

Non-pharmacological interventions in early schizophrenia: focus on cognitive remediation

Interventi non farmacologici nelle fasi precoci della schizofrenia: focus sul rimedio cognitivo

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Summary

Objectives

There is a growing body of evidence suggesting that barriers to functional recovery are associated with a host of neurocognitive impairments in both the early and later course of schizophrenia. Given the significant influence of cognitive functions on daily functioning, several cognitive training approaches have been developed to improve cognitive deficits in schizophrenia. Increasing amounts of data suggest that cognitive remediation leads to improvements not only in cognition, but also in functional outcomes of schizophrenia. Some researchers speculate that deficits in cognition are more amenable to remediation during earlier phases of the illness, rather than when chronicity has developed. Despite the widely cited benefits of cognitive remediation in long-term course patients, fewer studies have examined the extent to which cognitive remediation has practical implications in the early stages of schizophrenia. The aim of this paper is to review the available literature on cognitive remediation in the prodromal phase and the early course of schizophrenia.

Methods

This review summarizes findings of cognitive changes induced in the early course and the prodromal phases of schizophrenia by different cognitive remediation approaches. Electronic

searches were performed in the PubMed database, and all the studies published until January 2013 have been taken in account. Controlled studies of cognitive training are discussed in more detail.

Results

Few studies on the effects of cognitive training programs have been conducted in first episode or in early schizophrenia, and only three studies have been conducted in the prodromal phase of the disease or in subjects at risk for psychosis. The studies available support the usefulness of cognitive remediation when applied in the early course of schizophrenia and in subjects at risk for the disease.

Conclusions

Although preliminary positive results have been achieved, more empirical research is needed to confirm the efficacy of cognitive remediation in the early course of schizophrenia, and future studies should address the issue of the usefulness of cognitive remediation in the prodromal phases of schizophrenia or in subjects at risk for psychosis.

Key words

Schizophrenia • Cognitive remediation • First episode psychosis • Early intervention • At risk psychosis

Introduction

Impairments in a wide range of cognitive abilities have been consistently reported in individuals with schizophrenia¹. Deficits in cognitive functioning, including those in psychomotor speed, attention, memory and executive functions, are thought to underlie the severe functional disability associated with the disease^{2,3}. Subjects at risk for psychosis and in the prodromal phase of schizophrenia have been shown to be already impaired in cognitive functions, especially in verbal executive and memory functions⁴. According to the diathesis-stress model, the

cognitive deficits in the prodromal phase of schizophrenia can also trigger illness⁵. Early course patients perform 0.3 to 1.0 standard deviations better than long-term course patients on neurocognitive abilities⁶. Declines in neurocognition are observed in the first 10 to 12 years of schizophrenia despite good clinical outcomes⁷. The consolidation of cognitive functions enables patients with schizophrenia to better cope with stressful life and environmental events usually determining higher risks of relapses⁸. Taken together, these findings underline the importance of targeting neurocognitive impairments early in the course of illness to decrease the severity of

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associated functional disability. Furthermore, cognitive treatment may contribute to prevent or delay the onset of schizophrenia. Although pharmacological treatment has been shown to be effective in reducing the symptoms of schizophrenia, cognitive impairments have mostly been found to be resistant to such treatments⁹. Consequently, an important target of research regarding psychotic disorders is the development of effective methods for improving cognitive abilities¹⁰. In this context, cognitive remediation attempts to improve and/or restore cognitive functioning using a range of approaches. Cognitive remediation for schizophrenia has been recently defined as “a behavioural training based intervention that aims to improve cognitive processes (attention, memory, executive

function, social cognition or metacognition) with the goal of durability and generalisation” (Cognitive Remediation Experts Workshop – CREW, Florence, April 2010). In recent decades, a number of cognitive remediation techniques, computerized and non-computerized, designed for individual or group settings, have been developed and adopted in the multimodal treatment approaches to schizophrenia¹¹. Some of the main structured protocols of cognitive remediation in schizophrenia are shown in Table I. Several reviews of studies, mainly in adults with schizophrenia, have indicated that cognitive remediation is effective in reducing cognitive deficits and in improving functional outcomes with long-term benefits¹². Nevertheless, few studies examined the effect of cognitive reme-

TABLE I.

Models of cognitive remediation interventions in schizophrenia (from Vita et al., modified)¹¹. *Modelli di intervento di rimedio cognitivo nella schizofrenia (da Vita et al., mod.)¹¹.*

Cognitive remediation intervention	Target	Duration	Setting (Individual/Group)	Computer assisted/Not computer assisted	Individually tailored
Integrated Psychological Therapy (IPT)	Cognitive, functions, social skills and problem solving	Sessions of 60 min, 2-3 times a week (about 12 months)	Group (6-8)	Not computer assisted	–
Integrated Neurocognitive Therapy (INT)	Cognitive functions and social cognition	30 biweekly sessions, 90 min each	Group (6-8)	Computer assisted sessions and not computer assisted sessions	–
Cognitive Remediation Therapy (CRT)	Cognitive functions	40 sessions at least 3 times a week, 45-60 min each	Individual	Not computer assisted session	+
Cogpack*	Cognitive functions	Sessions variables in duration and frequency (starting from 2-3 weeks)	Individual	Computer assisted	+
Cognitive Enhancement Therapy (CET)	Cognitive functions and social cognition	Biweekly sessions (about 2.5 hours per week) for 24 months	Group (couples and then groups of 3-4 couples)	Computer assisted sessions and not computer assisted sessions	–
Neuropsychological Educational Approach to Remediation (NEAR)	Cognitive functions and problem solving	Sessions of 60 min, twice a week (about 4 months)	Individual/Group (3-10)	Computer assisted sessions and not computer assisted sessions	+
Neurocognitive Enhancement Therapy (NET)	Cognitive functions and social cognition	Sessions of 45 min at least 5 times a week (about 6 months)	Individual/Group	Computer assisted sessions and not computer assisted sessions	+
Cognitive Adaptation Training (CAT)	Cognitive functions	Variable (short weekly visits at home, lasting about 30 min)	Individual	Not computer assisted	+

* Cogpack is a typical computer-assisted cognitive remediation (CACR) technique.

diation, and follow-up outcomes, in the early course of schizophrenia, and its usefulness in the prodromal phase of the illness or in adolescents at high risk for schizophrenia. Early detection of schizophrenia, especially in young subjects, could allow timely assessment and intervention in what is considered a crucial period of the illness. This could potentially influence the course of schizophrenia, and justify the potential usefulness of cognitive remediation interventions in a period in which neural plasticity is thought to play a major pathoplastic role¹³.

Herein, the authors review the current scientific literature on cognitive remediation in first episode schizophrenia, in the early course of schizophrenia or in the prodromal phase of the disease, including possible interventions applied to subjects at risk for psychosis.

Materials and methods

Search strategy

Electronic searches were performed in the PubMed database combining the following search terms: “cognitive remediation”, “neurocognitive enhancement”, “cognitive rehabilitation”, “first episode psychosis”, “early psychosis”, “early schizophrenia”, “prodromal psychosis”, “at risk psychosis”, “high risk for psychosis”. Detailed combinations of the above search terms are available from the authors on request. Two of the authors (SB, GD) independently reviewed the database to avoid errors in selection of publications. In addition, the reference list of the included articles was carefully searched to further identify other studies of possible interest.

Selection criteria

All studies published until January 2013 were included, without any language restriction. Studies were included according to the following criteria: (a) an original paper published in a peer-reviewed journal; (b) contains experiments using a cognitive remediation technique in the early course or the prodromal phase of schizophrenia or in subjects at risk for psychosis as defined by international psychometric criteria¹⁴. Studies on psychological, psychosocial, and psychoeducational interventions only, without cognitive remediation, were not considered.

Results

Cognitive remediation in the early course of schizophrenia

Studies analyzing the effectiveness of cognitive remediation in the early course of schizophrenia are summarized in Table II.

An early study on cognitive remediation on adolescents in the early course of psychosis was a controlled randomized investigation by Ueland and Rund¹⁵. This study aimed to investigate the effects of cognitive remediation in addition to psychoeducation on cognitive performance, clinical status and psychosocial functioning in 26 adolescents with psychosis. All patients received a psychoeducational programme, while 14 also received cognitive remediation intervention, partially derived from the Integrated Psychological Therapy (IPT)¹⁶. No evidence of differential improvement between the two groups was found, but a within-group analysis showed a different profile of improvement in the two groups: the training group improved on five of the ten cognitive and three of the five functioning outcome measures, while the control group improved on three of the cognitive and one functioning outcome variable. The results indicate that the cognitive remediation programme might have beneficial effects for some specific aspects of cognition, and possibly an indirect effect on measures of functional outcome. However, based on the lack of between-group effects, the authors could not conclude that the addition of this cognitive remediation programme leads to better results than psychoeducation alone.

The same research group performed a second study to investigate the long-term effects of a cognitive remediation programme for adolescents with early onset psychosis¹⁷. All patients received a psychoeducational programme, while the experimental group (n = 14) received the addition of a cognitive remediation programme, composed of four modules, two from the IPT and two focused on attention and memory, respectively. A significant overall improvement for eight of ten cognitive and three of four outcome measures was found. Only long-term verbal memory and executive function did not improve over time in the sample as a whole. After controlling for IQ, the remediation group improved significantly more than the control group in early visual information processing from baseline to the 1-year follow-up. No other between-group differences were found, and no significant relationships between changes in cognitive functioning and changes in psychosocial functioning were reported.

Til Wykes et al.¹⁸ tried a different approach on cognitive remediation in subjects with a diagnosis of schizophrenia, with an onset prior to the age of 19 years and a duration of illness of less than 3 years. The aim of this randomized controlled trial was to verify the effects of Cognitive Remediation Therapy (CRT)¹⁹, an individual cognitive remediation programme that already been demonstrated to be effective in adult patients affected by schizophrenia. The study enrolled 40 patients, randomly allocated to CRT group or to treatment as usual (TAU) group. Although all cognitive tests showed an advantage for the CRT group, the effect was significant

TABLE II.

Studies analyzing the effects of cognitive remediation intervention in the early course of schizophrenia.

Studi che hanno analizzato gli effetti degli interventi di rimedio cognitivo nelle fasi precoci della schizofrenia.

Authors	Type of Study	N	Mean Age (years) (SD)
Ueland and Rund ¹⁴	RCT, adolescents with early onset psychosis	Cog Rem = 14 Ctrl = 12	Cog Rem = 15.2 (1.1) Ctrl = 15.4 (0.7)
Ueland and Rund ¹⁶	RCT, adolescents with early onset psychosis	Cog Rem = 14 Ctrl = 11	Cog Rem = 16.6 (1.1) Ctrl = 16.8 (0.7)
Wykes et al. ¹⁷	RCT, young patients with recent onset schizophrenia	Cog Rem = 21 Ctrl = 19	Cog Rem = 18.8 (2.6) Ctrl = 17.5 (2.2)
Eack et al. ¹⁹	RCT, early course schizophrenia or schizoaffective disorder	Cog Rem = 18 Ctrl = 20	Total = 26.14 (6.54)
Eack et al. ²⁰	RCT, early course schizophrenia or schizoaffective disorder	Cog Rem = 31 Ctrl = 27	Total = 25.92 (6.31)
Eack et al. ²¹	RCT, early course schizophrenia or schizoaffective disorder	Cog Rem = 31 Ctrl = 27	Total = 25.92 (6.31)
Lee et al. ²⁷	RCT, first episode of major depression or psychosis	Cog Rem = 28 Ctrl = 27	Cog Rem = 22.88 (4.0) Ctrl = 22.74 (4.7)
Bowie et al. ²⁹	RCT, early-course (≤ 5 years of illness) and long-term course (≥ 15 years of illness) schizophrenia patients	Early-course = 12 Long-term course = 27	Early-course = 28.1 (5.4) Long-term course = 45.4 (6.8)

CET: Cognitive Enhancement Therapy; Cog Rem: Cognitive Remediation group; CRT: Cognitive Remediation Therapy; Ctrl: Control group; EST: Enriched Supportive Therapy; IPT: Integrated Psychological Therapy; NEAR: Neuropsychological Educational Approach to Remediation; RCT: Randomized Controlled Trial; SD: Standard deviation; TAU: Treatment as usual; WCST: Wisconsin Card Sorting Test.

Cognitive Remediation Program	Duration of Cognitive Remediation	Assessment	Main Findings (Average Effect Size)
Cog Rem: IPT + specific modules + psychoeducation Ctrl: Psychoeducation	30 hours (3 months)	Cognitive, functioning, symptoms at baseline and at discharge (6 months)	No superior effects of cognitive remediation compared to psychoeducation ($p > 0.05$). The remediation program may have a within group effects on specific cognitive and functioning measures (Effect Size not reported)
Cog Rem: IPT + specific modules + psychoeducation Ctrl: Psychoeducation	30 hours (3 months)	Cognitive, functioning, symptoms at baseline and at discharge (6 months) and at 1 year follow-up after discharge	Possible long-term effects of cognitive remediation on early visual information processing ($p = 0.042$). No other between-group differences were found (Effect Size not reported)
Cog Rem: CRT+ TAU Ctrl: TAU	40 hours (3 months)	Cognitive, functioning, symptoms, self esteem at baseline, post therapy (3 months) and at follow-up (3 months post-therapy)	CRT can improve cognitive flexibility as measured by the WCST ($p = 0.04$; Effect Size: 0.55). Cognitive change due to cognitive remediation may lead to functional improvement
Cog Rem: CET + social cognitive group Ctrl: EST (personal therapy + psychoeducation)	60 hours computerized + 45 (1.5 hours) weekly sessions on social cognition (1 year)	Social cognition at baseline and post therapy (1 year)	CET is effective on social cognition ($p = 0.005$; Effect Size: 0.96)
Cog Rem: CET + social cognitive group Ctrl: EST (personal therapy + psychoeducation)	60 hours computerized + 45 (1.5 hours) weekly sessions on social cognition (2 years)	Cognition, social cognition, functioning, symptoms at baseline after 1 year of treatment and after 2 years of treatment	After 2 years, CET appears effective in improving social cognition (Effect Size: 1.55), neurocognitive function (Effect Size: 0.46), functioning (Effect Size: 1.53) and symptoms (Effect Size: 0.77)
Cog Rem: CET + social cognitive group Ctrl: EST (personal therapy + psychoeducation)	60 hours computerized + 45 (1.5 hours) weekly sessions on social cognition (2 years)	Cognition, social cognition, functioning and symptoms at baseline, after 1 year of treatment and after 2 years of treatment. Functioning after 1 year post-treatment follow-up	CET has a long-term effect on functioning ($p = 0.003$; Effect Size not reported)
Cog Rem: NEAR + TAU Ctrl: TAU	Once-weekly 2-hours sessions for a total of 10 weeks	Cognition, functioning and symptoms at baseline and after treatment	Cognitive remediation improves memory ($p < 0.01$) and psychosocial outcome ($p \leq 0.05$) in both major depression and psychosis. Effect Size is in the large range
Cog Rem: computer-based exercises, strategic monitoring and methods to transfer cognition to behaviour in small groups	2-hours per week for 12 weeks	Cognition, competence measures, real-world functioning and symptoms at baseline and after treatment	The early-course group had larger improvements in speed of processing (Effect Size, n^2 : 0.41), in executive functions (Effect Size, n^2 : 0.22), in adaptive competence (Effect Size, n^2 : 0.095) and in community/household activities measures (Effect Size, n^2 : 0.074)

only on the Wisconsin Card Sort Test (WCST; increase of 1.1 categories). Interestingly, the authors also showed data regarding the frequency of attainment of a normal score on cognitive tests. At baseline, subjects performing below normal were equally distributed between the two treatment groups. Memory results clearly favour CRT at follow-up (44% CRT group vs. 0% control group), but not at post-treatment. Conversely, for the WCST the superiority of the number of normal subjects in the CRT group at post-treatment reduced at follow-up: 33% of the CRT group and 8% of the control group at post-treatment, and 55% of the CRT group and 44% of the control group at follow-up, achieved a normal score. On the other hand, CRT showed no direct impact on symptoms, self-esteem, or functioning. However, symptoms decreased more in the CRT group in relation to planning improvements, while in the control group improved scores in cognition did not have beneficial effects on other outcomes. There was an overall effect of cognitive change on symptoms and psychosocial functioning, and only the WCST improvement resulted correlated with a variation in symptoms.

Another research group studied the effects of another paradigm of cognitive remediation, investigating the impact of cognitive training on different outcome measures and brain morphology in a number of studies²⁰⁻²⁵.

The first step on this path was a randomized controlled trial investigating the effects of specific cognitive intervention on social cognition²⁰. A total of 38 subjects defined as "early course schizophrenia" (n = 28) or schizoaffective disorder (n = 10) were enrolled in the study. Subjects were eligible if diagnosed within the last eight years (mean duration of illness = 3.75 ± 2.80 years). Subjects randomized to the Cognitive Enhancement Therapy (CET)²⁶ completed a computer training in attention, memory and problem solving, and participated in a weekly social-cognitive group focused on managing emotions, others' perspectives and appraising the social context. On the other hand, subjects randomized to the Enriched Supportive Therapy (EST) received an intervention focused on stress reduction strategies and psychoeducation. Computerized assessment was performed at baseline and after one year of treatment using Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT), a measure of social cognition already recommended by the NIMH-MATRICES (National Institute of Mental Health – Measurement and Treatment Research to Improve Cognition in Schizophrenia)²⁷. A significant superiority of CET over the other treatment was seen in social cognition, with medium to large effect sizes in three MSCEIT subscales. A series of analyses of covariance showed highly significant and large effects favouring CET for improving emotional intelligence, with the most pronounced improvements occurring in patients' ability to understand

and manage their own and others' emotions. The results of this study are of particular interest since they lend preliminary support to the previously documented benefits of CET on social cognition in schizophrenia, and suggest that such benefits can be extended to patients in the early course of the illness.

A subsequent randomized controlled trial investigated the effects of a two-year CET in a larger sample of patients with schizophrenia (n = 38) or schizoaffective disorder (n = 20)²¹. Early-course outpatients (mean duration of illness = 3.19 ± 2.24 years) with schizophrenia or schizoaffective disorder were randomly assigned to CET or EST. After the first year of treatment, subjects in the cognitive remediation group showed significant and medium to large differential improvements in dysfunctional cognitive style, social cognition, social adjustment and symptomatology compared with those in the EST. After two years of treatment, highly significant and large differential effects were observed favouring CET on the composite indexes of cognitive style, social cognition, social adjustment and symptomatology. In addition, CET participants showed significant and medium size improvement on the neurocognitive composite by the second year of treatment. A subsequent analysis examined differential rates of improvement at two years for the individual components of the composite indexes. Social cognition and functioning were widely improved, while differential improvement in neurocognition was seen in verbal memory, executive functioning and planning. A closer inspection of the effects on employment indicated that significantly more patients receiving CET (54%) were actively engaged in paid, competitive employment at the end of two years of treatment, compared with recipients of EST (18%) ($p = 0.026$). Results from this two-year trial support the hypothesis that a cognitive remediation programme, such as CET, may improve cognitive and behavioural outcomes in early schizophrenia.

A long-term follow-up study was then performed to verify the durability of the effects of CET after one year²². Of the 58 patients enrolled in the previous study²¹, 46 completed two years of treatment, and 42 (72%) were available at one year post-treatment follow-up. Results from intent-to-treat analyses indicated that CET effectiveness on functional outcome was broadly maintained one-year post-treatment, and that patients receiving CET continued to demonstrate highly significant differential functional benefits compared to patients treated with EST. Differential improvement favouring CET continued to be observed in four individual components of the social adjustment: relationships outside the household, participation in social leisure activities, major role adjustment and overall ratings of global functioning. Patients who demonstrated greater neurocognitive im-

provement during the active phase of treatment were significantly more likely to maintain gains in social adjustment during post-treatment follow-up. At one-year follow-up, employment rates for CET patients were similar to those observed during active treatment (48%). Taken together, these findings indicate that the beneficial effects of CET on functional outcomes in early schizophrenia can be maintained at least for one year after the completion of treatment.

Another study by Eack et al.²³ analyzed possible mechanisms and moderators of neurocognitive and social cognitive improvement on functional change during a 2-year trial of CET in early course schizophrenia. To accomplish this, a path analysis was performed, investigating the effects of treatment on neurocognitive and social-cognitive change, weighting the contribution of the potential moderators (neurocognitive and social-cognitive change) on the direct effects of treatment on functional improvement. Improvements over 2 years in the neurocognition and in the emotion management subscale of the MSCEIT were significantly related to improved functional outcome in early course schizophrenia patients. The authors underlined that improvements in neurocognition and social cognition that result from cognitive rehabilitation are significant mediators of functional improvement in early-course schizophrenia.

A recent study aimed to determine the effectiveness of cognitive remediation as early intervention in first-episode depressive and psychotic disorders²⁸. Patients were included if they had a lifetime history of a single episode of major depressive disorder or a psychotic disorder. Fifty-five patients were randomly assigned to either Neuropsychological Educational Approach to Cognitive Remediation (NEAR)²⁹ or TAU. In total, 36 patients completed the study, and analyses were conducted using an intent-to-treat approach. At baseline, patients with first-episode psychosis performed significantly worse than depressed patients on every cognitive composite score ($p < 0.005$). Patients undergoing cognitive remediation improved significantly more than TAU patients on attention and working memory ($p < 0.01$) and immediate learning and memory ($p < 0.001$). Only immediate learning and memory remained significant after controlling for diagnosis and baseline attention and working memory. Similarly, the cognitive remediation group demonstrated greater improvements than the TAU group in psychosocial functioning. Improvement in delayed learning and memory independently mediated and predicted psychosocial gains at the trend level ($p = 0.07$). Effect size in cognitive and psychosocial functioning was large, and generally greater than that identified in previous studies of chronic schizophrenia¹². This discrepancy may indicate a better treatment response when cognitive remediation is implemented at

earlier stages of illness. The authors underline that cognitive and functional improvements were still detected after controlling for the effects of diagnosis.

Bowie et al.³⁰, in a well-conducted study, evaluated the effectiveness and transfer to functional competence and everyday functioning of cognitive remediation in early course (within 5 years of first episode) and long-term (more than 15 years of illness) schizophrenia. Twelve patients with early psychosis (mean illness duration = 3.4 years) and 27 patients with a longer term psychosis (mean illness duration = 25.7 years) were enrolled. The early course group had larger improvements in measures of processing speed and executive functions, as well as larger improvements in adaptive competence and real world work skills. Duration of illness was significantly inversely correlated with change scores of the neurocognitive composite ($p = 0.001$) and with improvement in real world work skills ($p = 0.020$). These findings suggest that despite significant improvement in both groups, there is larger improvement in several cognitive domains and generalization to functioning for those in the early stages of psychosis.

Neurobiological correlates of cognitive remediation in the early course of schizophrenia

There are only two published studies on the neurobiological correlates of cognitive remediation in the early course of schizophrenia^{24,25}. The neurobiological correlates of the effects elicited by CET have been studied in a structural magnetic resonance imaging (MRI) study²⁴. Fifty-three of 58 subjects enrolled in the previously described study²¹ received structural MRI assessment prior to the initiation of treatment, and then annually during the two years of treatment. Voxel-based morphometric analyses using mixed-effects models showed three primary areas of differential grey matter change between patients who received CET and those who received EST during 2 years of treatment. Significant areas of differential effects included a cluster in the left medial temporal lobe, around the amygdala, parahippocampal gyrus, hippocampus, and fusiform gyrus; a cluster covering the bilateral anterior cingulate; and a cluster in right insula. Patients who received CET demonstrated significantly greater preservation of grey matter volume over 2 years in the left hippocampus, parahippocampal gyrus and fusiform gyrus, and significantly greater grey matter increases of the left amygdala ($p < 0.04$) compared with those who received EST. Less grey matter loss in the left parahippocampal and fusiform gyrus and greater grey matter increases in the left amygdala were related to improved cognition and mediated the beneficial cognitive effects of CET. This study directly supports the idea that cog-

nitive rehabilitation provides a neuroprotective effect against grey matter loss in key regions implicated in social and non-social cognitive impairment in schizophrenia. In particular, while patients who received EST demonstrated progressive loss of grey matter volume in the fusiform and parahippocampal gyrus, patients receiving CET demonstrated grey matter preservation in these areas, and significant grey matter volume increase in the left amygdala. These differential effects on grey matter changes were significantly related to improved cognitive outcome, with patients showing less grey matter decline and greater grey matter increases demonstrating greater cognitive improvement over the two years follow-up.

In a subsequent study, the same research group investigated if a greater neurobiologic reserve, as measured by cortical volume, would predict a favourable response to CET in the early course of schizophrenia²⁵. The main findings of this study indicate that higher baseline cortical surface area and grey matter volume broadly predicted social-cognitive (but not neurocognitive) response to CET. Greater neurobiologic reserve predicted a rapid social-cognitive response to CET in the first year of treatment, while patients with less neurobiologic reserve achieved a comparable social-cognitive response by the second year.

Cognitive remediation in the prodromal phase of schizophrenia or in subjects at risk for psychosis

According to our selection criteria, only three studies analyzing the efficacy of cognitive remediation techniques in the prodromal phase of schizophrenia or in subjects at risk for schizophrenia were identified (Table III)³¹⁻³³.

Rauchensteiner et al. performed a pilot, non-controlled, study to examine the differential effects of a computer-based cognitive training programme (Cogpack)³⁴ in 'prodromal' patients compared to patients with fully manifested schizophrenia³¹. Cognitive functioning was assessed by different tests controlling for memory, attention and logical thinking, i.e. Verbal Learning Test (VLMT), Continuous Performance Test, Identical Pairs version (CPT-IP) and a non-verbal attention test. Subjects at risk for schizophrenia significantly increased their performance in the VLMT, in the CPT-IP and in five out of eight Cogpack tasks, while patients with schizophrenia did not. The results indicate that prodromal patients can improve their long-term verbal memory, attention and concentration after cognitive training. In two delayed-recall tasks of the VLMT after Cogpack training, prodromal patients were able to memorize significantly more words than at baseline. In the attention and working memory test CPT-IP, the hit rates of prodromal patients in detecting target events among intrusive and distractive numbers or shapes

TABLE III.

Studies analyzing the efficacy of cognitive remediation in the prodromal phase of schizophrenia or in subjects at risk for schizophrenia. *Studi che hanno analizzato l'efficacia del rimedio cognitivo nella fase prodromica della schizofrenia o in soggetti a rischio per schizofrenia.*

Authors	Type of Study	N	Mean Age (years) (SD)
Rauchensteiner et al. ³⁰	Non-controlled pilot study, subjects at risk for schizophrenia and fully manifested schizophrenia patients	Subjects at risk = 10 Schizophrenia patients = 16	Subjects at risk = 27.2 (5.3) Schizophrenia patients = 30.1 (7.8)
Urben et al. ³¹	A single blinded 8-week RCT, subjects at risk for psychosis and adolescents with psychotic disorders	Cog Rem = 18 Ctrl = 14	Cog Rem = 15.2 (1.3) Ctrl = 16.0 (1.3)
Bechdolf et al. ³²	Multicentre, prospective RCT, young people with EIPS of psychosis	Cog Rem (IPI*) = 63 Ctrl = 65	IPI = 25.2 (5.4) Ctrl = 26.8 (6.2)

CACR: computer-assisted cognitive remediation; Cog Rem: Cognitive Remediation group; Ctrl: Control group; EIPS: early initial prodromal state; IPI: Integrated Psychological Intervention; RCT: Randomized Controlled Trial; SD: Standard deviation; *IPI consists of individual cognitive-behavioural therapy (CBT), modified social skills training (SST), cognitive remediation and multifamily psychoeducation.

also improved significantly. Subjects with at risk mental state could enhance their performance significantly more than patients with schizophrenia. Despite some limitations, this exploratory pilot study of differential cognitive training outcomes in prodromal patients with at risk mental state for schizophrenia, compared to patients with fully manifested schizophrenia, can provide a first glance on the effects of preventive non-pharmacological interventions during the early and prodromal stages of the disease.

To investigate short-term outcomes of a computer-assisted cognitive remediation (CACR) in adolescents with psychotic disorders or at high risk for psychosis, 32 adolescents (psychotic, n = 21; at high risk for psychosis, n = 11) were randomised to the treatment condition (CACR) or a control condition (a set of computer games)³². The results revealed significant differences between baseline and follow-up in executive functions/inhibition abilities and reasoning abilities, with better performances at follow-up only in the CACR group. Longer duration of CACR session was reported to be more effective in improving reasoning abilities (p = .024). These findings suggest that CACR has specific effects on some of the investigated cognitive capacities, with promising long term benefits. On the basis of these encouraging preliminary results, the authors concluded that studies with larger samples are

needed to determine whether the CACR is similarly efficient for adolescents with psychosis and for those at high risk, and whether CACR can prevent the conversion to psychosis in such cases.

A multicentre, prospective, randomised trial with two parallel groups assigned to alternative out-patient interventions was performed to investigate the effects of integrated psychological intervention (IPI) on the prevention of psychosis in the so-called “early initial prodromal state” (EIPS)³³. Of 168 eligible individuals, 128 help-seeking out-patients in an EIPS were randomized to IPI or supportive counselling. The primary outcome measure was progression to psychosis (incidences of subthreshold psychosis, first-episode psychosis and first-episode schizophrenia) at 12-month (post-treatment) and 24-month follow-up. The cumulative conversion rates to subthreshold psychosis at 12 months were 3.2% for IPI and 16.9% for supportive counselling and 6.3% for IPI and 20% for supportive counselling at 24 months. The time to conversion for the entire study period was significantly shorter for the supportive counselling group than the IPI group (IPI: mean 887.1 days; supportive counselling: mean 784.2 days; p = 0.020). At the 24-month follow-up, significantly fewer patients in the IPI group than in the supportive counselling group had developed psychosis (3.2% vs. 15.4%; p = 0.018) or schizophrenia/schizophreniform disorder (1.6% vs.

Cognitive Remediation Program	Duration of Cognitive Remediation	Assessment	Main Findings (Average Effect Size)
Cog Rem: computerized cognitive training program (Cogpack)	10 single sessions (1-hour) for 4 weeks	Cognitive and symptoms at baseline and after treatment (4 weeks)	Subjects at risk increased their performance in long-term verbal memory (p < 0.01), in attention (p < 0.04) and in five out of eight Cogpack tasks, while patients with schizophrenia did not (Effect Size not reported)
Cog Rem: CACR Ctrl: Computer games	Biweekly single sessions (45 min) for 8 weeks	Cognitive and symptoms at baseline and 6 months after the end of the intervention program	Better performances at follow-up in the CACR group, with significant differences between baseline and follow-up in executive function/inhibition abilities (p = .040) and reasoning abilities (p = .005) (Effect Size not reported)
Cog Rem: computerized cognitive training program (Cogpack) Ctrl: Supportive counselling	12 sessions (12 months)	Functioning and symptoms at baseline, post treatment (12 months) and at follow-up (24 months post-treatment)	IPI was superior in preventing progression to psychosis at 12-month follow-up (p = 0.008) and at 24-month follow-up (p = 0.019) (Effect Size not reported)

12.3%; $p = 0.033$). In summary, the incidence of and time to conversion to subthreshold psychotic symptoms, psychosis and schizophrenia/schizophreniform disorder during a 12-month treating period was significantly lower for patients who received specially-designed IPI than for those who were treated with supportive counselling. Furthermore, IPI appeared effective in delaying the onset of psychosis over a 24-month period in people with an EIPS. Since IPI covered a variety of psychological strategies, the trial design did not allow assessment of the relative contribution of each intervention, such as cognitive remediation.

Discussion and conclusions

The available studies support the usefulness of cognitive remediation when applied to young, first episode schizophrenic patients. Exposure to cognitive rehabilitation may be an essential component to early-intervention programmes in psychoses. Evidence emerging from the research literature indicates that targeting cognitive impairments early in the course of the disorder can result not only in cognitive improvement *per se*, but also in significant functional benefits in such critical domains such as social functioning, employment and major role functioning. These analyses also suggest that therapy may have clinical utility if integrated into treatment programmes for young people with schizophrenia within the “critical period” for early intervention, thus offering the possibility to alter the course of disease. This should be inscribed in the well defined notion of the need for the earliest treatment as possible to improve the course of disease, as derived from a large number of studies on the duration of untreated psychosis (DUP) as a moderator of clinical and functional outcome of psychoses³⁵. What could be added to this knowledge is that the utility of early intervention may not be confined to pharmacological approaches, but may well be applied also to cognitive remediation intervention strategies. Given that the onset of psychosis often occurs during a critical developmental period, cognitive remediation might hold potential for recovery to premorbid levels for those in the initial stages of schizophrenia. The “protective” role of early effective intervention on the neurobiological and clinical deteriorating course of the disease³⁶, proposed for treatment with antipsychotics, especially with the 2nd generation^{37–38} compounds, may be extended to non-pharmacological approach, such as those reviewed herein. This adds to the growing literature demonstrating the biological effects of other non-pharmacological therapies, such as psychotherapies or cognitive therapies^{39–40}. As with many studies of cognitive rehabilitation with chronic patients with schizophrenia, important questions remain open: first, the duration of the effects of these interventions, and

their persistence over time in case they are not continuously applied; second, the generalizability of the effects to broader areas of functioning; third, the possible mediators and moderators of response; fourth, the role of social cognition and metacognition involvement in treatment effectiveness; fifth, the possible differential effects of cognitive remediation in patients treated with 1st or 2nd generation antipsychotics. These are all areas in which further studies are needed.

The few studies analyzing the efficacy of cognitive remediation in the prodromal phase of schizophrenia or in subjects at risk for schizophrenia^{31–33} provide the first evidence of the potential advantages of delivering cognitive remediation at the putative earliest stages of the disease. Prodromal patients seem to exhibit a higher rehabilitative potential concerning cognitive functions in comparison to patients with fully manifested schizophrenia, and it is conceivable that cognitive training may facilitate neuroplastic phenomena and may thus have a neuroprotective effect. Moreover, since cognitive deficits occur before the onset of psychoses⁴ and are significantly associated with poor premorbid adjustment and functional outcome in ultra high-risk individuals and in the prodromal phase of schizophrenia⁴¹, there is a clear rationale for further research into cognitive remediation in these populations. Given the theoretical and clinical interest of the possible role of treatment for preventing the subsequent conversion in psychosis of subjects with “at risk mental states”⁴², the lively debate on the risk-benefit ratio and ethical concerns of exposing young people to antipsychotic treatment, it would be particularly relevant to examine whether non-pharmacological strategies of treatment could demonstrate a similar preventive efficacy.

In conclusion, given the evidence for debilitating cognitive and functional difficulties occurring at or even before the onset of psychosis and the clear relationship between these two dimensions, the maximal benefits of cognitive remediation are expected to occur early in the course of illness, even in the putative prodromal phase. This is based on the premise that the potential recovery may be higher in early psychosis due to on-going neurodevelopment in this phase of the patient’s life and stage of illness. Despite the fact that more research on the effectiveness of cognitive remediation applied in the prodromal phases of psychoses or in the so-called “at risk mental states” is needed together with rigorous experimental efforts, preliminary findings indicate that cognitive remediation should be considered as a key point for early intervention in schizophrenia.

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