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RESEARCH PAPER

Cognitive remediation therapy (CRT) benefits more to patients with schizophrenia with low initial memory performances

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Abstract

Purpose: Cognitive deficits in schizophrenia mainly affect memory, attention and executive functions. Cognitive remediation is a technique derived from neuropsychology, which aims to improve or compensate for these deficits. Working memory, verbal learning, and executive functions are crucial factors for functional outcome. Our purpose was to assess the impact of the cognitive remediation therapy (CRT) program on cognitive difficulties in patients with schizophrenia, especially on working memory, verbal memory, and cognitive flexibility. *Methods*: We collected data from clinical and neuropsychological assessments in 24 patients suffering from schizophrenia (*Diagnostic and Statistical Manual of mental Disorders-Fourth Edition, DSM-IV*) who followed a 3-month (CRT) program. Verbal and visuo-spatial working memory, verbal memory, and cognitive flexibility were assessed before and after CRT. *Results*: The Wilcoxon test showed significant improvements on the backward digit span, on the visual working memory span, on verbal memory and on flexibility. Cognitive improvement was substantial when baseline performance was low, independently from clinical benefit. *Conclusions*: CRT is effective on crucial cognitive domains and provides a huge benefit for patients having low baseline performance. Such cognitive amelioration appears highly promising for improving the outcome in cognitively impaired patients.

➤ Implications for Rehabilitation

- Cognitive impairment is observed in 70–80% of patients with schizophrenia a devastating disorder with high direct and indirect social costs and cognitive alterations are a crucial predictive factor for an inability to work.
- Cognitive remediation is an efficient technique to improve cognition, autonomy, and social functioning in patients.
- Individual structure programs are successful to improve working memory, verbal learning and flexibility in this study.

Keywords

Cognitive remediation therapy, schizophrenia, verbal learning, working memory

History

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Introduction

Cognitive deficits are among the core symptoms of schizophrenia [1,2]. They appear several years before the emergence of psychotic symptoms [3,4]. The impairment in cognition affects attention–concentration, memory and executive functions, with huge consequences on the management of daily life, social outcome, social relations, and rehabilitation [5–7]. If we consider predictive factors for outcome in schizophrenia; work or educational status is predicted by working memory, while residential status (independent living) is predicted by verbal memory [8]. In a recent meta-analysis, Tolman and Kurtz [9] reported a moderate but significant relationship between objective indices of quality of life assessed with questionnaires about occupation, social interactions, recreations/leisure, and crystallized verbal ability, working memory, verbal list learning, and executive functions.

Hence, it is of great interest to provide patients the best opportunity to alleviate their cognitive deficits, if possible very early in the beginning of the disease, and throughout its evolution. Despite the numerous available medications, cognitive disorders are only partially improved by pharmacological treatments. Therefore, in recent decades, psychosocial treatments emerged. Among them, cognitive remediation techniques help to improve cognitive capabilities and to provide patients with new strategies to reduce their difficulties. Several types of programs can be administered, with different approaches (cognitive training,

*Both contributing to the same extent.

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learning strategies, and/or compensatory aid), equipment (paper and pencil, video, computer program, role-playing games) and administration modalities (individual or group).

The Cognitive Remediation Therapy (CRT) is issued from the FEP (Frontal Executive Program) originally created by Delahunty and Morice [10] to treat executive dysfunctions. Delahunty et al. [11] adapted the FEP into ''CRT'', and CRT has been translated/back-translated into French [12] in 2008. The aim of CRT is to alleviate dysexecutive impairments (executive functions that include attention, cognitive flexibility, and planning).

In the literature, several randomized controlled studies used CRT in schizophrenia reporting benefits for patients with severe cognitive and social handicaps [13]. Moreover, positive effects were found in the CRT group in cognitive flexibility, memory, and planning [14]. Wykes et al. [15] also evaluated the durability of these effects and found that benefits of CRT lasted 6 months after the end of the program, especially for working memory (using the Digit span – WAIS III).

Most noticeably, positive effects were also observed in functional magnetic cerebral imaging with increased brain activation in regions involved in the right inferior frontal gyrus after a working memory task [16], in the dorsolateral prefrontal cortex, anterior cingulate, and frontopolar cortex [17] and, using diffusion tensor imaging (DTI), in the anterior part of the genu of the corpus callosum [18].

In a randomized controlled study of schizophrenia, Wykes et al. [19] assessed the cost-effectiveness of CRT, using as a primary outcome measure the percentage of ''improvers'', based on the WAIS-III digit span raw scores. Indeed, Bryson and Bell [20] observed that a two-point gain compared to baseline on this working memory measure could contribute to functional improvements. Hence, a substantial benefit in working memory associated with a better quality of social behavior was observed 6 months after the end of CRT. This benefit was associated with lower costs for care at post-treatment assessment [19]. Finally, Wykes et al. [21] compared two groups of patients with schizophrenia regarding their age (under versus over 40 years old). Older patients benefited less from CRT. They showed minimal improvement on the digit span test and no change in flexibility or planning [14]. However, none of these studies evaluated the differential components of working memory or verbal learning skills after CRT.

The CRT program specifically taps on working memory with the use of verbal and visuo-spatial spans exercises such as visual-kinetic span, delayed response, number sequencing, dual count, and serial search. Regarding verbal learning, the CRT method comprises several exercises that focus on verbal comprehension, recall and retrieval of short stories using drill and strategies to consolidate encoding and recall.

Our study is part of a multi-center clinical trial that took place in France and Switzerland between 2008 and 2011. It specifies at comparing the effects between two individualized 3-months cognitive remediation programs, one including only paper and pencil sessions, using CRT, and one with both computerized and paper–pencil exercises using RECOS (Cognitive Remediation for Schizophrenia) program [22]. An equal number of clinically stable patients were recruited in this group-parallel-randomized-clinical-trial. Assessments, blind to group allocation, were repetitively done before the beginning of the program, after treatment 3 months after the first assessment, and 6 months following the end of the program. The main treatment outcome measure was the profile score of the BADS (an ecological battery for dysexecutive syndromes) [14]. The results showed a significant improvement 6 months after the end of the two programs with no difference between CRT and RECOS [23]. In our study, focusing on a group recruited from three cognitive remediation centers, we intended to more specifically evaluate the effect of the CRT program on crucial measures for outcome, such as the verbal and the visuo-spatial working memory dimensions, verbal learning, and flexibility. Through the use of the separated sub-scores for forward and backward spans (BWs) of the Digit Span test, we tested varying degrees of the involvement of working memory based on the model of Baddeley [24]: little input from the central executive: information storage in the phonological loop with the forward span (FW) and manipulation of information requiring central executive intervention with the BW [25]. The visuo-spatial working memory span yields a measure of visuo-spatial short-term memory capacity with FW and BWs in the same way that verbal span yields a measure of verbal with more or less phonological short-term-memory capacity [26]. Our hypothesis stated that patients could show an improvement at the end of the program, on the different working memory dimensions and this improvement could even concern the most cognitively impaired patients.

Methods

Design and participants

Twenty-four outpatients with chronic stabilized schizophrenia (10 women and 14 men suffering from schizophrenia according to the *Diagnostic and Statistical Manual of mental Disorders-Fourth Edition*, *DSM-IV-R*) were recruited in Sainte-Anne hospital in Paris, and in Le Vinatier and Saint Jean de Dieu hospitals in Lyon. These patients fulfilled the following criteria: aged between 18 and 55 years old, native French language, clinically stable with the same treatment for at least 1 month before the inclusion in the study, no substance abuse or dependence except tobacco consumption, no patent somatic or neurological disease. Patients had no electroconvulsive treatment for at least 6 months. To be included, patients had to express subjective complaints about their cognitive abilities such as concentration, memory, or planning difficulties.

They were assessed in a test–retest design study at week 0 (before the beginning of CRT program) and week 14 (at the end of CRT program). A clinical evaluation was also assessed before and after CRT program with the Positive and Negative Syndrome Scale (PANSS) [27–29].

Therapy

CRT is an individually paper–pencil program provided for face-to-face sessions with a therapist. Its purpose is to improve cognitive flexibility, capacity of inhibition, process of organizing and planning, working memory, or attention. CRT is composed of three modules: cognitive flexibility, memory, and planning. Each module contains approximately 15 tasks with different gradual levels of difficulty (from level 1 to 5), which trains concentration, divided and sustained attention, or symbolic reasoning. During the exercises, the therapist teaches strategies for processing information, mnemonic techniques and how these strategies can apply into daily life functioning. It combines various training techniques, such as errorless learning, intensive, and positive reinforcement. Each exercise is tailored to the cognitive abilities of the subject over the course of the entire program. However, all the patients have to perform the three modules in the fixed order ''cognitive flexibility, memory, planning'', and the different exercises of each module have to be trained. The differences stand only in the number of repetition for each exercise during practice until a successful level of the task is fully completed. Indeed, if one patient is a good performer the therapist increases the level of complexity or will switch to another exercise.

In this study design, patients came to the center for cognitive remediation for two sessions per week, and one session was performed at home with homework exercises. The correct execution of this homework was checked with the therapist in the learning center, during the following session.

Main outcome measures

- *Working memory* was evaluated with two different neuropsychological tests:
- Digit span (WAIS-III, 1997 [30]): It is a common measure of short-term memory (Table 1). Patients have to recall forward and backward with different serials of numbers. The memory span corresponds to the largest serial of numbers recalled in the right order. Two scores were collected: the digit span forward and backward raw scores, and age-scaled scores.
- Visuo-spatial span (WMS-III, 1997 [31]): The spatial span task assesses the visuo-spatial dimension of working memory. It tests the manner of holding and manipulating information about places. Patients have to touch different cubes presented on a board in forward and backward order. Two scores were collected: forward and backward raw scores, and age-scaled scores.
- *Verbal memory* was evaluated with the Logical Memory test of the MEM-III where the patient has to memorize and recall a short story and the Rey Auditory Verbal Learning Test (RAVLT [32]), where lists of unrelated words have to be memorized and retrieved.
- *Cognitive flexibility* was evaluated by the number of categories achieved as well as perseverative errors of the Wisconsin Card Sorting Test (WCST) [33]. This test is composed with cards that could be sorted by color, number or shapes depending on the printed figures. The patient has to guess the right rule of assortment to sort out the consecutive cards. After 10 consecutive correct answers, the therapist abruptly switches to another rule of assortment without informing the patient, and once again the new rule must then be guessed. Table 1 summarizes the different neuropsychological tests and the dimensions they evaluate.
- *Clinical symptoms of schizophrenia* were evaluated with the PANSS. According to previous literature on PANSS clinical factorial solutions, our study focused on total score and the five factorial components: positive, negative, cognitive, depressive, and excitement dimensions [27–29].

Oral information of the program was provided for all participants, who gave written informed consent prior to trial's inclusion. The experiment was conducted in accordance with the Declaration of Helsinki. This study has been approved by the Local Ethical Committee of the Faculty of Medicine of Lyon. Clinical history and demographic characteristics were assessed during a clinical interview. Pre-morbid IQ was obtained using the F-Nart (National Adult Reading Test French version, NART) [34].

Statistical analysis

First, to show improvements on clinical and neuropsychological measures, we used the Wilcoxon test to compare subject's scores between week 0 and week 14. Second, to see if improvements were associated with baseline levels, we used Spearman's correlation between subject's baseline scores at week 0 and their degree of improvement between week 0 and week 14. Non-parametric statistical methods (Wilcoxon test and Spearman rank correlation coefficient) were used because no assumptions about the frequency distribution of the variables (normality) and the relationship between the variables (linear) were made. Indeed, we found the use of such statistical methods more appropriate to test for significant relations on variables between T1 and T2 in small sample and also to avoid difficulties emerging from non-normal distribution on some variables (floor or ceiling effect). For example, several neuropsychological tests based on span measures are especially concerned with ceiling effect. Finally, to compare degrees of improvement with one another, we used Cohen's *d* effect size. Data were analyzed using IBM SPSS 20 software (IBM SPSS Statistics for Windows, Version 20.0, IBM Corp., Armonk, NY).

Table 1. Neuropsychological tests assessed before and after CRT.

Neuropsychological tests	Aims and measures	Reference
Working memory (a1)		
Digit span total age-scaled score	Measure verbal short-term working memory (holding and manipulating verbal information)	Wechsler D. (1997). *WAIS III* [30]
Digit span total raw score		
Digit span forward raw score		
Digit span backward raw score		
Visuo-spatial span: total age-scaled score	Measure visuo-spatial short-term memory	Wechsler D. (2001). *MEM III* [31]
Visuo-spatial span total raw score		
Visuo-spatial span forward raw score		
Visuo-spatial span backward raw score	Measure visuo-spatial short-term working memory (holding and manipulating visuo-spatial information)	
Verbal learning (a2)		
Logical memory test total words recall	Measure the ability to memorize, store and retrieve short stories read by the assessor	Wechsler D. (2001). *MEM III* [31]
RAVLT immediate memory	Measure the ability to memorize and retrieve immediately a list of 15 words read by the assessor	Rey A. (1964). *Rey auditory verbal learning test* [32]
RAVLT delayed memory	Measure the ability to retrieve after a delay of few minutes the same list of 15 words	
Flexibility, planning, conceptualization and abstracts reasoning (a3)		
WCST categories	Number of series of ten consecutive correct responses made during the test (6 max)	Nelson H. (1976). *Wisconsin Card Sorting Test* [33]
WCST perseverative errors	Measure the degree of reactive flexibility to the feedback of the assessor	

For the digit span and visuo-spatial span, normative values cannot be shown because they are age-dependent.

Results

Sample socio-demographic, IQ, and clinical characteristics at baseline

A total of 14 men and 10 women, with a mean age of 38.1 ± 9.1 years old were examined. The mean years-of-study was 13.5 ± 0.6. Mean PANSS score was 69.8 ± 25.5. The mean duration of disease was 10.3 years ± 7.5 and mean dosage for their anti-psychotic treatments was 260.6 ± 147.1 mg chlorpromazine equivalent per day [35]. Concerning their general cognitive aptitude, the mean score for I.Q. estimated with F-Nart was 107 ± 6.9.

Clinical improvements

The clinical evaluation with the PANSS before and after the CRT program showed a consistent improvement in the whole sample (scores at week 0: mean 69.8 ± 25.5; scores at week 14: mean 58.6 ± 25.7; $p < 0.001$). This improvement was noticeable on positive symptoms (Sub-scores at week 0 = 13.3 ± 6.0; Week 14 = 11.4 ± 5.6; $p = 0.014$) on negative symptoms (sub-scores at week 0 = 21.9 ± 5.3; Week 14 = 20.3 ± 4.9; $p = 0.043$) and as a tendency for the PANSS-depression sub-score (score at week 0 = 11.2 ± 4.5; Week 14 = 9.4 ± 2.7; $p = 0.054$).

Neuropsychological improvements

Comparison of the performance between week 0 and week 14

Working memory. Foremost, our patients showed impaired working memory at baseline (digit span total age-scaled and visuo-spatial span total age-scaled scores) (Table 2). When we examined the digit span total (raw and age-scaled) scores, no significant difference was found between week 0 and week 14. However, when the backward and forward scores were separated, performances were improved for the backward digit span raw score. When looking carefully to the forward digit span scores, we observed that 19/24 subjects (79%) obtained normal values in reference to their ages at the first assessment. Among these subjects, only three subjects had an evolution of their scores at T2, the most important part of this group [16] remained in the normal range after the remediation program.

When we examined the visuo-spatial span total scores, we observed a trend for an increase in the total raw scores and the age-scaled score. Nevertheless, patients were statistically improved for the backward raw score of visuo-spatial span. Once again looking forward to the forward visuo-spatial scores, 20/24 subjects (83%) were in the normal range in reference to their age at T1. When observing the evolution at T2, the vast majority of the group, 17/20 patients had remained in the normal range.

Verbal learning. With the logical memory test, there was a significant increase in the total number of words recalled. While the RAVLT showed no difference in immediate memory, delayed memory was significantly improved.

Flexibility and planning. Performances examined with the WCST showed a trend to a significant difference in the number of categories achieved, and a significant difference for perseverative errors.

Correlation of neuropsychological improvement with scores at baseline

We examined, for each subject, the correlation existing between improvement in neuropsychological tests from week 0 to week 14 and the baseline scores (Table 3).

Hence, we found many significant negative correlations: digit span (forward raw score); visuo-spatial span (forward and backward scores). Significant negative correlations were also found for the total recalled words in the Logical Memory test, RAVLT delayed memory score, and WCST number of categories and perseverative errors.

Table 2. Clinical and neuropsychological improvement with 14 weeks of CRT program ($N = 24$).

Clinical and neuropsychological tests ($n = 24$)	Week 0 Means ± SD	Week 14 Means ± SD	Wilcoxon Test p	Cohen's d
Clinical improvement				
PANSS total	**69.8 ± 25.5**	**58.6 ± 25.7**	**0.001****	**0.67**
PANSS positive	**13.3 ± 6.0**	**11.4 ± 5.6**	**0.014***	**0.59**
PANSS negative	**21.9 ± 5.3**	**20.3 ± 4.9**	**0.043***	**0.47**
PANSS cognition	6.1 ± 2.4	6.1 ± 2.2	0.83	
PANSS depression	11.2 ± 4.5	9.4 ± 2.7	0.054	0.47
PANSS excitement	7.4 ± 1.9	7.1 ± 2.3	0.47	
Neuropsychological improvement: Working Memory (a1)				
Digit span: total age-scaled score	8.6 ± 2.3	8.8 ± 2.1	0.51	
Digit span total raw score	14.6 ± 2.8	15.1 ± 2.5	0.23	
Digit span forward raw score	9.1 ± 1.8	8.9 ± 1.6	0.70	
Digit span backward raw score	**5.5 ± 1.7**	**6.2 ± 1.8**	**0.030***	**0.49**
Visuo-spatial span: total age-scaled score	8.5 ± 2.8	9.2 ± 2.7	0.06	
Visuo-spatial span total raw score	14.2 ± 3.1	15.0 ± 2.9	0.052	0.41
Visuo-spatial span forward raw score	7.3 ± 1.9	7.5 ± 1.7	0.61	
Visuo-spatial span backward raw score	**6.9 ± 1.8**	**7.4 ± 1.7**	**0.044***	**0.40**
Neuropsychological improvement: Verbal learning (a2)				
Logical memory test Total Words Recall	**34.8 ± 15**	**39.7 ± 14**	**0.014***	**0.52**
RAVLT Immediate memory	46.7 ± 12.6	46.7 ± 12.1	0.8	
RAVLT Delayed memory	**10.7 ± 3.5**	**9.5 ± 3.1**	**0.023***	**0.48**
Neuropsychological improvement: Flexibility and planning (a3)				
WCST Categories	4.4 ± 2.4	5.3 ± 1.2	0.053	0.42
WCST Perseverative errors	**19.9 ± 16**	**15.6 ± 16**	**0.045***	**−0.32**

The bold value indicates statistical significance; level of significance: *$p \leq 0.05$; **$p \leq 0.01$.
Cohen's d was calculated also for domains close to level of significance

Table 3. Correlations of score differences in neuropsychological tests between baseline and week 14 with (a) baseline neuropsychological test scores and with (b) differences between PANSS scores pre- and post-intervention ($N = 24$).

Neuropsychological tests ($n = 24$)	Correlation (a) Baseline score	Correlation (b) Clinical improvement
Neuropsychological improvement: Working Memory (a1)		
Digit span: total age-scaled score	−0.37	0.19
Digit span total raw score	−0.30	0.25
Digit span forward raw score	**−0.49***	0.07
Digit span backward raw score	−0.25	0.36
Visuo-spatial span: total age-scaled score	−0.34	0.01
Visuo-spatial span total raw score	**−0.40***	0.35
Visuo-spatial span forward raw score	**−0.64****	0.40
Visuo-spatial span backward raw score	**−0.52****	0.02
Neuropsychological improvement: Verbal learning (a2)		
Logical memory test Total Words Recall	**−0.5****	−0.08
RAVLT Immediate memory	−0.35	−0.07
RAVLT Delayed memory	**−0.6****	0.26
Neuropsychological improvement: Flexibility and planning (a3)		
WCST categories	**−0.9****	−0.20
WCST Perseverative errors	**−0.53****	−0.33

The bold value indicates statistical significance; level of significance: $*p \leq 0.05$; $**p \leq 0.01$.
Correlations with clinical improvement were calculated with the PANSS Total score improvement; all correlations were calculated with the Spearman's rho.

In other terms, the highest improvements were seen in patients who showed the lowest initial performance in visual working memory scores and, to a lesser extent, in digit span score, verbal learning skills, and flexibility. We found no significant correlations between cognitive improvement and years of studies, sex ratio, baseline PANSS scores, or treatments. Finally, cognitive improvement was not correlated to clinical improvement.

Effect size for clinical and neuropsychological improvement (Table 2)

Cohen'd statistics indicated that the CRT program is effective for improving cognitive functions after 14 weeks, with statistically significant effect sizes ranging from small (0.32) to medium (0.67).

Discussion

In our study, CRT program improved patients with schizophrenia in working memory, verbal learning and flexibility, with significant increases of digit and visuo-spatial BWs scores, and as a trend, of the total raw and total age-scaled scores of visuo-spatial span test. Regarding verbal learning skills, patients showed improvement in the recall of the Logical Memory test and the delayed recall of the Rey Auditory Verbal Learning Test. In terms of flexibility, they also improved their performances by decreasing the number of perseverative errors of the WCST.

In neuropsychology, the BWs of the two working memory tests are known to request the intervention of the central executive component of verbal and visuo-spatial working memory coordinating multiple processes in order to manipulate the information. Several studies showed that these two working memories' components were impaired in schizophrenia [36–38], as we did observe at baseline in our study. Our initial assumption was that CRT would improve these working memories' components (verbal and visuo-spatial BWs) and our results confirm this hypothesis. The ability of CRT program to alleviate working memory impairments in patients suffering from schizophrenia is here illustrated by the BWs results. Indeed, the CRT memory module (Part A and Part B) proposes different exercises that require holding in memory simultaneously several sets of information. [13].

In the literature, several studies found an improvement in working memory after cognitive remediation training in patients with schizophrenia: in verbal as well as auditory word span-tests [39]. Bell et al. [20] showed improvement in the digit span backward scores after a 10-week training with verbal memory exercises, with a 6-month durable effect [20,40]. Greig et al. [41] demonstrated better performances on the digit span working memory test and executive function after a 1-year neurocognitive enhancement therapy + vocational program toward vocational program alone). Grynszpan et al. [42] using a computer-assisted cognitive remediation showed an improvement of social cognition but also in verbal memory, working memory, and attention/vigilance. All these studies tested verbal working memory without assessing the visuo-spatial working memory component. Only our study showed that improvement in verbal working memory could be extended to the visuo-spatial dimension.

However, few studies reported negative results putatively due to a more aged sample [43], or with a computerized method of remediation [44].

Although BWs were improved in our study, we found no improvement in the FWs (verbal and visuo-spatial working memory). First, it must be said that the verbal and visuo-spatial FWs does not explore the same neuropsychological dimensions than the backward ones. Digit forward constitutes a string of digits that could be stored in the phonological loop as a verbal sentence, analog to a letter span task [45]. The FW of the visuo-spatial task is exploring purely the visuo-spatial sketch pad namely the visuo-spatial storage component of the visual working memory task described by Baddeley [24]. When recalling the spatial path constituted by the different blocks designed by the experimenter, the subject only has to recall the visual path previously showed. These verbal and visuo-spatial subtests do not require real manipulation in working memory and hence very little intervention in executive functions. When looking carefully to individual data, the subjects who showed the lowest performance at baseline were also those who were the most improved at week 14. Moreover, in our sample, the average FW at baseline may be ''too high'' to reveal a significant improvement. We cannot confirm this assumption by comparisons with other studies because authors did not separate the backward from the FWs. We also

thought that patients' baseline results could be dependent from education level but digit span test is well known to be independent from it [46].

Patients also improved verbal learning abilities, in recall of a short story (Logical Memory test), or in ability to learn lists of new words as in the RAVLT. The former and later tests are not equivalent in the demanded cognitive effort: same version for the Logical Memory test at week 0 and week 14, while for the RAVLT different equivalent lists are proposed. Indeed in the former test a practice effect could occur, while in the RAVLT, the improvement found in the ability to retrieve words from a new list at the delayed recall constitutes a noticeable positive point. Sartory et al. [47] observed better performance with the Logical Memory test of the Wechsler Memory Scale Revised in patients after a computerized program versus classical treatment. Lindenmayer et al. [48], in a randomized control trial using the Cogpack program (COGPACK 6.0, Marker software, Ladenburg, Germany), found an improvement in the immediate recall of the RAVLT, but no improvement in the delayed recall. However, their patients were hospitalized for a long time, while our sample included stable outpatients.

Cognitive flexibility was improved with fewer perseverative errors in the WCST at the end of CRT program. This could reflect a practice effect between week 0 and week 14. However, the CRT method emphasizes for each session exercises with arrangements, categorization, or use of superordinate categories in order to assemble, memorize, or retrieve tokens, coins, or playing cards. Furthermore, parts of the basic rules of the WCST are trained at the end of nearly each session by the use of assembly and categorization exercises delineating at least one or two of the main rules of this test. This could exactly fit with what is required for a real benefit in a remediation program, namely exercises trained in a drill and massive practice way [49,50]. Penades et al. [51] also showed an improvement in the WCST after CRT program.

Patients were clinically improved after the CRT program. This was noticed in Wykes et al. [13], with arguments for a positive feedback perceived by the patients. In our findings, at week 14 patients have a reduction of positive symptoms, putatively through the reduction of hallucinations as in Wykes et al. [13], negative symptoms, and a slight improvement in depression sub-scores.

When considering the performance at baseline and the improvement patients made, we observed numerous negative correlations between these two parameters. This could lead to several explanations. First, one can suppose that the higher the cognitive benefits gained afterwards, the worse the abilities were before the cognitive remediation program. The second explanation could be that patients who had the lowest performance at baseline might be more sensitive to larger improvements during the program, as opposed to patients with a high baseline performance, which might reach a ceiling effect with some of the tasks. CRT technique is undoubtedly a flexible method that trains patients in their most important cognitive impairments. This assumption can be confirmed by Wykes et al. [19] who suggested that *nearly half of the people who scored at a very poor level on working memory performed within the normal range following therapy.* Wykes et al. [16] noticed in a study exploring the effect of the CRT on a working memory test (n-Back) with MRI, that a working memory benefit was observed in a group of patients selectively chosen for having social functioning and cognitive difficulties.

Bell et al. [20] in a comparison of subjects receiving either cognitive remediation (NET program) or not, associated with work therapy, observed at 6-months follow-up that the less impaired patients at the digit backward at baseline experienced a slight cognitive decline, while the most impaired patients at baseline continued to maintain their working memory improvement, 6 months later. However, this discrepancy highlights the heterogeneity existing in patients with regard to the benefit raised by cognitive remediation, also possibly due to motivation, or to the quality of comprehension of the instruction [52]. The effect sizes we demonstrated for the digit span, as well as verbal learning or WCST, even if this concerns a small group of patients, are small to moderate. They are comparable to those mentioned in McGurk et al. [49] or Wykes et al. [50] meta-analyses. This is probably because patients were trained for more than 3 months using, as recommended by Wykes et al. [50], drill and practice plus multiple strategies. These are crucial keys to obtain significant change in cognitive remediation.

Limitations of the study

Our study had several limitations. The first one was the restricted number of subjects. As this work was the first study published with the French version of the CRT program, and as it was the first study to focus specifically on a verbal and visual span improvement in working memory, and verbal memory with the CRT method, it seemed important to us to mention these results. Of course further studies are warranted to replicate these findings and to check if the improvement using CRT could also concern the other neuropsychological dimensions of working memory. Our group of subjects was middle aged. It could be very interesting to investigate younger subjects displaying more flexibility, in order to see if more striking improvement in working memory could be observed. Moreover, the design of our study did not include a control group using a classical treatment with no cognitive remediation. The second limitation concerned the absence of a control group for improvement comparisons. It would be helpful indeed for future studies to compare our data in a CRT versus a control design methodology, with clinical and neuropsychological evaluations blind to the treatment assignment (a waiting list, e.g. to ethically ensure that every patient will have the opportunity to be enrolled in a cognitive remediation program). Such study design would better show the effect of CRT and answer issues about significant improvement in our study for variables with ceiling effect in some patients. This could lead to explain improvement not because of therapy but only because of patient's low baselines scores. However, despite the ceiling effect for some patients, our study still shows significant differences between baseline and week 14 meaning that patients with lower scores were improved during therapy. Third, given that the preponderance of significant effect sizes were small to medium and that percentages of statistically significant findings were obtained on a small subject sample without a control group design, the effectiveness of CRT program on clinical and neuropsychological improvement should be interpreted with caution.

This study shows an improvement in working memory and verbal abilities in patients with schizophrenia after a cognitive remediation program. The generalization of such benefits in the everyday life is of crucial importance [53]. In the literature, Nuechterlein et al. [54] in a multiple regression analysis, with a group of first episode patients with schizophrenia reassessed after 9 months found that working memory, attention and early perceptual processing, verbal memory and processing speed explained 52% of the variance in return to work or school after 9 months and a clinical stabilization. Lindermayer et al. [48], who trained with the Cogpack program patients with significant functional and symptomatic impairments, noticed that improving attention, psychomotor speed and immediate learning was associated with more weeks worked, and more wages earned at the psychiatric center. Finally, Killackey et al. [55] showed that

visual organization, visual and verbal memory were significant predictors for a better chance to get a job, maintaining the same amount of work hours per day over a period of 6 months, after having completed a cognitive remediation and vocational program.

Conclusion

This study shows in a group of stabilized patients with schizophrenia, treated with a 3-month cognitive remediation program an improvement in verbal and visual working memory spans, in verbal learning and flexibility. This improvement is independent from the amelioration in symptomatology. Moreover, patients who experienced the greatest improvements were those who presented the lowest performance at baseline. This last result provides some issues for patients who display a huge generalized deficit. Although our results have to be replicated in a more extended population and confirmed with a randomized controlled trail study design, CRT program seems a useful technique to improve crucial cognitive disabilities for patients with schizophrenia.

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Declaration of interest

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