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A randomized, controlled trial of computer-assisted cognitive remediation for schizophrenia

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ABSTRACT

Objective: There is considerable interest in cognitive remediation for schizophrenia. Our study aimed to evaluate, in a large sample of patients with schizophrenia, the interest of a computer-assisted cognitive remediation program on cognitive performances of patients as well as in clinical and functional outcome.

Method: Seventy-seven patients with remitted schizophrenia were randomly assigned to 14 2-hours individual sessions of computer-assisted cognitive remediation (n = 39) or a control condition (n = 38). Remediation was performed using RehaCom ® software. Four procedures were chosen to train four cognitive functions involved in different stages of the information processing: attention/concentration, working memory, logic, and executive functions. Primary outcomes were remediation exercise metrics, neuropsychological composites (episodic memory, working memory, attention, executive functioning, and processing speed), clinical and community functioning measures.

Results: Cognitive performances concerning Attention/vigilance, verbal working memory and verbal learning memory and reasoning/problem solving improved significantly in the remediation condition when no difference was reported in the control condition between the 2 assessments. However, there were no significant benefits of cognitive remediation on non-verbal working memory and learning and speed of processing or functional outcome measures.

Conclusions: Cognitive remediation for people with schizophrenia was effective in improving performance, but the benefits of training did not generalize to functional outcome measures. Long term follow-up studies are needed to confirm the maintenance of such improvements.

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1. Introduction

Cognitive deficits are routinely evident in schizophrenia with an average degree of one standard deviation below the normative mean (Dickinson et al., 2007). Verbal memory, attention, working memory, problem solving, processing speed, and social cognition are the most heavily impaired domains (Palmer et al., 2009). Cognitive deficits are stronger predictor of long-term functional outcomes, such as work performance and independent living, than positive or negative symptoms (Kurtz, 2006). Both conventional and even second-generation antipsychotic medications are poorly effective on cognitive deficits (Woodward et al., 2005). Different pharmacological interventions to enhance cognition have been evaluated, including acetyl-cholinesterase inhibitor (Keefe et al., 2008), nicotinic agonist (Freedman et al., 2008), glutamatergic agents (Buchanan et al., 2007) but none of these results have been particularly encouraging (Harvey, 2009).

The finding of limited efficacy of pharmacological intervention has increased interest in a class of behavioural treatments known as cognitive remediation therapy (CRT) that specifically targets memory, attention, reasoning, and similar capacities, with the ultimate aim of enhancing everyday functioning. CRT has already proven effectiveness in the field of neurological impaired patients rehabilitation (Rohling et al., 2009). A number of approaches have been developed in the last fifteen years to remediate cognition in schizophrenia. Meta-analysis (McGurk et al., 2007) concludes that cognitive remediation in schizophrenia yields moderate improvements in cognitive performance, and that these neurocognitive gains translate to improvement in psychosocial functioning. Moreover, the intervention is well accepted amongst the patients (Rose et al., 2008) and the effects are durable up to 6 months after the withdrawal of the therapy (Hodge et al., 2010) and the intervention is well accepted amongst the patients (Rose et al., 2008). However, the remediation programmes used are very heterogeneous and most studies are of poor methodological quality; large randomised controlled trials remain scarce.

CRT programs differ in approaches (restorative versus compensatory, "bottom-up" or "top-down" strategies) in support (computer or paper and pencil), in number of sessions, group or individual work, individualised program to fit a given neuropsychological profile or a standardized program, combined or not with other rehabilitation programs. The question of which parameters are the most effective remains largely unresolved due to paucity and heterogeneity of studies. Twamley et al. (2003) have reported in their meta-analysis that effect sizes for computer-assisted remediation are generally higher than for paper-and-pencil techniques. Treatment intensity, patient's baseline work habit, clinician experience, and intrinsic motivation of patients all seem to be predictors of good response (Medalia and Choi, 2009).

Taking these results into account we developed a broadly targeted computer-assisted cognitive remediation program for a large group of patients with schizophrenia. We hypothesized that relative to a condition designed to control for non-specific treatment effects cognitive remediation would improve performance on cognitive abilities in patients.

2. Methods

2.1. Clinical trial design

In a multi-centric (3 centres), single-blind, randomized and controlled study, we compared a computerised cognitive remediation rehabilitation strategy added to the standard treatment versus the standard treatment alone (waiting list). Seventy-seven patients were randomised to either the active group (CRT patients, standard treatment and cognitive remediation program, n = 39) or to the control group (non-CRT patients, standard treatment only, n = 38). The CRT intervention took place over seven weeks during the interval. Clinical and cognitive assessments were realised at baseline and 3 months after treatment. The assessors were blind to the participants' assigned randomisation and had no other role in the project that would undermine the blinding.

2.2. Participants

Participants were enrolled from the hospitals of Bron, Saint Egrève and Clermont-Ferrand (public psychiatric hospitals of south-east France). Recruitment for the trial began in 2006 and concluded in 2009. Patients were eligible if they met the DSM IV criteria for schizophrenia, were clinically stabilized without any modification of their medication for at least one month, spoke French fluently and were aged between 18 and 40 years. Exclusion criteria were past or present neurological disorders or substance dependence or abuse, pregnancy, and not being able to give informed consent. We collected demographic and clinical information on age, gender, educational level, duration of illness and antipsychotic regimen. All subjects gave written informed consent and the study was approved by a local ethical committee (CPP Sud Est III, Lyon, France, 24 January 2006).

2.3. Intervention: computer-assisted remediation therapy (REHACOM® modules)

The therapy consisted of 14 individual two-hour sessions over a 7-week period providing supportive, graduated training and practice in selecting, executing, and monitoring cognitive operations. CRT was conducted by a psychologist on a computer with a special input panel (joystick and ergonomic pads) using RehaCom® software package (SCHUHFRIED, GmbH). RehaCom® is a computer-assisted therapy system for cognitive functions whose efficiency has been shown in evaluation studies involving patients with brain injuries (Puhr, 1997). The system consists of a basic program and a number of training procedures. This program enables patient progression and performance feedback. Based on results from our previous open study (Cochet et al., 2006), four procedures have been chosen from amongst the nineteen different procedures available in RehaCom®, to train four cognitive functions involved in different stages of the information processing: attention/concentration, working memory, logic, and executive functions. For more details about Rehacom modules, see the Rehacom website at http://www.hasomed.de.

2.3.1. Attention & concentration (REHA-AUFM)

In the procedure Attention & concentration (REHA-AUFM) a separately presented picture is compared to a matrix of pictures. The patient has to recognize a picture (symbols, items, animals or abstract figures) shown separately and select it from a matrix. The abilities to differentiate and to concentrate are trained simultaneously.

2.3.2. Memory (REHA-MEMO)

In the training procedure "topological (or visuo-spatial) memory (REHA-MEMO)", every training task is divided into two stages: the acquisition stage and thereafter the reproduction stage. In the acquisition stage, the patient's task is to memorise the content and the placement of the pictures. During the reproduction stage the pictures are "covered", with one picture displayed separately (without the cover). The patient's task is to locate the picture's pair from the matrix of covered pictures.

2.3.3. Logical reasoning (REHA-LODE)

The system for "logical reasoning (REHA-LODE)" uses problem solving exercises. The types of exercises used are 'completion of a series'. The principle behind the training is that the problem solving exercises are very graphic and vivid. The patient should learn to recognize the concepts underlying each problematic situation and to use these concepts to solve the logic problem (von Cramon et al., 1991). The aim of the training is an improvement in the conclusive thinking and in the problem solving.

2.3.4. Naturalistic executive function: Shopping (REHA-EINK)

The RehaCom procedure "Shopping" is a highly realistic training exercise. The client performs the same tasks on the computer that he would have to do when going shopping in a supermarket. A shopping list contains all the items that have to be bought. The client has to find these items and put them in a trolley. When all items are collected the client leaves the supermarket passing the cash register. The procedure aims at an improvement of the executive functions, particularly of the planning and acting competencies of realistic situations. Shopping is a highly realistic training procedure requiring basal as well as more complex cognitive skills. It uses memory intensively as well as memory relieving: the client may or may not have the possibility to have further looked at the shopping list.

2.4. Assessment

2.4.1. Clinical assessment

Clinical characteristics of patients were assessed by a blind investigator using the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987) and the Clinical Global Impression (CGI).

2.4.2. Neuropsychological assessment

In order to assess cognitive performances of included patients before and after CRT or control, we used standardized cognitive tests which were not used in the therapy itself. We used several tests from the computerized Cogtest ® battery test (Barua et al., 2002) (http://www.cogtest.com/home.html) to assess different domains of cognitive functioning. Subtests of this battery are equivalent to the NIMH-MATRICS (Green et al., 2004) which is an expert consensus neuro-cognitive battery tests for schizophrenia.

- *Attention / vigilance:* The Continuous Performance Test—Identical Pair version (CPT-IP). This requires a subject to respond whenever two identical stimuli appear in a row within a sequence of 150 rapidly flashed trials. We used the 2-digits version and the 4-digits version. We retained: (1) the index of perceptual sensitivity to signal to noise differences [d′ index] and (2) the response criterion, i.e. the amount of perceptual evidence that the subject required to decide if a stimulus is a target [natural log of beta].
- *Non-verbal Working Memory:* Spatial Working Memory test (SWM). The goal of the task is to determine how accurately subjects recall the spatial locations of briefly presented visual targets. A key measure was the long median which reflects the distance to the target;
- *Verbal Working memory:* Auditory Number Sequencing (ANS). The participants are presented with clusters of numbers (e.g. 936) of increasing length (from 2 digits to a maximum of 8 digits). They are asked to tell the tester the numbers in order, from lowest to highest. A key measure was the maximal span recalled;
- *Verbal learning and memory:* Word List Memory test (WLM). 16 words are presented auditorily by the computer to the subject who must then recall as many as possible. Key measures were the total recall on first trial and the total on delayed recall;
- *Visual learning and memory:* Face Memory Test (FMT). Key measures were the percentage of correct immediate recall responses and delayed recognition;
- *Speed of processing:* Finger Tapping Test (FTT). Key measures were the total taps with the left hand and with the right hand;
- *Reasoning and problem solving*: Strategic Target Detection test (STDT). This test is similar to the paper-and-pencil 'cancellation' tests or the 'cross-out' subtest of the WAIS-III, where subjects are required to cross-out target stimuli embedded among distracters. The subject must learn which the correct target is by choosing one of the stimuli and observing feedback that indicates whether the choice was right or wrong. This feature is similar to that used in the Wisconsin Card Sorting Test (WCST). Key measures were the four shape strategic efficiency (the shorter, the better strategy) and the total errors.

2.4.3. Psycho-social assessment

Quality of life was assessed by the self-report quality of life for people with schizophrenia (SQoL) (Wilkinson et al., 2000). We also assessed social autonomy of patients with a French scale: the Social Autonomy Scale (EAS) (Leguay et al., 1998).

2.5. Planned analysis

Demographic, neuropsychological and clinical characteristics at baseline were compared using two-tailed Student t-test except for gender for which Fisher chi square test was used. The first set of primary analyses tested the treatment effect (by two-tailed paired Student t-test for matched sample) on the 4 metrics that were derived from the remediation exercises (level at inclusion and level after the 14 training sessions for *REHA-AUFM, REHA-*

Table 1
Socio-demographical, clinical and neuropsychological characteristics of patients at baseline.

		CRT patients (n = 39)	Non-CRT patients (n = 38)	p*
Socio-demographical				
Gender (F/M)		10/29	9/29	1†
Age (years)		33.4 (6.9)	32.2 (6.0)	0.41
Educational level (years)		12.7 (4.4)	11.9 (2.5)	0.25
IQ		95.3 (14.5)	105.4 (14.9)	0.13
Clinical				
PANSS		73.3 (11.6)	75.7 (13.0)	0.62
Positive PANSS		15.5 (4.8)	16.2 (5.2)	0.57
Negative PANSS		20.7 (6.5)	21.4 (6.9)	0.69
Illness duration (years)		8.7 (6.6)	8.1 (4.5)	0.68
SQoL		120 (31)	112 (35)	0.34
Antipsychotic medication				
Chlorpromazine equivalent (mg/day)		337 (215)	441 (230)	0.06
Neuropsychological				
Attention/vigilance				
CPT-IP	2D-D prime	3.4 (1.9)	3.3 (1.4)	0.81
CPT-IP	4D-D prime	1.3 (0.7)	1.3 (0.7)	0.82
Verbal Working Memory				
ANS	Span	6.7 (0.2)	6.7 (1.1)	0.88
Verbal Learning and Memory				
WLM	First recall	6.8 (2.3)	7.0 (1.8)	0.89
WLM	Pr discrimination	0.35 (0.1)	0.35 (0.4)	0.99
Reasoning and problem solving				
STDT	Total error	33 (28)	24.5 (12.6)	0.51
STDT	Four shape strategic efficiency	15,622 (3658)	16,587 (3250)	0.07
Non-verbal Working Memory				
SWM	Long median	66.9 (20.3)	65.5 (23.8)	0.39
Visual Learning and Memory				
FMT	Immediate recall	0.7 (0.1)	0.7 (0.1)	0.34
FMT	Delayed recognition	0.7 (0.01)	0.7 (0.1)	0.34
Speed of processing				
FTT	Total left	225 (48)	243 (41)	0.43
FTT	Total right	242 (53)	256 (49)	0.16

*p: Two-tailed Student t-test except for gender († Fischer chi^2). Results are given as mean (standard deviation).

MEMO, REHA-LODE, and *REHA-EINK*). The second set of analysis tested the generalisation to neuropsychological tests assessing (by two-tailed paired student t-test for matched sample): attention, verbal and non-verbal working memory, speed of processing and problem solving function, tested using Cogtest®. Finally, we analysed whether cognitive remediation therapy could improve quality of life and social skill.

We then calculated the Cohen's d effect size of each of the assessments in the CRT group.

3. Results

3.1. Group characteristics

Concerning clinical and socio-demographical variables, we reported no difference between patient groups at baseline (Table 1).

CRT patients and non-CRT patients did not significantly differ for cognitive performances at baseline, as measured by the Cogtest ® battery.

3.2. CRT treatment effects

The difficulty level reached by the patient for each module was reported at the end of the CRT. The maximal number of levels for each module is: 24 REHA-AUFM (attention), 20 for REHA-MEMO (memory), 23 for REHA-LODE (executive functions: reasoning), and 18 for REHA-EINK (executive functions: planification).

We reported in all CRT patients a large effect of the training in the 4 trained procedures ($p<0.0001$) (Table 2):

- Attention & concentration (from an average level of 8.3 ± 1.9 to 21.8 ± 2.3),
- Memory (from 5.6 ± 1.1 to 10.7 ± 3.2),
- Logical reasoning (from 8.4 ± 2.6 to 19.0 ± 2.2),
- Naturalistic executive function (from 6.0 ± 1.6 to 17.2 ± 2.1).

Table 2
Effect of training on the level reached after 14 sessions compared to level at baseline for the 4 trained procedures.

	CRT patients (n = 39)		
	Before CRT	After CRT	p
Attention & concentration REHA-AUFM	8.3 (1.9)	21.8 (2.3)	<0.0001
Memory REHA-MEMO	5.6 (1.1)	10.7 (3.2)	<0.0001
Logic thought REHA-LODE	8.4 (2.6)	19.0 (2.2)	<0.0001
Naturalistic executive function REHA-EINK	6.0 (1.6)	17.2 (2.1)	<0.0001

3.3. Neuropsychological performances

Neuropsychological performances assessed by other tests than those used to trained patients (Cogtest® battery) revealed a significant effect of CRT on Attention/vigilance (measured by d′ index at the Continuous Performance Test—Identical Pair test; 2 and 4 Digits), verbal working memory (measured by Span at the Auditory number sequencing test) and verbal learning memory (measured by first recall and percent of discrimination at the World List Memory test) and reasoning and problem solving (measured by total errors at the Strategic Target Detection Test) (Table 3).

We reported no effect of CRT on Non-verbal Working Memory, Visual Learning and Memory and Speed of processing.

3.4. Clinical and social outcome

Whatever the group, we observed no improvement of positive or negative symptoms measured by Positive and Negative Syndrome Scale (PANSS). We also observed no improvement in general psychopathology and clinical global impression 3 months after the beginning of CRT (Table 4).

Finally, we reported no improvement in social autonomy in both CRT and non-CRT patients. The assessment of Quality of life by Wilkinson's SQoL show trends toward improvement in both groups.

3.5. Effect sizes

Impact of CRT on all clinical and neuropsychological assessments was calculated using Cohen's d effect size. We reported a large effect of CRT on verbal learning (1.55) and a medium effect size on Attention (0.42 and 0.48), verbal memory (0.52), and working memory (0.41) (Fig. 1).

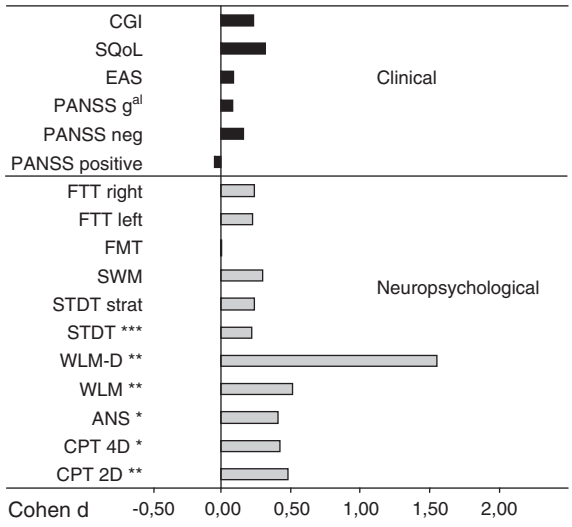

Fig. 1. Impact of CRT on clinical and neuropsychological assessments (Cohen *d* effect size). Clinical data: CGI: Clinical global impression; SQoL: Self-report Quality of Life; EAS: Social Autonomy Scale; PANSS: Positive and Negative Syndrome Scale. Neuropsychological data: FTT = Finger tapping test; FMT = Face memory test; SWM = Spatial working memory test; WLM = Word list memory test –D = delayed; STDT = Strategic target detection test; ANS = Auditory number sequencing; CPT = Continuous Performance Test Identical Pair. *: Two-tailed Student t-test for matched sample, $p<0.05$.

4. Discussion

We aimed to study if computer-assisted CRT is able to modify cognitive performances in remitted patients with schizophrenia. Using a program consisting of 14 training sessions of 4 cognitive functions (attention/concentration, topological memory, logical reasoning, and executive functions) by mean of the REHACOM®

Table 3
Neuropsychological performances in patients with or without CRT. CRT patient improved their performances in Attention/Vigilance, Verbal learning and working Memory while non-CRT patient did not displaye any changes.

Domains and tests		CRT patients (n = 39)			Non-CRT patients (n = 38)		
		Session 1	Session 2	p	Session 1	Session 2	p
Attention / vigilance **							
CPT-IP**	2D-D prime	3.4 (1.9)	4.3 (1.8)	0.004	3.3 (1.4)	3.4 (1.5)	0.8
CPT-IP**	4D-D prime	1.3 (0.7)	1.6 (0.7)	0.02	1.3 (0.7)	1.4 (0.6)	0.7
*Verbal Working Memory***							
ANS**	Span	6.7 (0.2)	7.0 (1.0)	0.04	6.7 (1.1)	6.8 (0.9)	0.3
Verbal Learning and Memory **							
WLM**	First recall	6.8 (2.3)	8.0 (2.3)	0.002	7.0 (1.8)	6.9 (2.6)	1
WLM**	Pr discrimination	0.35 (0.1)	0.70 (0.3)	0.007	0.35 (0.4)	0.6 (0.4)	0.9
Reasoning and problem solving **							
STDT**	Total error	33 (28)	27 (27)	0.0004	24.5 (12.6)	21.7 (9.5)	0.17
STDT	Four shape strategic efficiency	15,622 (3658)	14,745 (3561)	0.7	16,587 (3250)	15,165 (2462)	0.1
Non-verbal Working Memory							
SWM	Long median	66.9 (20.3)	60.5 (22.3)	0.08	65.5 (23.8)	60.6 (17.4)	0.2
Visual Learning and Memory							
FMT	Immediate recall	0.7 (0.1)	0.7 (0.1)	0.5	0.7 (0.1)	0.7 (0.1)	0.6
FMT	Delayed recognition	0.7 (0.01)	0.7 (0.1)	0.07	0.7 (0.1)	0.7 (0.1)	0.4
Speed of processing							
FTT	Total left	225 (48)	236 (46)	0.1	243 (41)	245 (48)	0.9
FTT	Total right	242 (53)	256 (44)	0.09	256 (49)	271 (45)	0.06

p; intra group comparison (Two-tailed Student t-test for matched sample) **: improved after CRT. Results are given as mean (standard deviation).
CPT-IP = Continuous Performance Test—Identical Pair, SWM = Spatial working memory test, ANS = Auditory number sequencing, WLM = Word list memory test, FMT = Face memory test, FTT = Finger tapping test, STDT = Strategic target detection test.

Table 4
Clinical and social assessment in patient with or without CRT. We observed no improvement in social or clinical abilities whatever the group.

	CRT patients (n = 39)			Non-CRT patients (n = 38)		
	Session 1	Session 2	p	Session 1	Session 2	p
PANSS						
Positive	15.5 (4.8)	15.3 (4.3)	0.7	16.2 (5.2)	16.3 (6.1)	0.9
Negative	20.8 (6.5)	21.9 (6.9)	0.2	21.4 (6.9)	20.8 (8.9)	0.5
General psychopathology	36.9 (9.5)	37.8 (11.1)	0.7	38.1 (11.6)	39.2 (14.0)	0.9
Social autonomy						
EAS	33.2 (12.5)	34.3 (10.8)	0.4	37.8 (16.1)	36.6 (15.4)	0.8
Quality of life						
SQoL (Wilkinson)	120 (31)	110 (31)	0.1	112 (35)	102 (33)	0.06
Global clinical impression						
CGI	4.0 (0.8)	4.2 (0.9)	0.2	4.4 (1.2)	4.6 (1.0)	0.3

PANSS: Positive and Negative Syndrome Scale. EAS: Social Autonomy Scale; SQoL: Self-report Quality of Life; CGI: Clinical Global Impression.
p: Two-tailed Student t-test for matched sample. Results are given as mean (standard deviation).

software, we reported that CRT could improve patients' performances in Attention/vigilance, verbal working memory and verbal learning memory and reasoning and problem solving. REHACOM® software was initially developed for rehabilitation after brain injury which can be a consequence of disease such as stroke or multiple sclerosis as well as trauma (Friedl-Francesconi and Binder, 1996). Our results support the efficiency of this tool in schizophrenia.

We observed no effect of CRT on non-verbal working memory and learning and speed of processing. This lack of efficiency could be explained by the remediation program itself which favours verbal strategy for problem solving even in the visuo-spatial REHA-MEMO where subjects were encouraged to name the pictures.

Those cognitive improvements have no effect on a clinical level, social autonomy or quality of life. However, the follow-up period is certainly too short to observed such effect which may take a relatively long time before becoming apparent. Nevertheless, these results are encouraging as verbal memory and card sorting test (Strategic Target Detection Test is similar) are cognitive parameters, which are linked to the functional outcome in schizophrenia (Green et al., 2000).

The lack of real placebo condition that controlled for non-specific elements of the remediation training, including supportive therapist interactions and exposure to interesting computer activities could not permit to conclude between a direct effect of CRT or an effect of management of the patient. However, our results replicate findings from such controlled study with another way of training (Cavallaro et al., 2009; Dickinson et al., 2010). Interestingly, our program is shorter in duration (28 h) than most of the alternative CRT strategies (36 to 40 h), which may translate in a better cost-effectiveness. Secondly, patients were not blind about their experimental condition due to the lack of non-specific intervention as a control procedure. Thirdly, as previously stated, a follow-up assessment would have allowed to study whether the remediation effects are durable and whether cognitive improvements have delayed beneficial effects on social behaviour and quality of life as suggested by a previous study (Wykes et al., 2007).

Thus, computer-assisted CRT for people with schizophrenia was effective in improving performance on verbal memory, verbal learning and reasoning. Benefits of training could be generalized to broader neuropsychological aptitudes except for non-verbal cognitive performances and for functional outcome measures. As the RehaCom ® exercises do not resemble the cognitive assessment tasks by Cogtest ®, the improvements in test performance cannot be due to a practice effect. Those results corroborate with other studies (Bell et al., 2001; Wykes et al., 1999; Kurtz et al., 2007; Cavallaro et al., 2009; Dickinson et al., 2010) and confirm, with a larger sample, our previous report (Cochet et al., 2006; Bor et al., submitted for publication). Further studies with a longer following-up period may be necessary in order to study whether cognitive improvements may generalize to functional outcome. A clinical trial comparing REHACOM CRT and another validated CRT method in a longitudinal study is needed to confirm the interest of this method.

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Funding for this study was provided by PHRC 2005 and had no further role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

M Saoud, T d'Amato and J Brunelin designed the study. I Jalenques, E Giraud-baro, M Pacaud troncin, F Augier-Astolfi, PM Llorca and A Cochet wrote the protocol and included participants. A Cochet and F Galland realized the acquisition. R Bation and J Brunelin analysed the data and wrote the first draft of the manuscript which was corrected by T d'Amato and M Saoud. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors declare that they have no conflicts of interest.

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