Associative working memory and subsequent episodic memory in Alzheimer's disease

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Recent studies indicate deficits in associative working memory in patients with medial-temporal lobe amnesia. However, it is unclear whether these deficits reflect working memory processing or are due to hippocampally mediated long-term memory impairment. We investigated associative working memory in relation to subsequent episodic memory formation in patients with early Alzheimer's disease to examine whether these findings reflect deficits in long-term encoding rather than 'pure' working memory processing. Nineteen patients with Alzheimer's disease and 21 controls performed a working memory task in which objects had to be searched at different locations. The subsequent episodic memory test required participants to reposition objects to their original locations. Patients with Alzheimer's disease were impaired on associative working memory and subsequent episodic memory, but they performed above chance at high-load episodic memory trials. This suggests that when working memory capacity is exceeded, long-term memory compensates. ***NeuroReport*** **23:119–123 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Deficits in episodic memory due to medial temporal lobe atrophy are a key characteristic of Alzheimer's disease, which includes the dementia phase of the disease as well as its prodromal stage of mild cognitive impairment [1,2]. However, it is less clear whether and to what extent working memory is affected. Standard neuropsychological working-memory tests (e.g. span tasks) generally reveal no deficits in patients with Alzheimer [3,4]. Conversely, patients with working memory deficits seem to perform well on at least some long-term memory tasks [5]. This double dissociation has led to the notion that memory can be divided into separate systems, in which working memory is predominantly supported by the prefrontal cortex and long-term memory by the medial temporal lobe [6].

In contrast to this dissociation, recent studies have demonstrated medial temporal lobe activation during working memory tasks [7,8], in particular when participants have to associate multiple items or features [9–11]. In addition, studies have shown that patients with early Alzheimer's disease are impaired on working memory tasks that require object–colour binding, colour–colour binding or object–location binding [12–14]. This suggests that the medial temporal lobe is not only involved in long-term memory function but also in working memory, and that working memory and long-term memory may not function totally independent of one another [15].

From a theoretical point of view, Baddeley's [16] working memory model is relevant. It contains auditory and visuospatial slave systems and a supervisory module, the central executive. Later, the episodic buffer was added to the model. It integrates information from various sources (i.e. binding) and transfers information into long-term memory [16]. In addition, the episodic buffer serves as an 'overflow buffer', providing extra storage capacity when the capacity of the slave systems is exceeded. It could therefore be argued that the medial temporal lobe involvement observed during associative working memory tasks reflects functions of the episodic buffer. Alternatively, medial temporal lobe involvement may simply reflect long-term encoding processes, as medial temporal lobe activation during working memory maintenance is found to predict subsequent episodic memory performance [7,8]. The aim of our study was to investigate this explanation.

As deficits in working memory for spatial associations have already been demonstrated in patients with early Alzheimer's disease in the mild cognitive impairment stage [14], the current study extends the literature by including patients in the dementia phase and by extending the paradigm with a subsequent memory test. Concerning the subsequent memory task, we hypothesize a general deficit in patients with Alzheimer's disease compared with controls. More importantly, by directly comparing associative working memory performance with

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subsequent episodic memory for the same stimuli, we are able to examine whether any long-term encoding has taken place during the working memory task as this should be reflected in above-chance performance on the subsequent memory task.

To our knowledge, no studies have directly compared associative working memory and subsequent episodic memory formation in Alzheimer's disease. In addition, investigating associative working memory may lead to a better understanding of the development of episodic memory deficits, as it has been suggested that episodic memory problems may result from difficulties in binding information into complex memories [17,18]. Furthermore, this setup may have clinical implications as well, as patients with early Alzheimer's disease show working memory problems that currently often remain undetected by standard neuropsychological tests.

Methods

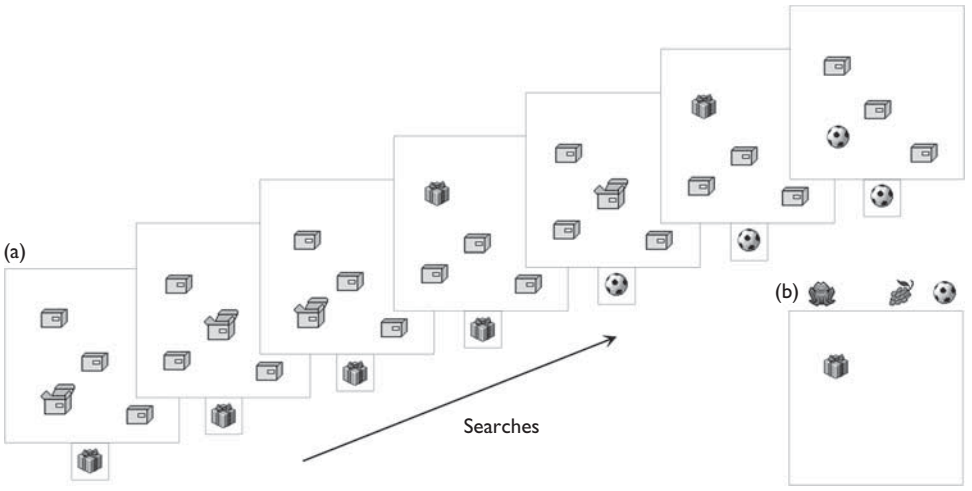
Nineteen patients diagnosed with (amnestic or multiple-domain) mild cognitive impairment ($n = 12$) [2] or dementia ($n = 7$) [1] due to Alzheimer's disease were recruited from Geriatrics and Neurology Departments of the Elkerliek Hospital, Helmond, The Netherlands (eight men; mean age 75.3, SD = 7.4; mode educational level classified using seven categories 5, range 3–7). The mean score on the Mini-Mental State Examination, a brief screening for cognitive impairment [19], was 23.7, range 17–29. Performance on the Digit Span working-memory subtest of the Wechsler Adult Intelligence Scale – Third Edition [19] was 11.35, SD = 2.27. Diagnoses were supported by neuroimaging, neuropsychological testing and clinical interview. General exclusion criteria were a history of any neurological or psychiatric disease (unrelated to Alzheimer's disease).

Twenty-one community-dwelling, high-functioning healthy volunteers were examined (eight men; mean age 72.7 years, SD 7.1 years; modus educational level 5, range 3–7) and were matched on age [$F(1,18) = 1.28$, $P = 0.27$], sex (Mann–Whitney $U = 191.5$, $P = 0.83$) and education (Mann–Whitney $U = 198.5$, $P = 0.98$). Exclusion criteria for the controls were subjective memory complaints and a history of neurological or psychiatric disease. All participants had normal or corrected-to-normal vision. The study was approved by the hospital's Institutional Review Board; all participants fulfilled the criteria for competence and provided written informed consent.

Working memory paradigm

All participants completed a computerized visuospatial working memory task (Box Task [20], Fig. 1a), in which pictures of closed boxes (1×1 cm) are presented at various locations within a 19×19 cm frame on a 15″ touch-sensitive monitor. Participants were instructed to search through the boxes to find a hidden target object by 'opening' the boxes. When a target was found, a new target object was presented that had to be searched. Participants were instructed that a previously found object remained hidden in its box. Thus, participants not only had to remember which boxes were recently searched but also which boxes contained previous targets. When all target objects were found, a new trial with a new spatial layout and an increased number of boxes started. The task included one practice trial containing three

Fig. 1



(a) Schematic overview of the working memory paradigm. The participant has to search for the target object. A within-search error is made when the participant returns to a box that was already found to be empty in that search. This error is displayed in the third panel. The sixth panel shows a between-search error: the participant opens a box that already contained an object from a previous search. (b) Schematic overview of one trial of the subsequent episodic memory task.

boxes and four trials containing 3, 4, 6 and 8 boxes, respectively. There was no time limit, but participants were motivated to respond within a reasonable time (i.e. within a few seconds).

Three error measures are computed (see Fig. 1a). First, *within-search errors* are made by returning to a box that was already opened within that search. This measurement reflects the ability to keep track of locations recently visited and is therefore assumed to reflect visuospatial sketchpad functioning [16]. Second, *between-search errors* are made by returning to a box that already contained a target from a previous search. This measurement reflects the ability to maintain object–location information for longer periods of time. Hence, the ability to avoid between-search errors is assumed to rely on the episodic buffer [14]. Third, the *strategy score* measures search efficiency by counting how often a participant starts a search with a different box. As following a predetermined search sequence would be more efficient, a low strategy score indicates an efficient search strategy [21].

Subsequent episodic memory task

After an unfilled delay of approximately 5 min, participants performed an unexpected delayed cued-recall test, developed using Object Relocation software [22]. In this task, participants had to place objects back to the locations where they were presented during the working memory task (see Fig. 1b). All objects were presented in random order above an empty square and could be placed at any location within that square. This task included one practice trial containing three objects and four trials containing 3, 4, 6 and 8 objects, respectively. Self-corrections were allowed and, again, no time limit was set.

Here, we measured the absolute distance in millimetres between the original location of an object and the location where the participant relocated that specific object. The absolute error is the total of these distances for all objects in a display [22].

Analyses

A doubly multivariate 2 (Group: controls vs. patients) × 4 (Set size: 3, 4, 6, 8) repeated-measures analysis of variance, with within-search errors, between-search errors and strategy score as dependent variables, was used to analyse the data from the working memory paradigm. Mauchly's test showed that the assumption of sphericity was violated, which is why the degrees of freedom were corrected according to the Greenhouse–Geisser estimate. For the subsequent memory task, a multivariate 2 (Group: controls vs. patients) × 4 (Set size: 3, 4, 6, 8) repeated-measures analysis of variance, with absolute error as a dependent variable, was used.

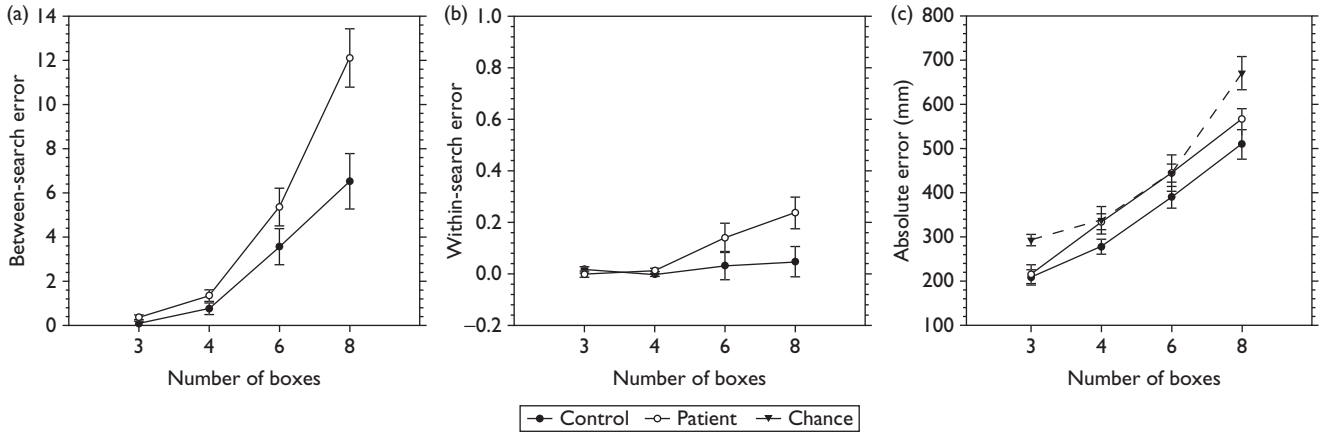
An α of 0.05 was used in all analyses. For all effects, effect sizes were calculated (η_p^2), which describe the proportion of variance explained by the factor in question. To check whether both groups performed above chance, 10 healthy students were asked to perform only the subsequent episodic memory task. Here, participants were instructed to place objects at the 'correct' location by guessing the most appropriate location, that is without having seen the original displays in the working memory paradigm. As none of these participants had any knowledge of the original locations of the objects, their performance was used as an estimate of chance performance [23].

Results

Working memory paradigm

Patients made more within-search errors than controls [$F(1,39) = 5.54$, $P = 0.02$, $\eta_p^2 = 0.12$; see Fig. 2a]. In addition, a main effect of set size was found, with more

Fig. 2



Results for the working memory paradigm [(a) and (b)] and the subsequent episodic memory task (c), for the increasing number of boxes in patients with Alzheimer's disease and controls. (a) Number of between-search errors. (b) Within-search errors. (c). Absolute error. Higher scores represent worse performance.

errors being made with increasing set size [$F(1.90,73.93) = 5.40$, $P < 0.01$, $\eta_p^2 = 0.12$]. The interaction effect of set size and group was marginally significant [$F(1.90,73.93) = 2.69$, $P = 0.08$, $\eta_p^2 = 0.07$], indicating that an increasing set size led to a greater increase in errors for patients than for controls.

With respect to between-search errors, patients made more errors than controls [$F(1,39) = 11.32$, $P < 0.01$, $\eta_p^2 = 0.23$], see Fig. 2b. More between-search errors were made in trials with a larger set size [$F(1.71,66.65) = 67.32$, $P < 0.001$, $\eta_p^2 = 0.63$] and an increasing set size led to a greater increase in errors for patients than for controls [$F(1.71,66.65) = 5.99$, $P = 0.006$, $\eta_p^2 = 0.13$].

Analysis of the strategy score showed a main effect of set size [$F(2.45,95.53) = 219.94$, $P < 0.001$, $\eta_p^2 = 0.85$], indicating that larger set sizes led to a higher strategy score. No group difference was found for strategy [$F(1,39) = 1.65$, $P = 0.21$].

Subsequent episodic memory task

Patients presented with a significantly larger absolute error than controls, reflecting a worse performance [see Fig. 2c; $F(1,39) = 5.81$, $P = 0.02$, $\eta_p^2 = 0.13$]. In addition, larger set sizes resulted in larger absolute error scores [$F(6,34) = 55.20$, $P < 0.001$, $\eta_p^2 = 0.91$]. Pair-wise comparisons showed that controls performed significantly above chance level [$t(29) = -3.49$, $P < 0.01$]. For the patients, a trend towards above-chance performance was observed [$t(27) = -1.95$, $P = 0.06$]. Further analyses showed that patients performed significantly above chance level when trials had either three [$t(26.35) = -3.05$, $P < 0.01$] or eight boxes [$t(27) = -2.45$, $P = 0.02$], but not for the conditions with four and six boxes ($P = 0.92$ and 1, respectively).

Discussion

The present study shows that patients with early Alzheimer's disease demonstrate clear deficits on an associative working memory task. Although subsequent episodic memory formation was found to be severely impaired, patients performed above chance on trials with either a low (three boxes) or a high memory load (eight boxes). The above-chance level performance on the three-box condition suggests that this condition is too easy. In the eight-box condition, this above-chance performance may indicate that the episodic buffer was successfully recruited during high-load working memory trials, which will be discussed in more detail below. These findings confirm the notion that patients with Alzheimer not only have long-term memory deficits but also deficits in working memory tasks that rely on the integration of information. Often, this remains undetected by standard neuropsychological tests. Indeed, Digit Span performance was unimpaired in these patients.

To our knowledge, this is the first study to assess both associative working memory and subsequent long-term memory formation with a similar task paradigm using the same stimuli. Compared with a previous study by Kessels *et al.* [14] that examined the same working memory paradigm in mild cognitive impairment patients (without the subsequent episodic memory test), more within-search errors and between-search errors were present in the current study. Although absolute differences are small, this may be the result of including patients who are already in the dementia stage of the disease and thus perform worse than patients in the mild cognitive impairment stage. Although it was not our aim to make specific claims about neural representations, previous studies have established that medial temporal lobe atrophy typically accompanies early Alzheimer's disease [24]. Our findings are in agreement with recent evidence showing that the medial temporal lobe plays an important role in associative working memory [9,10].

It remains to be clarified whether these associative working memory deficits in Alzheimer's disease are limited to object–location associations. That is, it could be argued that spatial features rather than the binding process itself lead to hippocampal involvement. However, previous results have shown binding problems with nonspatial features as well. For example, short-term memory for object–colour associations is compromised in patients with Alzheimer's dementia [12,13].

Our results can be interpreted in view of Baddeley's working memory model, specifically its episodic buffer [16]. Patients with early Alzheimer's disease have problems keeping track of recently visited locations in the working memory task, which may point to a deficit in the visuospatial sketchpad. No group differences were found for strategy usage. This finding is in line with previous studies [14,20] and indicates that executive functions are relatively spared in early Alzheimer's disease. As binding is a function of the episodic buffer, the impairment in associating objects and locations in working memory may be due to impaired functioning of the episodic buffer.

In addition, the overflow function of the episodic buffer may elucidate why an increasing working memory load affected patients more than controls. It may also explain why patients performed above chance level on subsequent episodic memory trials with eight boxes. In trials with fewer boxes, processing at the visuospatial sketchpad level may suffice, but when working memory capacity is exceeded, the episodic buffer may be recruited as an overflow buffer. As the episodic buffer is the interface between working memory and long-term memory [16], additional involvement of the episodic buffer may have resulted in activation of the residual long-term encoding processes in patients with Alzheimer's disease. This, in turn, may explain the improved subsequent memory on the eight-box condition. Although the underlying mechanisms of this episodic buffer deficit are still under

debate, impairments in working memory binding may underlie deficits in episodic memory formation, both of which rely on the medial temporal lobe [15].

Conclusion

In summary, episodic buffer dysfunction may result in associative working memory deficits in patients with early Alzheimer's disease. As associative working memory is especially impaired when memory load is high, the overflow function of the episodic buffer may be involved. This additional involvement may have resulted in some transfer of the information into long-term memory, which explains the better long-term memory performance for the high-load trial.

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Conflicts of interest

There are no conflicts of interest.

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