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Illness duration effect on Computer-Assisted Cognitive Remediation (CACR) efficacy in Schizophrenia: a preliminary report

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Summary

Computer-Assisted Cognitive Remediation (CACR) interventions are reliable and efficacious to improve the cognitive deficit in people with a diagnosis of schizophrenia (PSZ). Aim of this study was to investigate the illness duration effect on CACR efficacy. We divided a sample of 32 PSZ in those with a Short Duration of Disease (SDD; n = 12) and those with a Long Duration of Disease (LDD; n = 20). In the whole sample of 32 PSZ, cognitive, insight and functioning indices improved at the end of CACR intervention, as well as 3 and 6 month after the end of CACR program. No significant difference of cognitive, insight and functioning indices emerged between SDD and LDD during the 6-month follow-up period. Findings from this preliminary report revealed that CACR is an efficacious strategy to improve cognition, and consequently insight and functioning, in PSZ both in early-stage and chronic disorder.

Key words

CACR • Cognitive remediation • Schizophrenia • Cognition • Functioning • Insight • Psychosis

Introduction

Schizophrenia is widely believed a cognitive illness [1], despite to make a diagnosis of schizophrenia specific criteria describing cognitive deficits are absent in the current diagnostic classification systems. Cognitive impairment in people with a diagnosis of schizophrenia (PSZ) is present early in the course of illness, frequently preceding the onset of the full psychosis of several years. Moreover, deficits in PSZ's cognition have been clearly recognized to influence the everyday functioning and to determine the outcome in the "real-world" [2].

In rehabilitation setting of schizophrenia, cognitive remediation provides powerful and efficacious learning strategies (including errorless learning, scaffolding, massed practice, positive reinforcement and information processing strategies) to improve PSZ's cognition [3 4]. Computer-assisted cognitive remediation (CACR) offers a set of cognitive remediation tools through cognitive exercises with different difficulty levels customized on subjects' performance. CACR programs are commonly implemented in cognitive remediation setting for schizophrenia [3]. Meta-analytic evidence of cognitive remediation techniques (comprising CACR too) shows a significant improvement in cognition (including general and specific cognitive domains), as well as an overall effect on functioning and functional outcome [5-8].

Despite how PSZ's cognition becomes different during the course of illness is still under debate [1], brain structural and functional modifications are observed during the course of schizophrenia [2], sometimes differentiating specific stages of illness duration [9]. The influence of schizophrenic illness duration on CACR is not well investigated [10]. Aim of this preliminary study was to investigate the results of CACR intervention on PSZ's cognition, insight and functioning at different stages of illness duration.

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Methods

Subjects

People with a diagnosis of schizophrenia (PSZ) from an outpatient program for cognitive rehabilitation of "Tor Vergata" University Psychiatry Clinic were considered for the study. The inclusion criteria were: a diagnosis of schizophrenia according to DSM-IV, confirmed with the MINI-Plus [11]; an age between 18 and 50 years; a stable clinical and pharmacological condition from at least three months. The exclusion criteria were: history of head trauma; history of perinatal trauma; mental retardation; major neurological illness, included epilepsy; history in the last six months of alcohol and / or substance abuse. Thirty-two PSZ constituted the sample enrolled for the present study (12 women and 20 men; age: mean 33.09 and SD 7.22; education, in years: mean 12.84 and SD 2.69). In order to study the illness duration effect PSZ were divided in those with short disease duration (SDD; lower than 5 years from the first psychotic episode) and those with long disease duration (LDD; higher than 5 years from the first psychotic episode). The Positive and Negative Syndrome Scale [12] was used to assess the severity of psychopathology. In the week preceding the beginning the CACR intervention, psychiatrists, who followed each patient up in the outpatient clinical program but were not directly involved in the rehabilitation intervention, calculated the PANSS total score following a semi-structured interview and referring to the patient's clinical condition during the week before.

Assessments

Raters, not directly involved in the patients' CACR intervention, performed neurocognitive, insight and functioning evaluations (below described) during the week preceding the beginning ("pre") and during the week succeeding the end ("post") of the CACR intervention, as well as three and six months after the CACR end (respectively, "3m post" and "6m post").

Neurocognitive assessments

The neurocognitive battery was built to measure the cognitive domains mainly impaired in schizophrenia and that could improve with cognitive rehabilitation [5]: verbal learning and memory, speed of processing, working memory and executive functions. The neurocognitive tests were: the immediate and delayed Rey Auditory Verbal Learning Test (RAVLT), the Trail Making Test A (TMT-A), Trail Making Test B (TMT-B) and the derived index TMT-B minus TMT-A; letter fluency and category fluency; digit forward span and digit backward span. For each test, trained raters carried out the validated Italian version to PSZ. We decided to summarize the results of each test in a single, global cognitive index. For each time of assessment, we calculated the z-score for each test and then we averaged each single z-score obtaining, at the end of this process, an average z-score, named "cognitive composite z-score". In order to obtain z-scores, the reference values of means and SDs for cognitive test were derived from a convenience sample of twenty subjects without a personal and familiar history of psychiatric disorders. Additional inclusion criteria were: an age between 18 and 50 years; the absence of a history of head trauma, perinatal trauma, mental retardation and a major neurological illness, included epilepsy. The MINI-Plus was also used to confirm the absence of psychiatric diagnosis in the healthy control subjects (HCS). Enrolled HCS group did not differ respect to PSZ in gender (8 women and 12 men; $\chi^2_1 = 0.033$, p = 1.000), age (mean 35.00 and SD 7.83; $t_{30} = -0.896$, p = 0.374) and education (mean 12.50 and SD 2.76; $t_{30} = 0.444$, p = 0.659).
The Schizophrenia Cognition Rating Scale [13-15] was also used as a measure of general cognitive function in PSZ. SCoRS has shown to be a reliable and valid tool for assessing cognitive performance of the "real world" of PSZ, particularly evident by the observations of SCoRS correlations with several measures of functioning.

Insight assessment

The total score of Schedule for the Assessment of Insight [16] was used to have a general index about the insight and its change after CACR intervention.

Functioning assessment

The evaluation of patient's functioning was carried out with the total score of Life Skill Profile [17] and Personal Social Functioning Scale [18 19].

CACR intervention

The CACR was performed by the application of COGPACK® program (Marker Software®; www.markersoftware.com) [20], one of most used software packages among those programs available for CACR [21 22]. The COGPACK® has different neurocognitive exercises: domain-specific exercises, useful for training specific cognitive domains (particularly among those known to be impaired in schizophrenia: verbal memory, verbal fluency, psychomotor speed and coordination, executive function, working memory, attention); non-domain-specific exercises, that involve, at the same time, the use of various functions and involve culture, language and calculation skills. Most exercises are adaptive and, based on the patient's performance during the session course, the computer sets the level of exercise difficulty. In each session, the program archives the patient's performance, giving patients the opportunity to have, at the end of each session, a feedback on their performance in that session and, eventually, on their progress through the CACR sessions. Each patient received, by a trained cognitive rehabilitation expert, an individual COGPACK® session, administered twice a week, in 45-

55 min sessions, for 18 weeks. After the end of CACR treatment phase, PSZ did not receive any type of structured rehabilitation program, following scheduled clinical visits of outpatient program.

Ethics

Following a standard clinical procedure, all participants were informed about the CACR intervention and provided written informed consent. The current observational study was approved by the "Tor Vergata" University Hospital ethics committee and carried out in accordance with "Ethical Principles for Medical Research Involving Human Subjects" (Declaration of Helsinki, 1964).

Statistical analysis

We performed t-tests for independent samples (with two-tailed p-value) to test the differences between the means for the SDD and LDD groups, and chi-square statistics (with Fisher's exact test for a two-tailed p-value) were performed to test for significance of the association between grouping variables.

A general linear model approach was used to analyze the "between factor" x "within factor" interaction effect (between or grouping factor: SDD *vs* LDD; within factor, treatment time: "pre" *vs* "post" *vs* "3m post" *vs* "6m post") on cognitive, insight and functioning indices. To investigate the "treatment time" effect and "grouping × treatment time" interaction effect, separate models of repeated measures analysis of variance (rm-ANOVA) was employed (dependent variables in the separate models were: cognitive composite z-score, SCoRS, SAI, LSP and FPS). Univariate results were examined only if Wilks' Lambda multivariate significance criterion was satisfied. The sphericity of the covariance matrix was tested with Mauchly's test of sphericity; in the case of violation of the sphericity assumption, Greenhouse-Geisser epsilon (ε) adjustment was used. *Post-hoc* tests were performed to define which variables contributed to the measured effects using Bonferroni's confidence interval adjustment for multiple comparisons. Statistical significance was set at $p < 0.05$.

Results

Among 32 PSZ included in the study, those with a SSD were 12 whereas those with LDD were 20. Descriptive and univariate statistics of socio-demographic and clinical characteristics of the two groups are summarized in Table I. As expected SDD and LDD differed in age (younger age of the SDD group) and illness duration (longer by definition for the LDD group). It is interesting to note that cognitive, insight and functioning indices did not differ between SDD and LDD at pretreatment assessment.

In all rm-ANOVA models, the multivariate test showed a significant "treatment time" effect on cognitive (cognitive composite z-score: Wilks' Lambda = 0.086, $F_{3,28} = 99.322$, $p < 0.0001$; SCoRS: Wilks' Lambda = 0.183, $F_{3,28} = 41.658$, $p < 0.0001$), insight (SAI: Wilks' Lambda = 0.319, $F_{3,28} = 19.884$, $p < 0.0001$) and functioning indices (LSP: Wilks' Lambda = 0.169, $F_{3,28} = 45.754$, $p < 0.0001$; FPS: Wilks' Lambda = 0.114, $F_{3,28} = 72.297$, $p < 0.0001$). Also the univariate tests for repeated measure adjusted for the violation of the sphericity confirmed these results (cognitive composite z-score: $F_{3,90} = 159.579$, $\varepsilon = 0.667$, $p < 0.0001$; SCoRS: $F_{3,90} = 104.744$, $\varepsilon = 0.506$, $p < 0.0001$; SAI: $F_{3,90} = 27.996$, $\varepsilon = 0.733$, $p < 0.0001$; LSP: $F_{3,90} = 87.114$, $\varepsilon = 0.691$, $p < 0.0001$; FPS: $F_{3,90} = 86.009$, $\varepsilon = 0.735$, $p < 0.0001$). *Post-hoc* tests showed that, for all indices, the pairwise comparisons "post *vs* pre", "3m post *vs* pre" and "6m post *vs* pre" were highly significant different with p-values consistently < 0.0001 (cognitive composite z-score, Figure 1A; SCoRS, Figure 1C; SAI, Figure 1E; LSP, Figure 1G; FPS, Figure 1I).

The multivariate test of rm-ANOVA models of cognitive composite z-score, SCoRS and LSP showed a significant "grouping × treatment time" interaction effect (cognitive composite z-score: Wilks' Lambda = 0.436, $F_{3,28} = 12.099$, $p < 0.0001$; SCoRS: Wilks' Lambda = 0.508, $F_{3,28} = 9.042$, $p = 0.0002$; LSP: Wilks' Lambda = 0.733, $F_{3,28} = 3.396$, $p = 0.032$). For SAI and FPS rm-ANOVA models, the "grouping x treatment time" interaction effect was not significant at the multivariate test (SAI: Wilks' Lambda = 0.838, $F_{3,28} = 1.801$, $p = 0.170$; FPS: Wilks' Lambda = 0.897, $F_{3,28} = 1.073$, $p = 0.376$). The univariate tests for repeated measure adjusted for the violation of the sphericity did not confirmed the significant "grouping × treatment time" interaction effect (cognitive composite z-score: $F_{3,90} = 2.403$, $\varepsilon = 0.667$, $p = 0.099$; SCoRS: $F_{3,90} = 2.377$, $\varepsilon = 0.506$, $p = 0.117$; LSP: $F_{3,90} = 2.097$, $\varepsilon = 0.691$, $p = 0.130$), hence revealing no significant difference between SDD and LDD at the end of CACR intervention as well as at 3 and 6 month after the CACR end also for cognitive composite z-score, SCoRS and LSP. Post-hoc tests showed in fact that, for all indices in both SDD and LDD, the pairwise comparisons "post *vs* pre", "3m post *vs* pre" and "6m post *vs* pre" were highly significant different with p-values consistently < 0.0001 (cognitive composite z-score, Figure 1B; SCoRS, Figure 1D; SAI, Figure 1F; LSP, Figure 1H; FPS, Figure 1L). To note that, despite the presence of mean differences for cognitive composite z-score and SCoRS during the follow-up, particularly evident at "6m post" time, pairwise comparison post-hoc tests between SDD and LDD at "post", at "3m post" and "6m post" were not significant for cognitive, insight and functioning indices.

Discussion

Findings from this preliminary report show CACR intervention determines, over a six month period, a stable improvement in general cognition, insight and functioning

TABLE I. *Descriptive and univariate statistics of sociodemographic and clinical characteristics of sample.*

	SDD (n = 12)	LDD (n = 20)	Statistics
Gender (w/m)	5/7	7/13	$\chi^2_1 = 0.142$ p = 0.724
Age (years)	25.83 (3.42)	37.60 (4.62)	$t_{30} = -7.802$ p < 0.0001
Education (years)	13.42 (2.58)	12.50 (2.76)	$t_{30} = 0.932$ p = 0.359
Onset age (years)	22.58 (2.64)	21.50 (2.61)	$t_{30} = 1.132$ p = 0.266
Illness duration (years)	3.00 (1.41)	16.10 (4.99)	$t_{30} = -8.825$ p < 0.0001
PANSS total score	72.42 (10.27)	73.60 (15.75)	$t_{30} = -0.232$ p = 0.818
Antipsychotics (FGA/SGA)	2/10	7/13	$\chi^2_1 = 1.247$ p = 0.422
Chlorpromazine equivalent	241.67 (79.30)	240.00 (109.55)	$t_{30} = 0.046$ p = 0.964
Cognitive composite z-score	-0.99 (0.46)	-1.29 (0.61)	$t_{30} = 1.456$ p = 0.156
SCoRS	35.33 (6.79)	37.25 (7.02)	$t_{30} = -0.757$ p = 0.455
SAI	6.25 (2.09)	6.60 (2.56)	$t_{30} = -0.399$ p = 0. 693
LSP	123.75 (10.82)	121.70 (15.04)	$t_{30} = 0.411$ p = 0.684
FPS	58.33 (11.45)	55.30 (16.07)	$t_{30} = 0.046$ p = 0.964

LDD: people affected by schizophrenia with long duration of disease; SDD: people affected by schizophrenia with short duration of disease; FGA: first generation of antipsychotics; SGA: second generation of antipsychotics; SCoRS: Schizophrenia Cognition Rating Scale; SAI: Schedule for the Assessment of Insight; LSP: Life Skills Profile; FPS: Personal Social Functioning Scale. Data are frequencies and means (SDs).

both in early and chronic stages of schizophrenia. These results confirm evidence of cognitive remediation strategies in PSZ with a LDD5 as well as in PSZ with SSD [7 23].

Despite our CACR sessions and follow-up duration were different from other studies, including the absence of any type of other structured rehabilitation programs during the six month follow-up period after CACR end, improvement in PSZ's cognition and functioning reported in current preliminary study are in line with those results described by others using COGPACK® program [24-27]. We may explain these findings with the high level of efficacy generated by this CACR intervention, mainly based on (re)learning practical cognitive strategies through the high flexibility and adaptation of exercises in several cognitive domains based on PSZ's performances.

Our results are similar to those recently reported by Corbera et al. [10]. Within a randomized control trial design, these authors studied the effect of a computerized cognitive training program (sequence of computerized cognitive exercises) in PSZ with an early illness phase and in PSZ with a chronic illness phase, distinguishing an early-chronic group (corresponding to chronic phase group of our study) and a late-chronic group. Despite the methodological differences present in these two researches (mainly for a different type of CACR intervention and PSZ involved) both studies revealed PSZ with early and chronic (named early-chronic in Corbera et al.) stages of schizophrenia has an improvement in cognition after CACR.

Future perspectives in our CACR program of rehabilitation setting for schizophrenia might be: (a) a longer follow-up duration [26 27], that could give the opportunity to observe the effect of the single CACR intervention on cognition and functioning in schizophrenia, as well as on insight and psychopathology [28]; (b) more sophisticated cognitive and functioning assessments (as, for

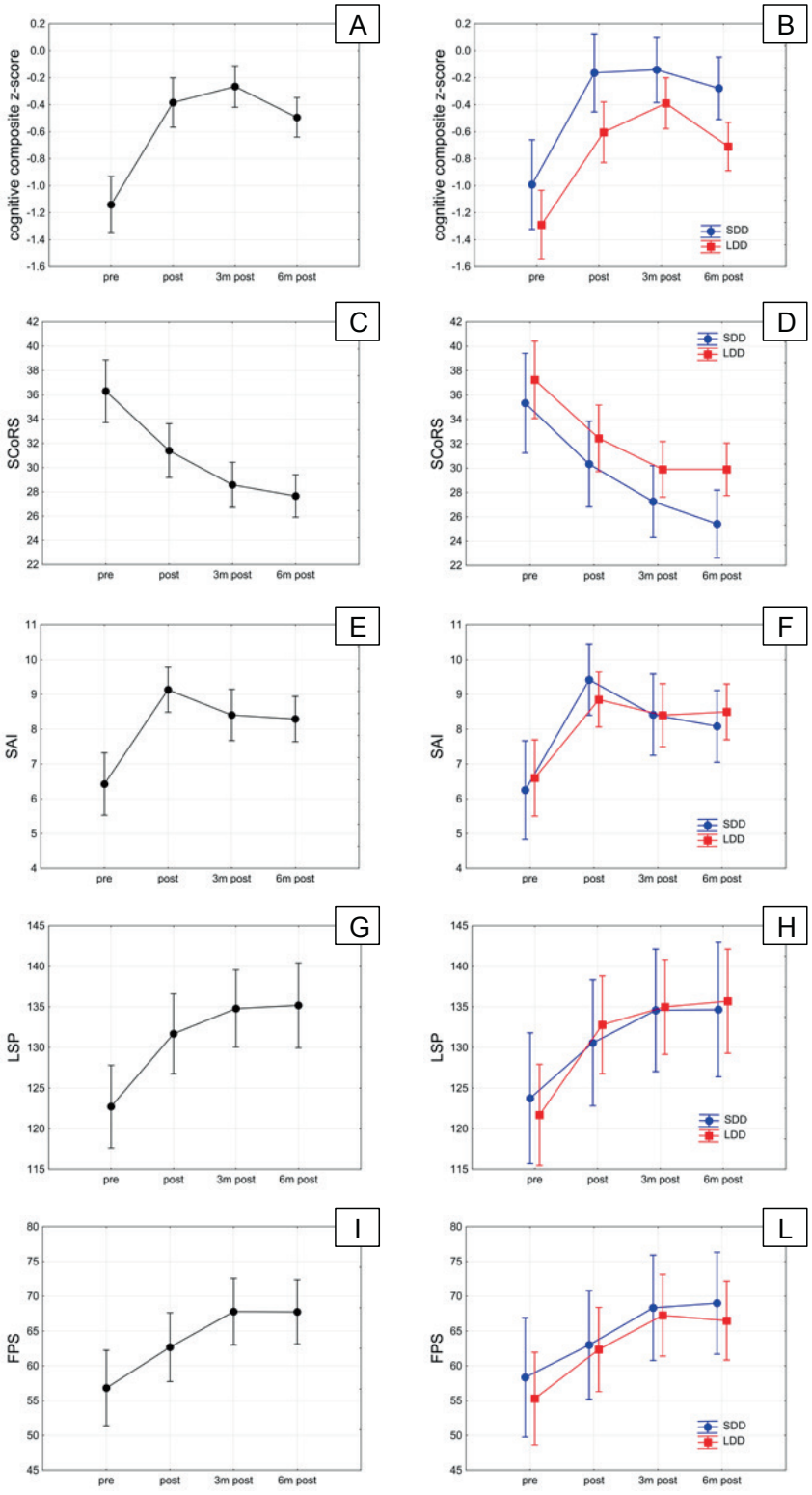

FIGURE 1. *Means (circles and squares) and 95% Confidence Intervals (vertical bars) of the cognitive composite z-score, SCoRS, SAI, LSP and FPS during the week preceding the CACR beginning ("pre"), during the week succeeding the CACR end ("post"), as well as three and six months after the CACR end (respectively,"3m post"and"6m post"), in the whole group (left side of the panel) and in SDD and LDD (right side of the panel). LDD: people affected by schizophrenia with long duration of disease; SDD: people affected by schizophrenia with short duration of disease; SCoRS: Schizophrenia Cognition Rating Scale; SAI: Schedule for the Assessment of Insight; LSP: Life Skills Profile; FPS: Personal Social Functioning Scale.*

example, the implementation of UPSA-B and SLOF) [29-31]; (c) an integration with different rehabilitation techniques during or after the CACR intervention [32].

In conclusion, according to the current findings from this preliminary report, subjects affected by schizophrenia, independently from stage of illness, may improve in cognition and everyday functioning capacity for several months after a single intervention with a computer-assisted cognitive rehabilitation strategy.

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Conflict of Interest

None.

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