Review

Cognitive Impairment Associated with Schizophrenia: insights and treatment perspectives

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SUMMARY

Cognitive Impairment Associated with Schizophrenia (CIAS) is a major determinant of clinical outcomes and everyday functioning in schizophrenia. As such, it represents a field of research that is currently showing a consistent and ever-growing intertest. A comprehensive assessment of CIAS is crucial for effective management of schizophrenia. In this regard, several validated assessment tools are now available; among these, the MATRICS Consensus Cognitive Battery and the Brief Assessment of Cognition in Schizophrenia are the most strongly recommended. An emerging and clinically meaningful paradigm in CIAS assessment is the systematic identification and treatment of potentially reversible contributors to secondary cognitive impairment, which may substantially improve real-world outcomes. Treatment should begin with the optimization of pharmacotherapy, followed by evidence-based non-pharmacological interventions, such as cognitive remediation and aerobic physical exercise, both supported by strong evidence. Further research and more effort are currently needed to raise awareness on CIAS and to foster the dissemination and the implementation of evidence-based approaches to its management and treatment.

Key words: CIAS, cognition, cognitive remediation, evidence-based, physical exercise, psychosocial interventions, schizophrenia

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Introduction

Schizophrenia is a severe mental disorder that often carries significant impairment in psychosocial functioning and poor real-world outcomes [1–5], high levels of both public and internalized stigma [6–11], and substantial excess mortality, mostly due to non-communicable diseases [12–15].

Cognitive impairment can be considered one of the core features of schizophrenia [16–18], and has been acknowledged as such even in the earliest conceptualizations of the disorder [19,20].

It represents a very frequent issue, as more than 80% of diagnosed individuals show a global cognitive performance that is at least one standard deviation below that of the general population [21,22], interesting both neurocognitive [23,24] and social cognition domains [25–27]. Moreover, this impairment can be observed since an early age, often predating the full onset of psychotic symptoms [28–31].

Considering the frequency, the relevance and the impact of this issue on the daily lives of people with schizophrenia, the use of the dedicated term "Cognitive Impairment Associated with Schizophrenia" (CIAS) is gaining traction within the scientific community [32–35].

The aim of the present narrative review is to provide insight into the most recent findings on the assessment, treatment and management in clinical practice of CIAS.

Impact Of CIAS

The relevance of CIAS and its interest in scientific and clinical contexts is determined not only by its frequency, but also by its considerable impact on the lives of people with schizophrenia.

First and foremost, CIAS represent one of the core determinants of impairment in psychosocial functioning in people living with schizophrenia: a consistent and ever growing body of literature attests that CIAS is one of the stronger predictors of worse functioning [36–38], accounting for 20-60% of the observed variance in measures of functional outcomes [1,39–41]. In fact, several studies report that the impact of CIAS on functional outcomes surpasses that of other core domains of schizophrenia, such as positive and negative symptoms [42,43]. Moreover, several studies attest that the negative impact of CIAS is not limited to measures of functional capacity and psychosocial functioning, but is consistently reflected in worse real-world functional outcomes [41,44–46].

Alongside the well-documented negative impact on psychosocial functioning, CIAS also plays a relevant role on more distal outcomes that are nonetheless considered important treatment goals for people with schizophrenia: in fact, CIAS has been consistently associated with worse quality of life [47–49]. Moreover, CIAS appears to represent one of the main determinants of reduced life engagement [50,51], a patient-reported outcome that is gaining increasing attention in recent literature [52,53]. CIAS has also been shown to directly act as a hindrance in the process of recovery, as it represents a barrier in the psychiatric rehabilitation of people with schizophrenia and a negative moderator of treatment response in several psychosocial interventions [54–56].

People living with schizophrenia are more frequently the victims rather than the perpetrators of violence [57–61]; nonetheless, schizophrenia diagnosis is associated with an increased risk of aggressive and of violent behavior, compared to the general population as well as to other psychiatric diagnoses [62–66]. In this context, CIAS, alongside other factors, is related to an increased risk of violent behavior [67–72].

Finally, recent evidence shows that CIAS even represents a significant risk factor for increased mortality in people with schizophrenia, including natural cause mortality: this may be related to a detrimental effect of CIAS on the ability to identify somatic illness symptoms, seeking and receiving effective treatment, and adhering to treatment regimens [73–75].

Assessment Of CIAS

Assessment represents the first and essential step in the clinical management of CIAS.

The European Psychiatric Association produced a guidance document dedicated specifically to the assessment of CIAS, reviewing and providing recommendations on different evaluation instruments [76]. Currently, the tool with the highest level of recommendation for the assessment of neurocognitive performance in people living with schizophrenia is the MATRICS Consensus Cognitive Battery (MCCB) [23]. The MCCB is a performance-based instrument that assesses all the six core neurocognitive domains that are interested in CIAS (attention/vigilance, processing speed, working memory, visual learning and memory, verbal learning and memory, executive functions/reasoning and problem solving) and also social cognition performance, showing good psychometric properties and correlation with functional outcomes [77–79]. The test battery and its administration and scoring manual [80] has been translated in 26 languages and normative data for several different cultural contexts are currently available [76].

However, while the MCCB can currently be considered the “gold standard” for the assessment of CIAS, its use in daily clinical practice may be consistently hindered by the long administration time (60-90 min) that such a comprehensive assessment entails. In this regard, while the MCCB should be considered the optimal measure in research settings and clinical trials, shorter and more agile instruments should be considered in real-world clinical settings.

The Brief Assessment of Cognition in Schizophrenia (BACS) [81] assesses only five neurocognitive domains, but it presents a much more contained administration time (about 35 min) while maintaining good psychometric properties, functional correlates and participant completion rates [82]. Having been translated and validated in 9 different languages, with available normative data for various settings, the BACS also represents a valid battery for assessment of CIAS [76].

An assessment tool with an even shorter administration time (about 15 min) is the Screen for Cognitive Impairment in Psychiatry (SCIP). Assessing four cognitive domains with good psychometric properties [83,84], this instrument is not recommend for a full assessment of cognitive performance in people with schizophrenia, but represents a valid screening tool to identify cases where a full, in-depth assessment is warranted.

Alongside performance-based instruments, interview-based instruments can also be considered in the assessment of CIAS. The strength of interview-based instruments is that they may capture elements that are more salient for patients, and, associated with objective measures obtained with performance-based instru-

ments, can provide a more comprehensive overview of the severity and impact of CIAS for specific individuals. In this respect, both the Cognitive Assessment Interview (CAI) [85] and the Schizophrenia Cognition Rating Scale (SCoRS) [86] have good face validity and psychometric properties and can be considered as co-primary outcomes alongside performance-based instruments in CIAS trials.

Alongside an assessment of neurocognitive performance, an assessment of social cognition should also be carried out to properly evaluate CIAS. However, valid measures of social cognition abilities are more limited than those for the assessment of neurocognition.

The Social Cognition Psychometric Evaluation (SCOPE) project [26,87,88] aimed precisely at the identification of measures of social cognition domains interested by CIAS (emotion recognition/processing, theory of mind/mentalization, attributional style/bias, social perception) that showed good psychometric properties and that could be reliably used in research and clinical setting.

The Bell-Lysaker Emotion Recognition Task (BLERT) [89] and the Penn Emotion Recognition Task (ER-40) [90] emerged as valid measures of emotion recognition and processing, while the Hinting Task [91] and the Reading the Mind in the Eyes Test (Eyes Test) [92] emerged as valid measures of theory of mind/mentalization. The Awareness of Social Inference Test (TASIT) [93] can be considered a measure of both emotion processing and theory of mind which also showed good psychometric properties and can be recommended for use in the assessment of CIAS.

However, all tools evaluating the attributional style/bias and social perception domains did not provide satisfactory psychometric properties: currently, no measure to assess these domains is valid enough to be recommended for use. More research is needed to develop and validate reliable measures of attributional style/bias and social perception in order to devise a comprehensive test battery for the assessment of the social cognition component of CIAS.

One important element that has to be also considered in the assessment of CIAS, beside the difference in evaluation tools, is that of timing. While available literature on this issue is currently limited, the consensus is that CIAS should be properly assessed at least once in every individual diagnosed with schizophrenia [76]. Ideally, a first full assessment should be conducted as soon as possible, during the earliest meetings with the patient, in order to assess the baseline level of impairment. The assessment should be repeated afterwards to monitor the individual's conditions. In particular, the assessment should be repeated at the start at the conclusion of specific interventions aimed at improving CIAS in order to assess the effectiveness of the treatment, if significant changes are noticed by the clinician, by the caregivers or the patient, or if concurrent medical comorbidities that could impact cognitive performance are diagnosed [76].

An opportunity that has recently surfaced in the field of CIAS assessment thanks to the development of novel technologies is that of remote assessment. Recent studies show that remotely administered MCCB, while not completely comparable to in-person administration, is equally valid for several subtests [94]. An application for the assessment of cognitive performance based on the BACS, the BAC App, has been developed and validated [95,96], and several other similar applications and mobile-based assessment tools are currently being devised and proposed to the scientific community [97–101]. However, more research is currently needed to appropriately compare the validity of these assessment tools to that of more well-established test batteries.

Finally, an aspect that has only recently being conceptualized but that could substantially impact on the management of CIAS, particularly in everyday clinical practice, in the assessment and recognition of secondary cognitive impairment.

Primary And Secondary Cognitive Impairment

As previously mentioned, CIAS represents an essential feature of schizophrenia, which is deeply rooted in the neurobiological alterations that determine the psychopathological characteristics of the disorder [16].

However, alongside these neurobiological alterations, which may determine a form "primary" cognitive impairment, people living with schizophrenia are also routinely exposed to factors that may independently impair cognitive performance, and that may be considered sources of "secondary" cognitive impairment. This "secondary" cognitive impairment could be superimposed to and worsen the "primary" one, contributing to a large extent to the overall severity and burden of CIAS [102].

Inappropriate pharmacological therapy may represent one of the main sources of secondary cognitive impairment in people living with schizophrenia. First-generation antipsychotics have been consistently shown to have worse cognitive outcomes than second-generation ones [103–106], with recent meta-analytic studies suggesting that some first-generation molecules could even have a direct detrimental role [107]. Prolonged exposure to consistently elevated dosages [108–111] and antipsychotic polypharmacy [112–114] could also a negative impact on cognitive performance. Total anticholinergic burden represents another clear source of cognitive impairment [115–117] that is strongly associated to worse functional outcomes [118,119]. Inappropriate use of benzodiazepines –

high doses for prolonged periods of time- could also have a negative impact on cognitive performance [120,121].
Another frequent potential source of secondary cognitive impairment is represented by substance use. Available literature show that a consistent negative effect on cognitive performance also in people with schizophrenia has been observed for the use of cannabis [122–124], cocaine [125–127], and tobacco smoking [128–130], and concomitant use of alcohol may directly affect the results of cognitive test [131,132].
Metabolic syndrome and metabolic conditions that represent individual components of the syndrome, such as diabetes, obesity and dyslipidemia, besides representing clear cardiovascular and cancer risk factors [133–135], have been shown to have a detrimental effect on cognitive performance in people living with schizophrenia [136–139]. In fact, insulin resistance has recently been hypothesized to represent a treatment target to improve CIAS [140].
Sleep disorders and sleep disturbances represent another frequent occurrence in people with schizophrenia [141–143] that have been shown to have a negative impact on cognition both in the general population [143,144] and in schizophrenia [145–148].
Social isolation and social deprivation are also elements that could contribute to cognitive impairment in people with schizophrenia [149–152].
Autistic features, which represent one of the other core dimensions of the disorder [153–158], have been associated with worse cognitive outcomes, particularly in social cognition domains [159–163] and represent a negative moderator of treatment response in interventions targeting social cognition [164] and pharmacological therapy [165,166].
Depressive symptoms have also been shown to be associated with worse cognitive performance in people with schizophrenia [167–170].
Finally, positive [171–175] and negative [176–181] symptoms themselves may contribute to cognitive impairment, an observation backed by a generalized, nonspecific positive effect of symptoms reduction on cognitive performance reported in meta-analytic assessments [107].
This conceptualization consisting in the separation of CIAS in a primary and secondary component carries a significant and clinically meaningful implication: that secondary cognitive impairment may be resolved or at least substantially reduced by treating the source issues [102]. In this regard, identifying and treating sources of secondary cognitive impairment may represent a relevant perspective both in research and in clinical settings. However, this model is recent and its clinical implications are still largely hypothetical: the dimension and the consistency of clinical benefits obtainable by integrating this approach in clinical settings currently require more dedicated research.
Furthermore, even a complete resolution of secondary cognitive impairment would not account for a total normalization of cognitive performance in the context of CIAS, as it would not target the primary component: in this regard, targeted treatment of CIAS with effective therapies currently remains a priority.

Treatment Of CIAS

The European Psychiatric Association also produced a guidance document dedicated to the treatment of CIAS: based on a meta-review of available literature, the guidance provides clear treatment recommendations based on the efficacy of evidence-based therapies [182].
The first step in the treatment of CIAS is the optimization of pharmacological therapy. As previously mentioned, several pharmacological treatments may have a negative impact on cognitive performance: first-generation antipsychotics [103–107], particularly at high doses [108–111], antipsychotic polypharmacy [112–114], high anticholinergic burden and anticholinergic medications [115–119] and prolonged high doses of benzodiazepines [120,121] all could contribute to the worsening of CIAS.
However, optimizing pharmacological therapy, while essential, represents a way to avoid secondary cognitive impairment rather than a direct treatment of CIAS.
In fact, even the most recently developed antipsychotic molecules do not appear to reliably present a positive effect on cognitive performance [107], and while several pro-cognitive pharmacological agents are currently being develop and investigated [183–186], none has currently provided sufficient evidence of effectiveness to be recommended as a direct treatment for CIAS.
However, the lack of pharmacological treatment does not mean that no effective treatment is currently available: in fact, psychosocial interventions dedicated to treatment of CIAS are available and have reliably and consistently provided evidence of effectiveness [182,187–189].
The treatment with the highest level of available evidence and recommendation is Cognitive Remediation (CR).
CR is a training-based psychosocial intervention that uses scientific principles of learning aiming specifically at the improvement of cognitive performance with the goal of improving real-world functional outcomes in a durable manner [190,191]. The interaction with an active and trained therapist, the repetition of cognitive exercises, the development of novel cognitive strategies and the transfer of cognitive improvements into real-word functioning all represent essential ingredients for its efficacy [190,192]. Several recent and large meta-analytic works have attested its effectiveness on both cognitive and functional outcomes [192–196], as well as its acceptability [189,197] and durability of effects [198]. It can be effectively im-

plemented in clinical practice even in contexts with limited available resources [199–201], as well as in low-income countries [202–205].

Despite the consistent evidence of effectiveness, CR is still implemented in clinical practice in a piecemeal manner, even in high-income contexts [206–208]: this appears to be mostly due to limited understanding of the benefits of CR on part of mental health professionals themselves and of regulatory entities [209–212]. To improve the dissemination and implementation CR in everyday clinical practice and rehabilitation services and to resolve this bench-to-bedside gap, a closer partnership between academic institutions and clinical services, as well as greater advocacy from service users, their families and carers, and of stakeholders organizations could represent essential future perspective [199,213].

Another important perspective for future research is represented by the use of novel technologies to improve the implementation and the delivery of CR. Remotely delivered CR interventions appear to be feasible and effective on both cognitive and functional outcomes [214–223]. App-based and smartphone-based CR programs with preliminary evidence of feasibility and efficacy are also emerging [224–227]. However, more evidence is currently required to better assess the effectiveness of this approach, particularly in comparison with more established and reliable CR administration methods. In particular, future research should also take into account cost-effectiveness parameters [228–231].

Another intervention that can be considered an evidence-based treatment for CIAS is Aerobic Physical Exercise (APE) [182].

APE-based interventions are well-recognized as treatments for improving metabolic and global health outcomes both in the general population and in people living with schizophrenia [134,232,233], and substantial meta-analytical evidence has shown that APE is effective in improving core dimension of schizophrenia such as positive and negative symptoms [234–236]. However, the benefits of APE apper to go beyond that of symptoms improvement in people with schizophrenia a: several systematic reviews and meta-analysis show that APE also provide consistent improvement in cognitive performance in the context of CIAS [234,237,238]. Recent meta-analyses have found that APE is more effective on CIAS when delivered by an active and trained therapist and have identified a threshold of intensity of 90 min per week for a duration of at least 12 weeks to provide effective results [239]; moreover, the positive effect of APE psychopathological domains and cognitive performance is translated into real-world functional improvements [240]. Interestingly, combining CR and APE provides superior benefits that each treatment alone, with a synergistic effect that grants faster improvements in CIAS [241–243]. On the contrary, direct comparisons between CR and APE as regards the improvement of CIAS are currently limited [244], and more research is needed on this issue.

Another approach that has recently emerged in the context of the treatment of CIAS is non-invasive brain stimulation [182].

Non-invasive brain stimulation in general operates by modulating brain activity through the use of magnetic or electric induction [245–247]: transcranial Direct Current Stimulation (tDCS), in particular, provides low-amplitude direct currents through electrodes applied to the scalp, and modulates cortical excitability in a nonfocal way by polarity-dependent shifts of neuronal membrane potentials [248–250].

Recent meta-analytic investigations show that tDCS can improve negative symptoms [251] and appear promising also in the treatment of CIAS, particularly in the working memory domain [252–256].

However, a high level of heterogeneity was observed in trials findings, which may result from substantial differences in electrode placement, administration intensity and treatment protocols. Current evidence shows that bilateral-bipolar prefrontal stimulation, with the anode placed on the left dorso-lateral pre-frontal cortex and the cathode contralaterally to other frontal areas may represent the optimal approach to treat CIAS with tDCS [251,257,258]. Moreover, recent evidence suggests that combining CR and non-invasive brain stimulation is feasible and could provide superior benefits that CR alone [259]. However, more research is currently needed in this field, are more studies are needed to properly define non-invasive brain stimulation as an evidence-based treatment for CIAS [182]

Conclusions

In conclusion, CIAS represents an issue that has a major impact in the clinical situation and in the daily lives of people with schizophrenia. As such, it represents a field of research that is currently showing a consistent and ever-growing research intertest.

A careful assessment of CIAS represents an essential starting point for its management, and several validated instruments are available to carry reliable evaluations; among these, the MCCB and the BACS represent those with highest levels of recommendation. In the assessment of CIAS, identifying and resolving sources of secondary cognitive impairment represents a novel but relevant paradigm, which could have a substantial impact in clinical practice.

Optimizing pharmacological therapy represents the first essential step in the overall treatment of CIAS, and CR and APE both represent effective evidence-interventions. More research and more effort are currently needed to raise awareness on CIAS and to foster the dis-

semination and the implementation of evidence-based approaches to its management and treatment.

Conflict of interest statement

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Ethical consideration

No ethical approval was required.

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