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A narrative review of treatment interventions to improve cognitive performance in schizophrenia, with an emphasis on at-risk and early course stages

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Abstract

Cognitive dysfunction is a core feature of schizophrenia (SCZ), which unfavorably affects SCZ patients' daily functioning and overall clinical outcome. An increasing body of evidence has shown that cognitive deficits are present not only at the beginning of the illness but also several years before the onset of psychosis. Nonetheless, the majority of treatment interventions targeting cognitive dysfunction in SCZ, using both pharmacological and nonpharmacological approaches, have focused on chronic patients rather than individuals at high risk or in the early stages of the disease. In this article, we provide a narrative review of cognitive interventions in SCZ patients, with a particular focus on pre-emptive interventions in at-risk/early course individuals when available. Furthermore, we discuss current challenges for these pre-emptive treatment interventions and provide some suggestions on how future work may ameliorate cognitive dysfunction in these individuals.

Keywords

Schizophrenia; Cognition; Early interventions; Pharmacotherapy; Cognitive remediation therapy

1. Introduction

Schizophrenia (SCZ) is a complex and often chronically impairing brain disorder with a tremendous economic impact both in the US and worldwide (Chong et al., 2016). SCZ typically emerges in late adolescence or early adulthood and affects several functional domains, including perception (e.g., auditory hallucinations), thought (e.g., paranoid

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delusions), emotion (e.g., blunted affect), and behavior (e.g., social withdrawal) (Tandon et al., 2009). Although psychotic symptoms, including delusions and hallucinations, are part of the diagnostic criteria of SCZ, remission of these symptoms can be achieved for the majority of patients (Buchanan et al., 2010; Dixon et al., 2010), whereas social and professional impairments generally persist after remission from psychosis (Harvey, 2014; Kahn and Keefe, 2013). Indeed, a substantial proportion of patients with SCZ experience marked, long-lasting impairments in daily functioning, affecting their ability to maintain social relationships, sustain employment, and live independently (Harvey et al., 2019). This is because the functional outcome of SCZ patients, rather than the psychotic symptoms, is strongly associated with the presence and severity of their cognitive dysfunction (Lepage et al., 2014). SCZ patients show impairments across virtually all cognitive domains, including speed of processing, attention/vigilance, working memory, visual and verbal learning, reasoning and problem solving, social cognition, and executive functioning, with varying degrees of deficit in different stages of the disorder (Guo et al., 2019; Harvey et al., 2003). These cognitive impairments tend to persist throughout the course of illness and are largely resistant to antipsychotic compounds or other treatments. Thus, cognitive dysfunction has been recognized as a core deficit of SCZ that urgently needs novel, more effective therapeutic interventions (Barlati et al., 2012).

While most interventions aiming to improve cognition in SCZ occur after the first psychotic episode, several studies showed that cognition impairments likely begin many years prior to the manifestation of psychosis. Children who developed SCZ as adults show a significantly lower intelligence quotient (IQ) already at 3 years of age (Cannon et al., 2002). Cognitive dysfunction in both general (i.e., IQ) and across specific (i.e., executive functions) domains (Fig. 1) can also unfold during early and late adolescent years, and such dysfunction represents a risk factor for the development of SCZ. For instance, a meta-analysis showed that individuals at Clinical high risk (CHR), who are uniquely enriched for risk of psychosis and SCZ, had impairments in both IQ and all cognitive sub-domains, except processing speed, relative to healthy comparison groups (Fusar-Poli et al., 2012b). The CHR includes different subgroups of Attenuated Psychotic Symptoms (APS, characterized by subthreshold psychosis-like positive symptoms, e.g., perceptual and thought disturbances), Brief and Limited Intermittent Psychotic Symptoms (BLIPS, defined by a history of fleeting psychotic experiences that spontaneously resolved within one week) and trait vulnerability plus a marked decline in psychosocial functioning (genetic risk and deterioration syndrome, GRD), and are often described as individuals at Ultra-high risk (UHR), given that this is the age range of highest incidence of psychotic disorders (Yung and Nelson, 2013; Fusar-Poli, 2017). Altogether, studies focusing on the lifespan of SCZ have provided evidence for early childhood cognitive impairments, robust impairment in UHR individuals, and significant cognitive deficits from the first psychosis episode through the course of the disorder (Sheffield et al., 2018). Several original and meta-analytic studies have shown the presence of cognitive deficits in CHR and UHR individuals (Catalan et al., 2021; Chu et al., 2019; Fusar-Poli et al., 2012b; Mayeli et al., 2022; Sheffield et al., 2018; Zheng et al., 2018b), thus indicating that cognitive deficits are already established during the prodromal phases of psychosis and schizophrenia (Bora et al., 2014). Furthermore, several studies have shown that the extent and persistence of cognitive impairments are especially taxing in SCZ when

compared to other psychotic disorders (Daban et al., 2006; Hill et al., 2013; Mollon and Reichenberg, 2018; Schatzberg et al., 2000). It is also important to point out that a strong cognitive impairment is present when schizophrenia is initially diagnosed. The existence of cognitive deficits in the early life of patients with SCZ therefore emphasizes the importance of providing effective interventions for their cognitive dysfunctions, especially early in the course of illness.

In this article, we will first review current evidence of treatment interventions (studies published prior to April 2022), which involve pharmacological and nonpharmacological approaches, for cognitive impairments in SCZ (Fig. 2), including CHR and early course individuals whenever available. We will then describe the limitations and challenges of these treatments. Finally, in the future directions, we will describe novel methods and strategies that are being developed to better address cognitive deficits in at-risk and early course SCZ patients, which may significantly improve their clinical outcomes and overall quality of life.

2. Current interventions for cognitive dysfunction in SCZ

2.1. Pharmacological interventions

Pharmacotherapy is the cornerstone of treatment for psychosis in patients with SCZ, but current antipsychotic drugs have minimal benefit for their cognitive impairments (Keefe et al., 2007). Several pharmacological compounds have been investigated for their potential efficacy in the treatment of cognitive dysfunction in SCZ. Clinical trials of these compounds have produced mixed results with a small to moderate effect size in the improvement of certain cognitive functions in patients (Choi et al., 2013). Commonly investigated compounds, described in detail below and in Fig. 2, include those that target neurotransmitter systems (e.g., glutamate, choline) or focus on neuroprotection, such as antioxidants.

2.1.1. Glutamatergic compounds—The glutamate system is hypothesized to contribute to the etiology and pathophysiology of SCZ, including its cognitive deficits (Moghaddam and Javitt, 2012). Pharmacological strategies to target the glutamate system through enhancement of N-methyl-D-aspartate (NMDA) receptor activity have produced promising but inconsistent findings for the treatment of cognitive symptoms in SCZ (Gargiulo and De Gargiulo, 2014; Hashimoto et al., 2013; Heresco-Levy, 2005). NMDA receptors are ionotropic glutamate receptors, and their activation requires the binding of both glutamate and either glycine or D-serine. In addition to administering these compounds, another strategy to stimulate the NMDA receptor is to increase the availability of glycine by inhibiting the glycine transporter (GlyT1) (Hashimoto et al., 2013). Numerous clinical trials have been performed utilizing NMDA receptor agonists (glycine and D-serine), the NMDA receptor partial agonist, D-cycloserine (Coyle and Tsai, 2004), and GlyT1 inhibitors (e.g., sarcosine and bitopertin) (Chang et al., 2020; Umbricht et al., 2014a). Initial studies showed improvement in cognitive function with NMDA receptor enhancers as an adjunct treatment to conventional antipsychotic drugs (Goff et al., 1999; Heresco-Levy et al., 1996, 1998; Kantrowitz et al., 2010; Tsai et al., 1998). Furthermore, a recent phase 2 trial found that 12 weeks of treatment with a GlyT1 inhibitor, BI 425,809, improved cognition in 509 patients

with SCZ (Fleischhacker et al., 2021). One meta-analysis found significant improvement of cognitive symptoms with glycine, D-serine, and sarcosine (Tsai and Lin, 2010). In contrast, a couple of more recent meta-analyses reported that NMDA receptor-enhancing compounds, including D-cycloserine, D-serine, D-alanine, sarcosine, and glycine, did not significantly improve cognitive symptoms in patients with SCZ (Chang et al., 2019; Iwata et al., 2015); however, subgroup analysis in younger patients (Levkovitz et al., 2009; Liu et al., 2014), were more efficacious and yielded medium effect sizes when assessing improvements in several cognitive domains (Table 1), thus suggesting that glutamatergic compounds may provide greater benefit in the earlier stages of SCZ (Chang et al., 2019).

Memantine is another pharmacological compound targeting the NMDA receptors (Parsons et al., 2007) that has pro-cognitive effects in patients with dementia (Knight et al., 2018) and Alzheimer's disease (Matsunaga et al., 2015), thus making it a potential candidate for the treatment of cognitive dysfunction in SCZ. A meta-analysis demonstrated that, across 8 randomized, placebo-controlled clinical trials, memantine significantly improved cognitive performance in patients with SCZ (Zheng et al., 2018a). Furthermore, recent studies have reported that memantine may be beneficial as an add-on intervention in treatment resistant SCZ by improv verbal recognition memory and paired associate learning in these patients (Veerman et al., 2016), an effect that was sustained over 1 year of treatment (Veerman et al., 2017). Also, Memantine added to clozapine demonstrated therapeutic benefit in patients with treatment-resistant SCZ, including improved cognitive functioning, as reflected by increased mini-mental state exam scores (De Lucena et al., 2009).

Pregnenolone is an endogenous neurosteroid that has been investigated for potential neurocognitive benefit through mechanisms of action that are not fully established but are thought to involve the positive modulation of NMDA receptors through its metabolites (Marx et al., 2011; Wong et al., 2015). Two clinical trials in chronic SCZ patients found that add-on pregnenolone was ineffective in treating cognitive symptoms, as measured by the Measurement and Treatment Research to Improve Cognition in SCZ (MATRICS) (Marx et al., 2009, 2014). In contrast, clinical trials using add-on pregnenolone in early SCZ have suggested that it may ameliorate cognitive deficits, including attention and working memory performance (Kreinin et al., 2017), corresponding to small effect sizes (Table 1). Overall, pharmacotherapy that targets the glutamatergic system via NMDA receptors shows promise for the treatment of cognitive dysfunction in SCZ. However, additional studies are needed to determine whether these pharmacological compounds are indeed effective in significantly improving cognitive impairments in SCZ patients, especially in the earlier stages of illness.

2.1.2. Cholinergic compounds—Compounds that target the cholinergic system, particularly via the α7 nicotinic acetylcholine receptor (nAChR), have also been investigated for the treatment of cognitive deficits in SCZ (Tregellas et al., 2019; Wallace and Bertrand, 2013). α7 nAChR is located on cell bodies and extra-synaptic areas to modulate neuronal activity and pre-synaptically regulate neurotransmitter release (Dani and Bertrand, 2007). In recent years, potential α7 nAChR-targeting compounds, such as tropisetron, ABT-126, and DMXB-A, have advanced to phase 2 and 3 clinical trials with mixed results. The majority of these trials have shown a significant efficacy often α7 nAChR agonists on cognitive symptoms only when looking at nonsmoking SCZ patients (Freedman et al., 2008; Haig

et al., 2016a, 2016b; Shiina et al., 2010; Zhang et al., 2012), whereas trials that did not separate smokers from non-smokers did not find α7 nAChR agonists to be effective for cognition symptoms (Umbricht et al., 2014b; Walling et al., 2016). This may be due to a desensitization effect on α7 nAChR receptors from chronic nicotine exposure (Tregellas et al., 2019). Additionally, an extended-release formulation of an α7 nAChR agonist showed no cognitive effects in both smokers and non-smokers (Kem et al., 2018). Altogether, these studies suggest that α7 nAChR compounds can be beneficial for the treatment of cognitive dysfunction in SCZ, but the benefits of α7 nAChR agonists, the most promising of those compounds, are likely limited to an immediate-release formulation in non-smoking patients.

2.1.3. Modafinil—Modafinil is a drug with widespread effects across neurotransmitter systems (Abi-Dargham et al., 2022) that is reported to improve attention, memory, and executive function in healthy individuals through inhibition of dopamine and norepinephrine transporters, which in turn leads to an increase in dopamine and norepinephrine efflux in several brain regions, including the prefrontal cortex (Minzenberg and Carter, 2008). Modafinil has also been shown to activate glutamate and inhibit GABA in these brain regions (Minzenberg and Carter, 2008), and it can indirectly activate the release of orexin neuropeptides and histamine from the lateral hypothalamus and tuberomammillary nucleus, respectively, all of which may contribute to heightened arousal (Ortiz-Orendain et al., 2019). Modafinil has been utilized in clinical trials as a cognition-enhancing intervention in patients with SCZ (Minzenberg and Carter, 2008). One clinical trial found that a single add-on dose of modafinil improved verbal and spatial working memory measures in patients with first episode psychosis (Scoriels et al., 2012). However, it was not found to significantly impact MATRICS measures in either chronic (Bobo et al., 2011; Kane et al., 2010; Michalopoulou et al., 2015) or early course (Lees et al., 2017) patients with SCZ. It also did not improve cognition in clozapine-treated patients based on a composite cognitive battery score (Freudenreich et al., 2009). Together, modafinil's cognitive effects in SCZ have been inconsistent, which may depend on the type of cognitive test utilized in the different studies (Yamada et al., 2019).

2.1.4. Antioxidants—Increased oxidative stress, and its interaction with neuroinflammatory processes, are thought to play an important role in the etiology of SCZ (Do et al., 2015). Animal models have further shown that interventions that reduce oxidative stress during periods of increased neuroplasticity (e.g., puberty) may be effective as early intervention treatments (Cabungcal et al., 2014; Gomes et al., 2016). For example, juvenile antioxidant treatment with N-acetylcysteine (NAC) significantly improved cognitive inflexibility (Maas et al., 2021) and pre-pulse inhibition deficits (Cabungcal et al., 2014) in rodent models of SCZ. Nutritional supplements that have antioxidative and anti-inflammatory properties, such as the glutathione precursor and NAC, have thus been examined as potential adjunctive treatments for SCZ. A meta-analysis of seven clinical trials of NAC treatment in patients ranging from early psychosis to chronic SCZ (Breier et al., 2018; Conus et al., 2018) found that NAC significantly improved the clinical symptoms, including working memory deficits and processing speed (with both improvements yielding small effect sizes, see Table 1), in these patients (Yolland et al., 2019). Building on the promising findings, additional clinical studies are needed to determine whether NAC

can represent a viable pharmacological option to improve cognitive dysfunction in SCZ, including in the early stages of the disorder.

2.1.5. Antipsychotics—While the role of antipsychotic compounds for CHR and UHR individuals remains unclear (Zhang et al., 2020), for people presenting with early course SCZ, antipsychotic treatment confers a range of benefits, including possible cognitive improvements. Prior work supports this finding, from the NIMH-funded clinical antipsychotic trials of intervention effectiveness study to large trials in early stages of SCZ, including recent metanalytic evidence (Keefe et al., 2007; Ohi et al., 2022; Trampush et al., 2015). However, it should be noted that these improvements in cognition may result from pseudo-specificity of cognitive enhancement secondary to amelioration of ross early psychotic illness will be crucial for determining the role of antipsychotic drugs in the therapeutic approach to cognitive dysfunction. Also, examining any cognitive improvement with novel, non-D2 receptor blocking antipsychotic drugs, such as xanomeline, lumateperone, and ulotaront will be needed (Brannan et al., 2021; Correll et al., 2020; Koblan et al., 2020).

Altogether, the pharmacological treatments discussed here have generally been assessed in chronic SCZ patients, when these interventions may be less effective, whether due to illness phase-specific pathophysiology (Krystal and Anticevic, 2015) or the influence of chronic drug exposure (Tregellas et al., 2019). Therefore, additional preclinical studies in neurodevelopmental animal models are needed to clarify the influence of these compounds on the development of neural circuits (Floresco et al., 2005; Sonnenschein and Grace, 2021a). Furthermore, future clinical studies in early course SCZ and at-risk individuals will be critical in determining whether these compounds may represent early, effective treatment interventions for cognitive dysfunction in SCZ throughout the course of illness.

2.2. Non-pharmacological interventions

2.2.1. Cognitive remediation therapy (CRT)—Cognitive remediation therapy (CRT) can be defined as “a training-based behavioral intervention that aims at improving cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goal of durability and generalization” (Wykes et al., 2011). CRT protocols vary in cognitive domains trained (i.e., attention, memory), sensory modalities utilized (i.e., visual, auditory, multi-sensory), and format of delivery (i.e., computerized, group-based, therapist lead). Additionally, CRT protocols can differ in strategies used, such as drill-and-practice training programs aimed at bottom-up training frameworks targeting lower-level cognitive processes versus top-down training approaches that emphasize the engagement of higher-order cognitive functions (e.g., problem solving, working memory) (Fig. 2).

Within the past several decades, a growing body of work has evaluated the efficacy of CRT in rectifying various cognitive dysfunctions in patients with SCZ. Across protocols, the most recent and comprehensive meta-analysis of CRT in SCZ, conducted in patients at different stages of illness and clinical conditions, identified 130 randomized controlled trials reporting 146 CRT vs. control intervention comparisons (Vita et al., 2021). Consistent with prior reports (Wykes et al., 2011), this meta-analysis found small to moderate effects of CRT on

global cognition and functioning, with smaller effects on clinical symptom severity. CRT demonstrated similar efficacy across the seven cognitive domains assessed by the MATRICS battery with smaller effects on attention and larger effects on verbal memory (Nuechterlein et al., 2004). In following a recent expert consensus on the four core elements of CRT in SCZ (Bowie et al., 2020), Vita and colleagues further demonstrated that: (1) the inclusion of an active and trained therapist and (2) the use of a structured development of cognitive strategies had a significant positive impact on cognitive and functional outcomes; whereas (3) repeated practice and (4) techniques facilitating the transfer of cognitive skills into real-world settings transfer were not beneficial (Vita et al., 2021). The same study, though, showed that the transfer technique integrating CRT with psychiatric rehabilitation had a significant positive impact on functioning, and the inclusion of all 4 core elements had the most positive impact on both cognitive and functional outcomes in patients with SCZ.

Concerning the effectiveness of CRT in SCZ across the different stages of illness, a systematic review and meta-analysis of CRT in early-course SCZ reported a positive, albeit small effect on global cognition, with specific improvements within the MATRICS domains of processing speed, working memory, and reasoning/problem solving (Revell et al., 2015) corresponding to small effect sizes (Table 1). A subsequent comprehensive review on CRT echoed this notion, reiterating the efficacy of CRT on cognitive outcomes in early-course and high-risk populations (Lewandowski, 2016). Since the publication of these reviews, nine additional randomized controlled trials (RCTs) assessing the efficacy of CRT (versus a control condition) have been conducted in first episode/early course SCZ patients. Of those RCTs, seven demonstrated significant improvements in cognitive functioning, including verbal memory (Chong et al., 2021; Vidarsdottir et al., 2019), verbal learning (van Duin et al., 2021), working memory (Chong et al., 2021; Nuechterlein et al., 2020; Vidarsdottir et al., 2019), visual memory (Cellard et al., 2016), processing speed (Chong et al., 2021; Loewy et al., 2021), attention (Cellard et al., 2016; Wojtalik et al., 2021), and social cognition (Wojtalik et al., 2021) with different effect sizes (see Table 1). Additionally, four studies demonstrated significant improvements in social (Ventura et al., 2019; Wojtalik et al., 2021) and occupational/educational (Nuechterlein et al., 2020; van Duin et al., 2021) functioning, and two demonstrated improvements in clinical symptoms, including positive symptoms (Loewy et al., 2021) and negative symptoms pertaining to social-emotional processes (Ventura et al., 2019). Most of the CRT interventions were administered simultaneously with, or integrated into, existing mental health services, potentially accounting for the one report of non-superiority to treatment as usual (Garcia-Fernandez et al., 2019). Given the high degree of service utilization in this population, the evidence suggests a potential confounding effect of other, more traditional interventions on the effects of CRT. At the same time, other interventions, including peer social interactions (Sandoval et al., 2019), meta-cognitive skills training (Breitborde et al., 2017), or aerobic exercise (Nuechterlein et al., 2016b) can have additive effects to CRT. Furthermore, when assessing the CRT effectiveness in different stages of SCZ, initial studies reported a greater response to CRT in early-stage vs. chronic groups (Bowie et al., 2014; Corbera et al., 2017; Deste et al., 2019; Vita et al., 2013). However, more recent work found no effect of illness duration on CRT outcomes, suggesting similar therapeutic effects of CRT throughout the course of SCZ (Lewandowski, 2016; Revell et al., 2015). Together, there

is clear evidence for the efficacy of CRT in early-course of illness, including first-episode populations; nonetheless, the added efficacy of CRT in these populations is clouded by other simultaneous interventions and the superiority of CRT in the early (vs. late) stages of illness needs to be further established.

Recent work has also begun to evaluate the efficacy of CRT in CHR populations, given that neurocognitive decrements during the UHR phase may predict functional outcomes and the transition to psychosis (Bolt et al., 2019). As such, the at-risk state represents a critical period for early intervention to maximize long-term functional outcomes. The most recent comprehensive review of CRT in UHR populations identified six reports (Glenthoj et al., 2017), of which four found cognitive improvements in verbal memory, attention, and processing speed (Choi et al., 2017; Hooker et al., 2014; Loewy et al., 2016; Rauchensteiner et al., 2011) with varied effect sizes ranging from small to large (see Table 1), and two reported improved functional outcomes in social functioning and adjustment (Choi et al., 2017; Piskulic et al., 2015). Notably, none of these studies demonstrated positive impacts on clinical symptoms, reiterating the rather selective impact of CRT on cognition and functioning. Two more recent RCTs have assessed the efficacy of CRT (versus control) in CHR populations. Friedman-Yakoobian et al., 2020 demonstrated improvements in social functioning and social cognition following an integrated neurocognitive and social cognitive training in a CHR population, yielded a large effect size (Table 1); however, no improvements in neurocognition were seen due potentially to the focus of the implemented training on social cognition, as well as to poor adherence rates (Friedman-Yakoobian et al., 2020). Glenthoj et al., 2020 demonstrated difficulties with the acceptability and feasibility of a different CRT integrating general neurocognitive remediation with standard treatment in a UHR population, potentially accounting for their lack of effect on cognition, functioning, or clinical symptoms (Glenthoj et al., 2020). However, some improvements in facial emotion processing speed immediately after the intervention, as well as better executive functioning and visual memory performances at the 12-month follow-up, were observed. Together, evidence for the efficacy of CRT in CHR populations is less clear, due in part to the limited acceptability and feasibility as well as to a high degree of heterogeneity within this population with regards to cognitive and functional performance (Glenthoj et al., 2020).

In addition to evaluating the impact of CRT on the cognitive and functional outcome measures, a growing body of literature has been examining its effects on the neural mechanisms underpinning cognitive outcomes, following CRT. It has been argued that these neurophysiological processes may be more sensitive and provide greater insight into the heterogeneity of response to CRT (Hochberger et al., 2019). To date, CRT has targeted a range of both lower-level and higher-order cognitive processes, with purported mechanisms ranging from early sensory processing (Javitt, 2009) to higher-order neural networks supporting executive functioning and working memory (Minzenberg et al., 2009; Perlstein et al., 2001). A recent activation likelihood estimation meta-analysis echoed this notion, identifying the insula and the thalamus associated with bottom-up sensory processing and frontoparietal regions supporting executive control and working memory as brain regions most implicated in response to CRT (Ramsay and MacDonald, 2015). Specific interest has been placed in the bottom-up impacts of auditory processing on verbal learning and memory (Adcock et al., 2009; Javitt, 2009). Hochberger et al., 2019 (Hochberger et al., 2019)

demonstrated that auditory-based targeted cognitive training resulted in a normalization of the auditory mismatch negativity and P3a event-related potential components, previously identified as markers of early auditory information processing that are disrupted in SCZ (Light et al., 2015). This normalization of auditory processing predicted later improvements in verbal learning and decreased positive symptom severity, identifying a potential neural mechanism supporting the response to targeted cognitive training that can be used to predict or improve clinical response. Concerning top-down regulation of cognition, special interest has been placed in the higher-order neural systems supporting working memory (Perlstein et al., 2001), as well as the impact top-down organizational strategies have on visual episodic memory (Cellard et al., 2016; Reeder et al., 2017). Specifically, the dorsolateral prefrontal cortex (dlPFC), which is implicated in working memory, memory retrieval, and emotional processing, has been repeatedly identified as a responder to CRT (Eack et al., 2016; Keshavan et al., 2017; Subramaniam et al., 2014), although more recent meta-analytic approaches have revealed broader neural networks implicated in CRT response, likely due to the modality of intervention and/or the targeted cognitive processes (Mothersill and Donohoe, 2019).

Taken together, the integration of neuroimaging in CRT research has yielded novel targets for treatment response indicators, as well as informed the advocation for early intervention (Puig et al., 2020). Indeed, despite heterogeneity in cognitive and functional outcomes in at-risk populations, there is an indication that early intervention with CRT may have neuroprotective effects on gray matter loss that is associated with better cognitive performance (Eack et al., 2010; Ramsay et al., 2017), and can regulate brain regions and associated neural networks implicated in these core cognitive processes. Moreover, the heightened neural plasticity in younger individuals suggests a sensitive period when CRT can have the most robust effect (Keshavan et al., 2014).

2.3. Physical exercise

Over the past decades, there has been increasing interest in physical exercise interventions, such as aerobic training and yoga, as an add-on approach for treating SCZ patients (Fig. 2). Although the focus of exercise intervention has been on improving the quality of life of these patients and mitigating their negative and positive symptoms, some studies have shown positive effects on global cognitive functioning (Acil et al., 2008; Mittal et al., 2017). Following an initial meta-analysis that reported no significant effects of exercise on different cognitive domains (Dauwan et al., 2016), a more recent, comprehensive meta-analysis revealed that exercise had a positive impact on cognition and significantly improved working memory, social cognition, and attention/vigilance (Firth et al., 2017). While most of those studies were conducted in chronic patients, three studies have assessed the effects of physical exercise on cognition in individuals with early course SCZ. In Hallgren's study, 91 first-episode psychosis outpatients underwent a 12-week supervised circuit-training program consisting of high-volume resistance exercises, aerobic training, and stretching (Hallgren et al., 2019). Using the Cogstate Brief Battery and Trailmaking tests, the authors reported significant post-intervention improvements in processing speed, visual learning, and visual attention, yielded small effect sizes (Table 1); although exercise frequency did not affect any cognitive outcomes (Hallgren et al., 2019). Lin et al. examined the impact of aerobic

exercise and yoga on 140 female first episode psychosis individuals (Lin et al., 2015). The authors found significant improvements in verbal acquisition, working memory, and attention in patients doing yoga exercise, and verbal retention and working memory in patients performing aerobic exercise, using Hong Kong List Learning, Digit Span forwards and backwards, and Letter Cancellation tests (Lin et al., 2015), yielded medium to large effect sizes (see Table 1). Nuechterlein et al. compared the effect of combining CRT with aerobic exercise and assigned 7 patients with a recent onset of SCZ to CRT and Exercise and 9 to CRT alone for a 10-week period. Their results showed a larger effect size in overall cognitive function, and especially in social cognition and working memory domains, assessed by MATRICS for combined CRT and exercise patients when compared to cognitive training alone (Nuechterlein et al., 2016a).

2.4. Neuromodulation

There has been a significant, growing body of literature demonstrating the potential therapeutic efficacy of various neuromodulatory approaches in schizophrenia (Fig. 2). Neurostimulation techniques, including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have demonstrated efficacy in engaging underlying neural processes and improving related cognitive functions (Aleman et al., 2018; Hasan et al., 2016; Kostova et al., 2020), with weaker evidence supporting the efficacy of neurofeedback on cognitive outcomes (Gandara et al., 2020). Specifically, 65% of reviewed tDCS studies demonstrated significant improvements in cognition, with most studies employing frontal stimulation to target either working memory or cognitive control/attention processing (Kostova et al., 2020). Similarly, while the majority of TMS intervention studies in SCZ had cognitive measures listed as secondary outcomes, with clinical parameters being the primary outcomes, there is evidence that repetitive TMS (rTMS) can improve visual and verbal memory, particularly when utilizing prefrontal stimulation (Aleman et al., 2018; Hasan et al., 2016). Like tDCS and rTMS, neurofeedback studies in SCZ have demonstrated efficacy in upregulating the targeted neural circuitry, although more work is needed to show whether non-invasive brain stimulation (NIBS) approaches can systematically improve related cognitive outcomes (Gandara et al., 2020).

Notably, despite data indicating the efficacy of NIBS in younger patients (Aleman et al., 2018), only one study has assessed the utility of it in early-course psychosis (Francis et al., 2019). Specifically, Francis et al. found significant improvements in general cognitive functioning both immediately and two weeks after bilateral prefrontal rTMS with small to medium effect sizes, as shown in Table 1, and these improvements were associated with baseline cortical thickness (Francis et al., 2019). While promising, additional studies are necessary to demonstrate the effectiveness of NIBS in high-risk and early-course populations. As these neuromodulation techniques are thought to induce neuroplasticity, future work will help elucidate the utility of early NIBS interventions to improve prognosis by protecting against progressive neural and cognitive decline over the course of SCZ. Also, as neuromodulation has been shown to augment the neural mechanisms underlying cognitive processes, studies integrating CRT with neuromodulation may provide a synergistic, augmentative effect (of neuromodulation) on the outcomes of CRT interventions in high-risk and/or early-course patient populations (Jahshan et al., 2017).

Note: Cohen's effect size or Hedge's g values for each intervention (pre- vs. post-intervention) were reported whenever any of the reviewed studies included either of those values. Otherwise, Hedge's g was calculated and reported for the studies wherein the mean and standard deviation of cognitive performance were provided for baseline and after-intervention assessments.

3. Discussion

In this study, we provided a narrative review of the most relevant findings of cognitive interventions in SCZ patients, emphasizing pre-emptive interventions in early-course and CHR individuals when these studies were available (Table 1). The most promising findings were observed when using CRT in both early-course and chronic patients, which resulted in an improvement in verbal learning, working memory, and social cognition in these patients. Even though the effects of illness duration on CRT outcomes have yet to be fully elucidated, early intervention should help the patients since cognitive deficits are present during the first episode of illness and even before the initial manifestation of full-blown psychosis in at risk states. It should be noted that around 25% of individuals at high risk developed psychosis within 3 years (de Pablo et al., 2021), and that this number is significantly higher than the prevalence of SCZ in the general population (less than 0.5%) (Pacific and Hasan, 2022). Also, several original and meta-analytic studies showed the presence of cognitive deficits in those individuals (Fusar-Poli et al., 2012b; Mayeli et al., 2022; Zheng et al., 2018b) and showed that cognitive deficits are already established before the prodromal phases of psychosis (Bora et al., 2014). Since, the focus of this study was pre-emptive cognitive interventions in SCZ, we included studies in CHR and UHR in this narrative review. Among pharmacological findings, compounds enhancing NMDA receptor activity have led to improvement in cognitive function, including in attention and working memory domains, in both early course and chronic patients. Neurostimulation and physical exercise have been utilized more recently, but several studies have provided some encouraging results about the potential of these interventions to enhance cognition in SCZ, although more evidence is needed, especially in individuals in the early stages of the disorder.

4. Challenges

Physical injuries are typically easy to diagnose. In contrast, cognitive deficits can have a more subtle onset and manifestation, which is often hard to recognize without using precise assessments. Cognitive alterations are one of the predictors of transition to psychosis and functional outcome in SCZ. Therefore, people working in mental health, from school psychologists, social workers, primary care physicians, and psychiatrists, should be aware of the importance of cognitive alterations. Cognitive dysfunctions should be properly recognized and targeted to change the trajectory of illness in individuals with SCZ. In case of diagnosis of cognitive deficits even at an early age, improving education for family members, teachers, school personnel, including psychologists and social workers, would be paramount (Fig. 3). Furthermore, a critical role can be played by pediatricians and child psychiatrists that should be more aware of how cognitive dysfunctions, especially if mild to moderate, may represent heralding signs of major psychiatric disorders, including SCZ, and should be promptly addressed. Additionally, people with severe disabilities such as SCZ

often encounter challenges when seeking effective, affordable, and accessible mental health care. Due to the severe burden of SCZ on patients and public health, it is crucial to provide accessible and affordable resources for early diagnosis and interventions for individuals who are at high risk for or in the early course of the disease.

5. Future directions

5.1. Promoting plasticity in the at-risk and early stages of SCZ

The high-risk period prior to the emergence of overt psychosis involves widespread deficits across multiple cognitive domains (Bora et al., 2014). Although cognitive impairment is often present years before the onset of psychosis (Keefe, 2014), it may be less severe in the early stages of the prodromal period compared to first episode patients (Simon et al., 2007). The goal of early intervention treatments is to limit the progressive decline in functioning that occurs over the course of SCZ. The early intervention strategy has growing support from preclinical research. Preclinical studies have suggested that early intervention with certain compounds, such as those that target the glutamatergic system or reduce oxidative stress, have the potential to prevent the emergence of phenotypes relevant to SCZ (Cabungcal et al., 2014; Gomes et al., 2016; Sonnenschein and Grace, 2021b). Indeed, subgroup analyses of clinical trials have provided additional support that pharmacological compounds targeting the glutamatergic system may be most effective in the early stages of SCZ (Chang et al., 2019; Kinon et al., 2015). Future clinical trials that specifically focus on the early stages of SCZ are therefore needed to confirm this possibility (Fig. 3). To date, preciously few clinical studies have examined early intervention pharmacotherapy in the clinical high risk period, where it is especially critical to prioritize candidates that are well tolerated, possess the minimal risk of adverse effects with long-term treatment, and have the potential to address psychiatric difficulties that impact functioning, regardless of transition to SCZ (Fusar-Poli et al., 2012a; Sommer et al., 2016; Thompson et al., 2015). Furthermore, capitalizing on the neural plasticity associated with an earlier age, including development and adolescence/young adulthood, when SCZ spectrum disorders tend to emerge and manifest themselves for the first time (Rapoport et al., 2005), neuromodulation has been identified as a potential therapeutic intervention to rectify these pathological processes. Specifically, neuromodulation-based early intervention at the neural level may be able to offer neuroprotective effects against later brain and related cognitive abnormalities (Hadar et al., 2018). To this end, further research is needed to investigate the effect of neurostimulation on CHR individuals and early stages of psychosis patients. Finally, one important type of intervention worth investigating in future studies is promoting habit formation. This would be especially helpful in relation to exercise, as achieving habitual, more automatic performance of activities may have the potential to bypass some of the cognitive limitations of working memory and attentional resources usually observed in patents with SCZ (Glisky, 2007).

5.2. Employing digital health technologies

We have seen rapid global growth in accessibility and capabilities of digital health technologies (DHTs) in the past few years, including recent developments in smartphone apps, virtual reality, social media, and chatbots (Torous et al., 2021). DHTs provide

a unique opportunity for using those technologies to remote monitor the patients, give timely treatment, and improve treatment decisions. Beyond monitoring the patient, DHTs can play an essential role in delivering time-sensitive intervention strategies due to the easy accessibility and cost-effectiveness. Despite some positive cognitive effects of such technologies in general SCZ patients (Clarke et al., 2019), because they are relatively new and undeveloped in potential, future research involving larger sample sizes and lower risks of bias is required for evaluating their effectiveness in both first and multiple episodes patients (Fig. 3).

5.3. Promoting multidisciplinary approaches and combined treatment interventions

In the past two decades, a team-based, multi-element approach to treating early-course psychosis, known as Coordinated Specialty Care (CSC) in the United States and Specialized early interventions (SEI) internationally, has been increasingly implemented worldwide. Despite the broad array of services provided, and although positive symptom-related and illness-related treatment outcomes have been reported (Correll et al., 2018), cognitive assessment and treatment are not a systematic part of these team-based programs. Cognitive health is crucial for SCZ treatment and should therefore be included in CSC and SEI programs. Furthermore, a coordinated specialty care framework can be extended for individuals at-risk for psychosis and SCZ to offer pre-emptive interventions (Fusar-Poli et al., 2017). Along with promoting multidisciplinary approaches, future efforts should be placed on combining treatment interventions for cognitive dysfunctions in SCZ. Specifically, randomized clinical trials combining pharmacological therapy or neuromodulation techniques with other cognitive-enhancing interventions will be critical to examining the synergistic effects of such interventions above and beyond the positive impact of each of them separately (Fig. 3). As proposed by Jahshan et al. (2017), targeting the underlying neurophysiological processes supporting cognition, either indirectly via exercise or directly via neurostimulation or pharmacotherapy, may foster neuroplasticity that, in turn, could facilitate cognitive remediation (Jahshan et al., 2017). In this regard, a recent review paper provided beneficial evidence for combining neurostimulation with cognitive therapy in psychiatric disorders and highlighted the paucity of these types of studies in patients with SCZ (Sathappan et al., 2019).

6. Conclusion

In sum, over the past three decades, several pharmacological and nonpharmacological approaches have been developed to improve cognitive function in SCZ patients. Despite deficits in several cognitive domains being present in the early stages of SCZ, as well as even several years before the first episode of psychosis, most of the studies conducted so far have examined the effectiveness of cognitive intervention in chronic SCZ. Furthermore, while we currently have a better understanding of the neural and molecular mechanisms underlying cognitive dysfunctions in SCZ, ranging from neurotransmitter imbalance to altered neural activity implicating different brain networks, much more needs to be established, especially in relation to the development and first occurrence of these neurobiological abnormalities. By characterizing the neurobiological underpinnings of cognitive dysfunctions and performing pre-emptive intervention in at-risk and early course

SCZ patients, future studies will have the potential to dramatically improve the prognosis and overall quality of life of these individuals.

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Abbreviations:

SCZ	Schizophrenia
IQ	Intelligence Quotient
CHR	Clinical High Risk
APS	Attenuated Psychotic Symptoms
BLIPS	Brief and Limited Intermittent Psychotic Symptoms
UHR	Ultra High Risk
NMDA	N-methyl-d-aspartate
nAChR	α7 nicotinic Acetylcholine Receptor
CRT	Cognitive Remediation Therapy
RCTs	Randomized Controlled Trials
dlPFC	dorsolateral Prefrontal Cortex
TMS	Transcranial Magnetic Stimulation
tDCS	transcranial Direct Current Stimulation
rTMS	repetitive TMS
NIBS	Non-Invasive Brain Stimulation

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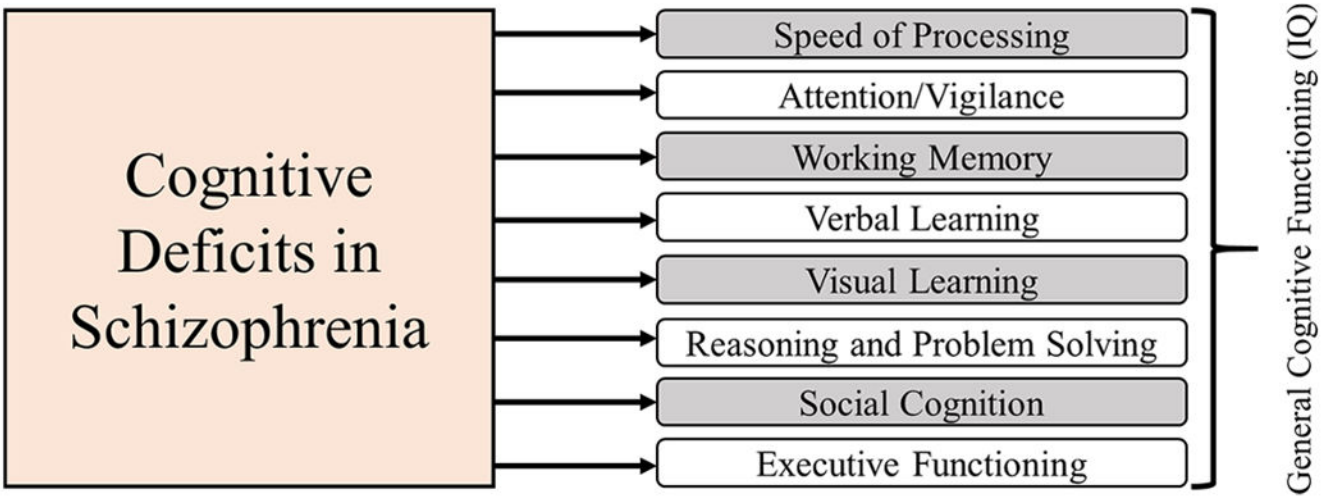

Fig. 1.
Cognitive deficits in Schizophrenia patients include specific domains and general cognitive functioning.

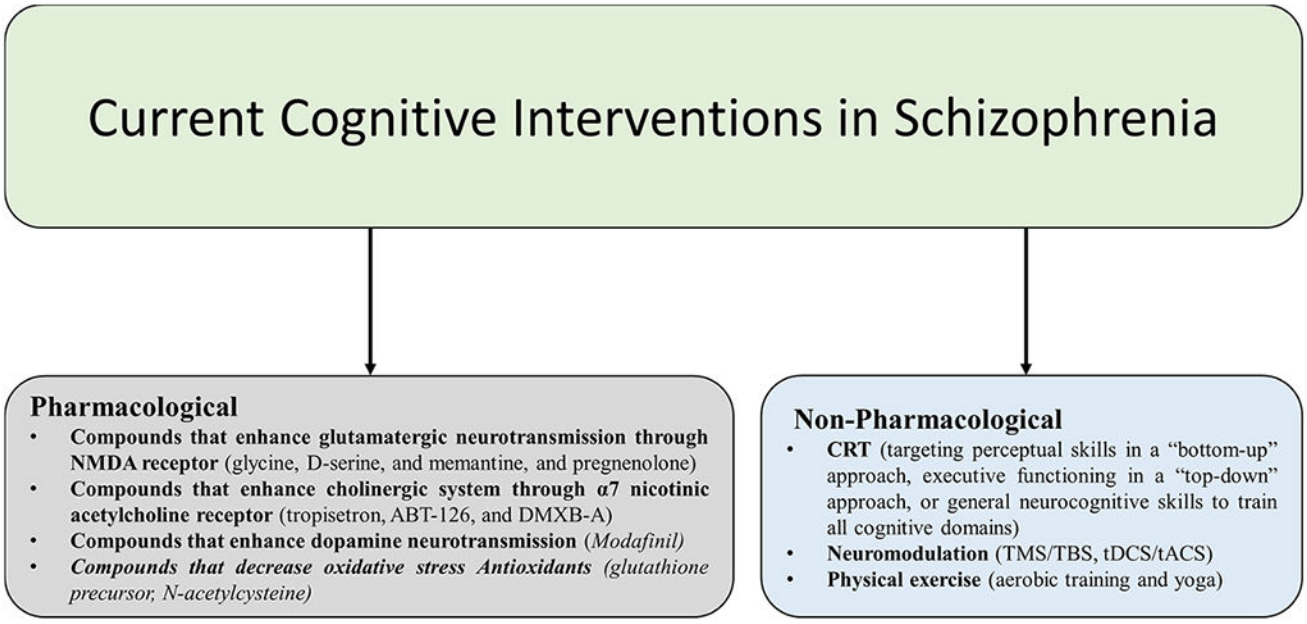

Fig. 2.
Current interventions for cognitive dysfunction in Schizophrenia.

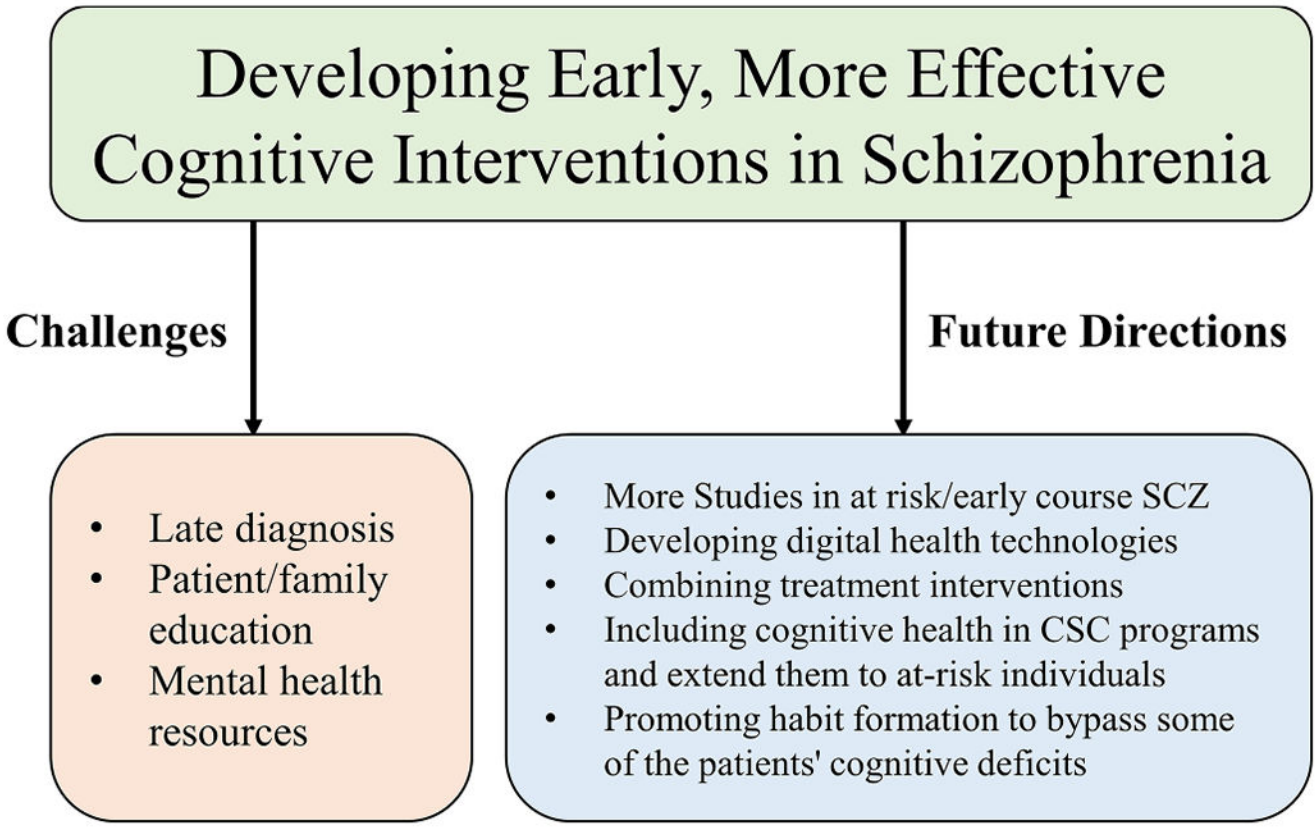

Fig. 3.
Challenges and future directions for pre-emptive cognitive interventions in Schizophrenia.

Table 1

Summary of characteristics of cognitive intervention studies in early course SCZ patients and at-risk for psychosis individuals.

Intervention	Study	Sample Size	Clinical Group	Intervention Details	Cognitive outcomes (versus control)
Pharmacological	(Levkovitz et al., 2009)	36 received minocycline, 18 received placebo	Early Psychosis	Patients were randomly assigned to either the minocycline or placebo groups in a 2:1 ratio. They underwent the 22-week add-on phase with minocycline or placebo (200 mg/d) being added to their atypical antipsychotic medication.	Minocycline improved cognitive functioning, mainly in executive functions (working memory [spatial working memory error; Hedges's g = −0.57], cognitive shifting [Intra-dimensional/ Extra-dimensional (ID/ED) Set Shift task-post-extradimentional errors; Hedges's g = −0.74], and cognitive planning [Stocking of Cambridge problems solved; Hedges's g = 0.66]).
	(Liu et al., 2014)	46 received minocycline, 46 received placebo	Early Psychosis	This was a 16-week, double-blind, randomized, bi-center, and placebo-controlled study. Patients were randomized to receive either 200 mg per day of minocycline or a placebo as additional therapy in a 1:1 ratio.	There was no significant difference between the seven cognitive domains assessed by MATRICS Consensus Cognitive Battery, except for the attention domain (Hedges's g = 0.56).
	(Kreinin et al., 2017)	29 received pregnenolone 31 received placebo	Early Psychosis	Patients were randomized to an 8-week, double-blind, randomized, placebo-controlled, 2-center trial. Participants received either pregnenolone (50 mg/d) or placebo added to antipsychotic medications.	Pregnenolone augmentation demonstrated significant amelioration of the visual attention deficit (matching to sample visual search [number correct; Hedges's g = 0.41]) in patients.
	(Lees et al., 2017)	46 EC-SCZ and 28 HC (Some received placebo, some modafinil, the exact number was not reported)	Early Psychosis	A double-blind, randomized placebo-controlled crossover design was used to compare the effects of modafinil in participants with early SCZ and related disorders and in matched healthy controls.	There was no significant effect on any cognitive domains in SCZ.
	(Breier et al., 2018)	30 received NAC, 30 received placebo	Early Psychosis	The study was a 52-week, double-blind, 1:1 randomization of placebo or the antioxidant N-acetylcysteine (NAC) (3600 mg/ day).	No cognitive improvements.
	(Conus et al., 2018)	32 received NAC 31 received placebo	Early Psychosis	The study was a 6-months, randomized, placebo-controlled, double-blind, 2-center trial comparing the antioxidant N-acetylcysteine (NAC) and placebo as add-on therapy to standard medication (antipsychotics, mood stabilizers, and/or benzodiazepine). All participants were randomized in a 1:1 allocation ratio to either NAC effervescent tablets (900 mg) at a dosage of 2700 mg/day (morning: 1800 mg; evening: 900 mg) or matching placebo tablets before meals.	Cognitive performance was assessed by MATRICS Consensus Cognitive Battery. Significant improvements were found in favor of NAC on neurocognition (processing speed; Hedges's g = 0.35).
Cognitive Remediation Therapy (CRT)	(Hooker et al., 2014)	14 CHR received CRT vs.	At-Risk	40 h/8 weeks of computer-based CRT in a single group of CHR participants. Exercises were	Cognitive performance was assessed by MATRICS Consensus Cognitive

Intervention	Study	Sample Size	Clinical Group	Intervention Details	Cognitive outcomes (versus control)
		14 Healthy controls		engaging computer games from two programs, the first targeted cognition, and the second one targeted social cognition.	Battery. Improved processing speed (Cohen's d effect size = 0.63); a trend toward improved visual learning/ memory (Cohen's d effect size = 0.54) and global cognition (Cohen's d effect size = 0.45).
	(Piskulic et al., 2015)	18 subjects received CRT, and 14 received a control intervention	At-Risk	The 40 h of the Brain Fitness Program (BFP, which involved auditory training exercises or computer game (for control group) activity, was expected to occur 4 days a week, over a period of 10–12 weeks.	A trend towards improvement in speed of processing (MATRICS Consensus Cognitive Battery; speed of processing) between baseline and 9-month follow-up (Hedges's $g = 1.39$) and at post-CRT compared to 9-month follow-up (Hedges's $g = 2.33$).
	(Glenthoj et al., 2017) (A systematic review)	Six studies; 324 subjects received CRT	At-Risk	This study systematically reviewed the evidence on the effectiveness of cognitive remediation in the ultra-high-risk population.	4 studies found cognitive improvements in verbal memory (Loewy et al., 2016; Rauchensteiner et al., 2011), attention (Rauchensteiner et al., 2011), and processing speed (Choi et al., 2017; Piskulic et al., 2015), and 2 reported improved functional outcomes in social functioning and adjustment (Choi et al., 2017; Piskulic et al., 2015).
	(Friedman-Yakoobian et al., 2020)	20 subjects were treated with CRT, and 18 subjects underwent a control intervention	At-Risk	6-month social cognitive and neurocognitive remediation intervention, including computer-based cognitive enhancement exercises, social cognitive group, individual coaching sessions, and online cognitive training exercises.	Improvement in social cognitive measures (global functioning social; Hedges's $g = 1.92$), but no improvements in neurocognitive.
	(Glenthoj et al., 2020)	73 subjects underwent CRT, and 73 received a control intervention	At-Risk	Total of 20 weeks of neuro- and social cognitive remediation, including intervention, consisted of manualized cognitive remediation comprising group training and social cognitive training.	No Global neurocognition improvement. Some specific improvements in facial emotion recognition processing speed immediately after the intervention, as well as improvements in executive functioning and visual memory at 12-month follow-up.
	(Rauchensteiner et al., 2011)	10 CHR and 16 SCZ patients underwent CRT	At-Risk and SCZ	Both groups were treated with a standardized computer-based cognitive training named Cogpack (which contains structured neurocognitive exercises grouped into themes, such as attention, memory, speed of apprehension, visual motor, and reaction) for 10 sessions (within a maximum of 4 weeks).	Long-term memory functions and attention after cognitive training improvement (verbal memory test, continuous performance test in two trials; Hedges's $g = 1.08$, and identical pairs version performance (hits), subtask 'shapes'; Hedges's $g = 0.71$) in prodromal patients, whereas in the group of patients with SCZ, no improvement occurred.
	(Revell et al., 2015) (A meta-analysis)	Eleven studies; 320 subjects underwent CRT, and 295 subjects received a	Early Psychosis except for one study, which also	This study systematically reviewed CRT trials in early SCZ to determine its efficacy on global cognition, functioning, and symptoms.	Improvement in the verbal learning and memory domain (Cohen's d effect size = 0.23) and an almost significant effect on the

Intervention	Study	Sample Size	Clinical Group	Intervention Details	Cognitive outcomes (versus control)
		control intervention	included a proportion of ultra-high-risk patients		social cognition domain (Cohen's d effect size = 0.30) and working memory (Cohen's d effect size = 0.19) along with processing speed (Cohen's d effect size = 0.19).
	(Ventura et al., 2019)	39 subjects received CRT, and 41 subjects received a control condition	Early Psychosis	The Cognitive Remediation Program included computerized cognitive training and a Bridging Group to facilitate generalization in a psychiatric rehabilitation program context. The computerized sessions involved 2 h per week of in-clinic CRT for a 6-month period, followed by once a week of CRT during months 7–9 and then CRT every other week during months 10–12.	Improvement in social functioning assessed by UCLA social attainment survey.
	(Vidarsdottir et al., 2019)	25 subjects underwent CRT and 24 received a control intervention	Early Psychosis	CRT was conducted twice per week over a 12-week period and consisted of 10–12 participants and four therapists. Three cognitive remediation approaches were used: Neuropsychological Educational Approach to Remediation, Compensatory Cognitive Training, and Social Cognition and Interaction Training.	The intervention group showed significant improvements in verbal memory (assessed using the Wechsler Memory Scale, 3rd edition Logical Memory immediate recall total score, delayed recall total score, immediate theme total score and delayed theme total score; Cohen's d effect size; between 0.29 and 0.45), cognitive flexibility (assessed using Trails B; Cohen's d effect size = 0.04), working memory (assessed using digit span working memory; Cohen's d effect size = 0.17), ToM (assessed using the Hinting task; Cohen's d effect size = 0.54), and a significant reduction in hostile attributions (assessed using the Ambiguous Intentions Hostility Questionnaire-Ambiguous items; Cohen's d effect size = 0.52), compared to the control.
	(Nuechterlein et al., 2020)	29 subjects received CRT and Medication and 31 subjects took Medication without CRT	Early Psychosis	Participants completed a 12-month randomized controlled trial of cognitive remediation and of long-acting injectable (LAI) risperidone. Cognitive remediation involved programs focused on basic cognitive processes as well as more complex, life-like situations. Healthy behavior training of equal treatment time was the comparison group for cognitive remediation, while oral risperidone was the comparator for LAI risperidone in a 2 × 2 design.	Superior overall cognitive (assessed by MATRICS Consensus Cognitive Battery total score; Hedges's g = 1.01) and work/school functioning improvement in cognitive remediation group. Cognitive improvement was significantly correlated with work/school functional improvement.
	(Chong et al., 2021)	109 first episode psychosis (of which 92 completed the	Early Psychosis	24-session CRT using Cogpack (which contains structured neurocognitive exercises grouped into themes, such as attention, memory, speed of apprehension,	Significantly improvement on the majority of the measures, including verbal memory, digit sequencing, and symbol coding.

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		study) received CRT		visual motor, and reaction) and Neuropsychological Educational Approach (which stresses short- and long-term goals that require patients to be insightful and motivated) were delivered over a period of 3 months, with two sessions per week in a group with a maximum of five clients in a session.	
	(Loewy et al., 2021)	80 subjects received CRT and 65 subjects underwent a control condition	Early Psychosis	8-week targeted auditory training consists of computerized exercises designed to improve speed and accuracy of auditory information processing while engaging auditory and verbal working memory as a cognitive remediation therapy vs. control condition; computer games in a double-blind randomized trial was assessed.	Significant improvement in global Cognition (Hedges's g = 0.47) and Problem-Solving (Hedges's g = 1.03). Speed of Processing improved at trend level significance (Hedges's g = 0.41).
	(van Duin et al., 2021)	34 subjects underwent CRT and 39 received a control intervention	Early Psychosis	The 40 sessions, 3 times a week web-based intervention program consisted of tasks targeting attention, memory, and planning. The program aimed to improve cognition through repetitive training (drill), learning strategies (strategy), and improving metacognition.	There was a significant beneficial effect of adjunctive CRT on executive functioning (assessed by Wisconsin Card Sorting Task nonperseverative errors; Hedges's g = 1.13) and subjective cognitive functioning (assessed with the Cognitive Failure Questionnaire; Hedges's g = 0.34).
	(Wojtalik et al., 2021)	58 subjects underwent CRT, and 44 subjects received a control condition	Early Psychosis	The CRT consisted of overall 18-months- 60 h of weekly computer-based neurocognitive training to improve attention, memory, and problem-solving and 45 small-group sessions to improve social cognition. The control group underwent individualized psychotherapy that utilized components of the basic and intermediate phases of personal therapy.	Improved overall cognition, social cognition, and attention/vigilance.
Physical Exercise	(Lin et al., 2015)	48 integrated yoga therapy group, 46 aerobic exercise group, and 46 waitlist control group	Early Psychosis	The 12 weeks intervention programs included integrated yoga therapy and aerobic exercise (walking and cycling).	Both types of exercise improved working memory in early psychosis patients (assessed by digit span test [forwards and backwards test]; Cohen's effect size ranging from 0.59 to 1.08), with yoga having a larger effect on verbal acquisition (Cohen's effect size of 0.97 compared to 0.83) and attention than aerobic exercise (assessed by letter cancelation test; Cohen's effect size of 0.69 compared to 0.22).
	(Nuechterlein et al., 2016a)	7 subjects had CRT and Exercise and 9 subjects had only CRT	Early Psychosis	Participants participated in 10-week interventions. CRT was used as coordinated sequences of neurocognitive and social cognitive exercises designed to enhance basic discrimination and processing skills and then generalize to more complex	Improvement in the MATRICS Consensus Cognitive Battery composite score for CRT&E patients and being higher relative to CRT patients (Cohen's effect size =0.48).

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				stimuli. The CRT & Exercise group also participated in an aerobic conditioning program for 30 min at the clinic 2 days/week and at home 2 days/week	
	(Hallgren et al., 2019)	91 Participants went through physical exercise program	Early Psychosis	Patients received usual care plus a 12-week supervised circuit-training program, consisting of high-volume resistance exercises, aerobic training, and stretching.	Significant post-intervention improvements were seen for processing speed, visual learning, and visual attention; all with moderate effect sizes (Hedges's g = ranging from 0.47 to 0.49).
Neuromodulation	(Francis et al., 2019)	10 repetitive transcranial magnetic stimulation (rTMS) and 10 Sham sessions	Early Psychosis	The effect of rTMS on cognitive function in early phase psychosis was tested. The subjects underwent 10 sessions of high frequency, bilateral, sequential rTMS targeting the dorsolateral prefrontal cortex over two weeks.	Improvement in overall cognition score (Brief Assessment of Cognition [BACS] total score; Hedges's g = 0.47), and motor speed (BACS token motor; Hedges' s g = 0.60).