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Positive effects of computer-based cognitive training in adults with mild cognitive impairment

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ABSTRACT

Considering the high risk for individuals with amnestic Mild Cognitive Impairment (A-MCI) to progress towards Alzheimer's disease (AD), we investigated the efficacy of a non-pharmacological intervention, that is, cognitive training that could reduce cognitive difficulties and delay the cognitive decline. For this, we evaluated the efficacy of a 12-week computer-based memory-attention training program based on recognition in subjects with A-MCI and compared their performances with those of A-MCI controls trained in cognitively stimulating activities. The effect of training was assessed by comparing outcome measures in pre- and post-tests 15 days before and after training. To evaluate the duration of training benefits, a follow-up test session was performed 6 months after memory and attention training or cognitively stimulating activities.

Outcome measures showed that the trained group, compared to control group, improved episodic recall and recognition. Six months after training, scores remained at the level of the post-test.

Since the training program was exclusively based on recognition, our results showed a generalization from recognition to recall processes, which are memory components that represent part of the core cognitive impairments in individuals at risk of converting to AD. Thus, cognitive training based on recognition holds promise as a preventive therapeutic method and could be proposed as a non-pharmacological early-intervention strategy. Future investigations need to focus on methodological constraints and delineating possible neuroplastic mechanisms of action.

1. Introduction

Cognitive enrichment early in life, as indicated by level of education, complexity of work environment, and nature of leisure activities, can promote better cognitive functioning that can be maintained into advanced age (Acevedo & Loewenstein, 2007; Brehmer et al., 2008). To combat age-related cognitive decline and prevent dementia, interventions based on increasing complex mental activity seem promising. Valenzuela and Sachdev (2006a, 2006b) reported that individuals with higher levels of mental activity have a reduced rate of incident cognitive decline and are at only about half the risk of developing dementia. These effects reflect increased cognitive functioning, which depends on the ability of the brain to compensate for pathological changes associated with aging. This compensatory ability is referred to as cognitive reserve. The cognitive reserve hypothesis suggests that cognitive enrichment promotes utilization of available functions (Christensen et al., 2008; Stern, 2009). The brain is malleable in response to one's environment, and the central nervous system is continuously adjusting to environmental experiences. Beneficial effects of environmental enrichment early in life have been observed in rodents and primates as structural correlates, which include more synapses in specific brain regions that lead to greater neuronal organization (for a review see Milgram, Siwak-Tapp, Araujo, & Head, 2006).

Research on interventions based on augmenting complex mental activity postulates that cognitive training (CT) acts by stimulating neuroprotective mechanisms (Valenzuela & Sachdev, 2009), anchoring the theoretical foundation of CT in the concept of synaptic plasticity and cognitive reserve. Our previous works on rodents support this view. During entry to senescence (around 15 months old) or after cholinergic damage, rodents show a wide range of cognitive deficits (McGaughy, Everitt, Robbins, & Sarter, 2000). We showed that housing in a long-term enriched environment had beneficial effects on cognitive performance (Paban, Jaffard, Chambon, Malafosse, & Alescio-Lautier, 2005) and that this correlated with an upregulated gene expression of neurotrophic signaling

Abbreviations: MCI, mild cognitive impairment; A-MCI-md, amnestic MCI-multiple domain; AD, Alzheimer's disease; CT, cognitive training

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molecules in frontal cortex and hippocampus (Paban, Chambon, Manrique, Touzet, & Alescio-Lautier, 2011). Lambert, Fernandez, and Frick (2005) found that cognitive stimulation in mice increased synaptophysin levels in the neocortex, hippocampus, and cerebellum. Electrophysiological measures of synaptic plasticity such as long-term potentiation are also increased (Artola et al., 2006). Interestingly, enrichment in transgenic Alzheimer's disease (AD) mice has been associated with as much as 50% less amyloid pathology (Adlard, Perreau, Pop, & Cotman, 2005; Costa et al., 2007). Studies in humans showed that CT in healthy older individuals can increase levels of putatively neuroprotective metabolites in the hippocampus (Valenzuela et al., 2003) and increase frontal lobe metabolism (Small et al., 2006). It is unknown whether mental training can delay hippocampal atrophy in AD, but Valenzuela, Sachdev, Wen, Chen, and Brodaty (2008) reported that lifetime levels of mental activity are inversely correlated to the rate of hippocampal atrophy in healthy older adults. Thus, there is increasing evidence in humans and animals of the role of environmental and lifestyle factors as moderators in cognitive aging and as protective agents for the development of AD. Given the involvement of such factors in the outcome of aging, it is reasonable to assume that cognitive intervention and particularly CT may play a role in normal aging and AD.

Persons with mild cognitive impairment (MCI) retain a large range of cognitive capacities and plasticity (Calero & Navarro, 2004), which makes them ideal for studying CT and its underlying mechanisms. Moreover, CT might serve in persons with MCI who are at risk of developing AD or other types of dementia.

To date, however, few studies have been conducted on CT and MCI. Memory strategies training resulted in limited improvement on objective memory and cognitive function (Rapp, Brenes, & Marsh, 2002; Troyer, Murphy, Anderson, Moscovitch, & Craik, 2008), suggesting that impaired memory function may be resistant to the benefits of a unimodal memory intervention. In contrast, multidomain CT in MCI showed positive effects on cognitive abilities and on mood and behavioral disturbances (Barnes et al., 2009; Cipriani, Bianchetti, & Trabucchi, 2006; Galante, Venturini, & Fiaccadori, 2007; Gunter, Schafer, Holzner, & Kemmler, 2003; Rozzini et al., 2007; Talassi, Guerreschi, Feriani, & Fedi, 2007). Traditional pen-and-pencil CT exercises are progressively being replaced by computer-based programs, which are superior in many ways. The computer facilitates multimodal and multidomain training, which seems to be a key factor for functional efficacy, and provides for individualized intervention, by gradually increasing task difficulty in a customized fashion. These features allow effective control of ceiling and floor effects, both important for successful cognitive exercise because individuals are continually cognitively challenged.

The specific goal of the present study was to develop, for subjects with MCI, a computer-CT program based on memory functions known to be deficient with the advance of AD but still preserved or slightly impaired in MCI, and then to conduct a pilot study to evaluate this program on episodic recognition and retrieval processes. The underlying hypothesis was that regular practice with specific tasks would strengthen the functioning of the targeted cognitive mechanisms, which are still relatively preserved, but vulnerable to AD. For this, we focused on median temporal lobe areas, which are vulnerable to early-stage AD (Braak & Braak, 1991; Delacourte et al., 1999) and developed training exercises to stimulate these areas. Based on the reported neuroprotective effects of CT (Valenzuela et al., 2003) and on the demonstration that neuroplasticity exists in persons with MCI (Calero & Navarro, 2004), we postulated that the stimulation of the brain regions vulnerable to early-stage AD could generate neuroprotective effects by stimulating residual neuroplastic pathways, reduce cognitive difficulties, and delay the cognitive decline.

2. Materials and methods

2.1. Patients

Twenty-two subjects with amnestic MCI multiple domains subtype (A-MCImd) referring to the Behavioral Neurology Department of Sainte-Marguerite Hospital, (Marseille, France) were selected. Inclusion criteria were as follows: (i) 65–90 years of age and (ii) meet definition criteria for A-MCI-md (Petersen, 2004). All patients had memory complaint, usually verified by an informant. Memory performances and those in one or more other cognitive domains (i.e. attention or executive domain) were below the normative data (see subsequent section for the description of neuropsychological tests). The cut-off scores for abnormality were 1.5 SD below the mean score for the corresponding age and education group, (iii) have normal general cognitive functioning as determined by a Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) score ≥ 24, and (iv) a global clinical dementia rating scale (Hugues, Berg, Danzinger, Coben, & Martin, 1982) score of 0.5. Exclusion criteria were (i) neurological, psychiatric, or medical disorders, (ii) moderate or severe depression as determined by a score > 11 (moderate depression) or > 19 (severe depression) on the Geriatric Depression Scale (Yesavage et al., 1983), (iii) relevant hearing, vision, motor or language deficits, and (iv) recent participation in cognitive stimulation/training.

All patients underwent a CT scan and routine biological screening. Activities of daily living were normal, as assessed through the Instrumental Activities of Daily Living (IADL, Barberger-Gateau et al., 1992). All patients underwent standard neuropsychological assessment. The neuropsychological battery assessed memory, attention, and executive skills. It included the following tests: The Rey Auditory Verbal Learning Test (RAVLT, Spreen & Strauss, 1998), the 16-item free and cued reminding test (RL/RI-16 test, Van der Linden et al., 2004), the copy and recall of the Rey Figure (Rey, 1959), the MMSE, the forward and backward digit span, the Trail Making Test (TMT, Reitan, 1958), Zazzo's cancellation test (Zazzo, 1974), Stroop test (Golden, 1978), the semantic (animals) and phonemic (letter P) verbal fluency test (Cardebat et al., 1990), the dual-task test of Baddeley (Baddeley et al., 1997), and the DO-80 naming test (Deloche et al., 1997). Behavioral assessment included the 30-item version of the Geriatric Depression Scale (GDS, Yesavage et al., 1983).

The 22 patients were randomly assigned into two groups (11 patients per group): a group that performed training (Trained group) and a group that participated in stimulating cognitive activities (Control group). Baseline demographic data are summarized in Table 1.

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

2.2. Intervention

2.2.1. Memory and attention training

2.2.1.1. Theoretical foundations. Because MCI individuals have mainly episodic memory deficits and their recognition memory mechanisms are at least relatively intact, our CT program used a familiarity-based forced-choice recognition procedure. Neuropsychological studies on A-MCI patients reported prominent deficits in episodic memory, characterized by impaired encoding and storage capacities in recall (for review, see Belleville, Sylvain-Roy, de Boysson, & Ménard, 2008), a pattern that is also characteristic in AD (for a review, see Lekeu & Van der Linden, 2005). These memory impairments are also reported for recognition (Alescio-Lautier et al., 2007; Dudas, Clague, Thompson, Graham, & Hodges, 2005; Perri, Carlesimo, Serra, Caltagirone, and the Early Diagnosis Group of the Italian Interdisciplinary Network on Alzheimer's Disease 2005), which involves recollection and familiarity processes. Other A-MCI studies revealed a significant deficit in recollection-based recognition but a selective preservation of familiarity-based recognition (Anderson et al., 2008; Serra et al., 2010; Westerberg, Paller, Mayes, Holdstock, & Reber, 2006).

Short-term memory is impaired in AD. In A-MCI-md, this deficit appears as increasing time between the encoding and recognition phase (Gagnon & Belleville, 2011), reflecting a difficulty in maintaining information, which consequently affects working memory. Subjects with A-MCI-md have preserved immediate memory and memory for short delays. To improve information maintenance during working

Table 1
Baseline demographic data of participants: mean ± SEM.

Characteristics	Trained group ($n=11$)	Control group ($n=11$)
Age (years)	75.09 ± 1.97	78.18 ± 1.44
Women/men (n)	5/6	6/5
Education (%) 1/2/3[a]	54/36/10	37/45/18
MMSE (/30)	27.36 ± 0.53	27.18 ± 0.40
CDR (/5)	0.5 ± 0	0.5 ± 0

[a] 1=primary school; 2=secondary school; 3=more than secondary school.

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memory, training was based on increasing the maintenance time. For this, we gradually increased the blank interval between memorization and recognition. This technique is used in the spaced retrieval method (Laudauer & Bjork, 1978), which is efficient for patients with mild AD (Camp & Stevens, 1990; Erkès, Raffard, & Meulemans, 2010). Because short- and long-term memory processes share similar neural mechanisms (Marklund et al., 2007; Nee & Jonides, 2011), we hypothesized that short-term memory training would help maintain information in long-term memory.

Based on the notion that remediation is better if participants are prevented from reinforcing their own errors, we endorse the definition of "error reduction" proposed by Fillingham, Hodgson, Sage, and Lambon-Ralph (2003). In this context, before and during training exercise, we used a procedure that reduces errors. Prior to training, the subjects were invited to perform a guided procedure that forced them to provide a good answer. This guided procedure was repeated until the subjects had acquired the automatisms to properly perform the task. Then, during training we used an approach whereby the task was manipulated to reduce incorrect responses. Subjects began with very easy discrimination, and task difficulty was increased gradually by the neuropsychologist (for more details see procedure section below).

We also focused on the practical implementation of mnemonic strategies, for example naming, repetition, categorization, or association. Indeed, MCI individuals may benefit from intervention programs to optimize their functioning through the use of cognitive and memory strategies (Belleville, 2008; Belleville et al., 2006).

The CT program incorporates, in addition to memory training, training of focused and divided attention and processing speed. In fact, besides memory deficits, A-MCI-md patients exhibit attentional deficits, particularly in attentional focus (Levinoff, Saumier, & Chertkow, 2005; Tales, Snowden, Haworth, & Wilcock, 2005), divided attention and attentional control (Belleville, Chertkow, & Gauthier, 2007; Danhausser et al., 2005), and/or speed of processing (Gorus, De Raedt, Lambert, Lemper, & Mets, 2008; Levinoff et al., 2005). Memory and attention are highly interactive and interdependent processes, due to their functional association and their shared circuitry. Attention is composed of hierarchical sub-components. High in the attention taxonomy are complex attention abilities such as working memory, divided attention, and the ability to shift attention between different tasks (Sturm, Willmes, Orgass, & Hartje, 1997). To enhance attention performances throughout training, we repeatedly administered several attentional tasks in a hierarchy based on the model of Van Zomeren and Brouwer (1994), which highlights areas of strength and selectivity of attention.

2.2.1.2. *Training exercises.* Training exercises were programmed in Java (Release 1.4) and conducted on a Microsoft Windows-based computer with a 12-in. tactile screen and a resolution of 1.024×768 pixels. The stimuli were pictures belonging to various categories (e.g., animals, flowers, objects of everyday life) and common words pronounced by the computer. Each picture was 256×256 pixels in size. Responses to training tasks were given using a tactile screen, a standard keyboard (using only 2 keys), and a computer mouse. For attentional training, we used response time tasks to yes/no choice; for memory training, we used recognition memory tasks with forced choice.

Memory training task:

Visual recognition task (v-RM)—The task lasted five minutes. Participants started the exercise with a number of pictures to memorize that was adjusted according to their performance in a pre-training session. There were three variants. In variant 1 (V1), participants were asked to memorize pictures and recognize them immediately after their presentation among distractors. Participants had to respond by clicking on the recognized pictures. Variant 2 (V2) was identical to V1 but memorization and recognition were separated by a blank interval of 10, 20, or 30 s. Variant 3 (V3) was identical to V2 but a distractor (multiple-choice-questionnaire based on semantic knowledge) was introduced during the interval (10, 20, or 30 s). We determined the percentage of correct responses.

Visuospatial recognition task (vs-*RM)*—The task lasted five minutes. Participants started the exercise with a number of pictures to memorize that was adjusted according to their performance in a pre-training session. There were three variants. In variant 1(V1), participants had to memorize the position of identical pictures and recognize this layout among two proposals: one was the layout and the other not. Participants had to respond by clicking on the model. Variant 2 (V2) was identical to V1 but memorization and recognition were separated by a blank interval of 10, 20, or 30 s. Variant 3 was identical to V2 but the multiple-choice-questionnaire distractor was introduced during the interval (10, 20, or 30 s). We determined the percentage of correct responses.

Visual recognition Working Memory Training Task (v-RWM)—This task lasted five minutes. At the beginning of the task, participants had to memorize one picture and, in the next trial, they were asked to memorize a novel picture and then to click on the old picture. In the next trial, the new pictures became the old pictures. This procedure was repeated throughout the task. We determined the percentage of correct responses.

Attentional training task:

Visual Focused Attention Task (v-FA)—The task lasted three minutes. There were three variants. In variant 1 (V1), participants had to concentrate on the middle of the screen to detect a target picture. Pictures (50% distractor, 50% target) appeared one after the other in the middle of the screen. Participants had to press on a key: "enter" for yes, it is the target, and "esc" for no, it is not the target. Participants were instructed to respond as fast and as accurately as possible. Variant 2 (V2) was identical to V1 but pictures (50% distractor, 50% target) also appeared in the periphery of the screen. Participants were instructed to ignore these pictures, even if it was the target picture. Variant 3 (V3) was identical to V1 but the target was a category, i.e. animals. We determined the percentage of correct responses and the response time (s).

Visuospatial Focused Attention Task (vs-*FA*)—The task lasted three minutes. There were three variants. In variant 1(V1), pictures (50% distractor, 50% target) appeared one after the other on the left or the right of the screen. Participants had to press a key: "enter" for yes, it is the target, and "esc" for no, it is not the target. They were instructed to respond as fast and as accurately as possible. In variant 2 (V2), two pictures appeared at the same time, one of which was pointed to by an arrow. The participants had to respond if the picture pointed to by the arrow was the target picture or not. They were instructed to ignore pictures that were not pointed to by the arrow even if it was the target picture. We determined the percentage of correct responses and the response time (s).

Divided attention task—The task was limited to six trials. Variant 1 (V1) consisted in concurrently performing one auditory short-term memory task (words pronounced by the computer) and V1 of the v-FA task. The recognition test took place after the dual-task. The subject had to recognize pictures that corresponded to the words heard among distractors. Variant 2 (V2) was identical to V1 but with V2 of the v-FA task. Variant 3 (V3) was identical to V1 but with V3 of the v-FA task. We determined the percentage of correct responses for the auditory short term memory task and the percentage of correct responses and the response time (s) for the visual focus attention task. Modulated parameters and cognitive processes trained by each task are given in Table 2.

2.2.2. *Cognitive activities*

Patients assigned to the control group were administered cognitive activities consisting of exercises in which they were asked to find names of countries and corresponding capitals, organize a list of purchases in categories, find similarities and differences, choose a newspaper article and bar all the letters "A", read a text and then answer questions, or tell a story or construct a sentence from a list of words in disorder, etc. All control patients performed the same sets of activities sessions. For training sessions, the control group was assigned the same number, frequency, and duration of cognitive activities sessions as the trained group.

2.2.3. *Procedure*

Training or cognitive activities sessions were supervised by a trained neuropsychologist who gave the instructions and managed the execution time for each activity. Each session had the same structure including 1—a welcome and a reminder of what had been done at the previous session, 2—training with two cognitive exercises or two cognitively stimulating activities, 3—teaching of memory strategies that can be applied in daily demanding memory situations (e.g., store the objects in the same place, take notes, etc.), 4—information on the cognitive functioning and on the effects of aging on cognitive functioning, and 5—a conclusion with feedback on performances or activities session.

Training consisted of 24 sessions of approximately 1 h that involved a memory task and an attention task (detailed presentation in Table 3). Both memory and attention tasks were performed using the following schedule: (a) read general information: participants read information about trained memory or attention process, e.g., definitions, examples in everyday life; (b) read the instructions for the task to perform; (c) view an example of the task: subjects performed some trials in which no mistake is possible, (d) practice the task: participants performed some trials of the task and were informed when they made a mistake. This step is based on trial and error learning technique, and (e) perform the task: participants performed the task and were informed at the end about their performance. Training was individualized for each patient by the neuropsychologist who had the opportunity to increase or decrease the difficulty of each task by modulating parameters such as the duration of image presentation, the number of pictures or words to remember, the choice of the target, or the addition of a distractor. These parameters were adjusted by the neuropsychologist at the phases "view an example of the task" and "practice the task". As patients improved across sessions, these parameters were manipulated so that the tasks would continue to challenge their abilities but without putting them in distress because they failed. Because of the adjustment of the level of exigency and complexity of the training according to the skills of the patients and their progress during training, the performances were never inferior to 70% and the feedback was always positive.

2.3. *Outcome measures*

Outcome measures included neuropsychological tests investigating verbal and visual memory. Verbal memory was assessed by the forward and the backward digit-span test, the 12-word-list recall test from the BEM-144 memory battery (Signoret, 1991), the 16-item free and cued reminding test (16-FR/CR test) (Van der Linden et al., 2004), and the subscore recall of the MMSE. Visual memory was assessed by the visual recognition subtest from the Doors and People memory battery (Baddeley, Emslie, &

Table 2
Modulated parameters and cognitive processes trained for each task. Two types of modulated parameters can be distinguished: those that were invariant and distinguished the variants of a task, and those that varied between subjects for a variant. Thus, throughout training, parameters were adjusted to the cognitive level of the patients. For memory exercises, the variation of (i) the number of pictures permitted us to act on memory load according to the attentional cost of the task, (ii) the number of distractors played a key role in the resistance to interference, (iii) the duration of model presentation acted on the speed and the quality of information processing, and (iv) the time interval promoted information maintenance. For attention exercises, the choice of the target pictures served to modulate the similarity between the target and the distractors in order to favor information processes training tasks Modulated parameters Trained cognitive processes.

Training tasks	Modulated parameters	Trained cognitive processes
Visual recognition memory task (v-RM)	***Specific to each subject*** – Number of pictures – Duration of pictures presentation – Number of distractors in the recognition test – ***Specific to each variant*** – Time interval (s) (V1) – Distractor during the time interval (V2)	– Selective attention – Encoding – Encoding strategies – Short-term storage – Visual recognition memory processes – Sensitivity to interference – Semantic knowledge
Visuospatial recognition memory task (vs-RM)	***Specific to each subject*** – Number of pictures – Duration of model presentation – ***Specific to each variant*** – Time interval (s) (V1) – Distractor during the time interval (V2)	– Selective attention – Encoding – Encoding strategies – Short-term storage – Visuospatial recognition memory processes – Sensitivity to interference
Visual recognition working memory task (v-RWM)	***Specific to each subject*** – Number of pictures	– Visual recognition memory processes – Updating – Flexibility – Inhibition processes
Visual focused attention task (v-FA)	***Specific to each subject*** – Target picture – Target category – ***Specific to variants*** – Target pictures (V1) – Target categories (V2) – Distractor pictures in the periphery (V3)	– Visual focus – Speed of processing – Inhibition processes – Resistance to the distraction – Categorization – Flexibility
Visuospatial focused attention task (vs-FA)	***Specific to each subject*** – Target picture ***Specific to each variant*** – Picture indicated by an arrow (V2)	– Visuospatial focus – Speed of processing – Inhibition processes – Alertness – Resistance to the distraction – Flexibility
Divided attention task (DA)	In addition to modulated parameters involved in the v-FA task: ***Specific to each subject*** – Number of words to memorize	In addition to cognitive processes involved in the v-FA task: – Allocation of attentional resources – Working memory – Short-term auditory memory – Recognition memory processes – Strategies to improve auditory memory

Nimmo-Smith, 1994), the DMS48 test (Barbeau et al., 2004), which is a delayed matching-to-sample task designed to assess visual recognition memory, and the recall of the Rey–Osterrieth Complex Figure (Rey, 1959).

2.4. Experimental design

All participants attended 24 individual 60-min sessions of training, 2 times per week for 12 weeks. The training and cognitive activities sessions took place in our laboratory. The effect of training and cognitive activities was assessed by comparing outcome measures in pre- and post-tests 15 days before (t0) and after (t1) training. To evaluate the maintenance of training benefits over time, a follow-up test session (t2) was performed 6 months after training or cognitive activities. Three trained neuropsychologists were involved in the study: one administered and scored the pre-tests, post-tests, and follow-up tests (this person was kept blind to the group membership of patients), one supervised training, and one supervised cognitive activities. Parallel versions were used at post-test and follow-up test for the 12-word-list recall test, the 16-item free and cued reminding test, and the MMSE (the list of words differed and semantic categories changed).

2.5. Statistical analysis

The STATISTICA 7.0 package (StatSoft, Inc.) and STATVIEW 5.0 package (SAS Institute Inc.) were used for data analysis. Training data were analyzed by repeated measures ANOVA for each variant that included Session as repeated factor. Correlation analyses (Pearson correlations) were carried out to investigate the relationship between the percentage of correct responses and the time interval in attention tasks. To evaluate the effect of training, neuropsychological test mean scores of the trained group were compared to those of control group at t0 (pre-test), t1 (post-test), and t2 (6-months follow-up) through an ANOVA with repeated measures that included Testing as repeated factor, followed by the post-hoc Newman–Keuls *t*-test with the Bonferroni correction for the significant effects. For the three free recall sessions of the 16-item free and cued reminding test, we performed repeated measures ANOVA for each test, i.e. t0, t1, and t2, including Free Recall as repeated factor to compare performances between the two groups. Effect sizes were calculated using η_p^2. Following Cohen (1988), η_p^2 above 0.01 reflects a small effect, above 0.06 a medium effect, and above 0.14 a large effect.

3. Results

3.1. Performances of training sessions

We postulated that training must generate ongoing cognitive dynamics that required continuous effort by the patient to be effective. Thus, parameters were manipulated so that training tasks would continue to challenge each patient's abilities without

Table 3
Organization of training. Training consisted of 24 training sessions. Memory and attention processes were concurrently stimulated. Each session included an attention task, either visual focused attention (v-FA), visuospatial focus attention (vs-FA), or divided attention (DA), and a memory task, either visual recognition memory (v-RM), visuospatial recognition memory (vs-RM), or visual recognition working memory (v-RWM). Training of memory promoted stimulation of visual and visuospatial modalities alternatively by using an adaptation of the spaced retrieval method. During these exercises, patients were encouraged to use mnemonic strategies like verbalization, association of ideas, and mental imagery. Training of attention was based on a specific approach that considered the sub-components of attention as being distinct, hierarchical, and independent. In this context, the hierarchical order was based on the theoretical model of Van Zomeren and Brouwer (1994), highlighting the intensity and selectivity axes of attention. With regard to the selectivity axis, we articulated our training on selective attention, divided attention, and working memory. For each hierarchical step of the selectivity axis, hierarchical steps of the intensity axis were embedded, i.e. alertness, vigilance, and sustained attention. Such hierarchies have been successfully used by Sturm et al. (1997) in the training of attention only. For the training of memory and attention components, the levels of exigencies and complexity were constantly adapted to the patients' progress during training. The advantage of using this procedure was suggested by Strache (1987) and was highlighted in the work of Sturm et al. (1997).

Sessions	Attention tasks	Variant	Memory tasks	Variant
1	v-FA	1	v-RM	1
2	v-FA	1	v-RM	1
3	vs-FA	1	vs-RM	1
4	vs-FA	1	vs-RM	1
5	v-FA	1	v-RM	2
6	DA	1	vs-RM	2
7	DA	1	v-RWM	
8	vs-FA	1	v-RWM	
9	v-FA	2	v-RM	2
10	v-FA	2	v-RM	2
11	DA	1	vs-RM	2
12	vs-FA	2	vs-RM	2
13		2	v-RWM	
14	v-FA	3	v-RWM	
15	DA	2	v-RM	3
16	DA	2	v-RM	3
17	vs-FA	2	vs-RM	3
18	v-FA	3	vs-RM	3
19	v-FA	3	v-RWM	
20	DA	3	v-RWM	
21	vs-FA	2	v-RM	3
22	vs-FA	2	v-RM	3
23	DA	3	vs-RM	3
24	DA	3	vs-RM	3

putting them in distress or causing them to fail. Examples of the evolution of the parameters manipulated are illustrated in Fig. 1A. The number of pictures to memorize during the training of the visual recognition task increased for V1, V2, and V3 (Fig. 1A1) for training performances (% of correct responses) between 85 % and 95% (data not shown). Similarly, the number of distractors in the recognition test increased (Fig. 1A2) for V1, V2, and V3 for the same range of performance. In the same way, the number of words memorized during the training of auditory memory increased in both the single (Fig. 1A3) and dual task situation (Fig. 1A4) for training performances (% of correct responses) respectively between 100% and 90–96% (data not shown). These data show that patients with MCI are able to maintain a high level of performance despite the increased mental load. Thus, participants improved their memory abilities during training.

Recall that to customize training, parameters were specifically adjusted to the cognitive level of the patient. Consequently, the evolution of training performances lies in a narrow range, and a stabilized performance should be interpreted as an improvement of the cognitive component trained since the complexity of the training was gradually adjusted according to the skills of the patients and their progress. An example is provided with the training of focalized attention. Performances are illustrated in Fig. 1B. In this task, we asked the subjects to respond as quickly as possible: yes, it is the target, or no, it is not the target. Since the subjects had to respond correctly and quickly, training consisted in finding a compromise between response accuracy, indicated by the percentage of correct responses (respectively for the visual and the visuospatial focalized attention: Figs. 1B1 and 1B2), and the speed at which the subject answered, indicated by the response times (respectively for the visual and the visuospatial focalized attention: Figs. 1B3 and 1B4). Repeated measures ANOVA on the percentage of correct response for the visual focalized attention showed a significant effect of Session for V1 [$F(2, 20)=3.51$, $p=0.05$; $\eta_p^2=0.26$] but no effect for V2 and V3 (respectively, [$F(1, 10)=2.94$, $p=0.117$; $\eta_p^2=0.22$, $F(2, 20)=1.42$, $p=0.265$; $\eta_p^2=0.12$]) (Fig. 2A). The post-hoc Newman–Keuls *t*-test ($p<0.05$) on V1 indicated that training performances on session 5 differed from those on sessions 1 and 2. The same analysis on the mean response times revealed a significant effect of Session for V1 and V2 (respectively, [$F(2, 20)=10.063$, $p=0.0001$; $\eta_p^2=0.50$], [$F(1, 10)=13.913$, $p=0.003$; $\eta_p^2=0.72$]), but no effect for V3 [$F(2, 20)=3.050$, $p=0.069$; $\eta_p^2=0.23$] (Fig. 2C). The post-hoc Newman–Keuls *t*-test ($p<0.05$) for V1 indicated that training performances on session 1 differed from those on sessions 2 and 5. Repeated measures ANOVA on the percentage of correct response for the visuospatial focalized attention revealed no effect of session for V1 [$F(2, 20)=0.30$, $p=0.741$; $\eta_p^2=0.03$] but a significant effect for V2 [$F(4, 40)=5.99$, $p=0.0001$; $\eta_p^2=0.37$] (Fig. 2B). The post-hoc Newman–Keuls *t*-test ($p<0.05$) indicated that training performances on session 12 differed from those of the next sessions. The same analysis on the mean response times showed no effect of Session for V1 [$F(2, 20)=2.829$, $p=0.082$; $\eta_p^2=0.22$] but a significant effect for V2 [$F(4, 40)=11.735$, $p=0.0001$; $\eta_p^2=0.54$] (Fig. 2D). The post-hoc Newman–Keuls *t*-test ($p<0.05$) indicated that training performances on sessions 17, 21, and 22 differed from those on sessions 12 and 13.

Correlation analyses showed a significant negative correlation between the percentage of correct responses and response times whatever the modality (visual vs. visuospatial) and the variant considered, V1–V3 ($r=-0.465$, $p=0.005$; $r=-0.377$, $p=0.029$; $r=-0.423$, $p=0.013$ respectively from variants 1–3 of the visual focused attention task and $r=-0.470$, $p=0.005$; $r=-0.759$, $p=0.0001$ respectively for variants 1 and 2 of the visuospatial focused attention task). Thus, as the percentage of correct responses increased, the response times decreased, suggesting improved attentional focus and processing speed over training.

Participants improved in all training tasks except for the visuospatial recognition memory task, which failed to train this modality of memory. For this task, it seems that training was too short to achieve positive results.

3.2. Performances on recognition and recall after training

Results are presented in Table 4. At pre-test (t0), the two groups did not differ significantly in memory neuropsychological test scores (see Table 4, t0 column; Newman–Keuls *t*-test, $p<0.05$).

3.2.1. Training effects on recognition

The *doors recognition subtest* of the doors and people battery were enhanced for both set A and B (set A: group effect [$F(1, 20)=7.534$, $p=0.012$; $\eta_p^2=0.27$]; testing effect [$F(2, 40)=1.990$, $p=0.149$; $\eta_p^2=0.09$]; group × testing interaction [$F(2, 40)=3.483$, $p=0.040$; $\eta_p^2=0.15$]; set B: group effect [$F(1, 20)=2.669$, $p=0.117$; $\eta_p^2=0.11$]; testing effect [$F(2, 40)=3.748$, $p=0.032$; $\eta_p^2=0.16$]; group × testing interaction [$F(2, 40)=4.387$, $p=0.019$; $\eta_p^2=0.18$]). The post-hoc Newman–Keuls *t*-test ($p<0.05$) showed that the

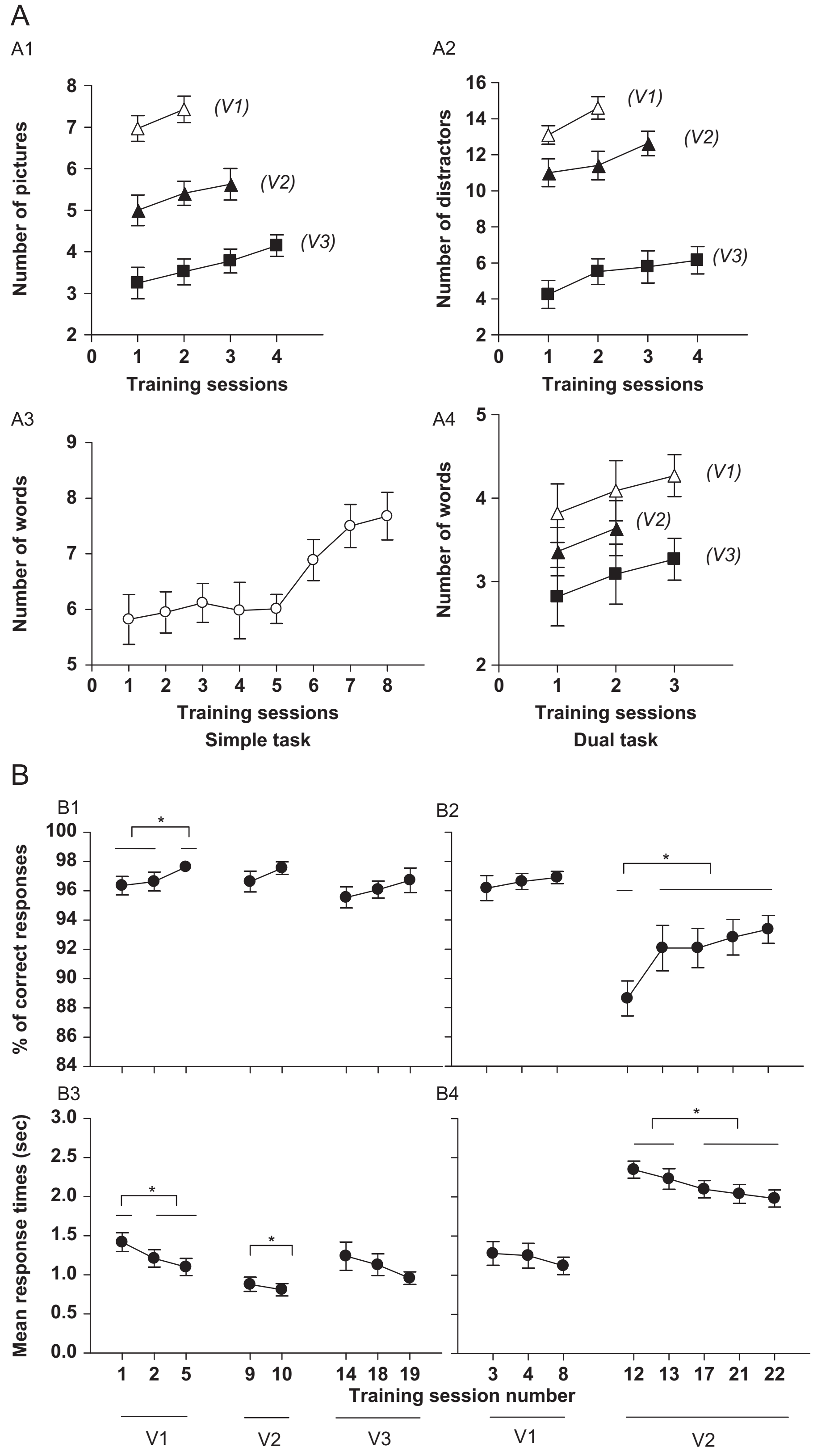

Fig. 1. Examples of the evolution of (A) manipulated parameters and (B) performances during training: (A) Number of pictures (A1) and distractors (A2) used respectively during memorization and recognition of the visual recognition task for each variant: V1 (empty triangles), V2 (solid triangles), and V3 (solid squares). Number of words used during auditory memory task respectively when the task was performed alone, simple task (A3, empty circles) and when the task was performed with attention task, dual task (A4), for each variant: V1 (empty triangles), V2 (solid triangles), and V3 (solid squares). (B) Results from focalized attention tasks. (B1) Percentage of correct responses and (B3) mean response times of the visual focalized attention task for the 3 variants (V1, V2, and V3). (B2) Percentage of correct responses and (B4) mean response times of the visuospatial focalized attention task for the 2 variants (V1 and V2). Note that the session number informs on the temporal location of each exercise during training. *Newman–Keuls *t*-tests, 5%, of the Session. Scatter plots with regression line between the percentage of correct responses and the response times of respectively the visual focalized attention task (*E*) and the visuospatial focalized attention task (*F*). *$p<0.05$, **$p<0.01$, ***$p<0.001$. Error bars represent SEM.

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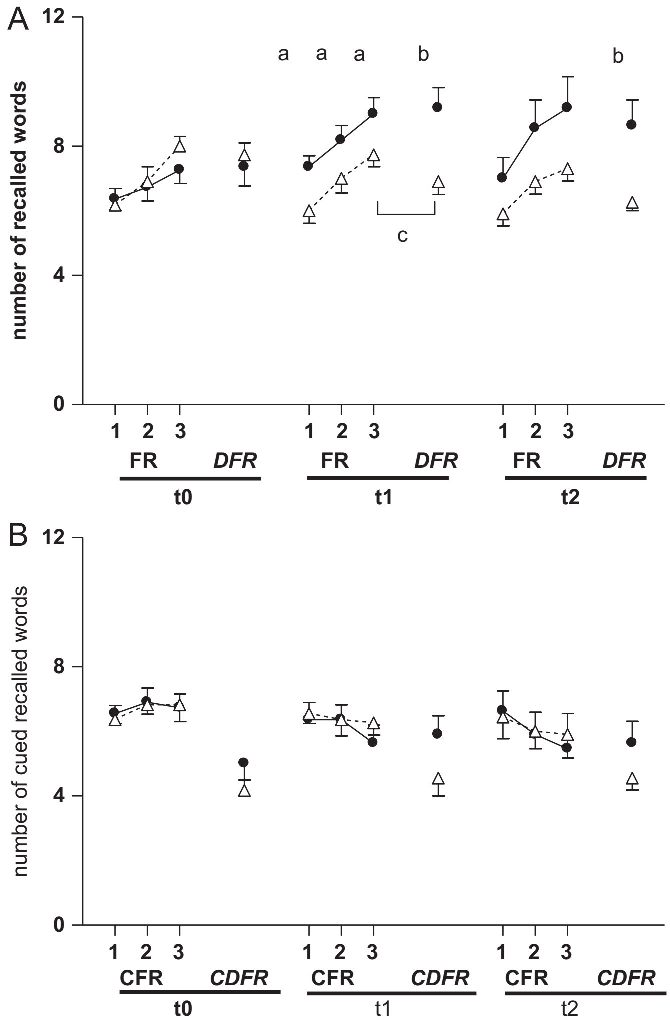

Fig. 2. Three free (A) and three cued (B) recall sessions of the 16-item free and cued reminding test. [a]Newman–Keuls *t*-tests, 5%, of the group × testing (t0, t1,t2) interaction; [b]Newman–Keuls *t*-tests, 5%, of the group × free recall (FR1, FR2, FR3) interaction for t1; [c]Newman–Keuls *t*-tests, 5%, of the group × free recall (FR3, DFR) interaction for t1. FR: free recall, DFR: delayed free recall, CFR: cued free recall, CDFR: cued delayed free recall. t0: pre-test, t1: post-test, t2: 6-month follow-up test (triangle = control, circle = trained). Error bars represent SEM.

Table 4
Mean scores and SEM for the cognitive outcome measures for control and trained groups at pre-test (t0), post-test (t1), and 6-month follow-up test (t2).

	Groups	Pre-test t0	Post-test t1	6-Month follow-up t2
Recognition		Mean ± SEM	Mean ± SEM	Mean ± SEM
Doors recognition subtest (*doors and people battery*)				
Set A/12	Control	7.45 ± 0.59	7.64 ± 0.47	7.18 ± 0.50
	Trained	8.18 ± 0.62	9.64 ± 0.53[a]	8.55 ± 0.39[a]
Set B/12	Control	4.82 ± 0.44	4.64 ± 0.45	4.27 ± 0.38
	Trained	4.91 ± 0.41	6.36 ± 0.66[a]	5.36 ± 0.45
DMS48 test (set 1): recognition score (%)				
	Control	92.91 ± 1.75	90.82 ± 1.56	85.60 ± 3.40
	Trained	91.09 ± 1.02	96.91 ± 0.58[a]	93.27 ± 2.53
Working memory				
Digit span test				
Forward condition	Control	4.36 ± 0.24	4.18 ± 0.12	3.91 ± 0.21
	Trained	4.45 ± 0.31	4.91 ± 0.21[a]	4.92 ± 0.23[a]
Backward condition	Control	3.82 ± 0.18	3.64 ± 0.20	3.45 ± 0.16
Trained	3.36 ± 0.24	4.00 ± 0.19	3.82 ± 0.18	
Recall				
BEM-144 12-word-list recall test				
Total recall score	Control	6.40 ± 0.46	6.05 ± 0.25	5.50 ± 0.32
	Trained	6.23 ± 0.35	7.28 ± 0.26[a]	6.86 ± 0.52[a]
16-Item free and cued reminding test				
Total score/48	Control	41.09 ± 0.44	39.91 ± 0.44	38.45 ± 1.53
	Trained	40.55 ± 0.41	42.91 ± 0.76[a]	41.82 ± 1.22
MMSE-recall of the 3 words				
Control	1.82 ± 0.24	1.55 ± 0.22	1.64 ± 0.26	
Trained	1.73 ± 0.20	2.45 ± 0.17[aa]	2.09 ± 0.22[a]	
Recall of Rey's complex figure/36				
	Control	11.86 ± 1.27	10.23 ± 0.87	9.73 ± 1.05
	Trained	10.09 ± 1.52	10.45 ± 1.36	10.14 ± 1.16

[a] Post-hoc Newman–Keuls *t*-test ($p < 0.05$) of the group × testing interaction.

trained group had better performances than the control group at both t1 and t2 for set A and only at t1 for set B.

The recognition score of the *DMS48* was also improved (group effect [$F(1, 20)=3.035$, $p=0.096$; $\eta_p^2=0.13$]; testing effect [$F(2, 40)=2.964$, $p=0.063$; $\eta_p^2=0.17$]; group × testing interaction [$F(2, 40)=3.858$, $p=0.029$]; $\eta_p^2=0.18$). The trained group improved performances at t1 (post-hoc Newman–Keuls *t*-test, $p < 0.05$). Note that at 6 months, differences did not reach significance, due to greater intra-group variability.

That the improvement persisted for set A at t2 suggests training had a strong effect on recognition. However, this effect needs to be consolidated concerning set B and DMS48.

3.2.2. Training effects on digit span

The *forward digit span* was improved in the trained group compared to control group over the three test sessions (Repeated measures ANOVA: group effect [$F(1, 20)=7.526$, $p=0.012$; $\eta_p^2=0.21$]; Testing effect [$F(2, 40)=0.283$, $p=0.754$; $\eta_p^2=0.05$]; group × testing interaction [$F(2, 40)=3.765$, $p=0.036$; $\eta_p^2=0.14$]). The post-hoc Newman–Keuls *t*-test ($p < 0.05$) indicated that the trained group improved their span at t1 and t2, showing that training preserved performances 6 months later. No effect of training was seen for the *backward digit span*.

3.2.3. Training effects on recall

The total score of the *BEM-144 12-word-list recall test* was improved in the trained group (repeated measures ANOVA: group effect [$F(1, 20)=5.582$, $p=0.028$; $\eta_p^2=0.22$]; Testing effect [$F(2, 40)=2.858$, $p=0.063$; $\eta_p^2=0.13$]; group × testing interaction [$F(2, 40)=5.085$, $p=0.011$; $\eta_p^2=0.20$]). The post-hoc Newman–Keuls *t*-test ($p < 0.05$) showed that the trained group improved performances at both t1 and t2, indicating training improved recall.

The total score of the *16-item free and cued reminding test* was higher in the trained group than the control group (repeated measures ANOVA: group effect [$F(1, 20)=5.165$, $p=0.034$; $\eta_p^2=0.22$]; testing effect [$F(2, 40)=1.176$, $p=0.318$; $\eta_p^2=00.13$]; group × testing interaction [$F(2, 40)=3.381$, $p=0.044$; $\eta_p^2=0.20$]). The post-hoc Newman–Keuls *t*-test ($p < 0.05$) indicated that, compared to the control group, the trained group improved its recall at t1, but this was not significant at t2. The score for the three free recalls are presented in Fig. 2A. Repeated measures ANOVA on data at t0 revealed that the two groups increased their score over the three free recalls (free recall effect [$F(2, 40)=12.324$, $p < 0.0001$; $\eta_p^2=0.38$]) in the same way (group effect [$F(1, 20)=0.231$, $p=0.635$; $\eta_p^2=0.01$]; group × free recall interaction [$F(2, 40)=1.369$, $p=0.265$; $\eta_p^2=0.06$]). At t1, the trained group had better performances than the control group (group effect [$F(1, 20)=5.191$, $p=0.033$; $\eta_p^2=0.20$]). Although the two groups started at different levels, performances improved over the three free recalls (Free Recall effect [$F(2, 40)=46.561$, $p < 0.0001$; $\eta_p^2=0.69$]) in the same proportion for both groups (group × free recall interaction [$F(2, 40)=0.136$, $p=0.873$; $\eta_p^2=0.07$]). Post-hoc analyses indicated that the increase in free recall in the trained group started at the first free recall and was maintained throughout the two subsequent free recalls. At t2, free recall was always higher in the trained group but the enhancement did not reach statistical difference, due to increased variability in the trained group relative to the control group. The scores for the three cued free recall tests are presented in Fig. 2B. Data showed that the number of cued recalled words was similar for the two groups whatever the test (t0, t1, or t2), suggesting that training had no effect on cueing. Regarding the delayed free recall (Fig. 2A) and the cued delayed free recall (Fig. 2B) for t0, t1, and t2, we found, as for free recall, that training improved delayed free recall but not cueing (group effect [$F(1, 20)=7.478$, $p=0.012$; $\eta_p^2=0.27$]; testing effect [$F(2, 40)=0.853$, $p=0.433$; $\eta_p^2=0.04$]; group × testing interaction [$F(2, 40)=5.052$, $p=0.011$; $\eta_p^2=0.20$] for the delayed free recall and Group effect [$F(1, 20)=0.170$, $p=0.685$; $\eta_p^2=0.01$]; testing effect [$F(2, 40)=3.386$, $p=0.105$; $\eta_p^2=0.05$]; group × testing interaction [$F(2, 40)=1.07$, $p=0.360$; $\eta_p^2=0.02$] for the cued delayed free recall). The beneficial effect of training seemed greater in delayed free recall than in free recall, since performances were still enhanced at t2 in delayed free recall (Fig. 2A) for the trained group, but not in total free recall. Then, to assess whether there was any performance gain between the last free recall and delayed free recall, a repeated measures ANOVA was performed on the third free recall and the delayed free recall for t1 and t2 (Fig. 2A). For t1, the analysis showed recall was better maintained in the trained group than in the control group (group effect [$F(1, 20)=26.406$, $p<0.0001$; $\eta_p^2=0.38$]; free recall effect [$F(1, 20)=0.363$, $p=0.553$; $\eta_p^2=0.02$]; group × free recall interaction [$F(1, 20)=5.806$, $p=0.025$; $\eta_p^2=0.19$]). The post-hoc Newman–Keuls *t*-test ($p<0.05$) indicated that the control group performed worse on delayed free recall than on the third free recall whereas the trained group maintained its performance. For t2, statistical analysis did not reach significance, due to the increased variability in the training group.

The recall of the three words of the *MMSE* (Table 4) was improved in the trained group (group effect [$F(1, 20)=7.646$, $p=0.012$; $\eta_p^2=0.28$]; testing effect [$F(2, 40)=1.416$, $p=0.254$; $\eta_p^2=0.06$]; group × testing interaction [$F(2, 40)=4.703$, $p=0.014$; $\eta_p^2=0.19$]). The post-hoc Newman–Keuls *t*-test ($p<0.05$) showed that the trained group performed better than the control group at both t1 and t2.

No effect was found for the recall of *Rey–Osterrieth Complex Figure*, suggesting that our training did not have any effect on visuoconstruction abilities.

4. Discussion

Our study revealed a positive effect of a computer-based memory and attention training program in subjects with A-MCImd. Interestingly, although only recognition was trained, both recognition and recall processes were improved, indicating a transfer of the training benefits between different mechanisms, recognition vs recall. This promising result may serve to delay cognitive decline in the pre-clinical stage of AD since recall is one of the core cognitive impairments. In this line, Rozzini et al. (2007) showed that CT combined with anticholinesterase inhibitor therapy induced more cognitive benefits than pharmacological treatment alone. Thus, the effect of training may be potentiated by the combination of a non-medicinal treatment and medication. This combination could be promising for preventing dementia. Surprisingly, despite the challenge, few studies have been conducted on the effect of CT in MCI subjects at risk of developing AD. Training of memory only has resulted in limited improvement (Troyer et al., 2008). In contrast, multidomain computer-based CT can significantly improve most cognitive functions, e.g., learning (Günther, Schäfer, Holzner, & Kemmler, 2003), behavioral memory (Cipriani et al., 2006), episodic memory and abstract reasoning (Rozzini et al., 2007), and long-term visual spatial memory (Talassi et al., 2007). However, these studies used a combination of several interventional approaches, which makes interpretation of results and comparison between studies difficult.

4.1. Beneficial effects on recognition

In the present study, the increased scores on neuropsychological tests assessing recognition might be expected since the CT program was exclusively based on recognition. However, note that according to dual processes models, recognition memory is supported by the dissociable processes of recollection and familiarity. Familiarity is thought to be spared in normal aging whereas recollection is not. The rare studies on this subject in patients with AD suggest the impairment of memory is due to deficits in both recollection and familiarity (Smith & Knight, 2002). Studies on A-MCI reported an impairment of recollection processes (Serra et al, 2010). Regarding familiarity, the data are conflicting. Some reported a preservation of familiarity (Anderson et al., 2008; Serra et al., 2010; Westerberg et al., 2006), while others reported an impairment (Ally, Gold, & Budson, 2009; Wolk, Signoff, & Dekosky, 2008). We previously showed that impairment of familiarity could depend on the nature of the modality tested i.e. visual or visuospatial (Alescio-Lautier et al., 2007). It has been suggested that the impairment of familiarity depends on the MCI subtype. Indeed, deficits were reported in A-MCImd (Ally et al., 2009; Wolk et al., 2008) but not in A-MCI single domain (Anderson et al., 2008; Serra et al., 2010). Since patients were A-MCImd in the current study, the positive effects we observed after CT based on familiarity forced-choice procedure suggest that there is still sufficient cerebral plasticity linked to this process to allow training.

Our results support the hypothesis of Westerberg et al. (2006) that enthorinal, perirhinal, and parahippocampal cortices are partially damaged but can nonetheless continue to support familiarity in A-MCI. Recent works suggested that sparing of familiarity is associated with a compensatory increase in perirhinal activity (Daselaar, Fleck, Dobbins, Madden, & Cabeza, 2006). Thus, it is likely that the CT, which focused on familiarity, increased compensatory perirhinal activities and consequently enhanced A-MCImd patients' performances. Particularly note that training using a familiarity procedure can enhance performance in a task that involves recollection. This was the case for set B of the Doors and People test. This set, in contrast to set A, could not be resolved on the basis of only familiarity. It also requires recollection processes (Holdstock, Gutnikov, Gaffan, & Mayes, 2000). According to this assumption, the improved performance in set B showed that our recognition training procedure was able to promote better recognition even though it requires, in addition to familiarity, recollection processes.

Attention training with the visual focused attentional tasks improved information processing, as shown by the decreased reaction time in the training tasks while the percentage of correct response increased (Fig. 1B1, B3). This effect was probably due to perceptual facilitation and better ability to detect details throughout the training. Thus, the increased recognition in set B of the Doors and People test in trained A-MCImd could also reflect better information extraction when similarity between target and distractors were increased. Indeed, set B is based on processing, which involves a large investment in attentional focus and selectivity and speed of information processing. Distractors are highly similar in color and form; to recognize the target door, one must be able to fully and promptly analyze the image.

4.2. Beneficial effects on digit span

Higher scores were found in the forward digit span test in trained MCI relative to controls. This effect could come from the progressive increase in CT of the number of pictures or words to memorize. In contrast, scores were not improved in the backward digit span test, which requires active memory processing in addition to immediate storage. We interpret this lack of improvement as an absence of transfer of the benefits of training from recognition to recall when the task is in working memory.

4.3. Beneficial effects on recall

Recall processes were improved in trained MCI. Remember that the CT program was exclusively based on recognition. Since recall was not trained, there was a generalization from recognition to recall processes. Interestingly, recall was improved for short- and long-term processes in trained A-MCImd.

Improvement of short-term retrieval processes in trained A-MCImd was shown by the increased scores in free recall. This is likely due to a deeper encoding through various strategies such as verbalization and association of ideas. In contrast, the lack of enhancement of cued recall suggests that training acts more on encoding than on retrieval processes.

Improvement of long-term retrieval processes in trained A-MCI-md was shown by the increased scores in delayed recall of the 16-item free and cued reminding test. Note that CT was mainly based on short-term memory training. Thus, it is likely that the enhancement of delayed recall could be explained by the use of the spaced retrieval method (Laudauer & Bjork, 1978), which promoted the maintenance of information. Belleville et al. (2006) reported improved delayed free recall of lists of words after 2-month multifactorial cognitive training. In this case, training was conducted in groups and focused on teaching episodic memory strategies such as visual imagery abilities, face-name associations, method of loci, and verbal organization like categorization and hierarchization. Note that delayed free recall is improved after many types of interventions: group or individual training, and training based on memory strategies or recognition processes. Because of the differences between the training by Belleville et al. (2006) and our training, it is likely that the positive effect was sustained by different cognitive mechanisms and consequently by different cerebral substrates.

4.4. Long-term beneficial effects

We found that improved recognition or recall lasted at least 6 months after training, suggesting a resistance to memory decline in A-MCI-md. This result supports the idea that CT could favor compensation mechanisms. However, note that memory performances become vulnerable in the absence of training, as shown by the increased variability in some scores. This leads us to think that, as the disease progresses, compensatory mechanisms established during training decline thereafter, resulting in lower cognitive performance. If patients do not sustain training, the transfer gains dissipate over time. This means that longer training could enhance or maintain training-related cognitive benefits over time and could generate a greater resistance to cognitive decline in A-MCI-md patients. Few studies have evaluated the maintenance of training. Long-term studies in healthy older subjects suggested that the positive effect of training is enduring. Willis et al. (2006) reported positive functional benefits at 5-year follow-up. Such long delays have not been tested in subjects with MCI. For this population, Rozzini et al. (2007) reported benefits in episodic memory at 3-month follow-up in a combined CT and medication treatment group compared with the medication-only and no treatment control group. To conclude, the beneficial effects we found on episodic recall at 6-month follow-up are encouraging, but future studies should fully document the long-term efficacy of CT in subjects with MCI and the impact on conversion to dementia.

4.5. Conclusion and prospects

Our results showed cognitive training improved episodic recall, one of the memory components in the core cognitive impairment in MCI patients at risk of converting to AD. These data are promising in view of developing training methods to delay cognitive decline in A-MCI patients. However, many points remain to optimize the effects of training. In particular, the training tasks that best predict improvement should be determined. We believe that the simultaneous training of memory and attention is an important parameter that may explain the beneficial effects of training. However, we are not able to specify whether the positive effects are the result of a particular memory and attention training task, or of several, or all. Note that parameters were manipulated so that training tasks would continue to challenge each patient's abilities throughout training. In our opinion, this is a prerequisite to promote the effects of training but, in retrospect, we may have applied this rule too frequently. It might have been more appropriate to promote stabilization of training performance, i.e. increase the repetition of the exercise without modifying parameters, before increasing the level of difficulty. We could probably give more power to training. Moreover, longitudinal and imaging studies should be conducted in particular on the long-term maintenance of the benefits of training, which may reflect a persistent change in the cerebral substrates involved. Finally, future research should focus on the effects of such training on participants' quality of life. Another group of A-MCImd patients who completed the same cognitive training as that presented in this study reported a positive impact on their self-esteem measured by the Rosenberg Self-Esteem scale (data not shown). It would be of particular interest to evaluate the effects of such interventions on objective measures collected in an ecological framework.

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