

Improvement of Episodic Memory in Persons with Mild Cognitive Impairment and Healthy Older Adults: Evidence from a Cognitive Intervention Program

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Key Words

Cognitive intervention • Memory training • Mild cognitive impairment • Episodic memory • Alzheimer's disease • Normal aging

Abstract

The efficacy of cognitive training was assessed in persons with mild cognitive impairment (MCI) and persons with normal cognitive aging. Forty-seven participants were included in this study: 28 with MCI and 17 controls. Twenty-one participants received intervention (20 MCI and 9 controls) and 16 participants (8 MCI and 8 controls) received no intervention (waiting-list group). The intervention focused on teaching episodic memory strategies. Three tasks of episodic memory (list recall, face-name association, text memory) were used as primary outcome measures. Results were analyzed using analyses of variance. The intervention effect (pre- and post-intervention difference) was significant on two of the primary outcome measures (delayed list recall and face-name association). A significant pre-post-effect was also found on measures of subjective memory and well-being. There was no improvement in the performance of groups of individuals with MCI and normal elderly persons

who did not receive the intervention. These results suggest that persons with MCI can improve their performance on episodic memory when provided with cognitive training.

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Introduction

Mild cognitive impairment (MCI) is characterized by memory complaints and impaired performance on memory tasks in older persons. These deficits occur in the face of preserved general cognitive function, an absence of significant functional repercussions and an absence of dementia [1]. MCI is common in older persons, with a prevalence of between 3 and 19% in the general population of older adults. Although persons with MCI do not meet the criteria for dementia, 20–50% of these persons will develop dementia over a period of 2–3 years [1, 2]. This is far greater than the conversion rate observed in the normal population (1–5% per year), or even in a population of persons who complain about their memory, but do not have memory deficits (0.3–6% per year). Hence, MCI appears to capture a group of individuals in a transitional state between normal aging and Alzheimer's disease (AD).

There are many reasons to believe that the provision of cognitive intervention may be crucial for persons with MCI. First, the initial wave of clinical trials for symptomatic drug treatment has been unsuccessful [3]. Thus, the management of MCI cognitive symptoms remains a critical and unresolved issue. Cognitive interventions may have strong potential if found effective, both as a single management strategy, and when combined with pharmacological treatment. In addition, the state of MCI is accompanied by feelings of depression and irritability [4]. The benefit is thus likely to be paramount for the quality of life of these individuals.

There are also reasons to believe that cognitive intervention may be successful in persons with MCI. Episodic memory training programs typically rely on the teaching of mnemonics and/or semantic elaboration procedures, which provide rich and distinctive encoding that promotes later recall [5]. The results generally indicate positive and lasting effects of intervention [6–16] in healthy older adults. Based on meta-analyses of the existing data, the average effect size (d') of memory intervention effects in normal older adults is large (about 0.7) on objective memory measures [16] and moderate (about 0.2) on subjective memory measures [17].

Only three studies have tested the efficacy of cognitive interventions in persons with MCI. One study reported positive intervention effects in 19 persons with MCI who were enrolled in computer-assisted training that targeted multiple cognitive processes [18]. Unfortunately, the study did not include a group that did not receive intervention. As a result, it is difficult to judge whether the positive effect was due to the intervention alone or to a practice effect on the cognitive outcome measures. When using a randomized trial with 9 persons with MCI treated with memory intervention and an additional 9 in a waiting list condition, Rapp et al. [19] found positive intervention effects on subjective measures of memory, but not on objective ones. Thus, the intervention alleviated the subjective complaints related to the MCI condition but did not succeed in actually increasing these individuals' memory capacities. However, it is important to note that the intervention used in the latter study was likely not optimal for unveiling intervention effects [16].

In a recent study, Olazaran et al. [20] completed a well-designed randomized controlled trial of a cognitive-motor simulation program in 72 persons with AD and 12 persons with MCI, all of whom were also treated with cholinesterase inhibitors. Patients in the intervention group maintained their cognitive status at month 6

through the intervention, whereas those in the non-treated group had declined. Unfortunately, the paper did not separate the data for participants with MCI and AD. Furthermore, the authors chose not to correct for multiple comparisons, which increases the risk of Type 1 error. Finally, it is important to note that the intervention did not incorporate strategy training, but involved stimulating cognition through various exercises.

In sum, there are reasons to believe that cognitive intervention can be both beneficial and successful in individuals with MCI, but there is clearly a need for additional data.

Cognitive intervention programs focus on the processes or functions that are impaired in the target population while building upon remaining capacities and strengths. Cross-sectional studies of cognition in MCI have indicated that episodic memory and control of attention are the cognitive components which are most severely impaired in this population [2, 21–25]. Thus, interventions should be designed to help individuals with MCI to develop and maintain efficient episodic memory encoding and retrieval strategies while supporting their attentional abilities. Developing efficient memory strategies in MCI can be done by relying on their semantic knowledge and visual imagery capacities, which are relatively well-preserved.

The major goal of this study was to assess the feasibility and potential efficacy of a 2-month multifactorial cognitive training intervention that specifically addresses the episodic memory deficit of persons with MCI and that includes components to optimize the efficacy of intervention in populations of older adults. The intervention program used here was modeled in part after that of Stigsdotter and Bäckman [7] and Yesavage et al. [8].

The intervention was multifactorial. First, it involved the training of both attention and episodic memory. The attentional training employed here was similar to that used by Kramer et al. [26] and that of Baron and Mattila [27]. Second the program was multifactorial in that different mnemonics were taught that could be applied to various materials and learning conditions. Third, the program includes other features, such as taking into account self-efficacy [28, 29], teaching individuals to form imagery-based associations and invoking stress management procedures. Lachman et al. [30] have shown that training on attitudes toward memory, in addition to memory training, increases the sense of control that participants have over their memory capacities. In addition, memory interventions that include relaxation and/or training on mental imagery are more effective in improv-

ing performance than memory interventions alone [8, 31].

Our primary outcome measure assessed proximal tasks by measuring the intervention effect on experimental tasks that were amenable to the technique taught during training. Distal generalization was assessed with secondary outcome measures that included a measure of subjective memory complaints that addressed various components of daily life, as well as a measure of well-being. To optimize generalization of the intervention effects outside of the laboratory (i.e., distal generalization), we incorporated a number of elements into the intervention: (1) Homework exercises to develop expertise and to practice the strategies in more ecological and diverse situations. (2) Teaching multiple mnemonics to increase the likelihood that components of training will be appropriate for, and therefore will transfer to, daily memory demanding situations. (3) Indication of the occasions when particular strategies can be used [32], because using mnemonics with inappropriate material is likely to reduce feelings of success and discourage participants from using the learned strategies in daily situations [5]. (4) There were two other significant aspects of our design. First, we provided intervention to aged persons without cognitive impairment (NI). By including normal participants, it was possible to assess the magnitude of the intervention effect in MCI as compared to that in elderly individuals with no cognitive decline (this was done by comparing the intervention effect across the two groups). It was also possible to measure whether the intervention actually normalized recall performance on tasks that were impaired in MCI prior to the intervention (this was done by comparing the post-intervention performance of persons with MCI to that of matched controls prior to the intervention). Second, in a different part of the study, we tested participants with MCI and normal participants who did not receive any intervention to determine the potential impact of test-retest effects on cognitive measures. These groups were equivalent to being in a waiting-list condition.

We hypothesized that prior to the intervention, participants with MCI would be impaired on memory measures relative to healthy controls. We expected that both healthy controls and participants with MCI would benefit from the intervention. Thus, performance on the primary outcome measures that were targeted by the training – which were memory measures – was expected to increase when comparing pre- to post-intervention scores. We predicted that the magnitude of the intervention effect would be similar across the two groups, resulting in parallel performance on the two test times.

We also conducted correlational analyses to assess the personal factors that are related to training efficacy. In healthy older adults, cognitive training efficacy is associated with higher mental status and younger age [8, 16]. Because our intervention was designed for older adults with impaired cognitive performance, it was important to assess whether mental status (as measured with dementia scales), age and education were related to intervention efficacy.

Method

Treated Participants

Participants with MCI were recruited from memory clinics. They were referred to the project by neurologists or geriatricians. Participants without cognitive deficits (NI) were healthy community dwelling older adults who participated voluntarily in the project and who were recruited through advertisements.

A clinical and neuropsychological assessment was conducted to support the research diagnosis, exclude dementia and characterize the participants. Participants with MCI received a complete clinical examination (e.g., CT-scan, blood analysis) to rule out major medical causes for their cognitive complaints. All participants completed the Hachinski scale, the Geriatric Depression scale [33, 34], the MMSE [35], the Mattis dementia rating scale (MDRS) [36, 37] and a test of episodic memory (BEM story immediate and delayed recall) [38]. Additional neuropsychological measures of language (DO-80 naming test) [39], executive functions (Stroop-Victoria) [40], and visuo-constructional praxia (Copy of the Rey Figure) [41] were used in persons suspected of having MCI. A test that had been completed in the patients' routine clinical investigation no more than 6 months prior to referral was not conducted again. In this case, the results contained in the clinical file were used. Testing was conducted by a senior research assistant trained in neuropsychology.

Persons with MCI fulfilled Petersen's most recent criteria for amnesic single domain MCI or amnesic multiple domain MCI [1] based on clinical and neuropsychological information. These patients had a memory complaint and performed 1.5 SD below the average level of persons of a similar age and education on the BEM story recall test (immediate and/or delayed recall). They had normal general cognitive functioning: they scored above the cutoff for dementia on the MMSE (score > 24) and on the MDRS (age and education based cut-off). Their cognitive difficulties had no significant repercussions on their functional independence, as assessed through clinical interviews with the patients and spouses. Participants with MCI were included in the study if they showed a memory deficit (amnesic single domain MCI subtype) or if they showed deficits of memory in addition to other domains (amnesic multiple domain MCI subtype). Participants with amnesic single domain MCI showed impaired performance on the memory task only (more than 1.5 SD below age/education norms on the BEM task), whereas patients with amnesic multiple domain MCI showed impairment on the memory task (more than 1.5 SD below age/education norms on the BEM task), as well as on any of the other cognitive tasks mentioned above (defined as performance that is more than 1.5 SD below norms). Thus, individuals

with MCI who did not exhibit a memory deficit on the BEM task (i.e., non-memory single or multiple domain MCI) were excluded from the study. Consistent with Petersen's criteria, the diagnosis for research purposes was made by consensus based on the referring neurologist's clinical judgment and the additional neuropsychological and clinical assessment. We excluded patients with AD on the basis of the DSM-IV and NINCDS-ADRDA research criteria [42], as well as patients with other forms of dementia.

NI participants were tested on a subset of the neuropsychological battery (MMSE, MDRS, BEM memory test) to document their cognitive functions and exclude participants with MCI (on the basis of the above criteria) or dementia. Additionally, the GDS and Hachinski scales were administered. The NI participants were matched to MCI participants on age and education.

All participants were Francophone, with normal or corrected visual and auditory acuity, no use of psychotropic medication known to impair cognition and no significant impairment of physical mobility or manual dexterity. Other exclusion criteria included intellectual deficiency, alcoholism or toxicomania, presence or history of severe psychiatric disorders, presence or history of significant cerebrovascular disorders, presence or history of a neurological disorder and general anesthesia in the last 6 months. During the initial contact, the details of the study were explained and only individuals who indicated that they planned to remain in the area for the duration of the study were retained.

Twenty participants with MCI and eleven persons classified as NI took part in the intervention component of this study. Two of the NI and two participants with MCI dropped out of the study shortly after beginning the intervention. One individual with MCI was excluded from the analysis at the outset of the study because it was found that she had arthritis, which impeded her attentional training. There were eight women in the MCI group and six women in the NI group.

Participants' consent was obtained according to the declaration of Helsinki and the Ethical Committee of the Institution in which the work was performed approved it.

Untreated Participants

To control for pre-post practice effects on repeated cognitive testing, a new consecutive group of eight MCI and eight NI participants was recruited with the same procedure as described above. They were tested on the objective cognitive measures with the same interval as the treated participants. However, they did not receive the cognitive intervention during the interval. Thus, they were equivalent to waiting list groups. There were six women in each group.

Intervention

The intervention was administered in 8 weekly sessions. Each session lasted approximately 120 min. Groups of 4–5 participants were formed. Training was conducted in groups, as this format was found to be more efficient than individual training [16, 43, 44]. There were three instructors. The three instructors were experienced clinical neuropsychologists. The general approach encouraged learning through tutoring and observation, as this is thought to be particularly effective in normal aged individuals [45]. We also used fading techniques in which the instructor provided decreasing support and cues to the participants.

In Session 1, the instructor presented an overview of the program and explained the different aspects of the cognitive changes

observed in normal aging. Care was taken to relate theoretical constructs to the particular training that the participants were to encounter during the intervention program, as well as to common activities of daily life. We introduced the view that older adults can cope with their memory problems and focus on the body of skill and knowledge that is preserved in aging. This aspect was also emphasized in any discussions that occurred during the training sessions. In the first session, participants were also given diaries that contained the training schedule of the intervention. In each session, they were given a written summary of the session, as well as the different homework exercises to put in their diaries.

Sessions 2 and 3 were devoted to computer-assisted attentional training. Divided attention was trained using a simplified adaptation of the program developed by Kramer et al. [26]. Participants were trained in a dual-task condition to allocate their attention according to different strategies. They were asked to combine a visual detection task and an arithmetic task. Participants were required to vary the attentional resources allocated to each task in the dual task condition to emphasize either the visual or arithmetic task. Speed of attention was trained with a modified version of Baron and Mattila's program [27]. In this task, participants perform a simple memory scanning task with increasing time constraints over a series of blocks of trials. The time allotted to report the answer on a given block corresponded to the 75th percentile of the time distribution from the previous block. Sessions 4–7 focused on episodic memory by teaching different methods to improve memory performance: interactive imagery, method of loci, face-name association and organization of text information (PQRST). In Session 4, a series of techniques to improve visual imagery abilities were taught as a pre-training phase [31]. In Session 5, the ability to learn face-name associations was taught by using imagery strategies. In Session 6, the method of loci was introduced. Participants had to generate and memorize a set of familiar locations in their home environments. They were later presented with words to remember and were instructed to link each word with a place in their mental map [6]. In Session 7, participants were instructed about hierarchical organization of texts. Participants were instructed to use a strategy known as the PQRST method (Preview, Question, Read, State, Test) [46, 47] to remember a short piece of text. In Session 8, the participants were involved in the learning of verbal organization on the basis of semantic proximity, categorization and hierarchization [7, 43, 46–48], which rely on verbal/semantic knowledge. In this last session, the different methods were also reviewed, as well as their application to daily life.

Compliance and Treatment Integrity

Participants who were present at all interventions and who completed at least 80% of the homework were judged as compliant. Treatment integrity and instructor quality control were dealt with in the following manner. First, the instructors were qualified clinicians who received training in clinical neuropsychology and who had clinical experience with elderly persons. A detailed training manual and audiotapes were constructed for each training session by the investigators who developed the training program. Prior to the study, instructors received specific training from the investigators who developed the training program. The training lasted approximately 7 h, in addition to 2 h of preparation prior to each session. The training included the presentation of

written material that provided step-by-step details of the organization of all sessions, and audio material in which the investigators recorded the content of each session. The material was also used by the instructors throughout the study. S.B., F.F. and L.G. directly supervised the instructors. During the study, treatment integrity was controlled by having regular meetings during which instructors and the investigators in charge of integrity control (S.B., F.F., L.G.) discussed the content of the training. At the outset of the training, participants filled out a questionnaire to assess their degree of appreciation of the instructors. Satisfaction was high for all instructors.

Outcome Measures

There was one pre-intervention assessment (Pre-intervention) and one post-intervention assessment (Post-intervention). The pre-test was conducted between 1 and 2 weeks prior to the intervention, while the post-test was conducted between 1 and 2 weeks following the end of the intervention. For each time-point, measures were taken in one testing session that lasted approximately 90 min. The order of presentation of the tasks was fixed across participants but in determining the order of presentation, care was taken to minimize interference between the memory tasks by introducing breaks between tasks. The individuals who conducted the testing in the pre- and post-intervention were different from the instructors who administered the intervention. Alternative versions of the memory tests were used at pre- and post-intervention testing. The alternative versions were crossed among participants so that each version would be used at pre-test for half of the participants and at post-test for the remaining participants.

Primary Outcome Measures

Three episodic memory tasks were used as primary outcome measures in the pre/post-intervention assessment. The episodic memory tasks were chosen so that the mnemonics that were taught during the intervention could be used to improve memory for the material. However, a different format and materials were used than that employed during the intervention. (1) Face-name recall was measured by presenting 12 black and white photographs of male faces associated with their written last names. Participants were given 45 s to learn each name. At the end of the study period, they were asked to count aloud backward for 20 s. They were then presented the faces and asked to provide the associated name. (2) Unrelated word list learning was tested by presenting two lists of 12 frequent and imageable words taken from the Côte-des-Neiges Computerized Memory Battery [49, 50]. All words were presented visually and simultaneously for a 3-minute study period. Thus, participants had time to use the strategies that they were taught at post-test. Recall was required after a 30-second delay, during which the participants were asked to count aloud, and again after a 10-minute delay filled with non-interfering tasks. (3) The Memo-text consisted of one short story presented visually to participants for a 3-minute study period. Participants were then asked to recall the text immediately and after a 10-minute delay filled with non-memory tasks. This task has been validated in French and distinguishes memory for main ideas (macro-structure) and memory for details (micro-structure) of the text [51, 52]. In the post-intervention testing, participants were instructed that they could make use of the strategies learned during the intervention.

Generalization Measures

A subjective memory questionnaire (Questionnaire d'auto-évaluation de la mémoire) [53] was used to assess the participant's judgement of changes in daily life following the intervention. The questionnaire is divided into ten sections that deal with memory difficulties in different areas of daily life (Conversations, Movies and Books, Slips of attention, People, Use of Objects, Places, Actions to Perform, Political and Social Events, Personal Events, General). Well-being [54] was also measured at pre- and post-intervention to assess the effect of the intervention on the general quality of life of participants.

Additional Measures

Our program focused on episodic memory training, but because it also included an attentional training we used one measure of attentional control, a computerized adaptation of the Brown-Peterson technique [55, 56]. Participants were presented with oral series of three consonants that they were asked to memorize. Recall was required upon an auditory signal that occurred after 0, 10, 20 or 30 s. During the delay, participants were asked to perform a simple task (articulation of the word 'bla' continuously) or a complex task (adding one to random numbers that were provided by the examiner). It was expected that the effect of the attention intervention would occur in the addition condition only because this was the condition that required attentional control.

Finally, a verbal fluency test was used as a control task. This was a task on which no improvement was expected to occur because its underlying processes were not targeted by our intervention. The task consisted of asking participants to produce as many words as possible that start with a particular letter (B, T and L) during a 90-second period of time.

Results

In the first set of analyses, the demographic characteristics of participants were compared. In a second set of analyses, the data on primary outcome measures for treated participants were analyzed separately for each task using mixed ANOVAs that included Group (MCI, NI) as a between-subject factor, as well as Intervention (Pre-intervention; Post-intervention) and experimental condition as repeated factors. A post-hoc HSD Tukey test for unequal sample size was used to locate differences in case of significant main effects or interactions. The Bonferonni correction (0.007) was used to compare pre-post-effects on primary outcome measures. In a third section, data analyses for the untreated participants are presented. These were analyzed separately because this was conducted as an independent experiment. As a result, assignment in the two conditions was not random, but consecutive, and participants were not matched on demographic and cognitive variables. In such conditions, running a single analysis is undesirable.

Table 1. Clinical characteristics of trained participants (SD in parentheses)

	MCI	NI or mean in normative data
MMSE (/30)	28.94 (1.2)	29.00 (0.8)
MDRS (/144)	139.44 (3.2) ^a	142.11 (1.7)
GDS (/30)	8.1 (3.8)	3.88 (8.3)
Hachinski	2.08 (2.05)	1.50 (1.8)
Story recall (BEM)		
Immediate (/12)	8.14 (1.7) ^b	10.06 (1.2)
Delayed (/12)	7.36 (2.0) ^b	9.67 (1.4)
Stroop 3 (s)	26.14 (10.9)	Norm mean = 31.74 (4.85)
Copy of Rey (/36)	31.03 (3.3) ^c	Norm mean = 34.11 (0.82)
Naming (DO-80)	78.4 (1.8)	Norm mean = 77.38 (1.50)

^a Indicates significant deficit ($p < 0.05$).

^b Indicates significant deficit ($p < 0.001$).

^c Indicates more than 1.5 SD away from norm mean.

Demographic and Clinical Characteristics of Participants

The mean age of the treated MCI participants was 62.33 years ($SD = 7.3$) and their mean education was 14.6 years ($SD = 5.0$). The mean age of the nine treated NI participants was 65.9 years ($SD = 6.0$) and their mean education was 14.6 years ($SD = 3.5$). There was no significant group difference in age, $t_{25} = -1.258$, NS, or education, $t_{25} = 0.00$, NS. Table 1 displays the clinical characteristics of the two groups of treated participants. Persons with MCI and NI did not differ on the MMSE. Participants with MCI performed slightly worse than NI on the MDRS. Furthermore, and as expected, persons with MCI were impaired relative to NI participants on immediate and delayed recall of the BEM memory test. Furthermore, their average score on the copy of the Rey Figure was more than 1.5 SD lower than the average performance based on standardized norms.

On average, non-treated participants were 69.38 ($SD = 10.7$) and 69.5 (9.9) years old (MCI and NI, respectively) and both groups had completed an average of 12 years of education ($SD = 3.2$ and 2.3 for the MCI and NI participants, respectively). The non-treated MCI and non-treated NI were comparable regarding both age and education, $t_{14} = -0.024$, NS, and $t_{14} = 0.180$, NS respectively. The average MMSE was 28.25 for participants with MCI and 28.75 for NI participants, $t_{14} = -0.748$, NS, and their MDRS scores were 134.6 and 139.9 for MCI and NI, re-

spectively. The score on the MDRS was significantly lower in persons with MCI than in NI participants, $t_{14} = -2.304$, $p < 0.05$.

Treated Participants

Primary Outcome Variables

Table 2 reports data for each task according to the different experimental conditions. The ANOVA on the face-name association task included Group (MCI; NI) as a between-subject factor and Intervention (Pre-intervention; Post-intervention) as a repeated factor. The ANOVA revealed a significant Intervention effect, $F(1,25) = 11.203$, $p < 0.01$, with greater recall at post-intervention than pre-intervention. However, neither the Main Group effect nor the interaction reached significance. Thus, the intervention improved recall in both MCI and NI participants. The intervention effect in MCI was significant when using the bonferroni correction for face-name associations ($p = 0.004$). The effect size for the intervention effect represents the magnitude of the effect present in the population. It is generally expressed in standardized units [63]. In case of a null hypothesis (no effect), a zero effect size is expected. If the null hypothesis is rejected, effect sizes of 0.2, 0.5 and 0.8 are considered as small, medium, and large, respectively. On the face-name association task, the effect size (Post-Pre/ SD) for the overall intervention effect was 0.59. A medium effect size such as the one found here is conceived as one visible to the naked eye.

The ANOVA on the number of words recalled in list recall was performed with Group (MCI; NI) as a between-subject factor and Intervention (Pre-intervention; Post-intervention) and Delay (Immediate, Delayed) as repeated factors. The results indicated a Main Intervention effect, $F(1,25) = 7.444$, $p = 0.01$, a Main Delay effect, $F(1,25) = 19.261$, $p < 0.001$ and a Main Group effect, $F(1,25) = 7.597$, $p = 0.01$. There was a Delay by Intervention interaction, $F(1,25) = 5.631$, $p < 0.05$, indicating that the intervention effect was larger with the delayed recall. In addition, there was a Group \times Delay \times Intervention interaction, $F(1,25) = 5.631$, $p < 0.05$. Post-hoc tests indicated that the improvement from pre- to post-intervention in participants with MCI was highly significant for delayed recall ($p = 0.0001$), but did not reach significance for immediate recall. In contrast, the intervention effect was found for both delays in NI persons ($p = 0.0026$ in both cases). Furthermore, in pre-intervention, persons with MCI differed from NI on delayed recall ($p = 0.0001$),

Table 2. Episodic memory tasks in persons with MCI and persons with no impairment (NI)

	A Face-name associations				B List memory			
					immediate		delayed	
	pre	post			pre	post	pre	post
MCI	5.78 (3.4)	7.56 (2.9) ^a			9.25 (1.6)	9.67 (2.0) ^c	7.39 (2.3) ^c	9.06 (2.4) ^{b, c}
NI	6.89 (2.76)	8.78 (3.15) ^a			10.22 (2.1)	11.61 (0.7) ^a	9.61(2.5)	11.0 (1.5) ^a
	C Text memory							
	Micro-structure				Macro-structure			
	immediate		delayed		immediate		delayed	
	pre	post	pre	post	pre	post	pre	post
MCI	12.78 (3.9)	13.78 (3.7)	12.11 (3.6) ^c	12.39 (3.3) ^c	18.06 (2.6)	17.06 (3.4)	16.78 (3.5)	16.39 (3.9)
NI	17.33 (2.7)	18.33 (2.3)	16.38 (2.39)	18.11 (2.3)	18.78 (2.7)	19.67 (2.4)	17.56 (2.6)	19.00 (2.2)

^a Significant intervention effect ($p < 0.01$); ^b significant intervention effect ($p < 0.001$); ^c significant group effect ($p < 0.001$).

but the effect just failed to reach significance on immediate recall ($p = 0.06$). Participants with MCI recalled fewer words than NI participants in post-intervention and the effect was significant for both delays ($p < 0.001$ in both cases). Interestingly, on delayed recall, the performance of individuals with MCI in post-intervention was equivalent to NI persons prior to intervention. This indicates that the intervention normalized the delayed recall of MCI persons. The intervention effect in delayed word list recall of participants with MCI was significant when using the bonferroni correction ($p = 0.006$). The effect size (d') for the intervention effect on delayed recall was 0.65 for both groups and 0.71 for individuals with MCI. These are medium to large effect sizes which indicate that almost half of the population areas are non-overlapping.

For text memory, the ANOVA included Group (MCI; NI) as a between-subject factor and Delay (Immediate; Delayed) and Intervention (Pre-intervention; Post-intervention) as repeated factors. There were two dependent variables: the number of elements recalled from the micro-structure and the elements recalled from the macro-structure. The analysis of the micro-structure indicated a Main Group effect, $F(1,25) = 16.819$, $p < 0.001$, and a Main Delay effect, $F(1,25) = 6.672$, $p < 0.05$. NI participants generally recalled more elements than those with MCI and all participants recalled more elements in immediate than delayed recall. None of the other effects

reached significance. The analysis of the macro-structure indicated a Main Delay effect, $F(1,25) = 13.292$, $p = 0.001$. Participants provided more elements in immediate than delayed recall. None of the other effects reached significance.

Generalization Measures

Performance on the subjective measures (QAM and well-being) is presented in table 3. Responses on the QAM were analyzed separately for each section with 2 (Group) by 2 (Intervention) ANOVAs. On this test, three participants (two with MCI and one NI) were excluded because they did not return their questionnaires. The analysis indicated that there were Group differences on four dimensions (Conversations: $p < 0.05$, Books and movies: $p < 0.05$, Personal events: $p < 0.05$, General: $p = 0.01$). On these dimensions, persons with MCI expressed a more severe level of complaints than those with NI. There was a Main Intervention effect on the Personal events section, $F(1,21) = 5.498$, $p < 0.05$, and a marginally significant effect on the Places and Political and social events dimensions ($p = 0.09$ in both cases). On these dimensions, interventions reduced the level of complaint. There were no Group by Intervention interactions on any of the variables, indicating that the intervention reduced the level of complaint with the same magnitude in individuals with MCI and NI. The effect size for the Main Intervention

Table 3. Secondary outcome measures in persons with MCI and persons with no impairment (NI)**A** Scores on the 10 areas of the subjective memory questionnaire (QAM)^a

	Conversations		Books and movies		Slip of attention		People		Use of objects	
	pre	post	pre	post	pre	post	pre	post	pre	post
MCI	2.59 (1.1) ^b	2.52 (0.8) ^b	2.80 (1.1) ^b	2.79 (1.1) ^b	2.87 (0.8)	2.77 (0.7)	2.62 (0.8)	2.55 (1.2)	2.67 (1.4)	2.60 (1.1)
NI	1.81 (0.5)	1.79 (0.6)	1.92 (0.6)	1.89 (0.4)	2.32 (0.7)	2.22 (0.9)	2.40 (0.7)	2.28 (0.8)	2.50 (0.8)	2.22 (0.8)

	Political and social events		Places		Actions to perform		Personal events		General	
	pre	post	pre	post	pre	post	pre	post	pre	post
MCI	3.15 (0.9)	2.79 (1.1)	2.23 (0.8)	1.90 (0.1)	2.56 (0.6)	2.38 (0.8)	2.76 (0.7) ^b	2.38 (0.8) ^{a, b}	3.86 (1.3) ^b	3.65 (0.8) ^b
NI	2.50 (0.8)	2.42 (0.9)	1.63 (0.5)	1.57 (0.6)	1.93 (0.6)	2.12 (0.9)	2.10 (0.5)	1.85 (0.5) ^a	2.76 (0.7)	2.69 (0.9)

B Scores on the scale of well-being

	pre	post
MCI	66.00 (14.4) ^b	68.9 (12.5) ^{a, b}
NI	78.83 (21.89)	84.67 (18.9) ^a

^a Significant intervention effect ($p < 0.05$); ^b significant group effect ($p < 0.05$).

tion effect for the personal events section was 0.44. This is a medium effect size value and it indicates that the effect is visible to the naked eye and has practical significance.

On the well-being scale (note that two participants with MCI were excluded because they failed to complete the questionnaire), there was a significant Group effect, $F(1,22) = 4.670$, $p < 0.05$, a significant Intervention effect, $F(1,22) = 4.957$, $p < 0.05$, and no significant interaction, $F < 1$. Overall, participants with MCI reported a generally lower level of well-being than NI participants. Furthermore, all participants reported a higher level of well-being at post-test than at pre-test. The effect size (d') for the Main Intervention effect was 0.23. This small effect size suggests the presence of extraneous variables which contributes noise in the data.

Additional Measures

Table 4 presents the data for the cognitive secondary outcome measures (Brown-Peterson procedure, fluency task). To assess the intervention effect on attentional control, an ANOVA was performed on the total number of items recalled in the Brown-Peterson procedure, using Group (MCI; NI) as a between-subject factor and Intervention (Pre-intervention; Post-intervention) and Interference (articulation, addition) as repeated factors. Only

Table 4. Additional cognitive measures in persons with MCI and persons with no impairment (NI)

	A Brown-Peterson procedure ^a			
	articulation		addition	
	pre	post	pre	post
MCI	30.78 (4.5)	30.28 (4.8)	27.61 (6.9)	29.11 (7.1)
NI	33.56 (2.7)	32.67 (4.4)	26.33 (4.8)	28.89 (4.5)

	B Verbal fluency ^b	
	pre	post
MCI	48.50 (16.0)	50.78 (15.9)
NI	48.90 (11.5)	49.89 (10.2)

^a The total recall (pooled over delays) of the Brown-Peterson procedure (control of attention) and, ^b verbal fluency (pooled over the three letters).

the interference effect was significant, $F(1,25) = 10.246$, $p < 0.01$. None of the other effects reached significance.

A two-way mixed ANOVA was applied to the total number of items provided in the fluency task with Group

Table 5. Episodic memory tasks in persons with MCI and persons with no impairment (NI) who received no intervention

	A Face-name associations				B List memory			
					immediate		delayed	
	pre	post			pre	post	pre	post
MCI	3.25 (3.8)	3.25 (4.3)			7.88 (2.6) ^a	6.75 (2.8) ^a	5.19 (3.5) ^a	4.88 (3.7) ^a
NI	4.38 (3.8)	4.0 (3.5)			8.31 (1.6)	9.25 (2.7)	6.50 (1.7)	7.50 (3.6)

	C Text memory							
	Micro-structure				Macro-structure			
	immediate		delayed		immediate		delayed	
	pre	post	pre	post	pre	post	pre	post
MCI	9.50 (4.2)	10.13 (6.1)	7.13 (3.8)	9.00 (6.6)	15.63 (5.8)	15.00 (5.0)	13.38 (5.1)	13.50 (6.4)
NI	14.50 (4.3)	13.63 (5.0)	12.38 (4.4)	12.25 (4.1)	17.00 (3.7)	17.13 (1.6)	16.75 (3.7)	16.75 (3.5)

^a Significant group effect ($p < 0.05$).

(MCI; NI) as a between-subject factor and intervention (Pre-intervention; Post-intervention) as a repeated factor. None of the main effects or interaction reached significance, $F < 1$ in all cases.

Correlates of Improvement

We used correlational analyses to assess which personal characteristics were associated with the pre-post-intervention effect in participants with MCI. This was done by deriving intervention effect scores (performance on post-intervention – performance on pre-intervention) for the variables on which positive intervention effects were found in persons with MCI. These were face-name learning, list recall (because immediate and delayed list recall were highly correlated, only the latter was used), QAM personal events, and well-being. Correlations were conducted between the four individual intervention effect scores and age, education, GDS score, performance on the MDRS, MMSE, number of words recalled on the BEM immediate task and number of words recalled on the BEM delayed task. Only two correlations were significant: younger age and a higher level of education were associated with a larger intervention effect score on delayed list recall ($r = -0.592$ and 0.698 , respectively, $p < 0.01$ in both cases). Age and education were not related to the other three intervention effect scores. Furthermore, neither overall baseline cognitive functioning (MDRS and MMSE), nor baseline episodic memory (BEM task)

correlated with any of the four intervention effect scores.

Non-Treated Participants

Results from the groups of participants who did not receive intervention were used to control for pre-post practice effects. These are presented in table 5. The data failed to reach significance on any of the tasks used. This indicates the absence of a practice effect on our cognitive tasks under the present testing conditions.

The ANOVA with Group and Time as factors on the face-name association task revealed that neither the main effects, nor the interaction, reached significance ($F < 1$ in all cases).

On word list recall, the ANOVA conducted with Group, Delay and Time as factors revealed a significant effect of Delay $F(1,14) = 51.391$, $p < 0.001$, and a significant Group by Time interaction, $F(1,14) = 5.432$, $p < 0.05$. The delay effect was due to an overall lower recall on delayed than immediate word recall. Inspection of the data in table 5, as well as post-hoc analyses, indicated that the Group by Time interaction was explained by a larger Group effect on Time 2 than on Time 1. This was due to a slight decrease in performance between Time 1 and Time 2 in participants with MCI, combined with a slight increase in performance between the two testing occa-

sions in NI participants. However, the Time factor failed to reach significance in both groups.

The ANOVA performed on the micro-elements of text recall indicated a Main Delay effect (immediate vs. delayed), $F(1,14) = 10.719$, $p < 0.01$, and a marginal Main Group effect $F(1,14) = 3.613$, $p = 0.08$. Neither the Time main effect, nor any of the interactions involving that factor, reached significance ($F < 1$). The ANOVA on macro-propositions revealed a Delay, $F(1,14) = 9.290$, $p < 0.01$, and a Group by Delay interaction $F(1,14) = 4.74$, $p < 0.05$ due to a larger delay effect in MCI persons.

Discussion

The goal of this study was to assess efficacy and feasibility of a multifactorial intervention in persons with MCI. The results indicate that this type of intervention is both feasible and has a high potential for assisting persons with MCI.

To What Extent Was the Intervention Efficient?

The findings of the study indicate that multifactorial intervention is efficient in improving the episodic memory performance of elderly persons with no cognitive decline (here, NI participants). This is consistent with many previous studies indicating that objective measures of memory are improved after cognitive interventions in healthy elderly participants [16] and that subjective measures can also show improvement, though of a lesser magnitude [17].

Importantly, our study also revealed positive intervention effects in persons with MCI. The pre-post-intervention comparison was significant on two out of three primary outcome measures. Participants with MCI showed improvements in delayed free recall of lists of words and in memory for a persons' name. The effect was highly significant and resisted to the control for Type 1 error. Importantly, these memory components are part of the core cognitive impairments in those MCI persons converting to AD [2, 22, 25, 57–59]. Thus, improvement in episodic memory following intervention is likely to have clinical validity in MCI by improving those cognitive components that are most likely to deteriorate. In contrast, performance was not improved on text memory. This lack of an intervention effect may arise from the lack of efficacy of the text training technique used here, the PQRST, a lack of congruence between the training used and the text outcome measure, or a combination of these two factors. The significant effect sizes obtained on ob-

jective memory measures for the intervention differences were in the medium to large range (0.59 and 0.71). This is generally conceived as reflecting an effect that is visible to the naked eye in the population and indicates that the areas of the two populations (treated and non-treated) are mostly non-overlapping. The effect sizes for participants with MCI were in the range of those previously reported with a similar paradigm in normal older adults. Verhaeghen et al. [16] reported an effect size average of 0.7 for the intervention effect in normal healthy adults using the same statistical procedure that we used here to derive effect sizes. Thus, importantly, the effect sizes in MCI were comparable to effect sizes in normal healthy older adults in spite of the fact that these persons are less cognitively proficient.

Our study design also included subjective measures of memory and well-being. The findings revealed that the intervention had a positive effect on some aspects of subjective measures of memory and on a measure of well-being, but the effects were less reliable than those obtained on objective measures. This finding indicates that, to some extent, the intervention has a positive impact on their subjective assessment of memory and their feelings of well-being. This positive effect on the subjective measures is at odds with previous studies that have reported few or no effects of cognitive intervention on the subjective memory or well-being of older healthy participants [17, 19, 48] (but see Rapp et al. [19], for positive effects in MCI). The finding of positive effects on both objective and subjective measures may result from the multifactorial nature of our intervention. The inclusion of pre-training on stress, self-efficacy and/or imagery that was part of the present intervention was correlated with an improvement in subjective memory in healthy older adults [17]. It can be argued that including these components in our intervention contributed strongly to the positive effects that were observed on subjective memory measures and well-being, see also [17, 30].

Of course, our study included a fairly restricted number of subjective measures and did not measure quality of life. In future research, it is important to use a larger range of non-cognitive measures, including measures of self-efficacy and self-esteem. Furthermore, the effect sizes obtained on the subjective measures (0.44 for the QAM and 0.22 for well-being) were of a smaller magnitude than those found on the objective measures. The finding of smaller effect sizes on subjective than objective measures is consistent with reports from existing meta-analyses. The effect size for the well-being measure was small, which suggests that uncontrolled variables introduced

undesired noise in the data. This may be due to inappropriate measures. It could also be related to the personal characteristics of our participants. There was some variability in the GDS scores of our participants with MCI. This may have contributed to increasing noise in our finding.

Finally, the findings of the present study support the feasibility of this type of intervention. We achieved a very high level of participation over time in both participants with MCI and NI. The attrition rate was relatively low in spite of the fact that the intervention was quite demanding. Of the initial group, only four participants (two MCI and two NI) dropped out of the study, which corresponds to an 11% attrition rate. Second, both MCI and NI participants were highly compliant. None were excluded on the basis of not reaching our compliance criteria. The successful intervention proposed by Olazaran et al. [20] was very long, spanning up to an entire year and consisting of up to 103 training sessions of 4 h each in length. Although this may have increased the efficacy of the intervention, it has practical limitations in that it may be too difficult to implement such long training regimens in typical clinical set-up, resulting in reduced feasibility. We found that using a much shorter regimen can still result in positive effects.

Who Benefited from the Intervention?

One important question concerns the characteristics of the population that is most likely to benefit from the intervention. In general, participants with MCI improved to the same extent as NI on the target variables. As a result, treated participants with MCI continued to perform more poorly than treated NI participants at post-intervention. However, a closer look at the data indicates that in some cases, the intervention brought individuals with MCI to the level of healthy controls prior to intervention. This was the case in the delayed recall of list memory. In pre-intervention, non-treated participants with MCI were impaired on delayed recall relative to non-treated NI. However, participants with MCI who received the treatment were comparable to non-treated NI. Thus, it is possible to envision cognitive intervention as a means to scaffold the performance of persons with MCI so that it is closer to that of typical non-MCI participants.

In terms of personal predictors of efficacy, we found no correlation between global cognitive status or clinical memory scores at baseline and training efficacy. In turn, significant correlations were found in participants with MCI between age, education and efficacy of the training, as a younger age and higher level of education were asso-

ciated with larger intervention gain. This is consistent with Verhaeghen et al.'s [16] meta-analysis, which indicated that in normal older adults, a younger chronological age predicts cognitive training success. In turn, the lack of correlation between global cognitive status and training efficacy was discrepant from some of their conclusions, suggesting that efficacy for cognitive intervention is positively related to mental capacity. Perhaps this finding can be explained by the fact that our intervention was adapted for individuals with MCI. It could also be due to the fact that we did not include patients with dementia, who would have had more severe cognitive difficulties than those with MCI. The question of the timeframe within which this type of intervention can be used in the MCI-to-dementia continuum is an important one. The present data indicate that the intervention is equally efficient within the range of cognitive decline experienced by persons with MCI. Whether this remains true as patients enter into the dementia process remains to be tested.

There is increasing evidence that different forms of MCI likely exist and that these different forms may very well have unique prognosis and evolution patterns [60–62]. Our study was restricted to amnesic MCI or multiple domain plus memory participants. One important question is whether the proposed intervention would also be effective for other forms of MCI. Although the efficacy of this intervention will have to be formally assessed in MCI subtypes, its multifactorial nature is likely an asset in terms of generalizability to other forms of MCI. For example, addressing non-cognitive components in addition to cognitive ones could make the intervention beneficial to dysthymic MCI. Along the same lines, attentional training similar to the one used here, but in a more intensive format, could be tested in persons with MCI whose impairments include mostly executive functions and/or attention.

Limitations

There are limitations and potential drawbacks in our study. First, the study included a relatively small number of participants, which likely limited its power. However, power is a function of both the N and effect size. Although our N was small, the effect sizes found on objective measures were in the medium to large range. This indicates that power was not a major limitation in our study, at least with regard to those measures. Group assignment was not randomized, but consecutive, and participants with MCI who were in the no-intervention condition were somewhat more affected than those who received the intervention.

In addition, alternative explanations for the intervention effects observed have to be addressed. One alternative account is that the effects are due to placebo or to reduced depression and isolation. This possibility cannot be entirely ruled out because we did not include a group with a placebo or psychosocial intervention. Furthermore, the average score of participants with MCI on the GDS depression scale was higher than that of controls. However, there are two reasons that make this unlikely. First, our effects are strikingly specific to episodic memory tasks, the ones that directly measure the focus of the intervention. No effect was found on attentional control, even though this is a task that is sensitive to depressive symptoms. If the effect on episodic memory was solely due to decreased depression, an effect would have been expected on that task as well. Furthermore, performance on the verbal fluency task was not changed by the intervention. The fact that participants improved on target measures and showed no improvement whatsoever on cognitive measures that were not addressed by episodic memory intervention is a good indication of the specificity of our effect. Such a selective impact would be unlikely if the effect were solely due to placebo or to the fact that participants benefited socially from the intervention. Finally, the GDS score at baseline was not correlated with efficacy of the intervention.

Another potential explanation of pre-post-intervention effects is that participants became familiar with the testing procedure and/or benefited from a task repetition effect. However, this explanation is highly unlikely given the finding that non-treated participants showed no improvement on the memory tasks and on the contrary, declined slightly on at least one measure. Although non-treated participants were relatively few in number and we may have lacked power to find significant time differences in non-treated persons, our data are certainly in the right direction.

The attentional measure failed to yield positive training effects. Although attention was not a primary target of our intervention, this is somewhat unforeseen because interventions on attention have been shown to yield positive effects in healthy older adults. However, there are sensible reasons why our intervention may not have had the same success. First, because we focused on episodic memory, attentional training was fairly restricted in time and it is quite plausible that it did not include a sufficient number of training trials. In addition, attentional training was the first component in the temporal sequence of intervention and preceded the post-intervention assessment by several weeks. If the effect vanishes rapidly with-

out practice or boosters, it is likely that this long delay between training and testing contributed to the negative finding. Finally, the population that we trained did not show signs of marked attentional deficits in our clinical testing (e.g., on the Stroop task) and this may have contributed to the reduction of power of the attentional training effect.

Finally, the issue of generalization and long-term benefits should be discussed. The current intervention focused on training specific strategies to be applied with specific material that was subsequently used in the evaluation. Thus, the effect found here is specific to the memory material that is tested in this particular context. We would not expect generalization on tasks that are not amenable to the training strategies that were taught in the present study. However, we expect generalization on tasks of daily life that are amenable to the particular strategies used here. To date, there is no functional scale that directly addresses memory activities amenable to those strategies. We have attempted to measure whether training can generalize to relevant activities in daily life by using a self-assessment memory questionnaire and we have noted some positive effects. However, there may be other ways to assess generalization. For example, future studies could inquire about the frequency of use of those strategies in daily life or require written records of their frequency and efficacy. One other possibility would be to use quality of life scales or measures of change scales with the participants or their spouses. The issue of generalization is critical to address in future studies. Finally, another limitation is that this is a short-term study and we have no indications on the long-term efficacy of the intervention. Long-term effects of a similar intervention have been reported in healthy older adults [9, 10, 12]. However, testing long-term maintenance of the benefits found in MCI is crucial because of the developmental nature of this condition.

Conclusion

Overall, our results suggest that patients with MCI can improve their episodic memory performance when provided with multifactorial memory training. These results also indicate that the form of intervention proposed here has a beneficial effect on some aspects of subjective memory and well-being of participants. Given that persons with MCI are at a high risk of developing AD, and given the scarcity of symptomatic treatment presently available for these persons, such results may have important clinical

cal implications. They indicate that this is a form of treatment that can have benefit for this population of older persons by reducing the severity of their symptoms. These findings also show that improvement remains possible even among a population of cognitively impaired older persons, which indicates that cognitive plasticity is present in elderly populations that experience cognitive decline.

Important questions remain to be addressed regarding cognitive interventions in MCI. One question concerns the characteristics of those sub-groups with MCI who are most likely to benefit from the intervention. Another question is to determine the limit after which intervention is no longer appropriate in the evolution of the disease as cognitive deficits accumulate in severity and quantity. The present study focused on short-term symptomatic improvement and another critical issue that is worthy of investigation is the extent to which intervention can delay the manifestation of the disease in those individuals who will evolve to AD. Answers to these

questions will necessitate the use of much larger sample sizes, as well as the follow-up of treated and non-treated patients. The present data suggest that this is a worthy endeavor.

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