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Review

# Non-pharmacological interventions to improve cognitive impairment and psychosocial functioning in schizophrenia: a critical review

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## SUMMARY

*Cognitive impairment represents one of the core features of Schizophrenia Spectrum Disorders (SSD) and has a significant negative impact on psychosocial functioning and real-world outcomes of people living with SSD. While currently available pharmacological treatments do not appear to provide significant improvements in cognitive performance, some non-pharmacological interventions have shown to reliably provide cognitive gains and consequent improvements of psychosocial functioning in SSD. The present critical review focuses on the evidence of effectiveness and on the limitations of these interventions. Cognitive remediation and physical exercise-based interventions appear to provide improvements in both cognitive performance and psychosocial functioning, with clear moderators of effects and with abundant scientific evidence supporting their clinical usefulness. Non-invasive brain stimulation techniques such as transcranial direct current stimulation and transcranial magnetic stimulation appear as promising interventions, but more research is currently needed to better assess the optimal modalities of delivering these treatments to people with SSD. More research is currently needed to better understand barriers and facilitators of implementation in clinical practice of these interventions, and more organization, policymakers and clinicians efforts are required to deliver them to people living with SSD in a consistent manner.*

**Key words:** cognition, cognitive remediation, functioning, non-invasive brain stimulation, physical exercise, schizophrenia

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## Introduction

Schizophrenia Spectrum Disorders (SSD) are severe and debilitating mental conditions, and people living with SSD often show limitations in real-world functional outcomes [1,2], reduced quality of life [3,4], high levels of internalized stigma [5-7] and low levels of life engagement [8,9].

Cognitive impairment represents one of the core features of SSD [10-12] that can be observed in the vast majority of diagnosed individuals [13,14] even before the clinical onset of the disorder [15-17], interesting both neurocognitive [10,18,19] and social cognition domains [20-22]. In fact, the prevalence and the relevance of cognitive impairment in SSD has recently led the international scientific community to devise and use with an increasing frequency the term Cognitive Impairment Associated with Schizophrenia (CIAS) [23].

The relevance of CIAS in a clinical perspective is also determined by the fact that it represents one of the main determinants of real-world functional impairment in SSD [24-27] and of worse long-term real-world outcomes [28-30].

Currently available pharmacological treatment appears to offer only minimal improvement in CIAS: while an accurate management of antipsychotic medications and of pharmacological therapy in general are essential

**TABLE I.** *Non-pharmacological interventions to improve cognitive impairment in schizophrenia.*

| Intervention | Definition | Main outcomes | Evidence of effectiveness |
|---|---|---|---|
| Cognitive Remediation | Behavioral training-based intervention targeting cognitive performance | Cognitive performance, with the aim of providing a durable improvement to psychosocial functioning | Cognitive performance and psychosocial functioning [43-45], acceptability [47] |
| Physical Exercise-Based Interventions | Interventions including elements of physical training, mostly aerobic exercise | Physical fitness, metabolic and health-related outcomes, but in people with SSD also cognitive performance, symptoms severity and psychosocial functioning | Metabolic and health related outcomes [70], cognitive performance [74,75], clinical symptoms and psychosocial functioning [71,73,76] |
| Non-Invasive Brain Stimulation | Stimulation of target brain areas through low-amplitude direct currents (tDCS) or focal electromagnetic pulses (TMS) | Neuronal firing rates and trophism in selected brain areas, resulting in improvement in core SSD dimension such as positive, negative and cognitive symptoms | Cognitive performance, mostly in the working memory domain [83-85], particularly for tDCS [86-88] |

*SSD: Schizophrenia Spectrum Disorders; tDCS: transcranial direct current stimulation; TMS: transcranial magnetic stimulation.*

to avoid further worsening of CIAS [31,32], and some interesting molecules have shown promising preliminary evidence of effectiveness [33-36], no pharmacological agent is currently indicated for the treatment of CIAS [37,38].

However, several non-pharmacological interventions have been developed and are provided to people living with SSD [39], and some of them have shown consistent evidence of effectiveness in treating CIAS and in translating cognitive gains into improvements in real-world psychosocial functioning.

The present paper aims to provide a critical review on the state of the art of non-pharmacological interventions in treating CIAS, focusing on the most recent evidence on the effectiveness and on the limitations of currently available treatments. A summary is reported in Table I.

## Cognitive remediation

Cognitive Remediation (CR) is a training-based behavioral intervention specifically designed to treat CIAS with the long-term aim of improving psychosocial functioning and real-world outcomes in a durable manner [40,41].

Several recent systematic review and meta-analyses have shown that CR interventions targeting neurocognitive domains and social cognition domains provide reliable improvements in CIAS that are well translated into functional gains [42-45]. The presence of an active and trained therapist delivering the intervention, the development of novel cognitive strategies and the use of techniques to facilitate the transfer of cognitive improvements in the real world, as well as the structured integration with psychiatric rehabilitation programs and the combination with other evidence-based interventions all represent elements that consistently improve the outcomes of CR; no patient characteristic appears to substantially limit the effectiveness of CR in rehabilitation contexts, but participants with a more compromised clinical presentation could obtain greater benefits [44]. In fact, an individual-patient meta-analysis including several different study samples showed that age does not represent a significant moderator of effect, suggesting that CR is feasible also in older patients [46].

This wealth of evidence attesting the effectiveness of CR on its main treatment targets and the identification of moderators of effectiveness resulted in the attribution to CR of the highest degree of recommendation in the European Psychiatric Association guidance dedicated to the treatment of CIAS [32].

Even more recently, another meta-analysis has shown that CR has a good acceptability profile, in line with that of other psychosocial interventions routinely used in the rehabilitation practice and delivered to people living with SSD [47]. A systematic review focused on factors influencing access and engagement of CR interventions, reporting that more severe CIAS and negative symptoms, lower intrinsic motivation and higher baseline self-efficacy resulted were observed in drop-outs [48]. A recent trial confirmed that CR is equally effective in pharmacological treatment responders and people with treatment-resistant SSD, further supporting the notion that subjects with a more severe clinical presentation might consistently benefit from receiving CR [49]. Another study focused on moderators of functional improvements after CR reported that participants who were more clinically compromised, older and with lower education level obtained greater improvements [50].

Despite the consistent evidence of effectiveness and the clear recommendation provided in international guidance to deliver CR to people living with SSD, this intervention, as well as other evidence-based non-pharmacological treatments, are still unevenly implemented

in the routine clinical practice of mental health services, even in high-income countries [51,52]. This is particularly problematic as recent evidence shows that CR interventions can be effectively implemented in day-to-day rehabilitation settings [53,54] even in contexts with limited available resources and low incomes [55].

In this perspective, future studies should focus on identifying and assessing facilitators and barriers to the implementation of CR in clinical practice, with particular attention dedicated to practical and feasible ways to strengthen facilitators and overcome barriers.

One possible instrument to facilitate access to services and to evidence-based treatment is represented by novel digital technologies, such as telemedicine: in fact, recent studies show that remotely delivered CR interventions appear to be feasible as well as engaging and well accepted by participants [56-59]. More research is currently needed and warranted in order to further attest the effectiveness of this approach on cognitive and functional outcomes: if this type of approach provided results that are similar to those obtained with in-person CR interventions in a reliable manner, it could represent a valuable asset to improve treatment access.

Another technology that could be of considerable interest in the context of delivering CR interventions is virtual reality: immersive virtual reality programs could provide more engaging exercises, improving participation and acceptability of the intervention, and ecologically valid scenarios could improve and facilitate the transfer of cognitive gains into real-world psychosocial functioning outcomes [60,61]. However, more high-quality studies are currently required in order to assess whether virtual reality CR interventions consistently provide superior effects compared to standard CR programs. The comparison between virtual reality and standard CR interventions should also take into account cost-effectiveness analyses, as virtual reality devices and programs are still currently characterized by elevated prices. In fact, cost-effectiveness analyses of CR represents another field that requires further studies: while several reports show that CR does indeed represent a valid intervention also in a cost-effectiveness perspective [62-66], the economic requirements of specific interventions and the available resources can change drastically over time and in different contexts, so more research is currently warranted regarding this aspect.

## Physical exercise

Physical exercise-based programs, and aerobic exercise in particular, can be considered to all intent and purposes as evidence-based intervention in people living with SSD, as they can reliably improve important outcomes such as metabolic and health-related parameters [67-69] but also core dimensions of the disorder [70-72].

In fact, the positive effects of physical exercise interventions in the treatment of CIAS are well documented in several large and high quality meta-analytic works [70,73,74]. The European Psychiatric Association guidance dedicated to the treatment of CIAS recommends the use of physical exercise interventions, but with a lower level of recommendation than that of provided for CR: despite the wealth of available evidence, this was mostly due to the lack of systematic assessments of the moderators of effects that could inform clinicians on which type of intervention should be implemented in routine rehabilitation practice and for the lack of systematic assessments of the effects on functional outcomes [32].

However, a recent meta-analysis explored specifically the potential moderators of effect of physical exercise interventions on CIAS: results showed that the most effective form of activity is aerobic exercise, delivered in a group context with the supervision of trained exercise professionals. Cognitive improvements provided by physical exercise also show a dose-response effect, starting from a duration of ≥ 90 min per week for ≥ 12 weeks: this observation strongly suggests that the observed cognitive improvements are directly related to physical exercise [75].

Moreover, another recent meta-analysis investigated the effects of physical exercise in people with SSD focusing specifically on functional outcomes: moderate-sized effects were observed for global functioning, social functioning and daily life functioning, with larger effects in aerobic exercise interventions of moderate to vigorous intensity [76].

In light of the results of these meta-analyses, physical exercise-based interventions can now be fully considered as evidence-based treatments targeting CIAS.

Recent studies show that physical exercise programs can also be easily combined with CR: these combined interventions appear to provide greater benefits than their individual components, granting faster improvements in cognitive performance [77-79].

As regards implementation in clinical services, physical exercise shares the same issues of CR and other evidence-based psychosocial interventions for people with SSD: they are currently implemented in a piecemeal manner and provided unevenly to service users, even in inpatients contexts [51]. On one hand, more research is currently needed to better understand facilitators and barriers that influence the implementation of evidence-based psychosocial interventions in clinical settings; on the other hand, greater efforts should be made at policymakers and service organization levels to reduce the bench to bedside gap.

## Non-invasive brain stimulation

Beside psychosocial intervention, another category of

non-pharmacological treatments that can be provided to people living with SSD consists in bran stimulation techniques, and in particular non-invasive brain stimulation. Non-invasive brain stimulation techniques that have been explored in the specific context of treating CIAS are mostly transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) [80].

TDCS consists in applying low-amplitude direct currents (usually 1-2 mA) through anode and cathode electrodes applied to the scalp, modulating cortical excitability in a nonfocal manner by polarity-dependent shifts of neuronal membrane potentials [81], while TMS provides focal electromagnetic pulses through a wire coil to focally stimulate target brain areas by inducing secondary electric current flows modulating neuronal firing rates [82].

Recent meta-analyses have shown that both tDCS and TMS could have positive effects in the treatment of CIAS [83,84].

In particular, both TMS [85] and tDCS [86-88] appear to provide small improvements in the domain of working memory, with tDCS having a more literature supporting in a consistent manner the evidence of effectiveness.

However, the stimulation protocols implemented in tDCS trials vary in a significant manner, with important differences as regards electrode placement, length and timing of stimulation sessions, and overall duration of the treatment: this methodological heterogeneity could mask the true potential of the treatment, and it can not be excluded that some treatment protocols could provide consistent benefits in CIAS as well as in other core SSD dimensions [89]. More studies are currently required in order to better identify the optimal treatment modalities and durations, allowing to properly assess the effectiveness of non-invasive brain stimulation. This represents an essential requirement in order to provide clear recommendations regarding its use in clinical practice.

Moreover, a recent systematic review and meta-analysis compared the effectiveness of combining non-invasive brain stimulation with CR to CR alone on cognitive and functional outcomes: while this work was conducted with a transdiagnostic approach and trials including samples of people with SSD represented a minority of included studies (5 out of 72 included studies), the combined approach appeared to provide superior benefits in the working memory domain [90]. This result suggests that a combined treatment approach may indeed be effective also in SSD: however, the Authors highlighted that the vast majority of included studies showed significant risk of bias. These issues warrant the need of further research on the effectiveness of this combination, particularly in SSD samples.

## Discussion

While CIAS represents a core feature of SSD that severely impacts real-world outcomes and shows little improvements with pharmacological therapy, different non-pharmacological approaches are currently available for its treatment.

CR and physical exercise-based interventions showed consistent benefits in improving CIAS and can be easily and effectively implemented in routine clinical practice, particularly in rehabilitation and impatient settings. CR directly targets CIAS and has wide literature supporting its consistent effectiveness [43-45]. Physical exercise also appears to reliably improve CIAS [74,75], and can also provide substantial benefits on metabolic and health-related outcomes [67,69].

Both interventions appear to provide larger benefits if delivered with an active and trained therapist: in this regard, the training and integration in rehabilitation services of therapists appears to be essential to properly treat CIAS and, consequently, to provide an optimal rehabilitation process and improve recovery in people living SSD. CR and physical exercise can also be combined into structured rehabilitation programs, if available resources allow it, to provide superior benefits [77-79].

Non-invasive brain stimulation, particularly tDCS, may also provide some measure of improvements, but more research is currently needed to better define the optimal stimulation modalities and treatment duration [32]. The combination of CR and non-invasive brain stimulation also appears promising, but more high quality studies in SSD samples are currently needed [90].

Despite the existence and the availability of these treatment options, more effort is currently needed to make sure that they are actually delivered to service users: evidence-based non-pharmacological treatments are still provided to service users living with SSD in an uneven and piecemeal manner also in high-income contexts [51].

To close, or at least reduce, this bench-to-bedside gap, several action are currently required: more research is needed on facilitators and barriers to treatments implementation; more effort is required at policymakers and service organization levels; national and international clinical practice guidelines should provide clearer and more univocal recommendations on the importance of these treatments; finally, practitioners in clinical settings should be educated on the existence and effectiveness of these treatments, and consider them as options in the routine treatment and clinical management of patients with SSD.

Moreover, even the most effective evidence-based interventions only provide moderate improvements in CIAS: constant effort in research settings is currently required to develop both pharmacological and non-pharmacological treatments that are able to provide larger benefits.

Despite these issues, the available treatments represent valuable assets to improve CIAS, and should be

carefully taken into account in the clinical management and in the process of treatment personalization and optimization to improve real-world recovery outcomes of people living with SSD.

## Conflicts of interest statement

The Authors declare no conflict of interest in the design, execution, interpretation, or writing of the manuscript.

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## Authors' contributions

SB, GD, GN, AV: study conceptualization and design; GN, ICP, LB, AC, NN, DZ, LP, JL, SB: literature search; GN: wrote the first draft of the manuscript; GN, SB, AV: supervision of the manuscript; all the Authors reviewed and approved the final version of the manuscript.

## Ethical consideration

Not applicable.

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