

COGNITIVE REMEDIATION IN THE PRODROMAL PHASE OF SCHIZOPHRENIA OR IN SUBJECTS AT-RISK FOR PSYCHOSIS

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Abstract

Objectives: Cognitive impairment is a key feature of schizophrenia with relevant consequences on patients' functioning. Several quantitative reviews and meta-analyses have established that cognitive remediation is effective in reducing cognitive deficits and in improving functional outcome both in chronic schizophrenia and in the early stages of the illness. Current literature underlines that subjects at-risk for psychosis already show an impairment in cognitive domains, that is associated with functional disability and conversion into schizophrenia. Thus, research in primary prevention of schizophrenia should focus its efforts in the improvement of these deficits, before the onset of the illness, with the goal to prevent the conversion to full-blown psychosis. Aim of the present review is to provide an up-to-date overview of current knowledge on the efficacy of cognitive remediation in the prodromal phase of schizophrenia or in subjects at-risk for psychosis, with particular focus on preventing the conversion to psychosis and the deterioration of functional outcome in this population. The secondary aim is the identification of potential areas worth to be investigated, useful for orienting future research.

Materials and Methods: English language and peer-reviewed publications were obtained by electronic searching PubMed/MEDLINE, PsycINFO, Scopus, Embase, and Web of Science database until June 2016, using the following keywords: "schizophrenia", "psychosis", "At-risk Mental State" (ARMS) or "Ultra High Risk" (UHR) or "Clinical High Risk" (CHR) or "prodromal phase" paired with "cognitive remediation", "cognitive training" and "cognitive rehabilitation".

Results: According to our selection criteria, eight studies analyzing the efficacy of cognitive remediation techniques in the prodromal phase of schizophrenia or in subjects at-risk for psychosis were identified. Despite some methodological limitations, the search results provide the first evidence of the feasibility and potential advantages of delivering cognitive remediation at the putative earliest stages of the disease.

Conclusions: Preliminary findings indicate that cognitive remediation should be considered as a key point for early intervention in schizophrenia. Further research on the effectiveness of cognitive remediation applied in the prodromal phases of schizophrenia is needed together with a more rigorous methodological approach.

Key words: schizophrenia, At-Risk Mental State (ARMS), Ultra High Risk (UHR), Clinical High Risk (CHR), prodromal phase, cognitive remediation, cognitive training, cognitive rehabilitation

Introduction

Cognitive impairment is a key feature of schizophrenia with relevant consequences on patients' functioning ^{1,2}. Evidences support that antipsychotic treatment has a limited influence on this domain and that there is the need of using psychosocial interventions as an integrated approach

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in the management of such impairment³. Given the relevant influence of cognitive performance on daily functioning, different cognitive training approaches have been developed to improve cognitive deficits and psychosocial functioning in schizophrenia⁴.

Several quantitative reviews have established that cognitive remediation (CR) is effective in reducing cognitive deficits and in improving functional outcome of schizophrenia^{5,6}. Furthermore, the available studies support the usefulness of CR when applied both in patients with longer illness duration and with early course schizophrenia⁷. According to the European and international health care policies, on research psychosis of last decades has focused not only on subjects with schizophrenia, but also on help-seeking persons who experience early signs of emerging psychosis, but do not fully meet diagnostic criteria for the disorder⁸. People at heightened risk for psychosis, usually referred to as Clinical High Risk (CHR), Ultra High Risk (UHR), psychosis prodrome or At-risk Mental State (ARMS), meet the following criteria: presence of attenuated psychotic symptoms (APS) and/or a family history of schizophrenia combined with problems in functioning and/or presence of one or more brief limited intermittent psychotic symptoms (BLIPS) such as delusions or hallucinations^{9,10}. The ultimate goal of this research approach, focused on people at-risk for psychosis, is to prevent this condition from converting to psychosis. A recent meta-analysis showed that the average 1-year transition rate to psychosis in this UHR group was 22%, increasing to 36% after three years¹¹.

An alternative set of criteria to detect at-risk patients is given by the so called “basic symptoms” (BS), which consist of subclinical subtle disturbances in stress tolerance, affect, thinking, speech, drive, perception and motor action occurring before the appearance of APS or BLIPS, thus allowing for detection of at-risk patients at an earlier stage¹²⁻¹⁴. The BS approach was developed to detect the risk for psychosis as early as possible, as indicated by the presence of the cognitive-perceptive basic symptoms (COPER) and the cognitive disturbances (COGDIS) criterion⁸. Current literature underlines also that subjects at-risk for psychosis and in the prodromal phase of schizophrenia show an impairment in cognitive domains, especially in verbal executive and memory functions¹⁵. These cognitive deficits are associated with functional disability and psychosis conversion, suggesting that the presence of cognitive deficits in the prodromal phase of schizophrenia can be considered as a vulnerability predictor¹⁶. Another possible

marker of the liability for psychosis is social cognition, defined through four core domains: emotional perception and processing, social perception and knowledge, Theory of Mind (ToM), and attributional style¹⁷. Impaired social cognition is considered to result in poor social functioning, a well-established risk factor for transition to psychosis¹⁸. Impairments in all of these domains have been consistently found in patients with chronic schizophrenia as well as in patients with first episode psychosis (FEP)¹⁹. Herein, the current scientific literature, emphasizes that the onset of psychosis can be prevented by intervening in the risk phase and treatment in the early stages of schizophrenia is significant to prevent the progression of the disease²⁰⁻²⁵. As for antipsychotic treatment, this is not indicated for the treatment of individuals at CHR, and the use of such medication for this population is controversial also for ethical consideration²⁶⁻²⁸. Because of their unfavorable side effect profiles, pharmacological interventions with antipsychotics should only be applied in individuals at CHR following thorough cost-benefit considerations, after obtaining consent by subject and family, and only for a limited time-period with the primary aim to achieve symptomatic stabilization as a starting point for psychological and psychosocial interventions, but not with the aim to prevent conversion to psychosis^{8,29}. On the other hand, several systematic reviews and meta-analyses explored the efficacy of different psychological and psychosocial treatments, such as cognitive behavior therapy (CBT) and family psychoeducation, in the prodromal stages of schizophrenia as early interventions to prevent conversion to psychosis, finding some positive results^{28,30-33}.

One of the evidence-based psychosocial interventions is CR³, that improves cognition and daily functioning in schizophrenia⁵. CR can be applied in all the phases of the illness, as highlighted by several meta-analytic studies^{5,6,34}. Revell et al., considering 11 studies with 615 participants, first reviewed quantitatively the efficacy of CR in early schizophrenia. Results show a significant effect of CR at this stage, with a positive effect on global cognition, especially on verbal learning and memory, and social cognition. Improvements nearing uncorrected significance were also seen in processing speed, working memory and in reasoning and problem solving. Furthermore, CR had a significant effect on symptoms and global functioning³⁴.

CR has been proposed also as a preventive intervention for at-risk subjects, because a prolonged duration of untreated CHR symptoms can compromise functional outcome³⁵. Thus, prevention has two prin-

to evaluate the state of the art of the research in this area of interest.

Objective

The aim of the present review is to provide an up-to-date overview of current knowledge on the efficacy of CR intervention in the prodromal phase of schizophrenia or in subjects at-risk for psychosis, with particular focus on the possibility to prevent the conversion to psychosis and the deterioration of functional outcome in this population. The secondary aim is the identification of potential areas still to investigate, that could be useful for orienting future research. Although there are numerous qualitative and quantitative and meta-analytic reviews on CR in patients with schizophrenia, also at the onset or in the early stage of illness, to our knowledge this is the first qualitative review on this topic in prodromal/high risk subjects.

Material and Methods

Electronic searches were performed on June 2016 PubMed/MEDLINE, PsycINFO, Scopus, Embase, and Web of Science database combining the following search terms (without time limit): [(treatment) OR (therapy) OR (rehabilitation) OR (enhancement)] AND [(neurocognitive) OR (cognitive)] AND [(risk) OR (prodrome)] AND [(psychosis) OR (schizophrenia)]. Two of the authors (SB, CA) independently reviewed the database in order to avoid errors in the selection of articles. In addition, the reference lists of the included articles were carefully hand-searched to further identify other studies of possible interest. Informations taken into account in this review include: study design, duration and setting; sample size and participant demographics; intervention details; outcome measures; follow-up; effect size.

Results

According to our selection criteria, eight studies analyzing the efficacy of CR techniques in the prodromal phase of schizophrenia or in subjects at-risk for psychosis were identified (Table I).

Rauchensteiner et al. performed a pilot, non-controlled, study to examine the differential effects of a computer-based cognitive training programme (Cogpack) in 10 'prodromal' patients compared to 16 patients with fully manifested schizophrenia. Cognitive functioning was assessed by different tests controlling for memory, attention and logical thinking, i.e. Verbal Learning Test (VLMT), Continuous Perfor-

mance Test, Identical Pairs version (CPT-IP) and a non-verbal attention test. Subjects at-risk for schizophrenia significantly increased their performance in the VLMT ($p < 0.01$), in the CPT-IP ($p < 0.04$) 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 also improved significantly. So, 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 prodromal stage of the disease³⁶.

To investigate short-term outcomes of an 8-week 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, CG). At the end of the intervention, improvement in visuospatial abilities was significantly greater in the CACR than in CG group ($p = 0.013$), corresponding to a large effect size ($d = 0.62$), with no other significant group differences. Furthermore, results revealed significant differences between baseline and 6-month follow-up in executive functions/inhibition abilities ($p = 0.040$) and reasoning abilities ($p = 0.005$), with better performances found only in the CACR group. A longer duration of CACR sessions was reported to be more effective in improving reasoning abilities ($p = 0.024$). 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, 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^{37 39}. Moreover authors evaluated in the same sample the relationship between mo-

Table I. Studies analyzing the efficacy of cognitive remediation in the prodromal phase of schizophrenia or in subjects at risk for psychosis.

Authors	Type of Study	N	Mean Age (years) (SD)
Rauchensteiner et al., 2011 ³⁶	Non-controlled pilot study, subjects at risk for schizophrenia vs fully manifested schizophrenia patients	Subjects at risk = 10 Schizophrenia patients = 16	Subjects at risk = 27.2 (5.3) Schizophrenia patients = 30.1 (7.8)
Urban et al., 2012 ³⁷	A single blinded 8-week RCT, subjects at risk for psychosis and adolescents with psychosis	Cog Rem = 18 Ctrl = 14	Cog Rem = 15.2 (1.3) Ctrl = 16.0 (1.3)
Pihet et al., 2013 ³⁸	RCT with subjects at high risk of psychosis and adolescent with psychosis	Cog Rem = 15 Ctrl = 13	Mean age = 15.69 (1.3)
Holzer et al., 2014 ³⁹	A single blinded 8-week RCT, subjects at risk for psychosis and adolescents with psychosis	Cog Rem = 18 Ctrl = 14	Cog Rem = 15.4 (1.3) Ctrl = 15.7 (1.4)
Bechdolf et al., 2012 ⁴⁰	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)
Hooker et al., 2014 ⁴¹	An uncontrolled pilot study investigating feasibility and potential behavioral benefits of computer-based TCT in a single group of CHR participant	Cog Rem = 18 Ctrl = 14 (tested at baseline to identify CHR deficits)	Cog Rem = 21.9 (4.2) Ctrl = 24.1 (3.2)
Piskulic et al., 2015 ⁴²	A single blind, randomized controlled pilot study tested the effectiveness in young people at CHR for psychosis	Cog Rem = 18 Ctrl = 14	Cog Rem = 19.72 (5.71) Ctrl = 17.5 (3.48)
Loewy et al., 2016 ⁴³	A double-blind RCT in two groups of CHR individuals	Cog Rem = 50 Ctrl = 33	Cog Rem = 17.76 (3.06) Ctrl = 18.73 (4.60)

AT: auditory training; CACR: computer-assisted cognitive remediation; CG: computer games; CHR: clinical high risk; Cog Rem: Cognitive Remediation group; Ctrl: Control group; EIPS: early initial prodromal state; ES: effect size; IPI: Integrated Psychological Intervention; RCT: Randomized Controlled Trial; SD: Standard deviation; TCT: target cognitive treatment; TM: treatment motivation.

* These studies have the same sample; † IPI consists of individual cognitive-behavioural therapy (CBT), modified social skills training (SST), cognitive remediation and multifamily psychoeducation.

tivation and treatment outcome, showing that a lower treatment motivation (TM) was predicted by more severe symptoms at baseline, and was associated with smaller improvements in symptoms and both cogni-

tive and psychosocial functioning at the end of the intervention. In particular, they found that more severe negative symptoms at baseline were associated with lower TM during the whole intervention, while higher

Cognitive Remediation Program	Duration of Cognitive Remediation	Assessment	Main Findings
Cog Rem: CACR (Cogpack)	10 single sessions (1 h) 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: CG	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 ($p = 0.040$) and reasoning abilities ($p = 0.005$) (Effect Size not reported)
Cog Rem: CACR Ctrl: CG	16 biweekly sessions (30-45 min) for 8 weeks	Cognitive, clinical, functional outcome and TM	Patients with higher TM improved attention and social-occupational functioning, and reported lower general psychopathology. Patients with increasing TM over the course of the intervention improve attention and visual-spatial abilities
Cog Rem: CACR Ctrl: CG	Biweekly single sessions (45 min) for 8 weeks	Cognitive, symptoms and functioning at baseline and post-intervention	Visuospatial abilities improved significantly more in CACR than in Ctrl group, with large ES ($d = 0.62$)
Cog Rem: CACR (Cogpack) Ctrl: supportive counselling	12 sessions (12 months)	Symptoms and functioning 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)
Cog Rem: online training from home (two programs, one with target on cognition and one with target on social cognition)	Four daily 15 minute sessions (1 h) for 5 days/week (total: 40 h/8 weeks)	Cognitive was assessed pre/post TCT. Symptoms and functioning were assessed pre-TCT and one-month post-TCT	Internet based TCT intervention is feasible and has potential cognitive benefits for CHR. Processing speed significantly improved after TCT ($p = 0.01$, $d = 0.63$) and predict a larger improvement in role functioning
Cog Rem: auditory processing cognitive remediation therapy Ctrl: CG	1 h sessions for 4 days a week (total: 40 h 10-12 weeks)	Clinical, functioning and cognitive measures at baseline, post-CRT (at 3 months) and at 9 month follow-up	Cog Rem group improved in global functioning between baseline and 9 month follow-up ($P < 0.05$), even though it was not correlated with cognitive functions. No other difference was found between the two groups. (Effect Size not reported)
Cog Rem: AT Ctrl: CG	40 hours session (1 h/day, 5 day/week, for 8 week)	Clinical, cognitive and functioning assessment at baseline and post-training	There were significant main effects for global cognition, working memory, visual learning and problem solving (small ES) and verbal memory (medium ES, $d = 0.61$). Both groups improved symptoms and functioning over time.

cial aims: the accurate identification of the target population and its effective treatment. Nonetheless, research in this field is only preliminary and optimal training parameters, including dose, intensity, and

setting, are still unknown. Herein, the authors report a qualitative review of the current scientific literature on CR intervention in the prodromal phase of schizophrenia or in subjects at-risk for psychosis, in order

positive symptoms predicted an increase and then a stabilization of TM and more motivated patients were more likely to show improvement in terms of attention, general psychopathology and social-occupational functioning. The authors concluded that these findings could lead to a significant contribution to the knowledge about determinants, dynamics, and effects of TM in adolescents at-risk or with psychosis within the framework of cognitive remediation ³⁸.

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). 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 the IPI and 16.9% for the supportive counselling group 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. 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 were 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 ⁴⁰.

An uncontrolled pilot study investigated the feasibility and the potential behavioral benefits of a 8-week internet/computer-based targeted cognitive training (TCT) in a single group of 32 individuals at clinical high risk (CHR) for psychosis. Cognitive functions were assessed immediately pre- and post-TCT,

while symptoms and functional outcome were assessed pre-TCT and one month post-TCT. Eighteen CHR participants were enrolled. At the end of TCT, CHR participants had a significant improvement in processing speed ($p = 0.01$, $d = 0.63$) and a trend improvement in visual learning and memory ($p = 0.06$, $d = 0.54$) and in global cognition ($p = .06$, $d = 0.45$). A greater improvement in processing speed predicted greater improvement in role functioning. Despite this is an uncontrolled pilot study, these findings provide evidence that an intensive, internet-based, TCT intervention is feasible and has potential cognitive benefits for CHR, supporting more extensive clinical trials ⁴¹.

A recent single-blind, randomized controlled pilot study tested the effectiveness of a 12-weeks auditory processing cognitive remediation therapy (CRT), the Brain Fitness Program (BFP - developed by Posit-Science), in improving cognition in a sample of 32 young people at CHR for psychosis. Participants were randomized to either BFP or a control treatment consisting of commercial computer games (CG) and clinical, functioning and cognitive measures were performed at baseline, post-CRT (at 3 months) and at 9-month follow-up (i.e. 9 months post-baseline or 6 months after post-CRT assessment). The BF group showed a trend of improvement in speed of processing between baseline and 9-month follow-up ($P = 0.06$) as well as at post-CRT compared to 9 month follow-up ($P < 0.05$), while the CG group showed a significant improvement in working memory between post-CRT and 9-month follow-up ($P < 0.05$). Furthermore, in the BF group there was a significant improvement in a global functioning social scale between baseline and 9 month follow-up ($P < 0.05$), even though this was not correlated with cognitive functions. No other differences were found between the two groups. Despite the small trend of improvement, the study confirms the feasibility of CRT for individuals at CHR and point up the need of additional RCTs, conducted with more attractive cognitive training programs specifically designed for young people ⁴². Finally, in a double-blind randomized controlled trial (RCT), 83 adolescents and young adults at CHR for psychosis were assessed as for clinical, cognitive and functional outcome variables at baseline and after 8-week auditory cognitive training (AT) or computer games (CG) application. Participants in the AT group showed, compared to CG group, improvement in global cognition, working memory, visual learning and problem solving with a small effect size and in verbal memory with a medium effect size ($ES = 0.61$). Symptoms and

functioning improved over time in both groups. The authors concluded that this study could improve the growing research literature on the issue of preventive approaches to psychotic illness, focusing on the identification of effective methods to improve cognitive dysfunctions, that contributes to poor outcomes in the CHR state⁴³.

Conclusions and further directions

The available studies support the effectiveness of CR when applied both in chronic patients with schizophrenia, in young first episode schizophrenia patients or in the early stages of the illness⁵⁶³⁴. Therefore, exposure to CR may be an essential component to early-intervention programmes in psychoses²⁸. 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 different critical domains such as social functioning, employment and major role functioning⁴⁴.

The few studies analyzing the efficacy of CR in the prodromal phase of schizophrenia or in subjects at-risk for psychosis provide first evidences of the feasibility and the potential advantages of delivering CR at the putative earliest stages of the disease process. Prodromal patients seem to exhibit a higher rehabilitative potential relative to cognitive functions in comparison to patients with fully manifested schizophrenia, and it is conceivable that cognitive training may facilitate neuroplastic phenomena and have a neuroprotective effect⁴⁴⁻⁴⁶. This is based on the premise that the potential recovery may be higher within the “critical period”, in which the on-going neurodevelopment increases the possibility to alter the course of disease. The “protective” role of early effective intervention on the neurobiological and clinical deteriorating course of the disease, proposed for treatment with antipsychotics – especially with the 2nd generation compounds – may be extended to non-pharmacological approaches, such as CR⁴⁷⁴⁸. Moreover, since cognitive deficits occur before the onset of psychosis and are significantly associated with poor premorbid adjustment and poor functional outcome in the prodromal phase of schizophrenia and in UHR individuals, there is a clear rationale for further research on CR in these populations⁴⁹. 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”, and 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 efficacy²⁷²⁸. 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 CR are expected to occur early in the course of the illness, and even in its prodromal phase⁴⁹.

The studies reported in this narrative review have numerous methodological weaknesses, such as the small sample size, the inclusion in the same sample of “at-risk” subjects and patients with schizophrenia, the difficulties in understanding the contribution of each single intervention in integrated approaches, the lack of control groups and the absence of follow-up periods. Furthermore, many important questions remain open: i) the actual efficacy of CR in delaying or preventing the onset of psychosis; ii) the generalizability of the effects to broader areas of functioning; iii) the possible mediators and moderators of response; iii) the role of social cognition and metacognition involvement in treatment effectiveness. Despite these limitations and the fact that further research on the effectiveness of CR applied in the prodromal phases of psychosis or in the so-called “at-risk mental states” is needed together with more rigorous experimental efforts, available findings indicate that CR should be considered as a key point for early intervention in schizophrenia.

Recently, it has been proposed a randomised, parallel group, observer-blinded clinical trial – the FOCUS trial – with an initial sample size of 126 patients meeting the standardised criteria of being at UHR for psychosis, with the aim to investigate whether CR can improve cognitive and psychosocial function in this population. FOCUS trial results will shed light on the effect of CR on cognition, functional outcome, and symptomatology, as well as long-term outcome in preventing transition to psychosis in subjects at-risk for psychosis⁴⁷.

Future research should use progress in cognitive neuroscience to identify neural circuits involved in the pathophysiology and in the treatment of CHR subjects, in order to develop new cognitive training strategies to prevent the onset of psychosis and to improve outcome. These CR programmes should be more engaging and appealing for young people yet without a diagnosed disease. Furthermore, there is the need to perform dose-response studies, estab-

lishing the time and the intensity of training necessary to generate clinically significant gains in cognitive and functional outcomes. Another key point for future research should be to identify more homogeneous groups of subjects at highest risk for psycho-

sis as potential target group for treatment. Finally, it will be relevant to consider CR approaches within other evidence-based psychosocial integrated interventions to better provide the generalization of any obtained effect.

Take home messages for psychiatric care

- Cognitive impairment is a key feature of schizophrenia with considerable consequences on patients' functioning. Several quantitative reviews and meta-analyses have established that CR is effective in reducing cognitive deficits and improving functional outcome both in chronic schizophrenia and in the early stages of the illness
- Current literature underlines that subjects at risk for psychosis already show an impairment in cognitive domains, that is associated with functional dysfunction and with psychosis conversion. Thus, research in prevention of schizophrenia should focus on the improvement of these deficits before the onset of the illness, with the goal to prevent the conversion to psychosis
- 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 have a neuroprotective effect, with the possibility to alter the course and trajectory of the disease. Thus, it has been proposed that exposure to CR may be an essential component of early-intervention programmes in psychosis
- Despite some methodological limitations, the few studies analyzing the efficacy of CR in the prodromal phase of schizophrenia or in subjects at risk for schizophrenia provide first evidences of the feasibility and the potential advantages of delivering CR at the putative earliest stages of the disease
- Although these findings indicate that CR should be considered as a key issue for early intervention in schizophrenia, many relevant questions still remain open and future rigorous research is needed for the implementation of more targeted interventions

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