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Visual and visuospatial short-term memory in mild cognitive impairment and Alzheimer disease: Role of attention

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Abstract

It has been proposed that visual recognition memory and certain attentional mechanisms are impaired early in Alzheimer disease (AD). Little is known about visuospatial recognition memory in AD. The crucial role of the hippocampus on spatial memory and its damage in AD suggest that visuospatial recognition memory may also be impaired early. The aim of the present study was to evaluate which modality, i.e. visual or visuospatial, is more implicated in the early memory impairment in AD. First, to determine onset of memory impairment, we compared the performances of patients with AD to those with amnestic mild cognitive impairment (MCI). Second, to determine the relative contribution of attentional impairment on the performance of MCI and AD patients, we tested the influence of a distractor in the interval between the memory image and recognition tests. Results showed that visuospatial short-term deficits appear earlier than visual short-term ones. In addition to mnemonic deficits, results showed attentional deficiency in both MCI and AD patients. Deficits of performances in visual modality seemed of attentional origin whereas those of visuospatial modality seemed of memory origin. The combination of attentional and mnemonic evaluation is likely to be a promising approach to finding predictive markers that distinguish MCI patients that convert to AD.

Keywords: Visual memory; Visuospatial memory; Attention; MCI; Alzheimer disease

1. Introduction

Alzheimer disease (AD) is characterized by progressive memory loss and other cognitive impairments, e.g. aphasia, apraxia, and personality changes. AD is neuropathologically characterized by neuritic plaques and neurofibrillary tangles and functionally by a decreased metabolic rate of neurons (Braak & Braak, 1991; Yilmazer-Hanke & Hanke, 1999). The density of neurofibrillary tangles correlates with the severity of the disease (Arriagada, Growdon, Hedley-Whyte, & Hyman, 1992; Delacourte et al., 1999). Despite the global nature of the cognitive dysfunction in AD, memory disorder is clearly the most prevalent and prominent feature of the early stages of the disease.

In the earliest stages of AD, memory difficulties are apparent when AD patients are confronted with every day tasks requiring episodic memory (Bondi, Salmon, & Butters, 1994). Memory impairments are apparent on tasks that require learning and retention of verbal or non-verbal information. AD patients present severe impairments on recognition and recall tasks. They have severe deficits in transferring information into a long-term storage system. Delis et al. (1991) reported that this anterograde amnesia is not primarily due to difficulties in retrieval mechanisms but instead that it reflects a defect at the level of consolidation. This defect may be mediated by damage to the hippocampus (Hyman, Van Hoesen, Damasio, & Barnes, 1984) and entorhinal cortex and by neurotransmitter changes in cholinergic system (Weingartner, Sitaram, & Gillin, 1979).

Accurately predicting the development of probable AD early in the course of the disease would have major implications for

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment; VSTM, visual short-term memory; VSSTM, visuospatial short-term memory; MI, memory image; PI, probe image

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maximizing treatment efficacy. For that, studies of cognitive deficiencies in patients with mild cognitive impairment (MCI) have recently emerged as the most promising approach. The concept of MCI was introduced by Flicker, Ferris, and Reisberg, (1991) and the Mayo Clinic group (Petersen, 1995) to fill the gap between cognitive changes associated with normal aging and those associated with dementia. MCI is defined as a state of cognition in which the deficiency is greater than expected for a subject's age and socio-cultural background, but not sufficiently severe to satisfy the criteria of nosographic classifications of dementia. The MCI definition most widely used is that of amnestic MCI (Petersen et al., 1999). It requires a memory complaint (preferably corroborated by an informant), objective memory impairment for age and education, largely preserved general cognitive functioning, essentially normal activities of daily living, and absence of dementia. Despite impaired memory performance, individuals with amnestic MCI do not meet diagnostic criteria for AD and other causes that could be at the origin of cognitive disorders (for example a depression). Many patients with amnestic MCI present a high risk of developing AD in a few years. The concept of MCI recently has been expanded to include three subtypes: (1) amnestic MCI, in which the patients suffer from isolated memory impairment; (2) multiple domain MCI, in which they may have mild impairments in several cognitive domains with or without a memory impairment; (3) single non-memory domain MCI, in which a person is impaired in a non-memory area such as executive function or language (Petersen et al., 2001). Individuals diagnosed with MCI typically have severe episodic memory deficits. Wang and Zhou (2002) reported impaired encoding and retrieval of episodic memory in MCI patients, with encoding being more impaired.

Specific cognitive evaluations in AD patients indicate that deficits may occur in attentional control as well as in episodic memory (Perry & Hodges, 1999). Several studies have examined the nature of attentional impairments related to the capacity to divide and focus attention (Gordon & Carson, 1990; Nestor, Parasuraman, & Haxby, 1991; Baddeley, Baddeley, Bucks, & Wilcock, 2001). Levinoff, Saumier, and Chertkow (2005) revealed that MCI and AD patients are impaired in tasks of focused attention. Tales, Haworth, Nelson, Snowden, and Wilcock (2005) reported AD and MCI patients have a deficit in visual search. Interestingly, those authors reported that only MCI patients who appear clinically to suffer exclusively from a deficit in memory also display a deficit in visual attention-related processing. Tales, Snowden, Haworth, and Wilcock (2005) reported that AD patients and amnestic MCI exhibited deficiency in the ability to disengage attention and to use a visual cue to produce an alerting effect.

For visual recognition tasks such as recognizing individual items in the visual field, the perirhinal cortex must be intact. Studies in monkeys have shown that lesions of the perirhinal cortex severely impair performance on visual recognition memory tasks (Meunier, Bachevalier, Mishkin, & Murray, 1993; Squire & Zola, 1996). The crucial role of the perirhinal cortex in visual recognition memory is also supported by human case studies (Aggleton & Shaw, 1996). The hippocampus is important in memory functioning (Squire & Zola-Morgan, 1991) and is involved in visual recognition memory. Hippocampus is known to be affected and atrophied early in the course of AD (Hyman, Van Hoesen, & Barnes, 1990). Degeneration of the hippocampus, as measured by volumetric magnetic resonance imaging correlates with poor visual recognition memory performance after long delays in a delayed matching-to-sample test in AD patients (Riekkinen et al., 1998). An impairment of visual recognition memory, based on the delayed matching-to-sample schedule, has been reported by Barbeau et al. (2004) in MCI and AD patients. For these authors, visual recognition memory is impaired early in the course of the disease.

Little is known about the visuospatial modality in the memory process of AD patients and to our knowledge no data exist on this modality in MCI patients. Simone and Baylis (1997) reported AD patients are severely impaired in a delay response task measuring spatial memory. Visuospatial processing is impaired in AD (Meguro, Shimada, Someya, Horikawa, & Yamadori, 2001; Rizzo, Anderson, Dawson, Myers, & Ball, 2000) and affects the patients' activities in daily living. Fujimori et al. (2000) showed that visuospatial disturbance was related to bilateral parietal metabolism and that visuoperceptual disturbance was related to right temporo-parietal metabolism in patients with mild to moderate AD. The model of short-term working memory proposed by Baddeley (Baddeley & Hitch, 1974; Baddeley, 1986) involves two subsystems for processing information (verbal and visuospatial) and a central executing system considered as a high-level limited-capacity processor. This processor is impaired in patients with AD (Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991). Grossi, Becker, Smith, and Trojano (1993) showed that the system for visuospatial information was also impaired in AD patients. The hippocampus plays a crucial role in spatial memory (McNaughton et al., 1996) and in the recognition of items' arrangement. Regarding the earlier damage of the hippocampus in AD, recognition memory might be also impaired in the early stages of AD. All these data in conjunction with the time course of the neurodegenerative process in AD led us to hypothesize that AD patients would be impaired in both visual and visuospatial recognition memory. In this respect, it is of interest to evaluate recognition memory for these two modalities in amnestic MCI.

The aim of the present study was first to determine which modality, i.e. visual or visuospatial, is more implicated in the recognition memory impairment in MCI and AD patients. For that we used a task for visual short-term memory (VSTM) and one for visuospatial short-term memory (VSSTM). In the VSTM task, patients had to encode a memory image (MI) constituted of individual images and to recognize these images among three successive recognition tests. For each recognition test, patients had to answer yes or no when asked whether it corresponded to the MI. To give a correct response, patients had to detect novelty, i.e. one or several images that had not been in the MI. In the VSSTM task, patients had to encode the location of the MI (always constituted of individual images) and to recognize this location among three successive visuospatial recognition tests. As for VSTM task, for each recognition test, patients had to answer yes or no when asked whether it corresponded to

the MI. To give a correct response, patients had to detect novel locations. Thus, in the VSTM recognition task, patients code images and, in the VSSTM task, patients code their location.

Moreover, attention and memory are interrelated cognitive processes. Impairments in one of these cognitive functions may influence performance in the other. This is particularly true for short-term and working memories, which are closely linked to attention. These memory processes cannot correctly function if the subjects cannot focus or divide their attention. Our paradigm involves these two aspects of attention. Second we determined the relative contribution of attention in the memory impairment of MCI and AD patients. For that, we tested the influence of a distractor in the interval between the model and recognition tests. The distractor tests the selective attention mechanism of subjects by forcing them to concentrate on the relevant information and to ignore the irrelevant information. The distractor may also have an impact on attentional capacity and resources.

2. Methods

2.1. Subjects

In this study, we included eight patients with AD, eight patients with MCI, and eight elderly healthy controls. Elderly healthy controls were similar to the MCI or AD group in age and gender (Table 1).

All patients were recruited from a memory clinic and underwent a full examination by a neurologist and a neuropsychologist. A head imaging study (CT scan or MRI) was performed on all patients. None of the patients had visual complaints in daily living or showed complete Balint's syndrome, or apperceptive or associative visual agnosia. No patients showed problems in understanding the instructions for the following assessments. None of the patients took any psychotropic medication during the time of the study.

Subjects in the AD group met the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's disease and Related Disorders Association Work Group (NINCDS-ADRDA) diagnostic criteria for 'probable' Alzheimer's disease (McKhann et al., 1984). Mean MMSE score of the AD group was 25.43 (mini mental state examination, Folstein, Folstein, & McHugh, 1975).

Subjects with MCI all met criteria for an amnestic form of MCI (Petersen et al., 1999) as all had memory complaint (usually verified by an informant), performed poorly on neuropsychological tests of verbal memory, and had normal general cognitive function. Activities of daily living were normal, as assessed through the instrumental activities of daily living (IADL, Barberger-Gateau et al., 1992) and they had a CDR score of 0.5 (clinical dementia rating, Hugues, Berg, & Danzinger, 1982). Mean MMSE score of the MCI group was 27.71.

The control group consisted of healthy elderly volunteers recruited by newspaper advertisement. They had no psychiatric, neurological, or cardiovascular history and did not use psychotropic drugs. All elderly healthy controls had a score of 30 points on the MMSE.

The study was conducted according to the declaration of Helsinki and the study was approved by the hospital research Ethics Committee. All subjects provided written informed consent prior to participation.

Table 1
Group characteristics

Population	*n*	Mean age	Women/men	MMSE
EHC	8	70.12 (70–80)	6/2	30
Amnestic MCI	8	73.12 (66–83)	5/3	27.71 ± 0.30
Mild AD	8	77.87 (70–80)	4/4	25.43 ± 0.32

MMSE: mini mental state examination; EHC: elderly healthy control; MCI: mild cognitive impairment; AD: Alzheimer disease.

2.2. Stimuli

Stimuli consisted of coloured line-drawing images (128×28 pixel) representing concrete objects or scenes of semantic categories of daily living. The image was randomly located in an imaginary 5×7 grid on a video monitor with a grey background. Images had no salient distinguishing features and colours. We used 1064 images, thus novel images were used for each trial.

2.3. Span control task

We used a span control task to determine the number of images with which patients should perform the recognition task. Thus, patients performed the recognition task at their memory capacity level and consequently were not in difficulty. Thus, memory impairment, if it existed, would not be explained by an exceeded memory capacity.

Before performing the recognition task, all patients were tested for their visual memory capacity by the span control task. It consisted in presenting to the patient 1 then 2, 3, 4, 5... images until he was wrong. For example, if the patient memorized three images and failed to remember four images, he performed the recognition test with three images.

2.4. Design

Each trial was composed of a memory image (MI) and three probe images (PIs) separated by a blank interval of 1, 10, or 30 s (Fig. 1). The MI contained 3, 4, or 5 images depending on the visual memory span of each patient. The images of the MI were presented at random locations within the background. The PIs always contained the same number of images as the MI. The patients' task was to detect whether images changed or not (visual short-term memory, VSTM) or were the same but changed or not in their location (visuospatial short-term memory, VSSTM). Thus, there were two types of PI: visual change or no change, and location change or no change (Fig. 1). In visual change, one or more images could change and their spatial location remains invariant. In location change, the whole image moved to a new position within the background and images remained invariant. Among the three PIs, there was always one PI in which no change occurred (no change) and two PIs in which visual or location change occurred (change) depending on the nature of the trial. In all cases, both visual and location changes never appeared in the same trial. Visual and location change trials were randomly distributed within the recognition task.

2.5. Procedure

For each trial, MI was associated with a sound stimulus to focus patient's attention on the MI and was presented for 3, 4, or 5 s according to the number of images (1 s per image). Patients were free to move their eyes. Each PI was presented until a response key was pressed. Patients were instructed to memorize images and their location on the MI and to detect whether images or their location on the PI was the same as on the MI. Each PI response was entered via key press: "Esc" for yes, PI was the same as MI; and "Enter" for no, PI was not the same as MI. Thus, for each trial we recorded three responses. Response times were also measured for each PI.

Each patient completed 30 trials, which were always presented in the same order for each patient without distractor (i.e. 15 trials in visual modality and 15 trials in visuospatial modality) and 30 trials with distractor (i.e. 15 trials in visual modality and 15 trials in visuospatial modality). Half of the patients performed the task first without distractor and second with distractor and conversely for the other half trials.

2.6. Distractor task

The distractor task consisted in pointing out yellow circles in alphabetical order (Fig. 1). The distractor was presented during all the time interval (TI). In other words, when the distractor was introduced during the 1 s TI, it appeared as a "flash" to the patients and they had no time to perform the task. When it was introduced during the 10 and 30 s TI, patients had time to perform it, one time or more depending on their skill. All patients were trained to perform the

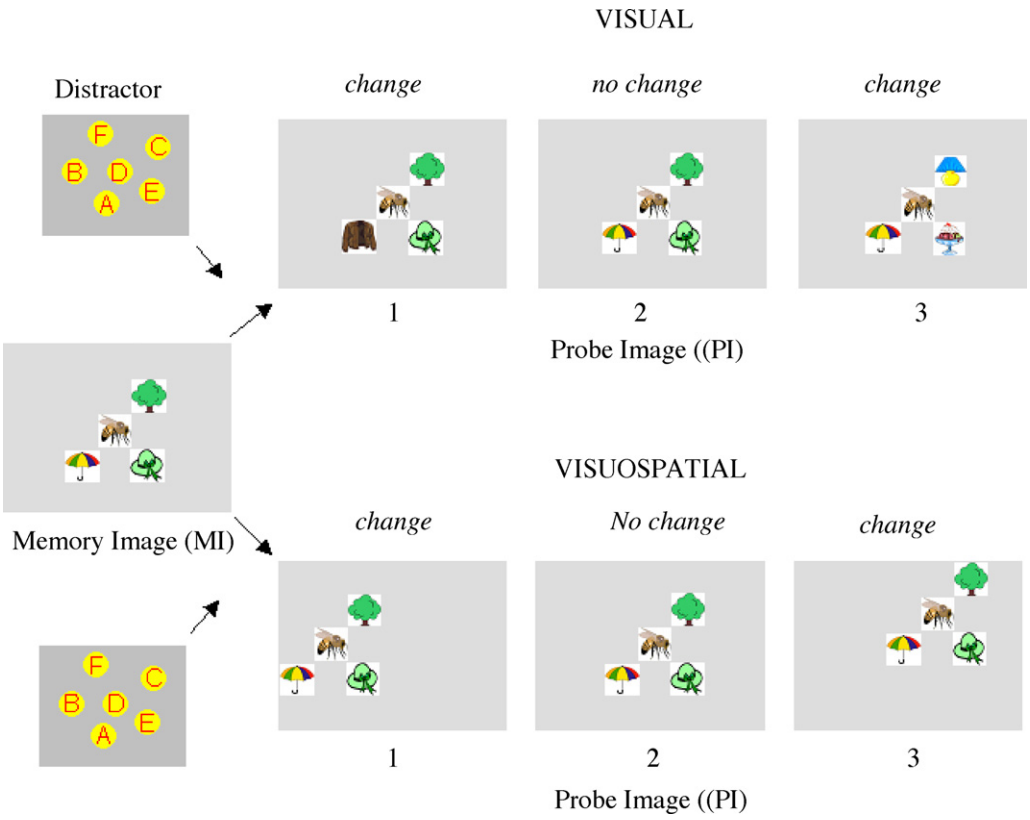


Fig. 1. Illustration of the images used for either visual or visuospatial trials. Each trial was constituted by a memory image (MI) that was different for each 15 visual and each 15 visuospatial trials. The MI was followed by a 1, 10, or 30 s interval and then three probe images (PIs) were successively presented. For each PI, patients must respond yes or no whether it corresponded to the MI. In the first condition, time intervals were blank. In the second condition, a distractor was presented during all the time intervals. The distractor task consisted in pointing out yellow circles in alphabetical order.

distractor task before doing the memory task. No performance was recorded during distractor task.

2.7. Equipment

All patients were tested individually in a room with normal interior lighting. All experiments were carried out on a PC computer with a 19-in. screen. The unrestricted viewing distance was approximately 50 cm; 1 cm on the screen corresponds to a 1° visual angle. The software was written by Gilhodes in Labview 6.1.

2.8. Statistical methods

Data were statistically analysed using analyses of variance (ANOVA), three of which within factors (modality, distractor, TI) and one between factors (group). When an interaction was observed, the global ANOVA was followed by a follow-up ANOVA.

For all ANOVAs reported hereafter, violations of the sphericity assumption (homogeneity of covariance) were corrected using the Huynh and Feldt (1976) procedure; the corrected P-value along with the epsilon correction factor (ε) are reported. When the H–F estimator is greater than 1, a value of 1 is used in all calculations for probabilities, and the H–F probabilities are not adjusted.

Then, one-way ANOVA was performed for each TI and no change and change condition followed by Newman–Keuls t-test (5%). We also determined the correlations between the number of correct responses and response times.

3. Results

Each subject's performance was expressed as the number of correct responses in the trial. For a response to be considered correct, patients had to give the correct response three times, i.e. at each PI. To better understand memory deficit in MCI and AD patients, we analysed two additional measures: the number of correct responses at each PI and the percentage of correct responses for PIs in which the image of the MI was presented, i.e. no change, and for PIs in which the image other than that to memorize was presented, i.e. change. Mean response times in the trials were also recorded.

Our approach for analysing results, when a deficit appeared in a trial, consisted in detecting in which PI it was present and in determining for that PI whether the subjects detected change or no change.

3.1. Visual memory span

The mean span of elderly healthy controls was 4 ± 0.29, 3.25 ± 0.17 for MCI patients and 3.38 ± 0.20 for AD patients. ANOVA showed no group effect.

3.2. Visual and visuospatial short-term memory task

In all analyses, the H–F epsilon correction factor is greater than 1, hence the probabilities are not adjusted.

ANOVA for repeated measures performed on the number of correct responses in the trial for all factors revealed a significant group effect [$F(2, 21) = 17.82$, $P < 0.0001$], a distractor

effect [$F(1, 21) = 26.20$, $P < 0.0001$], a modality effect [$F(1, 21) = 14.42$, $P < 0.001$], TI effect [$F(2, 42) = 7.43$, $P < 0.002$], and a distractor × modality × TI × group interaction [$F(4, 42) = 2.96$, $P < 0.03$], indicating that all factors differentially affected performances according to the group. Distractor was a more discriminative factor between groups and TIs than was the modality factor. Whatever the modality, as concerns TI, AD patients were always the most impaired. MCI patients' performance was between that of elderly healthy controls and AD patients. On the contrary, each group performed differently according to the absence or the presence of the distractor [distractor × TI × group interaction: $F(4, 42) = 5.07$, $P < 0.002$], the time course of the performance depending on whether groups performed the task with visual modality [distractor × TI × group interaction: $F(4, 42) = 5.18$, $P < 0.002$] or visuospatial modality [distractor × TI × group interaction: $F(4, 42) = 2.55$, $P \leq 0.05$].

3.3. Visual short-term memory

ANOVA for repeated measures performed on the number of correct responses in the trial (Fig. 2A) revealed a significant group effect [$F(2, 21) = 13.98$, $P < 0.0001$] but no TI or group × TI interaction. Indeed, whatever the TI, elderly healthy controls presented higher scores, MCI patients intermediate scores, and AD patients lower scores. This was particularly marked at both 10 and 30 s TI [respectively, one-way ANOVA: $F(2, 21) = 6.77$, $P < 0.005$; $F(2, 21) = 12.11$, $P < 0.0003$]. MCI patients presented performance deficit at only the 30 s TI, and AD patients at both 10 and 30 s TI ($P < 0.05$; *post hoc* Newman–Keuls *t*-test).

ANOVA for repeated measures on PI1 showed a significant group effect [$F(2, 21) = 9.11$, $P < 0.0014$] but no TI or group × TI interaction (Fig. 3). One-way ANOVA on each TI revealed a group effect on the 30 s TI [$F(2, 21) = 4.9$, $P < 0.01$]. MCI and AD patients had a visual recognition deficit ($P < 0.05$; *post hoc* Newman–Keuls *t*-test). No effect was found on PI2 and PI3; the three groups performed similarly.

Analysis of the percentage of correct responses in no change and change conditions for PI1 (Fig. 4) in which MCI and AD patients presented a deficit in their performance showed that AD patients clearly presented difficulty in detecting no change ($P < 0.05$; *post hoc* Newman–Keuls *t*-test).

ANOVA for repeated measures performed on the mean response times (Fig. 2B) revealed significant group effect [$F(2, 21) = 4.37$, $P < 0.025$], and TI effect [$F(2, 42) = 3.35$, $P < 0.044$] but no group × TI interaction. MCI and AD patients had similar response times and both were higher than elderly healthy controls ($P < 0.05$; *post hoc* Newman–Keuls *t*-test). Correlation analyses were performed on the number of correct responses and response times for the 30 s TI in which both MCI and AD patients presented altered performance. A significant neg-

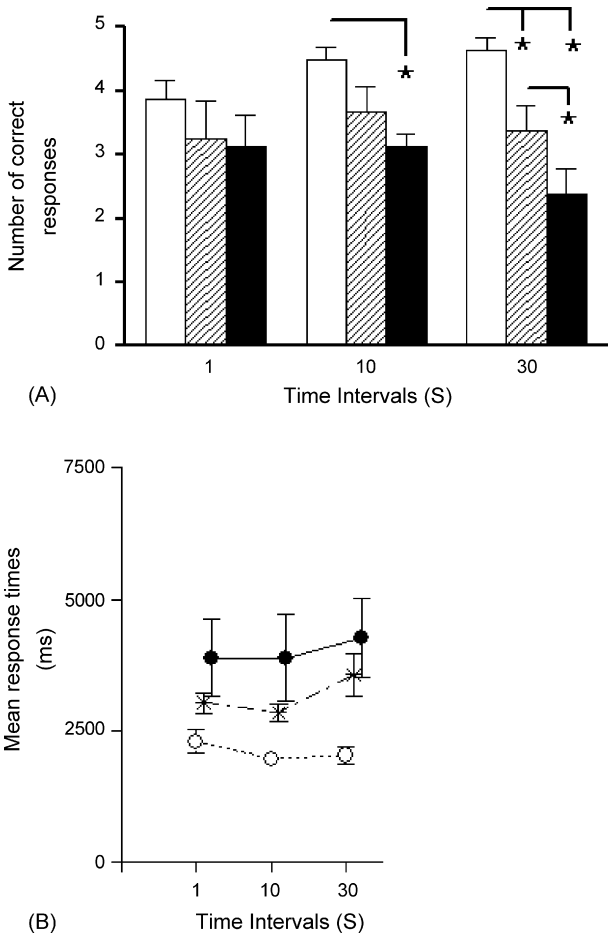


Fig. 2. Results from visual short-term memory (VSTM). (A) Number of correct responses in trial for the 1, 10, and 30 s time intervals (TIs) in elderly healthy controls (white bar), amnestic mild cognitive impairment patients (MCI, hatched bar), and mild Alzheimer disease (AD patients, black bar). (B) Mean response times in milliseconds (ms) for each three TIs at trial in elderly healthy controls (empty circle), amnestic mild cognitive impairment patients (MCI, cross), and mild Alzheimer disease (AD patients, dark circle). (*) Newman–Keuls *t*-test, 5%.

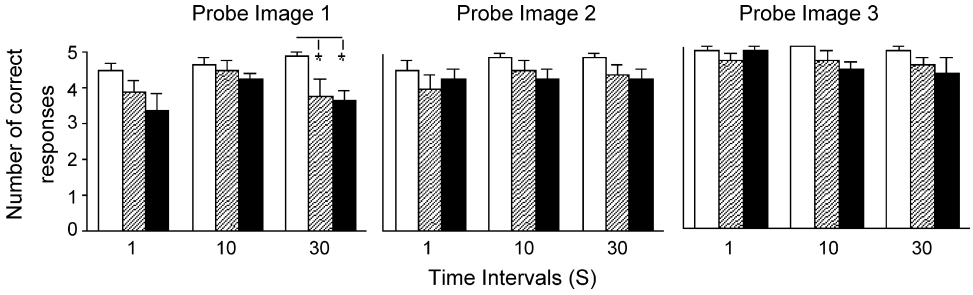


Fig. 3. Results from VSTM. The number of correct responses for each probe image (PI) and each TI in elderly healthy controls (white bar), amnestic mild cognitive impairment patients (MCI, hatched bar), and mild Alzheimer disease (AD patients, black bar). (*) Newman–Keuls *t*-test, 5%.

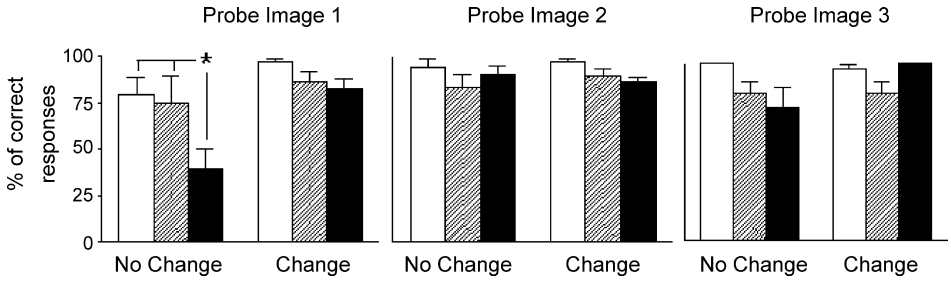


Fig. 4. Results from VSTM. Percentage of correct responses at each PI for visual no change and visual change in elderly healthy controls (white bar), amnestic mild cognitive impairment patients (MCI, hatched bar), and mild Alzheimer disease (AD patients, black bar). (*) Newman–Keuls *t*-test, 5%.

ative correlation was found between the number of correct responses and response times for MCI [$r(8) = -0.793$, $P < 0.016$ for performances at the trial and $r(8) = -0.796$, $P < 0.015$ for performances at PI1] but not for AD patients.

3.4. Visuospatial short-term memory

ANOVA for repeated measures performed on the number of correct responses in the trial (Fig. 5) revealed a significant group effect [$F(2, 21) = 8.58$, $P < 0.002$], a TI effect [$F(2, 42) = 7.81$, $P < 0.0013$] but no group × TI interaction. As for VSTM, elderly healthy controls presented higher scores, MCI patients intermediate scores, and AD patients lower scores whatever the TI [$F(2, 21) = 4.36$, $P < 0.026$ for 1 s TI; $F(2, 21) = 10.2$, $P < 0.0008$ for 10 s TI; $F(2, 21) = 3.97$, $P < 0.034$ for 30 s TI]. AD had impaired performance for all TI, and MCI patients for the 10 and 30 s TI ($P < 0.05$; *post hoc* Newman–Keuls *t*-test).

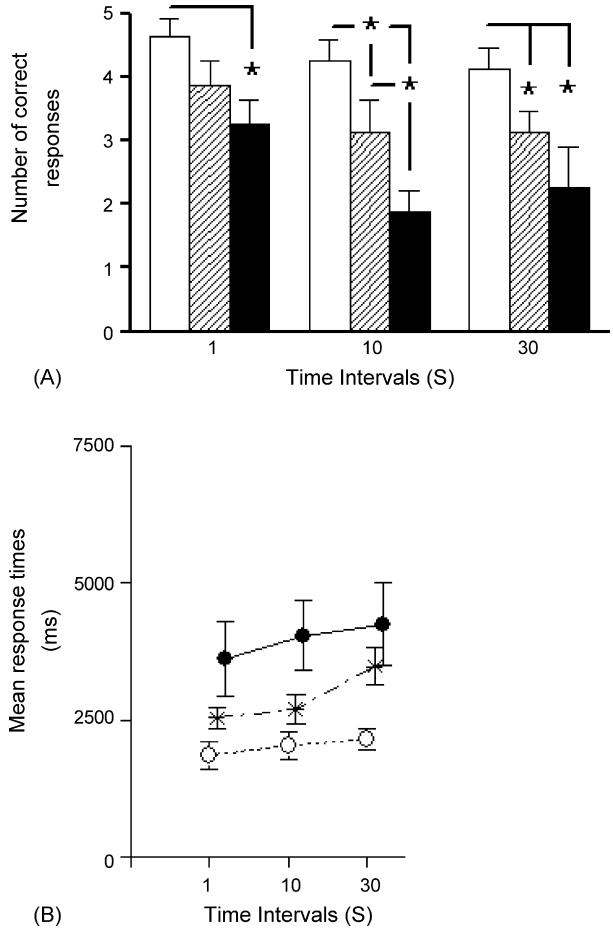


Fig. 5. Results from visuospatial short-term memory (VSSTM): (A) and (B) illustrate results for the same measures as in Fig. 2. (*) Newman–Keuls *t*-test, 5%.

ANOVA for repeated measures on PIs showed a group effect for the three PIs [respectively, $F(2, 21) = 6.92$, $P < 0.005$; $F(2, 21) = 9.33$, $P < 0.0013$; $F(2, 21) = 8.38$, $P < 0.021$]. *Post hoc* Newman–Keuls *t*-test ($P < 0.05$) revealed that ADs' performances were particularly affected (Fig. 6).

Analysis of no change and change conditions (Fig. 7) showed that MCI patients presented a deficiency in detection of no change only for PI1 whereas AD patients presented a deficiency in the detection of both no change and change for all PIs ($P < 0.05$; *post hoc* Newman–Keuls *t*-test).

ANOVA for repeated measures performed on the mean response times (Fig. 5B) revealed significant group effect [$F(2, 21) = 5.51$, $P < 0.012$], TI effect [$F(2, 21) = 6.39$, $P < 0.0038$] but no group × TI interaction. One-way ANOVA on each TI revealed a group effect [respectively: $F(2, 21) = 4.52$, $P < 0.028$; $F(2, 21) = 5.8$, $P < 0.09$; $F(2, 21) = 4.57$, $P < 0.022$]. AD patients presented higher response times than elderly healthy controls. Response times displayed by MCI patients were intermediate for the 1 and 10 s TI and were like those of AD patients for the 30 s TI ($P < 0.05$; *post hoc* Newman–Keuls *t*-test). Correlation analyses were performed for all groups on the number of correct responses and response times in trial for the 10 and 30 s TI. We found a significant negative correlation between these two measures for MCI and AD patients [respectively: $r(8) = -0.813$, $P < 0.011$ and $r(8) = -0.889$, $P < 0.015$ for the 10 s TI and $r(8) = -0.713$, $P < 0.0457$ and $r(8) = -0.78$, $P < 0.018$ for the 30 s TI]. Significant negative correlations were found in AD patients for each PI when they presented a decrease in the number of correct responses [$r(8) \leq -0.784$, $P \leq 0.011$].

The comparison of VSTM and VSSTM performances in the trial (Figs. 2A and 5A) revealed a greater deficit for MCI and AD patients in VSSTM [ANOVA for repeated measures: group effect, $F(2, 21) = 14.12$, $P < 0.0001$; modality × TI × group interaction: $F(4, 42) = 2.60$, $P < 0.05$].

3.5. Visual short-term memory with distractor

ANOVA for repeated measures performed on the number of correct responses in the trial (Fig. 8A) revealed a significant group effect [$F(2, 21) = 5.44$, $P < 0.013$] and a TI × group inter-

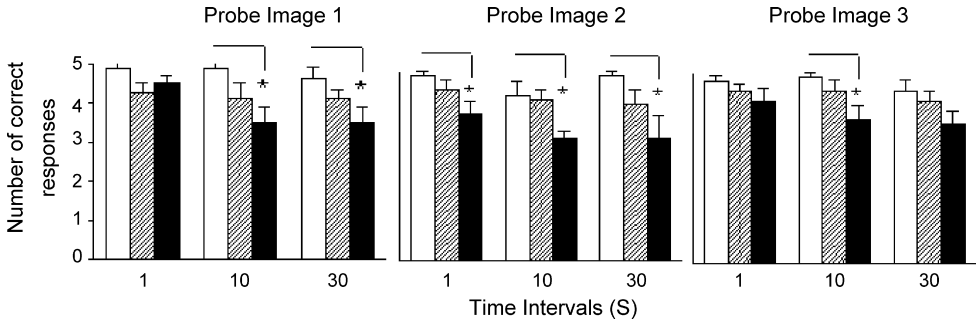


Fig. 6. Results from VSSTM. Results for the same measures as in Fig. 3. (*) Newman–Keuls *t*-test, 5%.

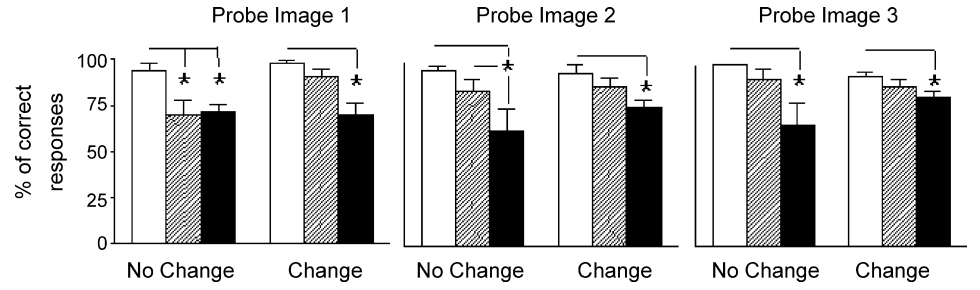
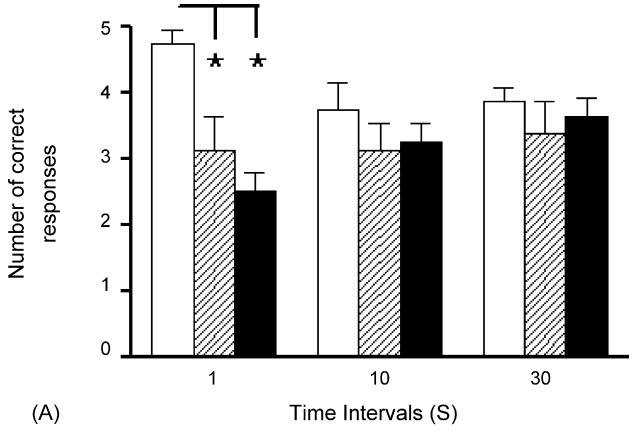


Fig. 7. Results from VSSTM. Results for the same measures as in Fig. 4. (*) Newman–Keuls *t*-test, 5%.



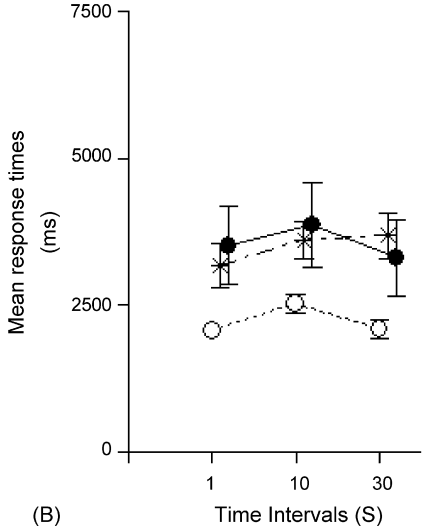


Fig. 8. Results from VSTM with distractor: (A) and (B) illustrate results for the same measures as in Fig. 2. (*) Newman–Keuls *t*-test, 5%.

action [$F(4, 42) = 3.10$, $P < 0.025$]. The three groups performed similarly for the 10 and 30 s TI whereas MCI and AD patients presented impaired performance for the 1 s TI [$F(2, 21) = 12.33$, $P < 0.0003$].

One-way ANOVA on PIs showed a similar deleterious effect on PI1 and PI2 for MCI and AD [respectively: $F(2, 21) = 4.82$, $P < 0.019$; $F(2, 21) = 3.86$, $P < 0.037$] (Fig. 9).

For PI1, MCI patients showed a deficiency in detecting no change ($P < 0.05$; *post hoc* Newman–Keuls *t*-test) whereas AD patients had a similar performance in no change and change conditions (Fig. 10).

ANOVA for repeated measures performed on the mean response times in the trial (Fig. 8B) revealed significant group effect [$F(2, 21) = 4.51$, $P < 0.023$] and TI effect [$F(2, 42) = 4.63$, $P < 0.015$] but no group × TI interaction. MCI and AD patients presented similar response times and both were more elevated than those of elderly healthy controls ($P < 0.05$; *post hoc* Newman–Keuls *t*-test). Correlation analyses were performed for MCI and AD patients on the number of correct responses and response times at the 1 s TI when the groups had lower performance. We found no significant correlation whatever the group.

The comparison between performances without (Fig. 2A) and with distractor (Fig. 8A) revealed that performances were differentially affected by the presence or the absence of the distractor according to the TI considered. Indeed, MCI and AD patients had weaker performances for the 10 and 30 s TI without distractor and for the 1 s TI with distractor [distractor × TI × group interaction: $F(4, 42) = 3.94$, $P < 0.0084$].

3.6. Visuospatial short-term memory with distractor

ANOVA for repeated measures performed on the number of correct responses in the trial (Fig. 11A) revealed a group effect

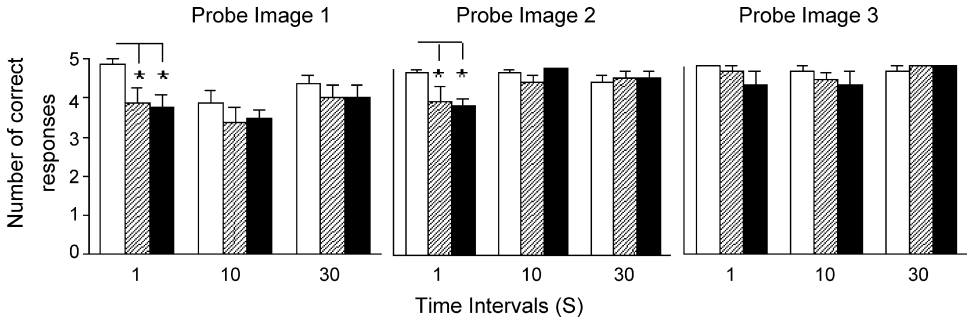


Fig. 9. Results from VSTM with distractor. Results for the same measures as in Fig. 3. (*) Newman–Keuls *t*-test, 5%.

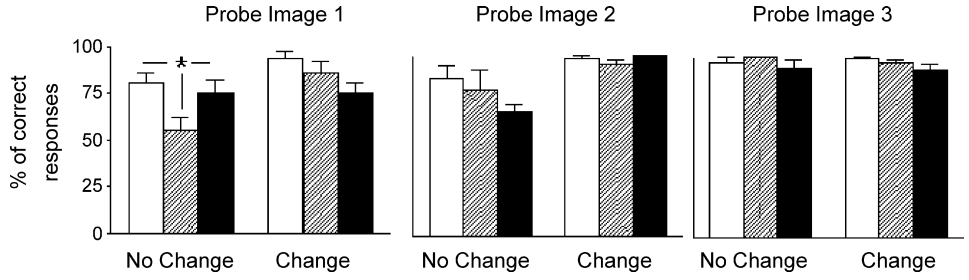


Fig. 10. Results from VSTM with distractor. Results for the same measures as in Fig. 4. (*) Newman–Keuls *t*-test, 5%.

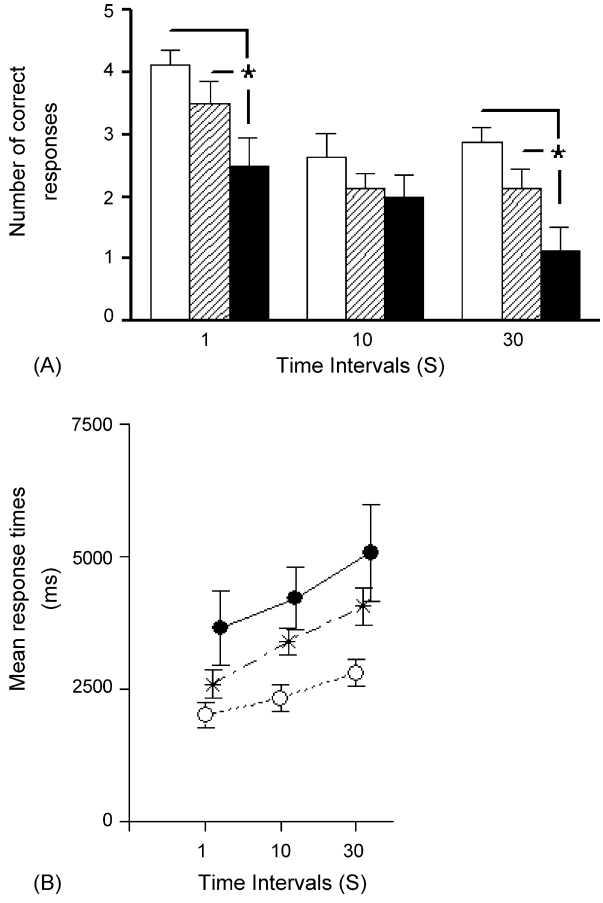


Fig. 11. Results from VSSTM with distractor: (A) and (B) illustrate results for the same measures as in Fig. 2. (*) Newman–Keuls *t*-test, 5%.

[$F(2, 21) = 10$, $P < 0.0009$] and a TI effect [$F(2, 42) = 18.63$, $P < 0.0001$] but no group × TI interaction. The performance of the three groups declined according to the TI, with again a higher score for elderly healthy controls, an intermediate score for MCI patients, and a lower score for AD patients. One-way ANOVA showed a group effect for the 1 and 30 s TI [respectively, $F(2, 21) = 5.98$, $P < 0.0088$; $F(2, 21) = 8.85$, $P < 0.0016$]. No difference could be detected for the 10 s TI between the three groups because of a generalized decrease in the performances.

Analyses of PIs (Fig. 12) showed that performances were particularly impaired for the 10 and 30 s TI of PI1 [respectively one-way ANOVA: $F(2, 21) = 4.58$, $P < 0.02$, $F(2, 21) = 3.83$, $P < 0.038$].

The percentage of correct responses of MCI and AD patients (Fig. 13) was weaker than that of elderly healthy controls in both no change and change conditions, but this difference reached statistical significance only for no change condition of PI1 for both groups and only for AD group on change condition of PI3 ($P < 0.05$; *post hoc* Newman–Keuls *t*-test).

Analyses on the mean response times (Fig. 11B) revealed higher RTs for AD patients and intermediate response times for MCI [ANOVA for repeated measures: group effect, $F(2, 21) = 5.3$, $P < 0.015$). Response times increased as TI progressed [TI effect, $F(2, 42) = 24.35$, $P < 0.0001$). These higher response times were similar for the three groups (no group × TI interaction). Because altered performances were observed whatever TIs and groups, correlation analyses were performed for the three TIs on the number of correct responses in trial and the response times. We found no significant correlation whatever the group and the TI.

The comparison between VSSTM performances without (Fig. 5A) and with distractor (Fig. 11A) showed lower scores with distractor for all groups [ANOVA for repeated mea-

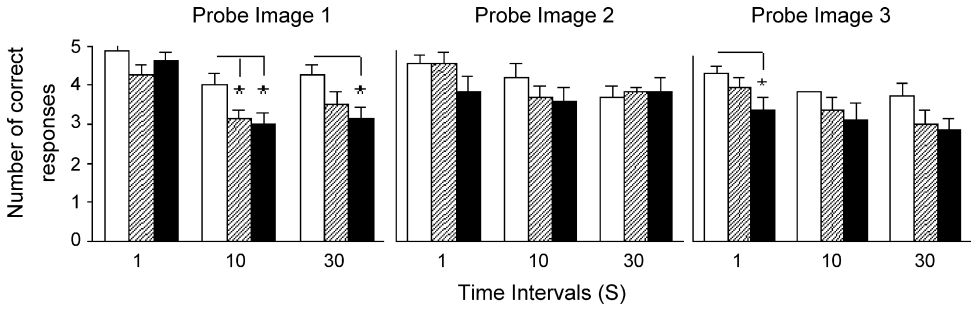


Fig. 12. Results from VSSTM with distractor. Results for the same measures as in Fig. 3. (*) Newman–Keuls *t*-test, 5%.

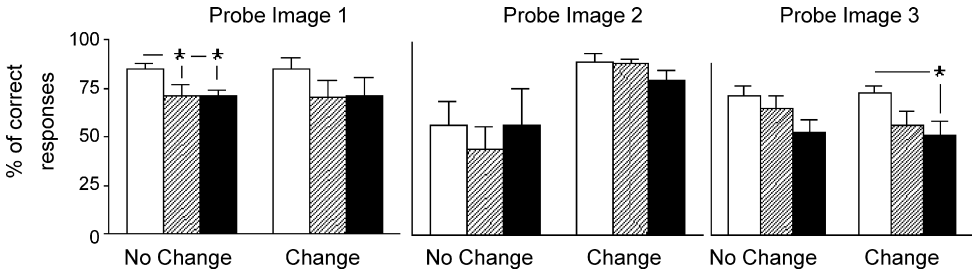


Fig. 13. Results from VSSTM with distractor. Results for the same measures as in Fig. 4. (*) Newman–Keuls *t*-test, 5%.

sures: interaction of group × TI × distractor interaction, $F(4, 42) = 4.31$, $P < 0.0052$].

The presence of the distractor affected the performance differentially depending on whether short-term memory was performed in visual (Fig. 8A) or spatial modality (Fig. 11A) [modality × TI × group interaction: $F(4, 42) = 4.31$, $P < 0.0052$]. Indeed, for trial scores, we noted a deleterious effect of the distractor for MCI and AD patients at the 1 s TI in VSTM against a deleterious effect for all TI in VSSTM.

4. Discussion

The results showed VSTM and VSSTM deficits in MCI and AD patients. In general, AD patients were always the most impaired and MCI patients had an intermediate performance between elderly healthy controls and AD patients. According to the conditions and/or the measures considered, MCI patients' performances were close to either AD patients or controls. The different measures for analysing results revealed that cognitive memory profile differed between MCI and AD patients according to the modality tested, indicating that performance deficit reflects an alteration of different processes. Indeed, MCI patients' retrieval processes were impaired in visual and visuospatial modality whereas those of AD patients were impaired in only the visual modality. Concerning the visuospatial modality, forgetting appears, which suggests that AD patients no longer access the memory trace or that they have not encoded the information. Attentional processes might be partly responsible for the deficit particularly in VSTM.

MCI and AD patients presented short-term memory deficits whose severity depended on the nature of the memorized information, i.e. visual versus visuospatial, and on the TI used. Visual recognition deficit appeared for the longest TIs. When the deficit worsened, i.e. in the visuospatial recognition, it extended to the shortest TI.

4.1. Visual short-term memory

VSTM deficits appeared at the 30 s TI for MCI patients and at the 10 and 30 s TI for the AD patients (Fig. 2A). This deficit corresponds to a decrease in the number of correct responses only at PI1 and for the 30 s TI (Fig. 3). Indeed, MCI and AD patients made few errors at PI2 and PI3 and consequently were able to give more correct responses. This could mean that the impairment of VSTM does not reflect a lack of encoding or forgetting but rather a transitory inaccessibility to the short-term memorized information. PI1 seemed to play the role of reminder stimulus. It reminded that PI1 can be the MI or not. In case if the PI1 was not the MI, it presented a change. One or several images can be changed but in no case all of them, hence only one image could serve as stimulus reminder. This raises the question of the nature of the information stored in VSTM. For certain authors the format of the storage units is object-based (Vogel, Woodman, & Luck, 2001) while for others the storage units are feature-based (Wheeler & Treisman, 2002; Vidal, Gauchou, Tallon-Baudry, & O'Rgegan, 2005). In the object-based theory, the storage capacity is determined by the number of objects; in the feature-based theory, the storage capacity is limited by the maximum number of features of a given dimension that can be stored simultaneously in parallel feature-specific memory stores. Thus, it is likely that at PI1 even only one image common to the MI is sufficient to play the role of stimulus reminder. Moreover, results from Jiang, Olson, and Chun (2000) suggest that units coded in a given presentation are not stored independently but rather as a function of the whole stimulus configuration. Consequently, it is not surprising that only one image and even more two or three permit access to the stored configuration. Thus, MCI and AD

patients were able to both encode and store visual information but they have difficulty retrieving information without a stimulus reminder. This difficulty in retrieving without a stimulus is part of normal aging (Craik & Jennings, 1992; Smith, 1996). Given the age difference between elderly healthy controls and AD patients, this retrieval difficulty might be partly related to normal aging. This hypothesis, however, is not supported by the fact that MCI patients also had a VSTM deficit, although their age differed by only 3 years relative to elderly healthy controls.

The analysis of the percentage of correct responses for the memory image (no change condition) and neighbouring image (change condition) at PI1 (Fig. 4) showed similar results for MCI in both conditions whereas AD patients had a lower percentage of correct responses for no change condition. This failure to detect no change was specific to PI1 and temporary since it did not persist in PI2 and PI3. The capacity of AD patients to detect change in PI1 strongly suggests they have encoded and retained MI. Data on change blindness, the failure to detect visual changes that occur during a disruption, showed that it can result from the absence of sufficient representations (Noë, Pessoa, & Thompson, 2000), from failure to retain a representation after forming it (Beck & Levin, 2003), or from the failure to compare representations of both pre- and post-change information (Mitroff, Simons, & Levin, 2004). Thus, since AD patients did not fail to detect change, we can assume that MI representation was stored and accessible. This assumption agrees with the capability of AD patients to detect no change at PI2 and PI3. The temporary incapacity to detect no change in PI1 may be explained by an attentional hypothesis. This phenomenon is described in the literature as attentional blink, a temporary functional blindness to the second of sequentially presented stimuli (Broadbent & Broadbent, 1987; Duncan, Ward, & Shapiro, 1994). The attentional blink can be explained by the attentional cost of attending to one visual stimulus, which may lead to impairments in identifying a second stimulus presented within approximately 500 ms of the first. Husain, Shapiro, Martin, and Kennard (1997) reported an increased attentional blink in visual neglect in which subjects could not identify the second target in a dual-target task until 1.440 ms after they had identified the first target. However, paradigms for which attentional blink have been described used shorter delays than some in our study. Perry and Hodges (2003) reported a normal attentional blink in MCI patients for variable intervals (from 0 to 2080 ms). In pathologies such as AD, this phenomenon might be extended for longer delays. Further studies will be necessary in early AD patients and notably, in addition to mnemonic paradigms, studies using a rapid serial visual presentation paradigm, which detect attentional blink (Broadbent & Broadbent, 1987; Raymond, Shapiro, & Arnell, 1992). This approach would serve to determine if the inability to detect no change in AD patients is due to attentional or mnemonic mechanisms.

Barbeau et al. (2004) reported an impairment of visual recognition memory in the DMS48 task in amnestic MCI and mild AD patients. The DMS48 task is based on the classic delayed matching-to-sample task in which patients have to choose between a target and a distractor during recognition. This impairment was found on a recognition test performed 3 min after encoding and on a delayed recognition test performed 1 h later. Those authors explained this deficit by a profound incapacity to store new information. This interpretation does not agree with our results. A plausible explanation for this discrepancy could be that our MCI and AD patients are earlier in the course of the disease than the patients of by Barbeau et al.

4.2. Visuospatial short-term memory

VSSTM deficit was greater for MCI and AD patients since, compared to VSTM, it was extended to two TIs for MCI patients (10 and 30 s) and to the three TIs for AD patients (Fig. 5A). In spite of their deficit on trial measure, MCI patients did not present a performance deficit whatever the PIs since performances were close to those of elderly healthy controls. Indeed, the worse responses were distributed among the three PIs (Fig. 6). Although results in the trial and results for each PI appear contradictory, they are not. Recall that for an answer to be considered correct, patients had to give the correct response three times (one for each PI). Thus, it was more difficult to have a correct response in the trial than in one PI. As MCI patients seemed to have, as for VSTM, difficulty accessing the shortly stored information, they may have partly recovered the information during PIs. Thus, they were able to correctly respond in one or two PIs but this was not sufficient to have a score of 1. The extended deficit at shortest TI, from 30 to 10 s, could reflect a greater difficulty in accessing the visuospatial information than the visual information. Thus, in MCI patients, visuospatial modality seems more deficient than visual modality. AD patients present a greater deficit in visuospatial modality than MCI patients. Indeed, their performance was altered for the three TIs in trials and for all PIs, suggesting that in this case patients have either not memorized or forgotten the information. The use of the span task may differentially affect the VSTM and the VSSTM task. In the VSTM task, the number of images in the MI and PI indicate that more comparisons need to be made during the PI, possibly leading to more errors. On the contrary, in the VSSTM task, the set of images can be considered as a whole, leading to fewer errors. Consequently, the difficulty in the VSTM task may depend on the span task whereas the difficulty level of the VSSTM task may be only slightly affected by the task. This means that the visuospatial deficit in MCI and AD patients could be linked more to the spatial component of the VSSTM task than to the visual one. If, as suggested above, the images as a whole could be shifted in the VSSTM task, one could hypothesize that a shift with fewer images is more difficult to detect than a shift with more images. This could partly explain the visuospatial deficit in AD and MCI patients. The difficulties in detecting no change or change increased in the visuospatial modality for AD patients (Fig. 7). Indeed, AD patients presented a deficit in the detection of both conditions in the VSSTM task whereas in the VSTM task they had deficiency only with no change detection. MCI patients presented difficulties in detecting no change in the VSSTM task whereas they presented no particular deficiency in the detection of both no change and change in the VSTM task (Fig. 4). It thus seems that the increase in the memory deficit according to the modality is closely linked to the capacity of the

patient to detect no change or change. Moreover, the deficiency in detecting no change appears earlier than that in detecting change and thus could be an early component of the memory deficit.

4.3. Visual short-term memory with distractor

When a distractor was presented during TIs, a VSTM deficit was observed at the 1 s TI for MCI and AD patients (Fig. 8). Surprisingly, no deficit was observed at the 30 s TI, in which MCI and AD patients presented a VSTM deficit when TI was blank (Fig. 2A). Because the presence of the distractor caused deleterious effect on the performance, this performance might have been more impaired at a TI in which it was already altered without distractor. This was not the case however. In fact, due to the TI, the distractor did not produce the same effect during the 1 s TI or the 10 and 30 s TIs. Indeed, at the 1 s TI, the distractor appeared quickly as a flash and the patient did not have time to perform the distractor task whereas at the 10 or 30 s TI, the patient had 10 or 30 s to perform the task. Therefore, for these two TIs, patients were in a paradigm of successive tests. Recall that the patient did not know the duration of the TI. Thus, when the distractor appeared, patients shifted their attention on the distractor task and formed an intention to perform it. At the 1 s TI, patients just prepared to perform the task when the distractor disappeared and was replaced by PI1. Thus, patients again shift their attention but here on recognition task. This double shift had deleterious effect on VSTM of MCI and AD patients. The sensitivity to the double shift may reflect impairment in disengaging–engaging attention in MCI and AD patients. Disengagement of attention has been investigated in AD patients in tasks that predominantly used paradigms according to the Posner model (1980). In the Posner model of visual orienting, the actual shift of visual attention is from one location to another. In our study, however, patients are requested to shift attention between or within objects and to shift a pattern of response and mental set, referred to as set-shifting. In the latter case, the impairment of MCI and AD patients may reflect attentional dysfunction that might be linked to executive functions. Performances in the PIs revealed that the deleterious effect of the "double shift" was temporary since MCI and AD patients performed well in PI3. Thus, this temporary deleterious effect of the distractor may rather reflect sensitivity to shift processes than a VSTM alteration. Further studies will be necessary to clarify this point.

When patients had the time to perform the distractor task (i.e. at the 10 and 30 s TI), their performance was not altered but with a blank 30 s TI the performance was worse. This apparently contradictory result may be explained by differences in attentional demands of the tasks. Indeed, the distractor puts MCI and AD patients in a situation where it was necessary to recruit more attentional resources than for a situation with a blank TI. This may explain why patients were able to perform well in a situation in which, when the TI is blank, they present a memory deficit. This deficit may represent a decrease in vigilance. A good performance when the distractor was present may reflect the preserved capacity of MCI and AD patients to recruit more attentional resources.

4.4. Visuospatial short-term memory with distractor

For MCI patients, the visuospatial modality was not as sensitive as visual modality to the influence of the double shift since there was no deleterious effect of the distractor. On the contrary, VSSTM deficit was found in AD (Fig. 11A). This was not surprising because, as suggested above, they have either not memorized or forgotten the information. At the 10 and 30 s TIs, where the distractor gave a successive test configuration to the task, the performance of the three groups was worse. We have explained the preserved performance at the 10 and 30 s TIs by patients' capacity to recruit sufficient attentional resources to perform the task well. If this is true, it was not sufficient to procure a good performance in patients with deficient visuospatial memory. Another explanation might be that the spatial component of the distractor interferes with that of location of the images in PIs. This interference process also may affect elderly healthy controls.

5. Conclusion

All these results suggest that MCI and AD patients present different cognitive profiles, which remain to be characterized.

Attention and memory are interrelated cognitive processes. Impairments in one domain may influence performance in the other. We showed in this study that both memory and attention were impaired in MCI and AD patients. Further studies will be necessary to better determine the role of attention in the memory deficits according the modality tested, more particularly to determine which attentional processes are involved.

Data suggest that VSSTM is more altered than VSTM. The deficit of performances in visual modality seems of attentional origin whereas that of visuospatial modality seems of memory origin. AD patients were more impaired in both VSTM and VSSTM than MCI patients, with a greater impairment for both groups in VSSTM, in which errors of memory show a much greater dependence on delay length than do errors in VSTM. On the contrary, no difference was found between MCI and AD patients in their errors of attentional origin in VSTM.

The combination of attentional and mnemonic evaluation is likely to be a promising approach to finding predictive markers that distinguish MCI patients that convert to AD. Further studies will be necessary to determine whether the evaluation of visuospatial memory would be a better predictor of AD than visual memory.

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