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Cognitive Stimulation of Executive Functions in Mild Cognitive Impairment: Specific Efficacy and Impact in Memory

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Abstract

Executive functions play an important role in the maintenance of autonomy in day-to-day activities. Nevertheless, there is little research into specific cognitive training for Mild Cognitive Impairment (MCI). We present the results of a program which aims to teach specific strategies and metacognitive abilities in order for patients to be able to carry out attentional and executive tasks. Two groups (A and B) were compared in a cross-over design. After the first evaluation, Group A (but not B) participated in a six month cognitive stimulation program. After a second assessment, only Group B received treatment and then a final evaluation was carried out on both groups. The results show that: i) both groups improved their performance as an effect of training; ii) improvements generalized to memory and general cognitive tasks; iii) in the interval without training, Group B's performance worsened and iv) Group A partially maintained their results over time.

Keywords

mild cognitive impairment, cognitive stimulation, executive functions, neuropsychological rehabilitation, strategy training, mental deterioration

Introduction

Interest in cognitive changes in the elderly individuals has been growing over the last few decades. This has allowed clinicians to progressively ameliorate the diagnostic instruments used to distinguish between physiological aging processes and incoming mental deterioration. Against this background, mild cognitive impairment (MCI) has been proposed as the clinical transition between normal age-associated cognitive changes and early dementia.[1] Mild cognitive impairment is a heterogeneous condition involving various cognitive domains, and various different subtypes have been identified.[2] Although most of the research carried out so far has aimed to investigate memory deficits, a subgroup of patients having MCI with predominant attention and executive deficits and relatively preserved memory has been identified.[3] Executive functions are conceptualized by Miyake and colleagues[4(p50)] as the "general purpose control mechanisms that modulate the operation of various cognitive subprocesses and thereby regulate the dynamics of human cognition." In other words, they are thought to be the key that organizes and regulates the processes underlying thought, behavior, and emotions.[4] Three frontosubcortical circuits, originating in the prefrontal cortex, have been identified as crucial to executive functions, namely (i) the dorsolateral prefrontal cortex, involved in working memory, planning, and supervisory attentional systems; (ii) the lateral orbital cortex, involved in response inhibition and self-regulation processes, motivation, and goal-directed behavior; and (iii) the mesial frontal cortex and anterior cingulate cortex that are activated in response conflict, motivation, and emotion processing.[5,6] Neuroimaging indicates that while the amnestic subtype of MCI is characterized by medial temporal lobe atrophy, the patients with MCI presenting with isolated attention/executive deficits show cerebral atrophy in the basal forebrain and prefrontal cortex.[7,8] The prevalence of cases of attention/executive MCI varies from 3% to 15%[3,9,10] based on various different recruitment and assessment criteria. These frontal symptoms impact the more complex functional abilities and are related to behavioral syndromes such as apathy.[11] Moreover, deficits in task planning, problem solving, cognitive flexibility, verbal fluency, response inhibition, and working memory were also found during in-depth assessments

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of patients with amnestic MCI, with a causative role in determining memory deficits.[12,13]

Although it has been suggested that disorders in executive functions are useful as a cognitive marker for tracking development in the pathophysiological processes of Alzheimer's disease,[14] controlled studies concerning the cognitive stimulation of these functions in MCI are to date meager.[5] Indeed, cognitive stimulation has so far mainly been targeted toward memory deficits.[15] Nevertheless, domain-specific improvements have been observed in MCI as the consequence of controlled training related to reasoning and the speed of processing.[16] Unfortunately, these improvements did not transfer into untrained domains, probably due to the nature of the programs that focused on specific task training rather than on cognitive strategies.

This study aims to verify the effects of a cognitive stimulation program that focuses on executive functions in patients affected by MCI. Any effects of generalization to general abilities and memory performance will also be ideally ascertained.

The program capitalizes on a previous study carried out by our group and integrates the following 3 rehabilitative methodologies: a metacognitive rehabilitative approach, the training of strategies, and training sessions that address the individual patient's problems.[17]

Initially devised for developmental disorders, the metacognitive approach[18,19] is also being progressively applied in the rehabilitation of adults, in particular patients with a traumatic brain injury.[20,21] In the training program described here, this approach was associated with the training of strategies.[22-24] In this case, strategies are not defined as knowledge relating to specific tasks but rather as concern in learning of rules and cognitive steps that are useful in order to deal with various different typologies of tasks. In other words, they do not consist of knowledge of information about tasks but involve learning cognitive processes,[17] which may be useful in day-to-day activities. Various different ways of dealing effectively with a particular task are thus explained and discussed with individual patients until those which are the most efficacious and the most pleasant to use for that individual are identified. The choice of strategies and training is thus highly personalized since it is directly related to the specific difficulties and needs of each individual patient or caregiver.[21]

As in the previous training program for memory abilities,[17] an important element in our program is the presence of the caregiver in all phases of the training. In this way, the caregivers are able to provide information concerning the patient's abilities in daily life activities and discuss with the therapist the best way to assist and support the patient when he or she encounters difficulties. The therapist offers useful and practical advice, gives emotional support, and recommends specific activities to be done at home.

The experimental crossover design employed here represents another element that is particular to this study. This design makes it possible to compare the 2 groups of patients affected by MCI and verify the hypothesis that the degree of decline over time is greater in the absence of cognitive stimulation. In addition, it can be established whether or not it is possible to reduce this decline by means of specific training programs.

Methods

The crossover design used in this study meant that the participants were divided into 2 groups after the first examination (T1). The first group (A) participated immediately in a rehabilitative training session that focused on enhancing executive functions and metacognitive strategies. The other group (B) did the same training session but took part in it after the second assessment (T2) which was carried out 6 months after the first. Initial neurological and neuropsychological assessments guaranteed that the 2 groups did not differ significantly in their abilities related to attention and executive functions. In this way, the 2 groups served as reciprocal controls of each other. In fact, the second comparison of their performance allowed us to verify the efficacy of the treatment in group A and, at the same time, observe the decline that occurred in group B. After the second phase, in which group B took part in a cognitive stimulation program, a further assessment permitted us to verify the degree of recovery in group B when compared to their previously recorded decline. This third assessment also enabled us to check whether the improvement in the performance of group A had been maintained over time or had declined.

Study Participants

Thirty people agreed to participate in the training program. They were recruited at the Centre for Alzheimer's and Cognitive Disorders at the University Hospital of Verona and were selected as part of a wider study concerning various aspects of neuropsychological assessment in MCI.

They met the Mayo criteria for MCI diagnosis, revised by Petersen[2] in 2008: (i) cognitive impairment described by the patient, relatives, or both; (ii) cognitive impairment objectified by means of a neuropsychological test battery (and interpreted in conjunction with the first criterion and the personal history of the patient); (iii) no impairment of activities in day-to-day life; and (iv) absence of dementia as defined by the *Diagnostic and Statistical Manual of mental disorders criteria* (Fourth Edition; *DSM-IV*).[25] As this program concentrated on executive functions, we selected not only those patients with the amnestic form of MCI but also all those with signs of deficits in executive functions on the basis of the revised Mayo criteria.[26]

All patients underwent a comprehensive assessment of their symptoms, mood state, and performance before being included in the study. The Mini-Mental State Examination,[27] the subtests of the Mental Deterioration Battery,[28] and a clinical interview with the patients and other informants were used to assess the cognitive status. The presence of mental deterioration was excluded by means of the Clinical Dementia Rating Scale (≤ 0.5)[29] and 2 interviews with the patient and with the informant (instrumental activities of daily living and basic activities of daily living).[30,31] Depression was excluded using the Geriatric Depression Scale.[32]

Table 1. Demographic Data and the Scores of Groups A and B in the T1 Neuropsychological Assessment.[a]

		Group A Mean (SD)	Group B Mean (SD)	P
Age		75.53 (±4.98)	74.13 (±8.45)	.59
Education		9.06 (±3.47)	10.06 (±4.57)	.51
General functions	Montreal overall cognitive assessment (MOCA)	25.33 (±2.96)	23.46 (±4.40)	.18
Executive functions	Tower of London (ToL)	29.93 (±5.84)	27.66 (±6.30)	.32
	Trail Making Test (TMT B-A)	155.26 (±156.00)	128.06 (±157.03)	.64
	Dual Task	0.71 (±0.32)	0.77 (±0.21)	.58
	TEA	8.26 (±1.94)	6.80 (±2.75)	.1
	Symbol–Number Association (WAIS)	11.80 (±2.42)	12.33 (±3.26)	.62
Memory	Rivermead Behavioral Memory Test (RBMT)	8.33 (±2.79)	7.93 (±2.84)	.7
	Listening Span Test (LST)	−0.16 (±0.80)	−0.97 (±1.29)	**.051**[b]
Language	Comprehension (AAT)	28.86 (±2.09)	29.80 (±0.56)	.11
	Denomination (AAT)	29.80 (±0.41)	29.73 (±0.59)	.72
	Repetition (AAT)	29.73 (±0.70)	29.66 (±0.89)	.82

Abbreviations: SD, standard deviation; *P*, values of statistical significance in Paired Samples *t* tests; TEA, the Attention Elevator Test; AAT, Aachener Aphasie Test; WAIS, Wechsler Adult Intelligence Scale.

[a] Details concerning the tests are reported in the main text. Only in the LST there is a tendency toward a statistical difference between the 2 groups, with better performance of group A than group B.

[b] The value given in boldface is for statistical significant comparisons.

Structural brain imaging (magnetic resonance imaging [MRI]) enabled us to exclude the presence of relevant underlying cerebrovascular disease. In addition, standard laboratory blood tests (thyroid function, complete blood count, blood chemistry, folic acid and vitamin B12, homocysteine, and blood lipid profile) were performed to rule out potentially reversible causes of cognitive impairment.

Other exclusion criteria were (i) current neurological and systemic diseases or a history of head injury with loss of consciousness; (ii) history or symptoms of psychosis or major depression (*DSM-IV*); and (iii) alcoholism or other substance abuse.[33]

All the patients were native Italian speakers and gave their informed consent to participate in the study. The procedures were approved by the local ethics committee (AOVI Prot N. 1855), and the study was carried out in accordance with the guidelines of the Declaration of Helsinki.

Assessment Schedule

After the first screening, the participants underwent a specific battery of neuropsychological tests to investigate cognitive functions and in particular executive functions, memory and language. Tests that are widely used in routine neuropsychological practice and are sensitive to early deficits in these cognitive domains were selected. General functions were assessed by means of the Montreal Overall Cognitive Assessment (MOCA).[34] For executive functions, the Tower of London (ToL),[35] the Trail Making Test,[36] the Dual Task,[37] the Attention Elevator (TEA) test,[38] and the Symbol-Number Association (SNA) test[39] were selected. Memory was investigated by means of a behavioral ecological battery (Rivermead Behaviour Memory Test [RBMT])[40] and a test of working memory, the Listening Span test (LST).[41] Finally, language was assessed by means of Comprehension, Denomination and Repetition subtests of the Aachener Aphasie test.[42]

All the test scores were corrected for age, sex, and education and compared with the values available for the Italian population. The mean scores of the 2 groups in the neuropsychological tests at T1 are shown in Table 1. The same assessment was repeated 6 months (T2) and 12 months (T3) after the first evaluation (Table 2).

Training Schedule

After the first assessment (T1), the patients were divided into 2 groups (A and B), according to the requisites for crossover designs. Group A received immediate training consisting of cognitive stimulation lasting for 6 months, followed by a second assessment (T2). After this, a 6-month period without training followed and then these patients were retested (T3). On the contrary, group B did not receive any specific training between T1 and T2 but participated in the cognitive stimulation program for a 6-month period between T2 and T3. The timeline is illustrated in Figure 1.

Participants were placed in 1 of the 2 groups as agreed with them and their caregivers in accordance with individual requirements (eg, family commitments, holidays, personal preferences, etc).

In Table 1, we see that in the first evaluation (T1), there was no statistical difference between the groups either in terms of personal data or in terms of the test scores. Only in the LST did group A perform better than group B with a difference near to statistical significance ($P = .051$; Table 1).

The 6 months of training were organized as follows. The first 2 months involved intensive treatment with 2 individual sessions per week. In this phase, strategies were explained and then tried out and practiced. Note that while the general methodology was common for all patients, the training and the

Table 2. The Results of Group A and Group B in T2 and T3 Assessments.[a]

	Group A						Group B					
	T2		T1 vs T2	T3		T2 vs T3	T2		T1 vs T2	T3		T2 vs T3
	M	SD	*P*	M	SD	*P*	M	SD	*P*	M	SD	*P*
Montreal overall cognitive assessment (MOCA)	26.73	2.71	**.01**[b]	26.71	2.79	.34	22.53	5.08	**.03**[b]	23.29	4.84	.51
Tower of London (ToL)	30.53	4.88	.22	30.42	5.17	.17	28.47	4.37	.31	29.93	4.05	**.001**[b]
Trail Making Test (TMT B-A)	126.33	159.26	.11	141.28	157.36	.07	113.53	135.41	.75	118.07	138.11	.57
Dual Task	0.72	0.2	.99	0.74	0.18	.30	0.49	0.19	**.00**[b]	0.53	0.19	**.01**[b]
TEA	9.53	0.92	**.02**[b]	9.7	0.73	.17	7.2	2.48	.61	8.21	1.76	**.03**[b]
Symbol-Number Association (WAIS)	12.67	2.97	**.04**[b]	12.86	2.88	.34	12.2	3.01	.83	12.29	2.76	.82
Rivermead Behavioural Memory Test (RBMT)	10.33	2.3	**.00**[b]	10.43	2.28	.67	8.07	3.17	.63	9.00	2.72	**.01**[b]
Listening Span Test (LST)	0.6	1.24	**.04**[b]	−0.35	2.07	**.05**[b]	−1.15	1.49	.46	−0.37	1.25	.17
Comprehension (AAT)	29.93	0.26	.07	30.00	0.00	[c]	29.33	0.82	.48	29.43	0.76	.34
Denomination (AAT)	30.00	0.00	.08	30.00	0.00	[c]	29.8	0.78	.58	29.79	0.8	[c]
Repetition (AAT)	30.00	0.00	.16	30.00	0.00	[c]	29.67	0.82	1.00	29.86	0.36	[c]

Abbreviations: SD, standard deviation; TEA, the Attention Elevator Test; AAT, Aachener Aphasie Test; WAIS, Wechsler Adult Intelligence Scale.
[a] The *t* test *P* values are reported for each test and group in comparisons between T1 (Table 1 for means and SD) and T2 and T2 versus T3.
[b] The values given in boldface are for statistical significant comparisons.
[c] Statistical analysis is impossible due to the absence of differences in the SDs in the 2 assessments.

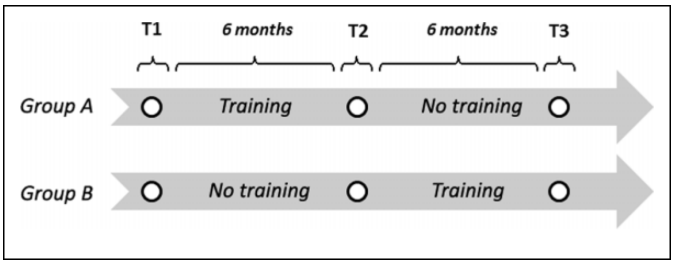

Figure 1. The timeline of the crossover design utilized in the study. T1, T2, and T3 refer to the 3 consecutive assessment sessions.

activities carried out were specific to each individual patient. This permitted us to focus on the patient's real needs and on the gap between perceived and real difficulties in everyday life. In the subsequent 4 months, only 1 session per week took place, but patients also practiced at home. This type of organization has a double function: It gives the patient the chance to use the strategies learned during training and permits the caregiver to provide support.

Methodologies

The program started with an in-depth discussion to identify the patient's difficulties in daily life activities and provide emotional support with the aim of helping them to accept the changes in cognitive functioning. The program was then discussed and planned with both the patient and the caregiver in terms of the timeline and contents. The importance of paying attention and employing specific strategies to face daily life tasks was emphasized as a preliminary necessity to be able to carry out the training program. At this point, cognitive strategies such as verbal and visual association, categorization, planning of complex tasks in specific steps, monitoring of execution, and intentional final check were devised by the therapist and tried out by the patients. They were subsequently put into practice in day-to-day tasks and simulated situations in which the patient was asked to resolve specific problems or situations. As these strategies need to be exercised over a period of time, the patients were expressly invited to use them systematically at home. In addition, specific activities for mental flexibility, maintenance of attention over time, and checks for impulsive responses were proposed.

Examples of the activities carried out during the cognitive stimulation sessions and at home are shown in Table 3. From the first session and in all phases of training, the caregivers accompanied patients participating in cognitive stimulation sessions. This enabled them to learn how best to help and give assistance to the patient. For example, they learned how, when appropriate, to encourage the patient to use external aids and the strategies they had previously learned. This is particularly important since executive functions have a central role in the maintenance of autonomy in most day-to-day activities.

Data Analysis

For each test, scores were analyzed by means of a repeated-measure analysis of variance (ANOVA) 3 $\times$ 2, with the test session as a within-subject variable (3 levels: T1, T2, and T3) and group as a between-subject variable (2 levels: A and B). In the case of a significant main effect of the test session factor, or a significant interaction of the 2 ANOVA factors, we performed repeated contrasts or repeated interaction contrasts, respectively, across the levels of the test session factor

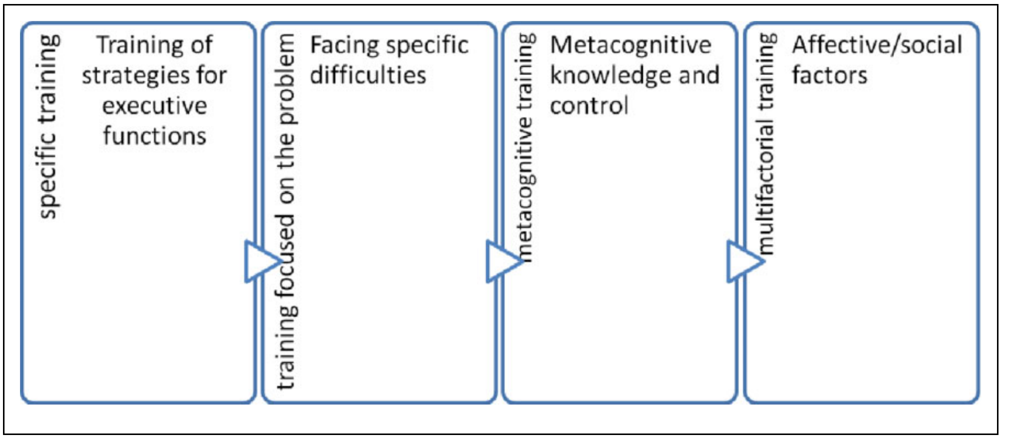

Figure 2. The methodology of the training. Various different approaches are integrated during the training sessions with the aim of providing a personalized program of cognitive stimulation.

Table 3. Examples of the Activities Proposed During the Training Program and Suggested as Possible Tasks to do at Home.

Cognitive Function	Examples of Activities
Cognitive flexibility	Shifting between two or more tasks (switching activities at an external signal, for example, "When you hear this sound, stop drawing and write 10 words" and "When you are watching TV, stop and answer the telephone"). Alternation of mental forward and backward counting (eg, "Count forward using the 3 times table and alternate this with a backward count from 100, 2 by 2, starting thus 0, 100, 3, 98, 6, 96, 9, 94 . . ."). Being aware of checking repetition (eg, indicating the elements of a scene without putting two objects of the same category in sequence. At home, "Check and record the moments when you find it difficult to change from one activity to another")
Maintenance of attention over time	Attention tasks requiring progressively longer time spans (eg, "Raise your hand when you hear the name of an animal in this story," progressively increasing the length of time that the activity lasts. At home "Try to progressively increase the length of time you spend reading or doing other cognitive activities")
Multi-tasking	Execution of 2 or more activities simultaneously ("While you are completing this picture, raise your left hand when you hear the number 5"). At home, practicing the execution of 1 activity and remembering to do something else at an external signal (eg, "While you are cooking, try to listen a radio program and then remember what it was about")
Inhibitory control	Automatic response inhibition tasks (eg, Denomination of verbal sequences modifying the order of elements, for example, "Say the names of the months in the reverse order"). Go/no go tasks. At home, "Only try to change the order in which you do something in routine activities"
Categorical thinking	Similarities. Phonemic and Semantic fluency. Metaphors and Idiomatic comprehension. Abstraction. At home "Try to organize your activities into different categories" (eg, things to do at home, shopping, social contact . . .), "While reading, try to categorize the information you want remember"
Verbal-logical reasoning based on previous knowledge	Identification of semantic differences in similar words and synonyms, analysis of proverbs, "nonsense" games, classifications. At home: comments, discussions, and critical comparisons about newspaper articles, books, or movies
Spatial and topographical planning	Working out how to follow a maze, activities involving constructive apraxia, planning a tour around a town or a journey to a foreign country. At home: "Try to plan a useful way to organize your wardrobe or your garage . . . ," "Try to plan a visit to your town for a friend who is arriving from another town . . . "
Planning of activities	Identification of the specific steps required to successfully carry out an activity. Monitoring of the execution and final evaluation of the results. At home: "Try to plan and prepare a dinner for your friends without help from other people," "Try to plan and execute all the things you have to do next week"
Problem solving	Simulation of real-life situations in which the person has to face a new problem for which he or she doesn't have a previous solution (eg, "Try to identify which of these two shops is the cheapest when you want to buy something; try to organize your kitchen in a new way")
Working memory	Mental problem solving, remembering information that may be useful in specific situations, remembering the various steps of an activity
Decision making	Making decisions in simulated situations of conflict. Making decisions while considering the consequences for oneself and other people. At home, "Try to participate in the decisions made in your family, take your time to think about them and express your opinion"

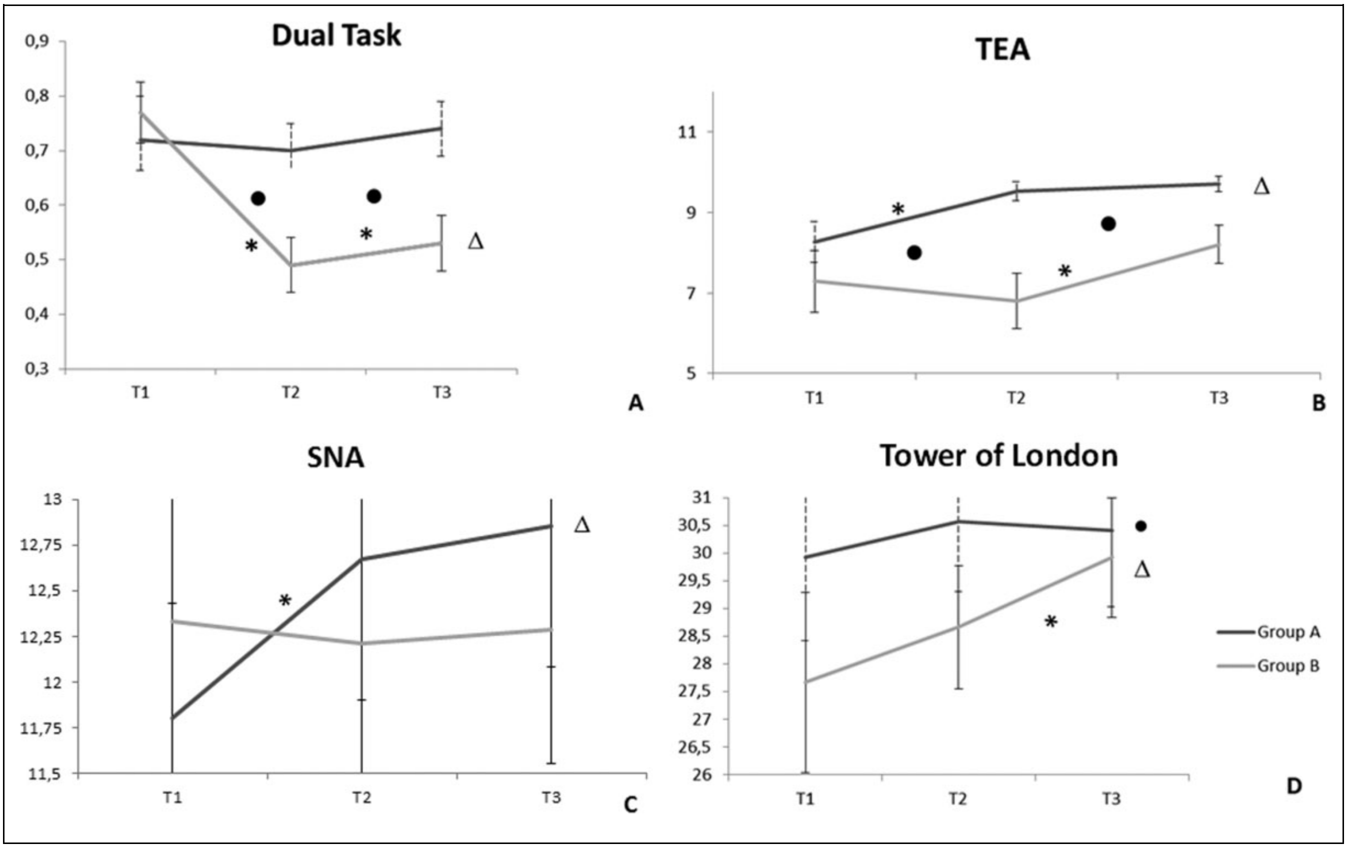

Figure 3. The effects of training on executive functions. The means and standard errors of the 2 groups in the 3 assessments are reported. A indicates Dual Task; B, Attentional Elevator Test; C, Symbol-Number Association; D, Tower of London; •, Contrasts $P < .05$; *, T-tests $P < .05$ in within-group comparisons (T1 vs T2 and T2 vs T3); Δ, *t* tests $P < .05$ in within-group comparison between T1 and T3.

(group × T1 vs T2, group × T2 vs T3, or group × T1 vs T3). This permitted us to identify whether the differences were specifically linked to the cognitive stimulation training.

Thus, in order to explain significant 2-way contrasts (or interaction contrasts), the differences between the scores in the 2 assessment sessions for the same group were tested by means of *t* tests. In the same way, *t* tests were used to explain differences between the scores of the 2 groups in the same assessment session. Unfortunately, it was impossible to collect quantitative data concerning caregiver coaching, but their qualitative reports on the program are discussed in the Results section (Figure 2).

Results

The mean scores and standard deviation (SD) for each group and test are shown in Tables 1 and 2. It is to be noted that 1 patient in each group did not complete the T3 assessment due to personal problems. Thus, the analysis concerning the T3 assessment refers to 14 participants per group.

Executive Functions

The results show a positive effect of cognitive stimulation on executive functions, although this is not homogenous for the 2 groups. Indeed, only in attention shifting (TEA) did both the groups improve their performance as a result of the training. Group A also improved in executive speed (SNA), while in group B the effects are more evident in Dual Tasks and planning (ToL). In addition, it was confirmed that in group B the absence of specific stimulation resulted in a decline in performance, in particular in the Dual Task. Planning and executive speed appear to be more resistant to the initial cognitive decline. The results of the individual tasks are as follows (Figure 3).

In the Dual Task, the ANOVA indicates an effect of interaction between test session and group ($F_{27,2} = 4.35$; $P = .018$), with a significant main effect both of group ($F_{27,1} = 4.6$; $P = .041$) and session ($F_{27,2} = 4.59$; $P = .042$; Figure 3A). In effect, the performance of the 2 groups across the test sessions is different. Interaction contrasts show that the 2 groups differ between T1 and T2 ($F_{27,2} = 5.67$; $P = .025$) and between T2 and T3 ($F_{25,2} = 4.65$; $P = .040$).The performance of group A does not change over time, maintaining the same results both after stimulation and in the follow-up. In contrast, group B shows a significant decline between T1 and T2, when no training is carried out ($t_{14} = 4.38$; $P = .001$). This is partially recovered between T2 and T3 ($t_{13} = 3.09$; $P = .009$). The comparison between T1 and T3 in group B confirms a general decline in performance ($t_{13} = 3.68$; $P = .003$) that training can only in part mitigate.

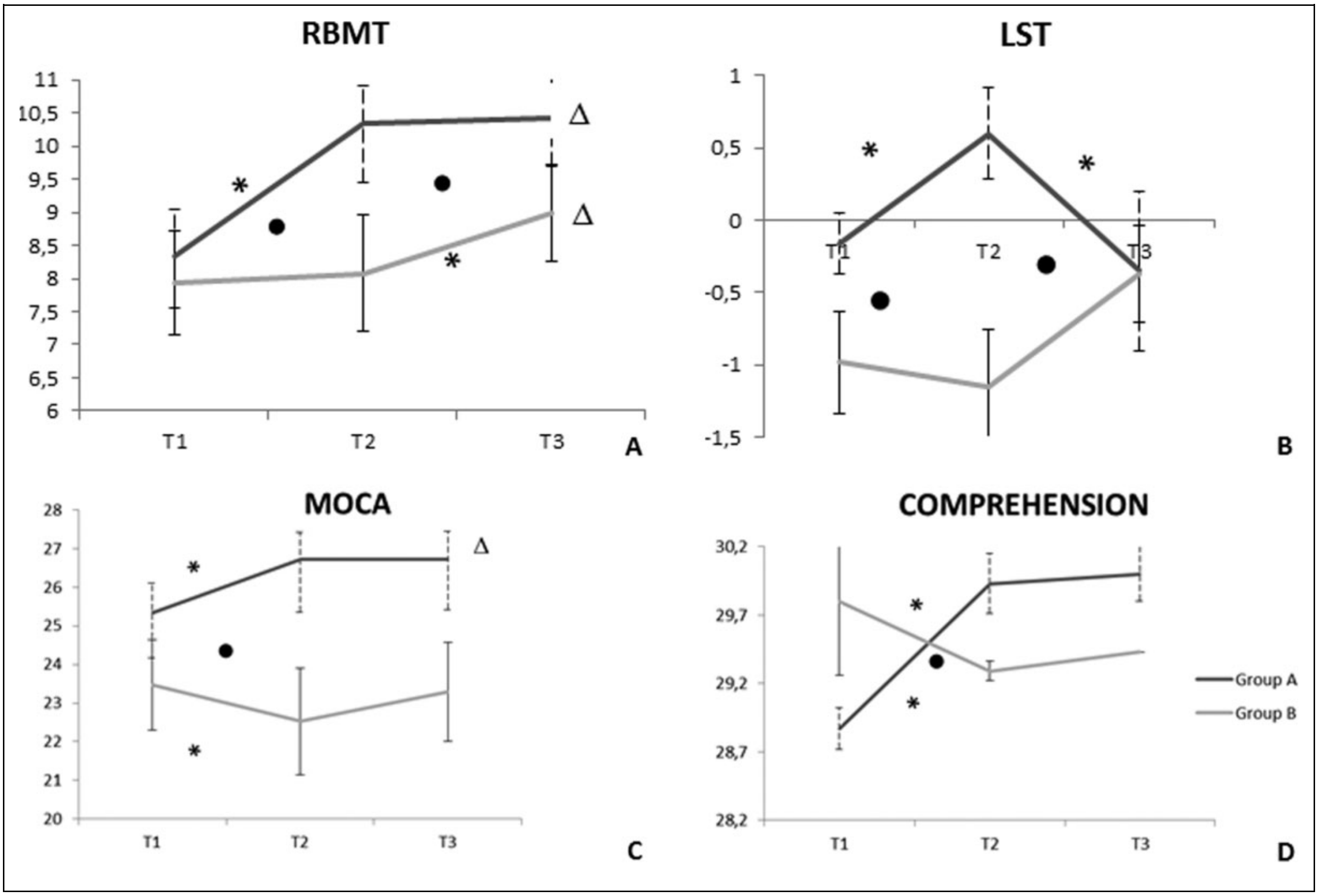

Figure 4. The effects of training on memory, general functions, and language. The means and standard errors of the 2 groups in the 3 assessments are reported. A indicates Rivermead Behavioural Memory Test; B, Listening Span Test; C, Montreal Overall Cognitive Assessment; D, Comprehension of phrases (Aachner Aphasia Test); •, Contrasts $P < .05$; *, t tests $P < .05$ in within-group comparisons (T1 vs T2 and T2 vs T3); $\Delta = t$ tests $P < .05$ in within-group comparison between T1 and T3.

An effect of interaction also emerges in the TEA between the testing sessions and group variables ($F_{27,\ 2} = 3.94$; $P = .025$), with significant main effects for session ($F_{27,\ 2} = 6.85$; $P = .002$) and group ($F_{27,\ 1} = 6.12$; $P = .02$; Figure 3B). In effect, the interaction contrasts show that the performance of the 2 groups significantly differs between T1 and T2 ($F_{27,\ 2} = 6.45$; $P = .017$) and between T2 and T3 ($F_{25,\ 2} = 4.22$; $P = .05$). Using this test, it is possible to hypothesize a specific effect of the training. In fact, group A improves in the interval between T1 and T2 ($t_{14} = 2.68$; $P = .018$) and maintains this recovery over time, showing a significant difference also between T1 and T3 ($t_{13} = 2.74$; $P = .017$). The performance of group B appears stable between T1 and T2 but improves after training ($t_{13} = 2.51$; $P = .026$).

In the SNA test, the variability between patients is notably extensive as indicated by the SDs reported in Figure 3C. Thus, the interaction between groups and sessions and contrast effects between the groups does not reach statistical significance. Nevertheless, group A seems to respond to the training with a significant improvement between T1 and T2 assessments ($t_{14} = 2.3$; $P = .037$) and maintains this recovery over time (T1 vs T3, $t_{13} = 2.52$; $P = .026$). The performance of group B on the other hand does not show any changes before and after training.

Finally, the interaction between groups and sessions in the ToL test does not turn out to be significant either. Nevertheless, although group A remains stable in their performance, group B shows a significant effect of the training (T2 vs T3, $t_{13} = 4.27$; $P = .001$). The contrast between the 2 groups is significant in the comparison between T1 and T3 ($F_{25,\ 2} = 5.57$; $P = .026$).

Memory

An effect of interaction emerges in the global scores of the RBMT between the testing session and group variables ($F_{27,\ 2} = 7.1$; $P = .002$), with a significant main effect for session ($F_{27,\ 2} = 24.17$; $P = <.001$) but not for group (Figure 4A). In effect, these contrasts show that the performance of the 2 groups differs significantly between T1 and T2 ($F_{27,\ 2} = 12.26$; $P = .002$) and between T2 and T3 ($F_{25,\ 2} = 7.5$; $P = .011$). Group A significantly improves after training ($t_{14} = 4.97$; $P < .001$) and maintains the recovery over time, showing a significant difference between T1 and T3 ($t_{13} = 4.94$; $P < .001$). Group B is stable in the time interval in which no training is carried out but improves as an effect of the training (T2 vs T3, $t_{13} = 3.37$; $P = .005$).

In the LST, the ANOVA indicates an interaction between testing session and group ($F_{27, 2} = 3.42$; $P = .041$), with a significant main effect for group ($F_{27, 1} = 4.67$; $P = .041$) but not for session (Figure 4B). The contrasts indicate that the 2 groups behave differently both in the intervals between T1 and T2 ($F_{27, 2} = 6.97$; $P = .014$) and between T2 and T3 ($F_{25, 2} = 6.22$; $P = .020$).

In Figure 4B, we see that these results are mainly due to performance of group A. Indeed, this group shows an immediate and significant recovery after training ($t_{14} = 2.3$; $P = .037$) which unfortunately does not resist over time ($t_{13} = 2.15$, $P < .051$). Group B also improves after training, but the difference does not appear to be statistically significant.

General Functioning and Language

Results from the tests for general functions and language show both the effects of cognitive stimulation and decline over time in the absence of specific training (Figure 4C and D).

In the MOCA test, the ANOVA indicates an effect of interaction between session and group ($F_{27, 2} = 5.75$; $P = .006$) with only the main effect of group close to significance ($F_{27, 2} = 4.11$; $P = .053$). The contrast effect between T1 and T2 ($F_{27, 2} = 13.86$; $P = .001$) is due to the improvement in performance of group A ($t_{14} = 2.3$; $P = .037$) and the simultaneous decline in group B ($t_{14} = 2.43$; $P = .029$). In the interval between T2 and T3, group A maintains their recovery. For group B, the recovery after training is not significant (Figure 4C).

Finally, the only aspect of language that seems to be influenced by training is comprehension. The interaction indicated by the ANOVA ($F_{27, 2} = 5.79$; $P = .005$) is explained by the contrast between the groups in the interval T1 to T2. Indeed, without stimulation group B declines in comprehension ($t_{14} = 2.17$, $P = .048$), while with training, group A tends to improve ($t_{14} = 1.98$; $P = .068$). In the interval T2 to T3, both the groups' scores are stable.

Individual Results

As expected, the pattern of performance was not homogeneous between the patients. In group A, 10 patients improved their personal performance in flexibility/attention shifting and in the Dual Task. This improvement was maintained over the 6-month interval period (for 11 patients in attention shifting and for 12 patients in the Dual Task). Although the scores in planning were globally quite good in both the groups, 5 people in group A responded to the training and all of them maintained the same scores in the follow-up.

Planning and attention shifting were stable in group B during the 6 months in which the patients did not participate in the training sessions. In fact, 11 patients did not change their scores in the ToL test and the same went for 7 of them in the TEA test. Some of them showed improvement as an effect of the stimulation (5 in planning and 7 in attention shifting). The others, except 1, remained stable during the period of cognitive stimulation. In contrast, the performance of 10 patients in the Dual Task declined between T1 and T2 and only partially recovered with training. Indeed, with stimulation, 3 patients improved their performance and 10 remained stable.

There was a statistical improvement in speed of execution after cognitive stimulation in group A, but this effect was probably due to the fact that the scores only relate to a small number of participants. Indeed, only 2 patients in group A and 3 in group B improved after training, while all the others remained stable.

In contrast, working memory turns out to be very responsive to training but only in the short term. In both the groups, the changes due to training are statistically significant and the number of patients responding to the stimulation is very high (11 in group A and 9 in group B). Unfortunately, this improvement did not resist over time. Indeed, in 8 patients the performance declined. Only 6 patients in group A showed an improvement in the comparison between T1 and T3.

Both groups significantly improved in the RBMT after training (8 patients in group A and 7 in group B), and this recovery resisted over time in all the patients in group A. In the MOCA, the scores of both groups improved (9 group A patients between T1 and T2 and 6 group B patients between T2 and T3). In group A, all the patients maintained recovery over time. Note that in the T1 to T2 interval, group B showed a decline in their performance in this test.

In the comprehension test, the period without stimulation also led to a decline in performance in group B. Unfortunately, group B did not recover after their decline, even with cognitive stimulation, while improvement in group A resisted over time.

In terms of general diagnosis, 8 patients showed an evolution in Alzheimer's-type dementia after the end of the training program. Among these, the performance of 6 people declined in the Dual Task and 1 person's performance declined in the attention-shifting tasks, during the period of the study.

Perceived Efficacy and Caregiver Reports

Unfortunately, we were unable to record any quantitative data concerning the effect of perceived efficacy due to the lack of suitable instruments. Nevertheless, a qualitative interview was carried out and clinical reports were collected. These indicate that the patients perceived some improvement in cognitive functions, in particular in attention and memory. In addition, they realized the importance of using specific strategies in daily life activities, although they also mentioned the difficulty in using them in a systematic way. The caregivers reported that they perceived some improvement in their own assistance skills and that they were more aware that the patients need to be autonomous in the activities that they are still able to perform.

Discussion

This study demonstrates the efficacy of a stimulation program that specifically focuses on the executive functions of patients affected by MCI. The results indicate that an improvement in these functions may have a positive effect on memory and general cognitive abilities. The benefits of the program are evident both immediately afterward and, at least in part, at a follow-up check 6 months later (group A). This is an important index of the successful maintenance of newly learned behaviors confirming the results of a previous study concerning the same methodology employed in a stimulation training program that focused on memory abilities.[17]

Another result (previously demonstrated and here confirmed) comes from the comparison between groups A and B (with group B receiving training after a delay of 6 months). It shows that without specific stimulation, the performance of patients with MCI declines over time and that after stimulation the recovery is only partial. Although the variability in terms of cognitive profiles and the evolution from MCI to mental deterioration is known to be extensive, a decline in executive functions is considered to be a significant risk factor in terms of the fast development of dementia.[13] Our data indicate that executive functions need to be stimulated right from the early stages of mental deterioration and that the precocity of cognitive stimulation may represent a crucial factor for the intervention to be successful. For this reason, specific controlled training programs that can prevent further mental decline are needed.[15]

Programs for executive functions have to date been used for rehabilitation in patients with acquired brain injury,[43] stroke,[44] schizophrenia,[45] and in children with developmental stuttering.[46] Nevertheless, to the best of our knowledge, only a few studies have specifically focused on training programs for attention control in patients with MCI,[16,47] while in the other cases, cognitive stimulation aimed to contribute toward memory improvement or offered multicomponential nonspecific activities.[7,48,49] In this study, working memory and planning (dorsolateral prefrontal cortex) and attention shifting plus divided attention (lateral orbital cortex and anterior cingulate cortex) were specifically assessed and trained[6] by means of specific tasks associated with the learning of cognitive strategies applied to day-to-day problems.

The executive functions that responded best to training were attention shifting and working memory (although the second only in the short term), while planning and execution speed did not seem to change with stimulation (but see[48,49]). In the Dual Task, data of group B show a significant deterioration during the period in which the patients did not participate in the training sessions. This confirms the most recent research demonstrating that poor Dual Task performance may be a critical prognostic index in older adults at risk of dementia.[50]

In general, we suggest that executive functions need to be continuously stimulated over time since training has a strong impact in the short term but not always enough of an effect to maintain efficient functioning in the long term. These results thus appear to be different from our results in the memory training sessions where learning strategies had more marked effects on functions trained, both immediate and delayed.[17]

Indeed, it is worth noting that our program focused on general cognitive strategies related to dealing with specific day-to-day problems rather than on repeated sessions of exercises for specific cognitive functions. For this reason, we would expect the effects of the intervention to involve a more strategic use of functions rather than a specific improvement of trained functions.

The results of the RBMT are also very interesting. This is an excellent test that investigates memory abilities in day-to-day contexts. Various memory tasks are mixed up with each other in a way that is very similar to normal daily life. For this reason, the test is very sensitive to memory deficits that are not shown by patients with MCI in other psychometric measurements. In addition, this test involves executive functions, as it requires the distribution of individual cognitive activity among various different tasks simultaneously. We therefore suggest that the improvement recorded in our patients in this test does not reflect a specific improvement in memory but rather a more efficient and strategic use of memory abilities which has been learned during training. Indeed, a training session concerning task planning, divided attention, inhibition of interferences, and monitoring of task execution may have a strong impact on the organization of the information that the patient has to remember, with a positive secondary effect on memory. The same explanation may also apply to the results for general cognitive abilities as measured by the MOCA.

To sum up, our data support the idea that executive abilities in patients with MCI can at least in part benefit from specific stimulation. In addition, they show that this improvement has indirect effects on general cognitive functioning and memory. Evidence demonstrating a capacity for neural plasticity in MCI is to date still meager.[51,52] Nevertheless the indications are that the behavioral changes recorded after cognitive stimulation may be trigged by neuroplastic effects. We consider that these potential changes may concern the general organization of cognitive reserve[53] rather than specific frontal-executive networks. Temporary activation of specific networks may explain the short-term improvement that does not resist over time (ie, working memory). However, in terms of the biological correlates of the more efficacious individual use of functions, we suggest that our training facilitates the activation of alternative, preexisting networks in the individual cognitive reserve not spontaneously recruited by patients. A recent functional MRI study[54] found extensive nonspecific hyperactivation in frontostriatal networks associated with better performance in executive functioning suggesting that this activation can support functional reorganization of a compensatory nature. More specifically, the authors suggest that in the early phase of MCI increased activation and compensatory neural reorganization may support cognitive functioning. The breakdown of these mechanisms signals a critical moment in brain deterioration and the progress of dementia. It is possible that our training activates these mechanisms linked to plasticity, acting on compensatory neural networks that are not involved in the pathological process and addressing them toward the maintenance of those cognitive abilities that are essential to daily life functions. The success of our program is due to a number of factors.

First, the training program was carried out in individual sessions. This meant that it was possible to target the training and strategies directly relating them to the needs and cognitive style of each individual patient. This also helped in terms of motivating each individual which is crucial to this and every rehabilitative program, as it allowed us to provide emotional support in moments of frustration. This program is very demanding in terms of energy and time, both for the operators and above all for the patients and their caregivers (2 sessions a week for 2 months and 1 weekly session for the other 4 months). For this reason, a high degree of drop out was expected. However, only 1 patient did not complete his or her follow-up assessment in group A and in group B another individual decided after the second assessment not to participate in the training sessions. All others regularly participated in the training sessions and assessments. As already discussed in the previous study on the subject of memory stimulation,[17] during the intensive phase of training, a very close relationship evolves between the operator, the patient, and the caregiver, with a therapeutic form of alliance that helps in terms of motivating the patients and encouraging their efforts.

A second factor contributing to the success of the program is the presence of caregivers. The caregiver is a key factor in the training of abilities and the use of strategies in the context of daily life. Indeed, the caregivers inform the operators about the real needs of each individual, reporting also on which activities he or she can do alone, in which he or she needs supervision (checking) or assistance in order to carry out and which he or she can no longer perform. At the same time, they can be instructed on how to encourage and assist patients to use the strategies they have learned at home.

Literature on the patient confirms the importance of the duration of a training program: the length of time needed is absolutely crucial, since executive functions are strongly influenced by the effects of training.[55]

Finally, another strength of the study design was the crossover paradigm that permitted us to monitor (i) the immediate results by means of posttraining assessments; (ii) the delayed effects in group A when comparing the pre- and posttraining assessments with the final evaluation; and (iii) decline in group B during the period that they did not participate in the training sessions.

With respect to subjective outcome measurements (self-reported questionnaire), participants reported a high level of satisfaction concerning the training and a high level of perceived usefulness concerning the strategies they had learned. Nevertheless, they also reported their difficulties in developing a personalized program to ensure regular practice of these strategies.

The study has some limitations. Unfortunately, it was not possible to obtain data from functional neuroimaging in order to document the neural correlates to behavioral changes. Other limitations of the study are the small number of patients and the lack of quantitative measurements concerning the use of strategies. In addition, the questionnaire employed to assess the patients' perceived well-being and sense of efficiency did not provide sufficient information. Nevertheless, qualitative feedback from patients indicated an improved sense of control regarding cognitive functioning and increased confidence in their abilities. This was confirmed by caregivers who also reported increased confidence in their assistance skills. However, in this case too, our results are limited by the lack of quantitative data. Further research is needed to identify specific tools that will enable us to compare neuropsychological results not only with neuroimaging evidence but also with subjective measures of well-being.

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