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Cognitive deficits and psychosocial functioning in schizophrenia: role of computer-assisted cognitive remediation

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Summary

Objective. The aim of this study was to evaluate the effectiveness of a computer-assisted cognitive remediation program (CACR) (through the use of the Cogpack software) on cognitive outcomes, symptomatology, and real-world functioning compared to a control active group following 24 weeks of treatment in a sample of outpatients with stable schizophrenia.

Materials and methods. Forty-four outpatients took part in the study: twenty-three of them were allocated to CACR and twenty-one to the control active group. First, we calculated chi-square tests for categorical variables and the univariate analysis of variance (one-way ANOVA) analyses of variance for continuous variables. Second, an ANOVA for repeated measures was performed for clinical and psychosocial variables.

Results. A significant improvement over trial duration (within-group effect) was observed for both treatments in positive (PANSS-P), negative (PANSS-N), general symptoms (PANSS-G), and verbal learning (HVLT-R). CACR was found superior to the control active group (between group effect) in improving specific cognitive domains: processing speed (TMT, BACS, fluency); verbal learning (HVLT-R); reasoning and problem solving (NAB); visual learning (BVMT-R); attention/vigilance (CPT-IP); social cognition (MSCEIT-ME); social acceptability (SLOF social acceptability). No differences were found between groups for the other clinical outcomes' measures.

Conclusions. Our data suggest that the use of CACR is important to implement not only specific cognitive functions, but also functioning in daily life and social cognition in patients with stable schizophrenia.

Introduction

Cognitive deficits have been considered a nuclear feature of schizophrenia: they are already present at the onset of the disorder, but also in the prodromal phase and tend to be stable over time. The impairment of cognitive performance is, on average, two standard deviations below healthy controls [1] and only 15-30% of patients are not deficient in neuropsychological tests, despite having a reduced cognitive functioning based on the premorbid level and the level of parental education [2]. Cognitive deficits are the most important determinant in the impairment of the daily functioning of patients with schizophrenia: they explain, globally, from 20 to 60% of the variance of functioning, with differences ascribable to the heterogeneity of the samples and the evaluation tools adopted [3 4]. An impairment in cognitive domains such as processing speed, attention, episodic memory, working memory and executive functions is strongly associated with poorer psychosocial functioning, including quality of social relationships, role functioning, self-care skills, and independent living [5 6].

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Moreover, cognitive impairment attenuates response to psychiatric rehabilitation, such as supported employment and social skills training [7].
To treat cognitive deficits and, later, act on the functioning of patients with schizophrenia, cognitive remediation (CR) methods have been developed and evaluated [8]. The most common of these methods include strategy coaching to improve performance on cognitive exercises, teaching cognitive compensatory (or self-management) strategies to reduce the effects of impaired cognitive functioning in everyday life, and drill-and-practice of cognitive exercises [9]. The goal of strategic training is to improve performance by explicitly learning and applying cognitive strategies, such as mnemonics [10].
On the other hand, the principle of drill and practice training has been adopted in the design of computer-assisted cognitive remediation CR programs (CACR) for patients with schizophrenia-spectrum disorders (e.g. CogPack and CogRehab). These computer programs are flexible and have several advantages over the pen and pencil programs, such as the enhancement of motivation due to the sensory variety that these exercises present [11 12], and the possibility of providing immediate feedback [13]. Other important features of CACR are its presentation of custom-tailored and adaptive tasks that can take into account the patient's deficits and their evolution over the course of therapy (specific sets of exercises can be individualized for the individual cognitive functions in which the patient is deficient, it is possible to modulate the difficulty based on individual answers) [14], standardization of instructions, and the possibility to perform the training with only little help from therapist, thereby containing costs [15].
However, evidence for the efficacy of such programs in improving (cognitive) functioning remains unclear.
Three meta-analyses including both drill and practice and strategic training and coaching showed that CR in general was effective in a broader sense on cognitive functioning in patients with schizophrenia-spectrum disorders [10 16 17]. More specifically, Wykes et al. (2011) showed that both drill and practice and strategic training improved cognitive outcomes; McGurk et al. (2007) found a larger effect on verbal learning and memory for drill and practice training alone, rather than combined with strategic training. Lastly, Grynszpan et al. (2011) performed a meta-analysis on 16 randomized controlled trials evaluating CACR and showed positive results on general cognition, with small effect sizes on verbal memory, working memory, attention/vigilance and speed of processing and a significant medium effect size for social cognition. Interestingly, cognitive domains that were specifically targeted by the interventions did not yield higher effects than those that were not, suggesting a "non-specific" effect of CACR.
A more recent metanalysis [11] including 24 studies specifically focused on computerized drill and practice programs showed that computerized cognitive training had a superior effect on attention and working memory, as well as on positive and depressive symptoms, when compared to a control condition. Furthermore, small to moderate, but only marginally significant effects were found for processing speed, verbal fluency, and verbal and visual learning and memory. No convincing evidence for improvement in general cognition, reasoning and problem solving, social cognition, and functional outcomes has emerged. Moreover, while longer illness duration was related to larger effect sizes for attention, shorter treatment duration was related to higher effect sizes on working memory and visual and verbal learning and memory. Thus, the dubious effects on social cognition and functional outcomes questions the generalization of cognitive improvement to other domains.
Therefore, in light of these considerations and the growing interest in CR programs, the objective of the present study was to evaluate, in a sample of outpatients with schizophrenia, the effectiveness of a CR program (through the use of the Cogpack software) in addition to standard therapy on cognitive outcomes compared to a control active group and to highlight a possible effect on symptomatology and real-world functioning.

Materials and methods

Subjects

The present study was conducted at the Dipartimento di Neuroscienze "Rita Levi Montalcini", Università degli Studi di Torino, Dipartimento di Neuroscienze e Salute Mentale, Struttura Semplice Dipartimentale Coordinamento Assistenziale Psichiatrico Ospedale-Territorio, AOU Città della Salute e della Scienza - Presidio Molinette, Torino, Italy and the Dipartimento Interaziendale di Salute Mentale ASL TO3 & AOU San Luigi Gonzaga, Italy, in the period between October 2017 e March 2019. Patients, initially evaluated by a psychiatrist, if they met the DSM-5 criteria for diagnosis of schizophrenia, were subsequently visited by our research group. The patients examined were aged between 18 and 65 years. The study was conducted on a sample of outpatients with diagnosis of schizophrenia in stable phase of illness.
The exclusion criteria were the following: a) co-presence of a diagnosis of intellectual disability and learning disabilities; b) hospitalization in psychiatric facilities in the six months prior to evaluation, and significant change of antipsychotic medications during the previous three months (according to clinical judgement).
Participants were recruited through referrals from attending psychiatrists or clinical staff at the psychiatric medical facilities where the study was conducted.
Written informed consent was obtained from all subjects after a complete description of the study. All patients were submitted to standard care provided in community mental health centers in Italy (pharmacological treatment, clinical monitoring at least on a monthly basis, home care when required).

Interventions

All patients recruited in the trial were allocated to one of the two interventions, computer-assisted CACR (Cogpack) and control active group.
In this trial, patients were considered completers if they attended at least 80% of the planned sessions.

Control active group

This condition was designed to control for nonspecific treatment effects. It specified an equal number of one-on-one computer sessions with the same trainers who conducted the CACR sessions, using the same schedule as the treatment arm: two-hour biweekly sessions. It offered supportive trainer interactions and matched experience with computers and varied computer activities. Control activities were selected for game-like properties and low cognitive demand. Participants in this condition did not receive problem-solving training or guided practice on the exercises used in the remediation condition. The control sessions were also videotaped and reviewed in supervision meetings.

Cognitive remediation group

The CACR group received 48 sessions computerized rehabilitation using Cogpack software, performed twice weekly, for a total of 24 weeks of treatment, in addition to standard therapy.
Cogpack is a computer-assisted cognitive remedy that requires the use of different abilities, including: visuomotor speed, understanding, concentration, alertness, language, memory and other cognitive functions. The exercises are grouped according to the cognitive domains that are tested: visuomotor skills, vigilance, language, memory, logic and calculations, daily skills, culture and special element orientation. The Cogpack software includes 64 different tests that can be composed to generate 540 different rehabilitation programs, so that it is possible to personalize the rehabilitation adapting it to the neuropsychological deficit found in the patient. Based on the results obtained by the patients in the previous tests, the exercises can be modulated in a programmed way or self-modulated by the software itself so that it can always improve individual performance. The variability of the exercises in the same category also makes it possible to rehabilitate the same neurocognitive function by using new tasks as soon as the patient manages to solve all the levels of the same exercise. The therapist has a fundamental role, because he allows learning without errors (as the patient with schizophrenia shows poor learning and trial skills); he must also set the initial level of the task to allow greater chances of success and finally he must not miss a continuous positive reinforcement that helps the patient to understand the reasons of possible failures and to improve himself. We also conducted a weekly group session designed to promote the transfer of improved cognitive functioning to real-world situations. The trained therapists also provided participants teaching compensation strategy or prompting additional practice if needed.
Additionally, at least one therapist at each site had to take 1-day training course to learn the CACR program before the study was started. Therapists involved in the intervention were psychologists, and technicians of psychiatric rehabilitation who were familiar with psychiatric rehabilitation for schizophrenia, and supervised during the study period by members of the research team who had several years of experience with CR. Internet conferences between members of the research team were also held during the study period. Using computer software and the manual also minimizes the disparity of efficacy in cognitive remediation.
In the CACR training, participants were directed to practice a wide range of cognitive domains in both the early and later phases of remediation, and each participant could choose either preferable tasks or unskilled tasks to enhance their interests or self-efficacy in the later phase. In the groups, participants talked about their weak tasks, and discussed with each other strategies to complete tasks using some cognitive functioning in the early phase. In the middle and later phases, they also discussed social goals and how to transfer gained cognitive skills to achieve their goals.
The trial was carried out in accordance with the Declaration of Helsinki of 1995 (as revised in Edinburgh in 2000) and was approved by the Local Ethical Committee.
Patients were evaluated using a semi-structured interview to assess demographic and clinical features. Data were collected to determine age, gender, years of education, status of employment, marriage or an equivalent long-term relationship, length of illness, number of hospitalizations and antipsychotic treatment.

Psychiatric assessment

All subjects were evaluated at baseline (T0) and after six months (T1) with the following evaluation instruments: the *Positive and Negative Syndrome Scale* (PANSS); The *Calgary Depression Scale for Schizophrenia* (CDSS); the *MATRICS Consensus Cognitive Battery* (MCCB); the *Specific Levels of Functioning Scale* (SLOF).
Current levels of psychopathological symptoms were assessed using the PANSS, which includes positive symptoms (PANSS-P), negative symptoms (PANSS-N), and general psychopathology (PANSS-G) subscales. The CDSS was used to measure depressive symptoms [18].
Neurocognition was measured according to the 7 cognitive domains of the MCCB [19-21], derived from scores on 10 cognitive measures: speed of processing (*Trail Making Test Part A*; *Brief Assessment of Cognition in Schizophrenia*: Symbol Coding; *Category Fluency Test*: animal naming), attention/vigilance (*Continuous Performance Test*: Identical Pairs), working memory (*Wechsler Memory Scale*; spatial span subset; *Letter Number Span Test*), verbal learning (refers to immediate verbal memory, *Hopkins Verbal Learning Test (HVLT)-Revised,* immediate recall), visual learning (refers to immediate visual memory, *Brief Visuospatial Memory Test-Revised*), reasoning and problem solving (*Neuropsychological Assessment Battery* (NAB), mazes subtest).
The assessment of SC included a test contained in the MCCB: the *Mayer Salovey Caruso Emotional Intelligence Test* (MSCEIT) [22], managing emotion section, which examines the regulation of emotions in oneself and in one's relationships with others by presenting vignettes of various situations, along with ways to cope with the emotions depicted in these vignettes. It was integrated by the *Facial Emotion Identification Test* (FEIT) [23], which examines emotion perception, and *The Awareness of Social Inference Test* (TASIT) [24], which is a TOM test consisting of

7 scales (positive emotions, negative emotions, sincere, simple sarcasm, paradoxical sarcasm, sarcasm enriched, lie), organized into three sections: Emotion Recognition; Social Inference (minimal); Social Inference (enriched). The manual of the TASIT was translated into Italian by a psychiatrist of the Department of Psychiatry of the University of Campania "Luigi Vanvitelli", Naples, who gained experience in the use of the English version of the instrument during his stage at the Department of Psychiatry and Biobehavioral Sciences at University of California, Los Angeles (UCLA), as part of his PhD Course. The videotaped vignettes of the TASIT were dubbed in Italian at the Fono Roma Studios (www.fonoroma.com), a prestigious society in the field of film industry. As to the FEIT, the adaptation of the Italian version required the translations of the six emotions reported on the screen above the stimuli.
Real-life functioning was measured using the SLOF [25-27]. The original SLOF is a 43-item self- or informant-rated scale of a person's behavior and functioning which was abbreviated to assess the following domains: Interpersonal Functioning (e.g. initiating, accepting and maintaining social contacts; effectively communicating), Independent participation in Everyday Activities (shopping, using telephone, paying bills, use of leisure time, use of public transportation), and Vocational Functioning (e.g. employable skills, level of supervision required to complete tasks, ability to stay on task, completes tasks, punctuality). The SLOF consists of 43 items. Each of the questions is rated on a 5-point Likert scale, indicating the level of assistance the participant needs to perform the task, with higher score indicating better functioning. Scores on the instrument range from 43 to 215. The SLOF differs from the other outcome measures in emphasizing patient's current functioning and observable behavior, as opposed to inferred mental or emotional states, and focuses on a person's skills, assets, and abilities rather than deficits that once served as the central paradigm guiding assessment and intervention for persons with disabilities. Moreover, the SLOF does not include items relevant to psychiatric symptomatology or NC dysfunctions [25 27].

Statistical analysis

Statistical analyses were performed using the Software System Statistical Package for the Social Sciences, SPSS, version 25 for Windows (SPSS, Chicago, IL, USA). Data are expressed as average and standard deviation or percentages.
Analyses were planned in two stages. In stage 1, we performed chi-square tests for categorical variables and the univariate analysis of variance (One-way ANOVA) analyses of variance for continuous variables, in order to examine whether the two groups differed in baseline socio-demographic and clinical variables.
In stage 2, an ANOVA for repeated measures was performed for clinical and psychosocial variables. The between-subject factor was the group (CACR/control active group), and the within-subject factor was time (T0; T1). Effects of time (longitudinal dimension), group (cross-sectional dimension), and time by group (interaction effect) were examined.

Results

Forty-four outpatients meeting DSM-V criteria for schizophrenia took part in the study.
Twenty-three of these patients were allocated to CACR and twenty-one of them to the control active group. Five patients dropped-out from the CACR group and six from the control active group. Therefore, the final sample included 18 patients in the CACR group and 15 subjects in the control active group. Statistical analyses were performed on patients who completed the sessions of treatment. There were no significant differences with one-way ANOVA and chi-square test in socio-demographic, cognitive, and clinical characteristics between the two treatment groups, except for age, as patients in the active control group were older than those in the CR group. In addition, the severity of symptoms at baseline measured with the PANSS was not significantly different between groups.
Socio-demographic, cognitive, and clinical variables of the two treatment groups at baseline are shown in Table I. Results of the evaluation scales for the two treatment groups at T0 and at T1 are displayed in Table II. A significant improvement over trial duration (within-group effect) was observed for both treatments in positive (PANSS-P), negative (PANSS-N), general symptoms (PANSS-G) and verbal learning (HVLT-R).
CACR was found superior to the control active group (between group effect) in improving specific cognitive domains: processing speed (TMT, BACS, Fluency); verbal learning (HVLT-R); reasoning and problem solving (NAB); visual learning (BVMT-R); attention/vigilance (CPT-IP); social cognition (MSCEIT-ME), social acceptability (SLOF Social Acceptability).
No differences were found between groups for the other clinical outcomes' measures.

Discussion

This study was aimed to assess the effectiveness of CACR versus a control active group on specific clinical and functional domains in a sample of outpatients with schizophrenia spectrum disorders. The CACR group was contrasted with an active experimental condition that controlled for nonspecific elements of the remediation training, including supportive therapist interactions and exposure to interesting computer activities. Outcomes were assessed at three levels: proximally, on the remediation training exercises; intermediately, on neuropsychological measures not involved in the training; and more distally, on proxy measures of everyday functioning. The two groups taking part in the study were well matched at baseline assessment on demographic (except for age) and clinical confounding variables (i.e. depression) that could negatively impact the outcome measures and made biased the study results.
We found that CACR and active control group can be considered both effective treatments for patients suffering from schizophrenia spectrum disorders. In fact, both interventions showed a significant and similar efficacy in improving symptomatology.
Nevertheless, some specific differences between the two

Table I. Socio-demographic, clinical, cognitive and functioning characteristics of the sample at time zero.

Variables	TAU	Cogpack	F/χ^2	p
Age (years)	42.72±8.47	36.46±7.31	5.10	.03
Sex (male*)	10	3	1.09	.30
Single*	8	2	.28	.59
Employment*	21	10	1.22	.27
Scolarity (years)	11.08±3.82	13.23±3.47	2.88	.10
Age of onset	25.68±7.49	26.54±4.21	.15	.70
Duration of illness (years)	17.04±9.88	10.00±5.18	5.73	.02
PANSS-P	15.24±6.92	11.23±3.09	3.91	.06
PANSS-N	22.00±7.11	24.31±6.96	.95	.33
PANSS-G	36.08±9.98	36.54±10.63	.02	.90
PANSS total	72.96±17.95	72.85±16.69	.00	.98
CDSS	1.80±2.04	3.46±4.27	2.66	.11
Speed of processing	24.48±9.99	27.69±9.23	.93	.34
Social cognition	27.40±10.74	28.62±6.33	.14	.71
Working memory	29.64±11.16	31.38±9.94	.36	.55
Verbal learning	33.36±8.64	34.08±8.94	.06	.81
Reasoning/problem solving	32.28±4.71	34.00±9.46	.57	.46
Visual learning	35.92±14.06	36.92±17.34	.04	.85
Attention/vigilance	28.36±9.03	34.08±11.02	2.95	.09
SLOF total	179.12±17.35	175.00±18.70	.46	.50

*Data are expressed as mean ± standard deviation. * data expressed as a number. Statistical analysis: One-way ANOVA for continuous variables; χ^2 for categorical variables.*
PANSS-P: Positive and Negative Syndrome Scale, positive symptomatology; PANSS-N: Positive and Negative Syndrome Scale, negative symptomatology; PANSS-G: Positive and Negative Syndrome Scale, general symptomatology; PANSS total: Positive and Negative Syndrome Scale, total; CDSS: Calgary Depression Scale for Schizophrenia; SLOF total: Specific Level of Functioning, general functioning.

groups were observed. In particular, the CACR therapy group presented improvements, after six months of treatment, in specific cognitive domains (processing speed, verbal learning, reasoning and problem solving, visual learning, attention/vigilance), social cognition, and social acceptability, whereas the active control group did not. Working memory remained unaffected by both treatments. Lastly, while verbal learning improved in both groups over assessment occasions, a significant time×group interaction was evident, suggesting an advantage for CACR training in this specific neurocognitive domain.

Several studies have been performed to examine the effectiveness of CACR therapy in addition to usual treatments in patients with schizophrenia and they obtained discordant results. The lack of consistent findings across studies is not surprising considering the methodological limitations of the studies published thus far [8]. Most of them have had modest sample sizes of under 60 participants receiving a particular type of cognitive remediation [28-32], and two studies combined participants receiving different types of CR [31 33]. Three studies evaluated CR interventions with as few as one [32] to ten sessions [28 29]. Moreover, CR studies are conducted on inpatients [34-36] and outpatients [37-40]. Although evidence indicates that the patient status is not of importance, it may, however, be essential for a massed treatment schedule as adherence is more difficult to ascertain in outpatients [14]. Lastly, CACR have the potential to be performed independently by the patient. Many papers did not provide sufficient information on this topic and it is not possible to assess the effect of the amount of therapist involvement on training efficacy.

The positive findings regarding the amelioration of attention and vigilance, processing speed, verbal and visual learning and reasoning and problem solving reported in the present study are in concordance with several other studies that have utilized the CACR in patients with schizophrenia [11]. Processing speed is related to the ability to carry out the activities of daily life, to the degree of independence achieved and to the ability to get a job and therefore seems to be the basis of the poor performance of other cognitive tests and the impairment of global functioning [41]. The advantage of CR for processing speed, attention/vigilance and verbal and visual learning in the present study suggests, however, that at least some additional neurocognitive benefit may derive from the careful titration of task difficulty of cognitive exercises to ensure appropriate cognitive challenge, the rapid repetition of exacting exercises, and the frequency of reinforcement associated with achievement of intermediate and overall task goals characteristic of this condition. The hierarchical nature of the training program, starting with training in elementary attention skills and then graduating to considerably more complex episodic and verbal memory tasks may also play a role in the advantage of this condition [42].

Thus, the finding of a no advantage of CACR on work-

Table II. Analysis of the variance of scores variations of clinical, cognitive and functioning evaluation scales in the two treatment groups.

	TAU	Cogpack	ANOVA within groups F (p)	ANOVA between groups F (p)
PANSS-P				
T0	15.24±6.92	11.23±3.09	**3.38 (.04)***	1.72 (.20)
T1	12.00±3.91	11.77±4.30		
PANSS-N				
T0	22.00±7.11	24.31±6.96	**5.60 (.00)***	.01 (.91)
T1	21.52± 6.47	19.31±3.33		
PANSS-G				
T0	36.08±9.98	36.54±10.63	**4.86 (.03)***	.28 (.60)
T1	33.88±11.95	31.23±6.31		
CDSS				
T0	1.80±2.04	3.46±4.27	.94 (.39)	.17 (.68)
T1	3.68±3.73	1.77±2.52		
Speed of processing				
T0				
T1	24.48±9.99	27.69±9.23	2.32 (.11)	**6.28 (.02)***
	24.68±7.11	34.15±14.59		
Verbal learning				
T0	33.36±8.64	34.08±8.94	**12.39 (.00)***	**11.55 (.00)***
T1	31.84±6.01	47.62±9.86		
Working memory				
T0	29.24±10.76	31.38±9.94	1.05(.35)	1.87 (.18)
T1	29.64±11.16	35.62±11.13		
Reasoning and problem solving				
T0	32.28±4.71	34.00±9.46	1.94 (.15)	**9.84 (.00)***
T1	30.08±3.90	39.23±8.17		
Visual learning				
T0	35.92±14.06	36.92±17.34	1.51 (.23)	**5.20 (.03)***
T1	33.24±12.19	48.23±16.15		
Attention/vigilance				
T0	28.36±9.03	34.08±11.02	.19 (.83)	**4.64 (.04)***
T1	27.40±7.27	33.62±13.96		
Social cognition				
T0	27.40±10.74	28.62±6.33	1.40 (.25)	**6.72 (.01)***
T1	25.52±5.90	32.69±10.34		
SLOF phisical conditions				
T0				
T1	24.60±1.04	24.85±.38	.69 (.50)	2.47 (.12)
	24.40±.91	24.92±.28		
SLOF self-care				
T0	32.76±2.77	31.31±3.75	.29 (.75)	.32 (.57)
T1	32.27±2.49	32.46±2.22		
SLOF Int_Rel				
T0	22.12±4.29	20.62±6.07	.78 (.46)	.87 (.36)
T1	20.80±5.31	22.92±5.96		
SLOF Soc_Accet				
T0	34.54±.87	31.44±4.12	2.58 (.08)	**5.22 (.03)***
T1	34.77±.44	32.80±3.86		
SLOF Activities				
T0	47.76±5.67	44.31±6.74	1.48 (.23)	.12 (.73)
T1	44.48±6.96	44.31±5.14		
SLOF Work_skills				
T0	19.64±5.37	16.38±5.72	.54 (.59)	.045 (.83)
T1	20.34±4.89	19.92±5.60		
SLOF totale				
T0	179.12±17.35	175.00±18.70	.59(.55)	.14 (.71)
T1	175.84±16.77	178.62±11.76		

*Data are expressed as an average (standard deviation). Statistical analysis: ANOVA with repeated measures. * Significant value: p≤0.05. PANSS-P: Positive and Negative Syndrome Scale, positive symptomatology; PANSS-N: Positive and Negative Syndrome Scale, negative symptomatology; PANSS-G: Positive and Negative Syndrome Scale, general psychopathology; CDSS: Calgary Depression Scale for Schizophrenia; SLOF physical conditions: Specific Level of Functioning, physical abilities; SLOF Self-care: Specific Level of Functioning, self-care skills; SLOF Int_Rel: Specific Level of Functioning, interpersonal relationships: SLOF Soc_Accet: Specific Level of Functioning, social acceptability; SLOF Activities: Specific Level of Functioning, daily activities; SLOF Work-skills: Specific Level of Functioning, work skills; SLOF total: Specific Level of Functioning, general functioning.*

ing memory (a skill related to holding information in mind and manipulating that information), but accompanying evidence of a commensurate advantage in the reasoning/executive-function and problem solving domain in the CACR group is paradoxical as several studies have shown a close link between more elementary working-memory functions and higher-level reasoning and problem-solving skills [43]. Indeed, no effect was found in the domain of reasoning and problem solving when comparing computerized cognitive training to a control group in the meta-analysis of Prikken and colleagues (2019). This might be not surprising, as problem solving is a complex skill which is of great importance in everyday functioning [44]. Teaching strategies used by the therapist during and after CACR sessions in our study could explain our results. Indeed, the one-to-one interaction with a therapist who can explicitly encourage "bridging" strategies, as well as provide nonspecific support and motivational coaching form a meaningful components of the CACR therapy.

The same applies to social cognition: we found significant effect for this domain in the CACR group compared to the control active group. Social cognition is the set of mental functions that allow individuals of the same species to interact with each other, is defined as the ability to understand, predict and respond appropriately to the thoughts, feelings and behavior of others in social contexts different and often unfamiliar [45 46]. In literature, there are some studies that have tested the effects and possible improvements in social cognition, after CACR. Almost all agree that when coupled with rehabilitative programs focused on emotional intelligence, the benefits on recognition of emotions and the ability to interpret the feelings and behavior of others are more [47 48]. The three studies included in the meta-analysis of Prikken and colleagues did not detect a connection between CACR treatment and an improvement in emotional intelligence [11].

Moreover, the analysis regarding functional outcome resulted in a very small effect, as CACR was effective in improving only *SLOF Social Acceptability subscale*, in which are evaluated different aspects: the possible presence of verbal, physical abuse, physical aggression towards oneself, reiteration of certain behaviors (steps, oscillations, etc.), whether the subject destroys goods, whether the patient shows fear, cries or appropriates the property of others without authorization. A treatment period of a maximum length of 6 months may have been too short to rate more functioning differences between treatment groups, as some changes in the real-world functioning may take a relatively long time before becoming apparent, such as one year or more.

Conflicting results are reported in literature. Small to moderate, but only marginally significant effects on functional outcomes were found in the meta-analysis of Prikken et al. (2019), in contrast with other ones, that included also studies using strategy training, showing larger and significant effects [10 16 17].

This might suggest that CACR training alone might not be sufficient to improve daily functioning. Learning strategies might be a prerequisite for generalization of CACR treatment effects, as improvement of NC does not translate into improved social functioning [49 50]. It has been hypothesized that CR improves capacity to learn through increased verbal memory or executive functioning, and in the absence of concerted learning opportunities, improved cognitive functioning does not automatically lead to improved psychosocial functioning, as discussed in McGurk et al. [9 51]. Indeed, it was then demonstrated that CR is more likely to influence functioning when patients are given the opportunity to train cognitive skills in the context of a social learning environment through transferring skills from laboratory to real world and if it is combined with other psychosocial rehabilitation programs [16 50]. Our protocol study also focused on transferring learned abilities to the real world through 10-minutes discussion with the therapist at the end of each CACR session.

Moreover, the differences in literature could depend on the different scales administered to patients.

Finally, our results corroborate those of previous studies which showed a non-specific impact on symptoms in the CACR group [52-54] and are only partially consistent with evidence from Prikken et al. (2019), who showed a significant improvement of positive symptoms after CACR relative to a control condition, whereas small to moderate, but only marginally significant effects on negative symptoms were found. No effect of CACR on general symptoms was detected.

This study presents limitations and strengths. As for the formers, a first limitation of this study is its relatively small sample size: further studies on larger populations would be necessary to investigate more closely the relationship between type of treatment and cognitive functions, functioning in real life and symptomatology. Secondly, in this study only patients in stable phase of disease were included: it remains unclear to what degree these findings would generalize to patients earlier or later in the course of their illness, in long-term inpatient or nursing home care, or who are in comorbidity with substances abuse. Third, there was no independent randomization. But NC and symptoms were assessed blind to group allocation which strengthens our results. However, as our study was not blinded and patients receiving the intervention were offered increased attention, clinical care, and individualized contact on a frequent basis, this may have possibly influenced the positive cognitive outcomes in this group. Fourth, another factor that theoretically has the potential to influence whether CACR is found to be effective or not is choice of the control intervention. Although use of an active control may be desirable, it is important to ensure that the control task is sufficiently different from therapy to avoid it itself having positive beneficial effects on cognition [55]. The control active group we employed engaged cognitive functions, not of a drill and practice type. It makes at most minimal demands on executive function, and while it does require memory, this is procedural memory, which is universally considered to be dissociable from episodic memory as trained in CACR [56]. Also arguing against the possibility that our control intervention was therapeutic is the fact that we found significant differences at the end of the trial between the CACR and the active control group on some neuropsychological measures. Fifth, the fact that the study was conducted in an open unit, where patients had an opportunity to go out to the community might have

impacted the results, introducing uncontrolled variables, i.e., time spent in the community. Future studies could ensure that the active control task does not contain any form of cognitive training, although this could be extremely hard to accomplish. Sixth, the study could be viewed as lacking enough power to detect eventual differences between CACR and control group. This is a common problem in CACR trials, as detection of small effects requires large samples. Recruitment of large groups of patients is a great challenge, especially if it is conducted in a single unit. The duration of the study would substantially extend given that interventions take several weeks [57]. Lastly, we did not evaluate the long-lasting effects of these treatments after their discontinuation.

Some strengths of this study should be noted, including the well-matched baseline clinical, demographic, and cognitive characteristics of the two groups; the strict inclusion criteria; the absence of comorbid conditions that may have biased the study outcome measures; the accurate evaluation of cognitive functions, performed through the MCCB, and real-world functioning, evaluated through the *Specific Level of Functioning Scale* (SLOF), indicated as the best scale to estimate psychosocial functioning of schizophrenia patients among those included in the VALERO program. Lastly, diagnoses were based on structured clinical interviews and all patients were evaluated by trained raters.

In conclusion, if confirmed, our data suggest the importance of CACR aimed at implementing cognitive skills, social cognition and functioning in daily life in patients with schizophrenia.

Future studies are necessary to determine the durability of the improvements. While the effectiveness of the CACR has been demonstrated, further studies are needed to assess the effects over time.

Declaration of interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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