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A pilot study for rehabilitation of central executive deficits after traumatic brain injury

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Abstract

Primary objective: An impairment of the central executive system (CES) of working memory (WM) is a common consequence of traumatic brain injury (TBI), and may also explain deficits in divided attention, long-term memory and executive functions. Here we investigated the efficacy of a rehabilitative program (working memory training: WMT) targeting the CES in improving WM and other cognitive functions dependent on this system.
Methods and procedures: Nine TBI patients with severe WM deficits underwent the WMT (experimental training). The WMT was preceded by a general stimulation training (GST; control training). Patients' cognitive performance was evaluated at the admission, after the GST and at the end of the WMT.
Main outcomes and results: Whereas the GST had no effect on patients' performance, after the WMT patients improved in all the cognitive functions dependent on the CES, but not in those functions not thought to tap this system. Importantly, a beneficial WMT effect was found on patients' everyday life functioning.
Conclusions: The results support the efficacy of the WMT in recovering CES impairments.

Keywords: *Traumatic brain injury, working memory, working memory training, central executive system, Glasgow Coma Scale*

Introduction

Cognitive impairment is the most frequent cause of disability after traumatic brain injury (TBI) in patients with moderate or good neurological recovery [1, 2]. Patients with TBI typically exhibit deficits in various cognitive domains, such as attention [3–5], executive functions [6–8] and memory [9–11]. The real life disorganization caused by such deficits is often associated with negative psychosocial outcomes [12]. For this reason, in the last few years, the field of TBI rehabilitation has experienced a rapid growth [7, 13].

So far, the main approach that has been used to treat cognitive deficits after TBI is to restore impaired cognitive functions by requiring participants to complete a series of repetitive exercises engaging the purported functions, in order to promote the recovery of underlying neural circuits [2]. As such, most rehabilitative interventions target a specific aspect of patients' cognitive impairment, such as attention, executive functions or memory deficits [7, 13]. For example, Sohlberg and Mateer [14] developed a training program (APT) for patients with attention deficits, involving repeated focused, sustained, selective and divided attention tasks, which led to a significant improvement of attention (see also [15, 16]). As far as executive functions are concerned, Von Cramon et al. [17] developed a problem solving training (PST) based on 'problem orientation, definition and

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formulation', and compared it to a control training, involving memory exercises, in remediating executive deficits of TBI patients. Only patients who received the PST showed gains on various problem solving tasks. The efficacy of the treatment was corroborated by a later study by Levine and colleagues [18, 19], who demonstrated the generalization of the effects of a rehabilitative program derived from the PST [17] to real-life activities (i.e., meal preparation). As for memory rehabilitation, interventions may include training in mnemonic strategies, such as rehearsal, organization strategies, visual imagery, and use of mnemonics [7, 13, 10, 20].

Given the typical copresence of multiple cognitive deficits in TBI patients, many authors have recognized the need to develop treatments targeting multiple areas of cognitive functioning simultaneously, by providing sequentially specific intervention for each deficit [7]. These multimodal rehabilitative programs, however, may result in long training sessions and great effort for patients [7, 21]. It is worth noting that these 'serial' approaches to rehabilitation of TBI symptoms rely on the assumption that specific cognitive functions need specific training to be restored [16]. An alternative approach is however possible if one has reasons to postulate a hierarchical model by which training in one cognitive system would generalize to other systems, which are functionally dependent on the trained one.

The present study presents preliminary results concerning the effectiveness of a rehabilitative intervention for multiple cognitive deficits after TBI based on such an approach. In a previous study [22], we have demonstrated that a complex pattern of cognitive deficits, still present in the chronic phase of TBI and involving WM, divided attention, executive functions, and long term memory deficits, depended on an impairment of the central executive system (CES; [23, 24]). According to Baddeley [23, 24], the CES subserves several cognitive functions. Indeed, this system seems to have a role in dividing attention resources among concurrent tasks [25], in coordinating cognitive functions during problem solving [22, 24], and in processing and organizing incoming information to be stored in long-term memory [26]. Consistent with this theoretical model, by using regression analyses, we found that patients' performance on a test tapping CES functioning predicted performance on tasks requiring divided attention, executive functions and long-term memory. In contrast, no relation emerged between CES functioning and measures of more basic abilities, such as sustained attention or speed processing, which do not share the same need for executive resources [22; see also 25, 27, 28].

Based on these findings, it is possible to speculate that a rehabilitative treatment acting on CES functioning may be effective in improving simultaneously all the cognitive functions dependent on the CES, i.e., WM, divided attention, long-term memory and executive functions, while leaving unaffected those functions not thought to tap this system, i.e., sustained attention and speed processing [22].

Nine TBI patients presenting WM deficits underwent the WMT (experimental training). The treatment consisted of three working memory tasks, i.e., the PASAT [29] and two alternative versions of this task [30]. The WMT was preceded by a 'general stimulation training' (GST; control training), during which patients performed simple decision tasks, requiring low executive demands, and progressively familiarized with the testing setting.

To evaluate the efficacy and the specificity of the WMT, the scores obtained in a battery of neuropsychological tests at the admission (screening session), after the control training (GST; intermediate session) and at the end of the experimental training (WMT; final session) were compared. If the WMT is effective in recovering CES deficits, a significant improvement in WM as well as in the other cognitive functions dependent on this system, i.e., divided attention, long-term memory, and executive functions, should be found between the intermediate and the final session. In contrast, no change is expected in more basic attention abilities, such as sustained attention and speed processing, which are not thought to be dependent on the CES [22]. Such a 'selectivity' of improvement would argue: (i) for the specificity of the WMT in recovering CES deficits, and (ii) against any possible interpretations of the WMT effect as due to general cognitive stimulation or practice effects.

To provide further support to the efficacy of the WMT, and elucidate the mechanism underlying the performance improvement, the effect of the WMT has been compared to that of the GST. If, as we suspect, the WMT effect was unequivocally determined by the massive training of the CES provided by the WMT, no significant performance improvement should be found after the GST, which involved tasks not thought to tap the CES. In contrast, if the WMT effect was due to the mere presence of unspecific cognitive stimulation or to relational and psychological factors, a significant performance improvement should be observed also after the GST, during which patients performed basic cognitive tasks and received psychological support.

The second aim of the present study was to investigate whether the improvement obtained in neuropsychological tests after the WMT also generalized to daily living activities. Most rehabilitation studies report an amelioration of cognitive performance of TBI patients but they happen to ignore their real-life functioning that may be more informative about the specific difficulties patients encounter in everyday life [7, 21]. Therefore, in the present study the effects of WMT were evaluated not only in relation to conventional neuropsychological tests, but also in the context of everyday life. In particular we used the 'Rivermead Head Injury Follow-Up Questionnaire' (RHFUQ, [12]), that assesses patients' subjective experience of everyday difficulties, and the 'Patient Competency Rating Scale' (PCRS; [1]), in which patients evaluate their everyday functioning. These psychosocial outcome scores obtained before and after the WMT were then compared.

Method

Subjects

Table I shows patients' demographic data and cognitive outcomes. Nine TBI patients participated in the study. Participants were selected among a sample of patients referred to the Centro Studi e Ricerche in Neuroscienze Cognitive, Cesena, for evaluation and treatment secondary to diagnosis of TBI. Participants underwent a standardized battery of neuropsychological tests evaluating sustained attention, speed processing, WM, divided attention, executive functions and long-term memory (see below). Patients were selected on the basis of a severely impaired performance in WM (percentile value ≤ 5). Patients voluntarily participated to the study. Participants involved in the study were at least 6 months post-injury, to minimize the effects of neurologic recovery. Patients with other neurological disease, emotional or psychiatric disturbance, as well as patients with communication problems were excluded from the study. Patients gave their informal consent to participate according to the Declaration of Helsinki (BMJ 1991; 302:1194) and the local Ethical Committee.

The sample included 6 males and 3 females, with a mean age of 34 years (range 16–57) and a mean level of education of 12 years (range 8–18). The mean elapsed time between date of the injury and date of the neuropsychological examination was 28 months (range 6–61). The severity of the injury was evaluated according to the Glasgow Coma Scale at the admission (GCS; [31]). Mean GCS score at the admission was 10 (range 5–15). Duration of PTA was not considered as an index of trauma severity because it was not available for all patients. As far as severity of brain lesions is concerned, patients were classified according to Marshall's method [32] into one of the following classes:

(1) Diffuse Injury I: Intracranial pathology not detectable at the CT/MRI scan.
(2) Diffuse Injury II: Cisterns present, with midline shift <5 mm and high or mixed-density lesions <25 cc.
(3) Diffuse Injury III with swelling and IV with shift: Cistern compressed or absent, midline shift, high or mixed-density lesions >25 cc.
(4) Evacuated + Non-evacuated Mass lesion: High or mixed-density lesion >25 cc.

Six patients were classified as DI1. For the three patients presenting intracranial pathology detectable at the CT/MRI scan (DI2), lesion site is shown in Table I.

Table I. Patients' demographic and clinical data. Patients' demographic and clinical data according to gender, age, level of education, severity of TBI (GCS < 9 = severe, GCS 9–12 = moderate, GCS > 12 = mild), severity of brain injuries (DI = intracranial pathology not visible on CT/MRI scan, DII = cisterns present, with midline shift of 0–5 mm, lesion present but no high- or mixed-density lesion > 25 cc), time from TBI, and level of performance (in percentile value) for speed processing (SP), sustained attention (SA), working memory (WM), divided attention (DA), long term memory (LTM) and executive functions (EF = Letter Fluency; EF2: Tower of London).

Case	Sex	Age	Level of education (years)	Time since injury (months)	Severity of trauma (GCS)	Severity of lesion (Type)	Site of Lesion	SP	SA	WM	DA	EF1	EF2	LTM
M.A.	M	25	12	61	15	DI1	\	73	31	1	37	54	0	39
S.U.	M	32	18	6	6	DI1	\	42	31	1	22	30	2	0
L.C.	F	47	13	23	13	DI2	Left temporal	0	31	1	7	23	60	39
R.M.	F	29	8	78	5	DI2	Left frontal	31	16	0	22	2	8	0
V.R.	M	57	13	20	15	DI1	\	0	23	5	66	58	75	17
L.S.	F	20	13	19	5	DI2	Right frontal	8	31	4	17	6	25	0
D.S.	M	16	8	22	5	DI1	\	38	22	2	7	7	3	0
A.V.	M	31	13	15	15	DI1	\	50	2	5	16	35	75	35
E.C.	M	48	8	13	12	DI1	\	5	27	4	7	4	75	35
Mean	/	33.9	11.8	28.6	10.1	/		27	24	3	22	24	36	18

Neuropsychological assessment

To assess speed processing, 'Alertness' subtest from the Testbatterie zur Aufmerksamkeitsprufung (TAP [33]; see [34] for Italian normative data) was used. This test measures reaction times (RTs) with or without a warning signal. Subjects were required to press a button as quickly as possible as a target appeared in the middle of the computer screen. There were 4 blocks of trials, for a total of 80 trials. Mean RTs to stimuli presented without a warning were used as a measure of speed processing.

Sustained attention was evaluated by using the 'Optical vigilance' subtest from TAP [33, 34]. In this task, a bar moved up and down with a 1.8 cm oscillation in the center of the computer screen. Subjects were required to press a button whenever the bar showed a larger oscillation. The test lasted 10 minutes, and the target rate was about one stimulus per minute, for a total of 10 targets. The number of omissions was adopted as index of sustained attention performance, since it has been demonstrated to be highly reliable [8].

To assess divided attention, the 'Divided Attention' subtest from TAP [33, 34] was used. In this test, two simultaneous tasks, one visual and one acoustic, were administered. With regard to the visual task, a series of 10 by 10 cm matrices were displayed on a computer screen, each for 2 seconds. A matrix consisted of an array of dots, with 7 'X's randomly superimposed over them. Subjects were requested to press a button whenever 4 'X's formed a square. On the acoustic task, subjects listened to a continuous series of a high tone followed by a low tone and were requested to press a button whenever a repetition of two identical tones occurred. Thirty targets were given (15 acoustic and 15 visual). As measure of divided attention performance the number of omissions was taken into account, since it has been demonstrated to have the highest reliability [34].

To evaluate working memory, the 'Working memory' subtest from TAP [33, 34] was used, which consists in a 2-back task. In this task, a randomly ordered sequence of 100 digits appeared in the middle of a computer screen at the rate of one stimulus every 3 seconds. Subjects were required to press a button whenever the presented digit matched the stimulus occurred two positions back in the sequence. Fifteen target stimuli were given. The sum of omissions and false reactions was adopted as measure of WM performance.

The Buschke–Fuld Test ([35]; Italian version by Spinnler and Tognoni [36]), was used to assess long term memory performance. More specifically, the Consistent Long Term Retrieval score (CLTR), i.e., the number of words which were repeatedly recalled without need for further reminding until the last trial, was taken into account, because it has been demonstrated to be a highly sensitive measure of long term memory impairment after TBI [22].

Finally, to assess executive functions, two tests were used. In the Letter Fluency test [37], the total number of generated words was considered as a measure of executive functioning. In the Tower of London Test [38], the 'total move score', i.e., the number of moves executed by the subject minus the minimum number of solution moves was taken as an index of executive performance.

When possible, different standardized versions of tests were used in the three neuropsychological evaluations in order to minimize practice effects. Scores obtained in each test were converted into the respective percentile values. A percentile value <5 indicated a severely impaired performance; a percentile score ranging from 5–10 a mildly impaired performance, and a percentile value >10 a normal performance.

Psychosocial assessment

Two psychosocial outcome scales were used to assess patients' everyday functioning: The Rivermead Head injury Follow-Up Questionnaire (RHFUQ, [12]) and the Patient Competency rating Scale (PCRS, [1]).

The RHFUQ [12] lists 10 aspects of everyday life commonly affected by TBI. For each item, patients are required to rate the degree to which their efficacy in such activities had changed since brain injury, ranging from 0 (no change) to 4 (complete change). The sum of ratings obtained on all items was taken as measure of patients' everyday efficacy.

The PCRS [1] lists 30 activities of daily living, involving both cognitive abilities and physical functions. Patients are requested to use a 5-point Likert scale to rate their difficulty in a variety of everyday life activities, ranging from 0 (easy) to 5 (impossible). The sum of the ratings on all items was taken as measure of patients' everyday functioning.

Rehabilitative program

Working Memory Training (WMT; experimental training). The WMT was based on the repeated administration of the Paced Auditorily Serial Addition Test (PASAT; [29, 39]), which has been demonstrated to tap CES processes [40–42], and of two experimental tasks we derived from the PASAT, i.e., the 'Months task' and the 'Words task' [30].

The PASAT was administered by presenting auditorily a long sequence of digits, one at time. Patients were required to add each new number to the immediately preceeding one and say aloud the answer. Thus, if the first two digits presented were

5 and 6 the participants had to say 11 (5 + 6) and if the third digit was 3 the participants had to say 9 (6 + 3).

The 'Months task' was administered by presenting auditorily a sequence of months' names, one at time. The patients' task was to say aloud which month between the last and the immediately preceeding one come earlier in the calendar. Thus, if the first two months presented were *January* and *June* the participants had to say *January* (January ⇒ June) and if the third month was *August* the participants had to say *June* (June ⇒ August).

The 'Words task' was administered by presenting auditorily a sequence of common words, one at time. The patients' task was to extract the third letter of the last word and to produce a word beginning with that letter when the next word was presented. Thus, if the first two words presented were *Spaghetti* and *Pomodoro* the participants could say for example *Aglio* (Sp-*A*-ghetti) and if the third word was *Sole*, the participants could say for example *Mare* (Po-*M*-odoro).

In order to vary the difficulty of the tasks, the interstimulus interval (ISI) was varied (4000 msec; 3000 msec; 2600 msec; 2200 msec; 1800 msec): Patients initially performed the slowest version of the tasks and when they achieved a level of performance (i.e., number of correct responses) comprised between 1 and −1 standard deviation from that of normal controls (normal criterion), the ISI was reduced. Normative data for the PASAT, the 'Months task' and the 'Words task' relative to each ISI were obtained by submitting the three tasks to a large sample of healthy Italian subjects varying in age from 15–70 years and in level of education from 3–20 years [10]. The WMT was considered concluded when patients achieved the normal criterion in the three tasks in relation to each ISI level.

General stimulation training (GST; control training). The initial GST sessions were directed toward providing the patients with a description and an interpretation of their cognitive impairments with the aim to increase patients' awareness of their cognitive deficits and disabilities. The relation between cognitive deficits and symptoms such as anxiety, irritability and fatigue was also explored [1].

In addition, during the GST, three simple decision tasks were repeatedly administered to patients. These tasks involved the same material used for the WMT tasks, but with a crucial difference: Whereas the three training tasks used during the WMT required the continuous manipulation and updating of information in WM and therefore tapped CES processes, the tasks used during the GST only required basic-level attention demands, like the ability to maintain vigilance on a task over a long period of time.

The 'Even task' was administered by presenting auditorily a long sequence of digits, one at a time. After the presentation of each number, patients had to say, as quick as possible, 'even' if the number was even or 'odd' if it was odd.

The 'Winter task' was administered by presenting auditorily a sequence of months' names, one at time. After the presentation of each stimulus, patients had to say, as quick as possible, 'winter' if that month occurred in winter (December, January, February) or 'no winter' if it was one of the remaining months.

Finally, the 'Consonant task' was administered by presenting auditorily a sequence of common words, one at time. After the presentation of each word, patients had to say, as quickly as possible, 'consonant' if the first letter of that word was a consonant or 'vowel' if it was a vowel. The interstimulus interval (ISI) was sistematically reduced (4000 msec; 3000 msec; 2600 msec; 2200 msec; 1800 msec) across the GST sessions.

Procedure

Neuropsychological profile of TBI patients was evaluated at the admission (screening session), after the GST and at the end of the WMT. Results from the screening session allowed us to recruit experimental patients on the basis of their severely impaired WM performance, as tested by the 'Working Memory' subtest from TAP [33] (percentile value ≤5). After the screening session, patients underwent the GST, which consisted of four sessions a week, over a period of 4 weeks. During each GST session, patient received 6 tasks' administrations (2 for the 'Even task', 2 for the 'Winter task' and 2 for the 'Consonant task'). Patients received 15 tasks' administrations at each ISI, and the total amount of administrations patients received during the GST was 75 (see Table II). When the GST was concluded, a new neuropsychological

Table II. Experimental and control training data. Mean number of task administrations (cumulated across training tasks) received during the working memory training (WMT) and the general stimulation training (GST) in relation to each ISI level.

	Number of task administrations	
ISI (msec)	WMT	GST
4000	19.8 (±4.4)	15
3000	13.2 (±2.7)	15
2600	10.2 (±2.3)	15
2200	11.2 (±2.1)	15
1800	14.3 (±2.1)	15

evaluation was performed (intermediate session). In the same context, the psychosocial outcome of patients was evaluated. After the intermediate session, patients underwent the WMT, which consisted of four sessions a week, and usually lasted 4 weeks (see below). At the end of the WMT patients received a new neuropsychological and psychosocial assessment (final session).

The neuropsychological assessments (screening, intermediate and final session) and the rehabilitative program (GST + WMT) were conducted by two different neuropsychologists, who were blind to the experimental hypotheses.

Data analysis

Patients' scores in neurpsychological tests were firstly transformed into percentile scores and then analyzed by a within-subjects ANOVA with Function (speed processing, sustained attention, WM, divided attention, long-term memory, and executive functions, i.e., Letter Fluency and Tower of London) and Session (screening, intermediate, final) as factors.

Results

Results related to the experimental and control training

Patients' performance in the three GST tasks in relation to each ISI was errorless. As far as the WMT is concerned, the mean number of tasks' administrations (cumulated for PASAT, 'Months task' and 'Words task') necessary to reach the normal criterion in relation to each ISI level was calculated. As a group, patients needed 19.8 (±4.4) [mean ±standard deviation)] administrations to achieve normal scores in relation to the 4000 ms ISI, 13.2 (±2.7) for the 3000 ms ISI, 10.2 (±2.3) for the 2600 ms ISI, 11.2 (±2.1) for the 2200 ms ISI, and 14.3 (±2.1) for the 1800 ms ISI. The total amount of tasks' administrations patients received during the WMT was 69 (±10.4) (see Table II).

Results related to the neuropsychological outcome

To investigate the effects of WMT (experimental training) and that of the GST (Control training) on WM, divided attention, executive function, long term memory, sustained attention and speed processing, an ANOVA was performed on performance level with Function (speed processing, sustained attention, WM, divided attention, long term memory, and executive functions, separately for Letter Fluency and Tower of London scores) and Session (screening, intermediate, final) as within-subject factors.

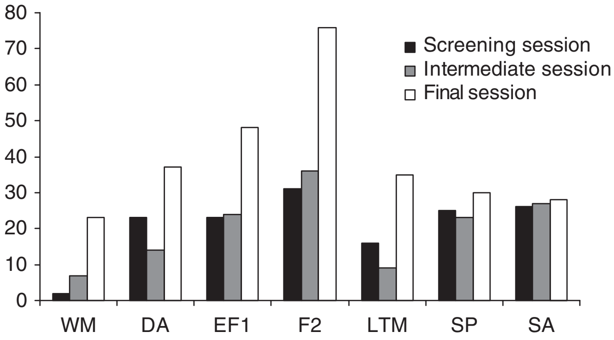

Figure 1. Experimental and control training effects. Patients' performance (expressed in percentile value) at the admission (screening session), after the GST (intermediate session) and after the WMT (final session). WM = Working memory; DA = divided attention; LTM = long-term memory; EF1 = executive functions, Letter Fluency; EF2 = Tower of London; SP = speed processing; SA = sustained attention.

The ANOVA revealed a significant effect of Session [$F(2, 16) = 20$; $p < 0.0001$]. Post hoc comparisons revealed a significant performance improvement from the intermediate to the final session (20 vs. 39 respectively; $p < 0.0005$), i.e., after the WMT, while no difference was found between the screening and intermediate session (21 vs. 20 respectively; $p = 0.46$), i.e., after the GST. More importantly, the interaction Session x Function was significant [$F(12, 96) = 2$; $p < 0.05$]. Post hoc comparisons, performed with the Duncan test, revealed that, compared to the intermediate session, in the final session patients significantly improved in WM (7 vs. 23; $p < 0.05$), divided attention (14 vs. 37; $p < 0.05$), executive functions (Letter Fluency: 24 vs. 48; $p < 0.05$; Tower of London: 36 vs. 76; $p < 0.005$) and long term memory (9 vs. 35; $p < 0.05$), but not in speed processing (23 vs. 30; $p = 0.37$) and sustained attention (27 vs. 28; $p = 0.8$; see Figure 1). In contrast, no significant difference was found between the scores obtained in the screening and in the intermediate sessions, i.e., after the GST, in all the cognitive functions investigated ($p > 0.15$ in all comparisons; see Figure 1).

Results related to the psychosocial outcome

To investigate the effect of the WMT on the psychosocial outcome of TBI patients, repeated measure t-tests were performed on the scores obtained in the 'Rivermead Head Injury Follow-up Questionnaire' (RHFUQ) and in the 'Patient Competency Rating Scale' (PCRS) before and after the WMT (intermediate vs. final session).

A significant difference was found between the RHFUQ scores obtained before and after the WMT

(22 vs. 10; $t(8) = 3.7$; $p < 0.001$). Similar results were found for the PCR scores, that were higher in the final than in the intermediate session (125 vs. 116; $t(8) = 2.4$; $p < 0.05$).

Discussion

Several studies [6, 40, 43] have indicated that TBI patients show an impairment of the central executive system (CES) of working memory (WM). More recent is the evidence that a unique CES impairment is at the core of a characteristic pattern of symptoms following TBI, involving WM, divided attention, executive functions and long-term memory deficits [22]. This evidence is in line with the Baddeley's model of the CES, which seems to be involved in regulating the distribution of limited attentional resources, selecting and organizing goal directed behaviours, and processing information to be stored in long term memory [23, 24].

Based on our previous findings [22], the main aim of the present study was to investigate whether a rehabilitative treatment (WMT) acting on CES functioning could be effective in recovering simultaneously all the cognitive functions dependent on the CES, i.e., WM, divided attention, executive functions and long-term memory, while leaving unaffected those cognitive processes not thought to depend on this system, like speed processing and sustained attention. With this aim, nine TBI patients with severe WM deficits underwent the WMT which consisted of performing three tasks with high executive demands until the achievement of normal scores [30].

The results of the present study support the efficacy and the specificity of the WMT in improving the cognitive functions dependent on the CES. First, we found a significant improvement in WM after the WMT. That is, all patients, who showed severely pathological WM performance (percentile value ≤ 5), at the end of the WMT obtained normal scores in a 2-back task (percentile value ≥ 10), which requires the continuous monitoring and updating of information in WM.

Next, the effect of the WMT generalized to the other cognitive functions dependent on the CES [22]. More precisely, after the WMT patients showed a better divided attention performance, suggesting an enhanced ability to distribute attentional resources among concurrent tasks. Moreover, after the WMT a significant performance improvement was detected in two tests tapping executive functions [37]. Indeed, patients showed an improved ability to initiate and guide a lexical search according to a given phonemic cue (Letter Fluency) and to select the moves necessary to rearrange three beads from their initial position to the one requested by the examiner (Tower of London test). The finding of improved performance on the Tower of London test is particularly important to demonstrate an improvement of executive functions after the WMT. Indeed, while the improvement in Letter Fluency might be, at least partially, attributable to a task-specific treatment effect (i.e., the 'Words task' requires the production of words beginning with a given letter), this reasoning cannot be applied to the amelioration found in the Tower of London test, which clearly does not share any feature with the training tasks. However, this conclusion should be taken with caution, since some of the improvement shown in the Tower of London might also depend on practice effect. Finally, as far as long-term memory is concerned, in line with our predictions after the WMT patients were able to store a higher number of items, thus exhibiting an improvement of long-term memory performance.

These results are in line with previous research on training programs targeting the CES [40, 44]. For example, in a study by Cicerone [40], a training program based on increasingly demanding *n*-back tasks was found to improve, beyond working memory, also several measures of attention. Our results extend this evidence, by showing that a CES recovery generalized to *all* the cognitive functions subserved by this system, in accordance with the most up-to-date model of the CES as the superordinate controller of many cognitive domains [24], including memory [26].

It is important to note here that the performance improvement observed after the WMT is unlikely to be due to general cognitive stimulation, practice effects, or to any possible role played by psychological and relational factors [21], since these factors were not effective during the control training. The same reasoning applies for another plausible effect as a possible explanation for the improvement, i.e., the motivation for being involved in a research study. Indeed, patients were informed that the GST was a part of the treatment for their deficits. It is worthwhile remembering, indeed, that the basic-level cognitive stimulation provided by the GST did not produce the amelioration observed after the WMT, nor did a putative reduction of psychological and relational symptoms, such as anxiety and irritability.

We therefore argue that the improvement in WM, divided attention, long term memory and executive functions found after the WMT was unequivocally related to the specific CES training provided by this treatment. The results concerning the specificity of the WMT are relevant to this idea. At variance with the cognitive functions dependent on the CES, sustained attention and speed processing did not improve after the WMT: Patients presented similar reaction times to a visual target and the same amount of omissions in a vigilance task before and after the experimental treatment. The generalization of the effects of the WMT to the cognitive functions dependent on the CES, but not to those functions not thought to tap this system, suggests that the WMT effect was not mediated through an unspecific increase in arousal or response speed, but through specific factors promoting the recovery of CES integrity.

A similar specific effect was observed by McDowell and colleagues [45] with regard to a pharmacological, rather than cognitive, treatment of CES deficits. The authors administered bromocriptine, i.e., a dopamine receptor agonist thought to enhance prefrontal functions, to a sample of TBI patients. Bromocriptine was found to improve performance on some tasks subserved by prefrontal functions, such as WM, divided attention and executive functions tasks, but not on tasks without significant executive demands, such as those requiring sustained attention or passive mainenance of information in short-tem memory. These results are much in accordance to ours in showing that some executive processes are linked to one another by overlapping neurochemical and functional substrates, and thus may be recovered simultaneously [45].

A second aim of the study was to investigate whether, and to what extent, the cognitive improvement found after the WMT also generalized to daily living activities. To this aim, the results obtained by patients in two psychosocial outcome scales before and after the WMT were compared. The results showed a significant improvement of RHFUQ [12] and PCRS [1] scores, suggesting an enhanced everyday functioning and perceived self-efficacy in patients after the WMT.

In summary, the results from the present study confirm that a treatment acting on CES functioning is effective in ameliorating not only WM but also, and in parallel, the other cognitive functions thought to depend on this system, i.e., divided attention, long term memory and executive functions. Importantly, since in the present study only chronic patients were studied, our results indicate that recovery of CES processes can occur even after stabilization of cerebral damage.

One main issue should be considered before a final conclusion. This treatment is based on a specific model of cognitive deficits after TBI. The selection of patients is of great importance in order to predict the outcome: Only patients showing a well defined cluster of TBI symptoms, i.e., a set of impairments depending on CES system, might benefit of WMT; whereas patients with different impairments probably require a different intervention. Therefore, inclusion criteria, based on a well detailed neuropsychological assessment, should be established before starting the treatment in clinical practice.

Finally, one limitation of the present study is the relativelly small sample size. Future research should be conducted with a larger sample of TBI patients: This would allow the confirmation and extension of the present data and the discovery of possible individual, clinical or demographic characteristics able to discriminate patients who may or may not benefit from the treatment. Morever, future fMRI investigation would be useful in verifying whether rehabilitative interventions targeting CES contribute to re-establish the appropriate functional connectivity upon which this system relies, which is altered in TBI patients [46–48].

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