Chi-square test; comparisons for remaining variables were established with Mann-Whitney's U test (abnormal distribution), except for fluency that was compared with Student's t-test (normal distribution).

Table 2.

Item memory and source memory on immediate recall and following interference and minimal interference in Alzheimer's disease (AD) and control participants

	AD	Controls
Item memory		
Immediate recall	46.79 (11.80)	67.86 (13.36)
Interference	18.91 (14.44)	41.07 (11.09)
Minimal interference	29.81 (11.34)	50.00 (13.03)
Source memory		
Immediate recall	31.09 (8.68)	47.32 (16.34)
Interference	9.62 (8.40)	23.21 (9.80)
Minimal interference	10.90 (7.73)	25.90 (10.72)

Note. Standard deviations are given between brackets; performance referred to percentage of correct responses.