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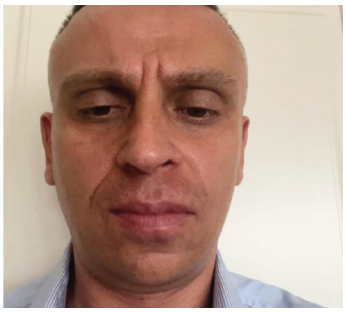
Review



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New strategies to improve cognitive symptoms in schizophrenia

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Summary

Cognitive impairment has a key role in schizophrenia outcome: both neurocognitive and social cognitive deficits are related to severe functional disability. As a matter of fact, cognitive deficits seem to explain 20-60% of the variance of everyday functioning. In order to restore cognitive deficits in schizophrenia, different pharmacological and non-pharmacological approaches were developed. Whereas pharmacological interventions include approved treatments and under-study molecules, non-pharmacological interventions include cognitive remediation, non-invasive brain stimulation techniques and physical activity. The aim of the present narrative review is to provide a comprehensive overview of the current available treatments for cognitive impairment in schizophrenia, focusing on pharmacological treatments and cognitive remediation techniques. Our purpose is to increase the knowledge and to understand the principles and methodology of these interventions, also highlighting the evidence of their effectiveness. Findings show that promising results were achieved in this field, but more research is needed to develop specific treatments to improve cognitive symptoms in schizophrenia.

Key words: antipsychotics, cognitive function, cognitive remediation, recovery, schizophrenia, treatment

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Introduction

Cognitive impairment, in past decades, has been consistently reported in patients with schizophrenia. Neurocognitive disability appears early in the course of the disease, even in prodromal phases, and these deficits are widely present in different stages of the illness whether in patients and in their first-degree family members [1]. In 2004, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project has identified seven distinct cognitive domains that are impaired in patients with schizophrenia: speed of processing, attention/vigilance, working memory, verbal and visual learning, reasoning and problem solving and social cognition [2]. Moreover, in the third meeting of the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) project, it was cleared that six areas of cognitive domains are damaged in patients with schizophrenia: perception, working memory, attention, executive functions, long-term memory and social cognition [3]. Regarding social cognitive deficits, they include impairments in facial affect recognition, in perceiving and interpreting social cues, in theory of mind (ToM) and in the ability to make appropriate causal attributions for events. Several studies have shown

that both neurocognitive and social cognitive deficits are among the major causes of severe functional disabilities in patients with schizophrenia and they are also related to a worse outcome of the disorder. In a comprehensive literature review, Green et al. [4] underlined that different cognitive deficits might have an impact on specific areas of psychosocial functioning. As a matter of fact, cognitive deficits seem to explain 20-60% of the variance of everyday functioning [5]. A more recent meta-analysis by Halverson et al. [6] explored relationships between functional outcome in schizophrenia spectrum disorders and different domains of neurocognition and social cognition. Overall, this work confirmed associations between social cognition, neurocognition, and functional outcome showing significant small-to-medium effect sizes. Similar associations between neurocognition and social cognition with functional outcome were detected also in the early stages of illness and in first episode patients (FEP). The influence of cognitive reserve as a mediator between cognitive domains and function in FEP was shown by Amoretti et al. [7] and by Gonzalez-Ortega et al. [8]. The influence of cognition on functional outcomes may happen through its influence on functional capacity, the ability to perform critical everyday living skills. Thus, functional capacity may actually be considered as a proxy measure between neurocognition and everyday functioning and it has been found to be quite strongly associated to cognitive performance [9]. Recent studies have shown how cognitive impairment predicts functional outcome even more than positive and negative symptoms and how it is associated with disability in phases of clinical remission too [1,10]. From the greater and detailed knowledge of the role and meaning of cognitive impairment in schizophrenia, its improvement became an essential target in the treatment and in the clinical management of the illness. In order to restore cognitive deficits in schizophrenic patients, there are different pharmacological and non-pharmacological approaches developed. Whereas pharmacological interventions include approved treatments (e.g. antipsychotics and antidepressants) and under-study treatments, non-pharmacological interventions include cognitive remediation, non-invasive brain stimulation techniques and physical activity techniques [11-14].

This review will focus on the analysis of various pharmacological treatments and cognitive remediation techniques, as regards non-pharmacological interventions. We decided to not include other non-pharmacological (eg, aerobic physical exercise) and / or somatic (e.g. brain stimulation) techniques potentially effective, or at least promising, for improving cognitive functioning in schizophrenia. Our aim is to increase the knowledge and understanding of the principles and methodology of these interventions for schizophrenia and to highlight the evidence of effectiveness of such interventions deriving from the current scientific literature.

Pharmacological treatment to improve cognitive functioning in schizophrenia

Cognitive functioning in schizophrenia: focus on treatment management

An important prerequisite for the success of cognitive enhancement interventions in schizophrenia is the stabilization of symptoms through an optimal use of antipsychotics and other psychotropic medications. An ideal pharmacotherapy includes a global assessment, an integrated care plan, and careful attention to therapeutic alliance, in addition to an appropriate choice of the medication(s), adherence, evaluation of comorbidities, and side effects. Avoiding unnecessary or excessive use of medications, as well as reducing the use of drugs with possible negative cognitive effects (for example, anticholinergics), could lead to cognitive benefits [15].

Cognitive functioning in schizophrenia: focus on metabolic profile

The relationship between cognition and the metabolic side effects of antipsychotic medications is complicated. The available literature regarding this topic is sparse, but it suggests a relationship between metabolic comorbidities and worse cognitive function in patients with schizophrenia [16]. Generally, the impact of the metabolic syndrome on cognitive functions is more pronounced in patients with severe negative symptoms. Meta-analyses have further confirmed the effects of metabolic syndrome and type II diabetes mellitus (T2DM) as determinants of poor overall cognition in schizophrenia [17]. Better cognitive performance at baseline has also been associated with a favorable metabolic profile at follow-up in schizophrenia [18]. Individual metabolic syndrome constituent components may exert distinct effects on specific cognitive domains in schizophrenia. For example, a higher waist circumference has been correlated with decreased motor speed and attention/vigilance, while hypertension and elevated triglycerides have been associated with poorer verbal memory. This relationship appears to be very important, considering the increased risk of developing metabolic syndrome in schizophrenic patients.

Cognitive functioning in schizophrenia: focus on first- and second-generation antipsychotics

Treatment with antipsychotics in schizophrenia is often limited to the reduction of positive symptoms, while negative symptoms and cognitive impairment may persist throughout life. First-generation antipsychotics (FGAs), especially, have relatively little influence on cognitive and negative symptoms and may cause adverse side effects, such as extrapyramidal motor symptoms (EPS), tardive dyskinesia, weight gain and sedation. More specifically, FGAs treatment seems to improve certain executive functions on the short period, but there is a decline

relative to baseline of moderate to large effect size (ES) on the long period and, finally, long-term treatment with FGAs can cause cognitive deterioration as a side effect [19]. More specifically, in the randomized NeSSy trial, second-generation antipsychotics (SGAs) presented an advantage over FGAs in cognitive function during medium-term treatment for schizophrenia. Findings also highlighted a distinction between progression to the harmful effects of FGAs with prolonged treatment as opposed to more persistent cognitive benefits with SGAs treatment [19]. This is in line with recent findings from meta-analysis studies on neuroimaging and antipsychotics in schizophrenia patients [20]. SGAs drugs may partially improve cognitive dysfunction, which may be related to their relatively high affinity for serotonin 5HT2A receptors compared with D2 receptors [21]. The apparent cognitive enhancement may be related to one or more of the following effects of atypical antipsychotics agents, not shared by FGAs: increased release of dopamine (DA) and acetylcholine (ACh) in the prefrontal cortex (PFC) and hippocampus; antagonism of 5-HT2A, 5-HT2C or 5-HT6 receptors and stimulation of 5-HT1A receptors. An increased release of DA may particularly lead to stimulation of D1 and D3 receptors, with a possible beneficial effect on cognition, assuming that these receptors are under-stimulated in schizophrenia [22]. An increased release of Ach might lead to enhancement of M1, M4, or α7 nicotinic acid post-synaptic receptors, all of which have been indicated as potentially involved in cognitive impairment in schizophrenia. However, cognitive improvements observed with SGAs may reflect an avoidance of potentially deleterious effects associated with FGAs rather than a specific enhancement of cognition [23]. A meta-analysis by Woodward et al. [24] demonstrated that SGAs improved overall cognitive function to a greater extent than FGAs. McGurk et al. [25] demonstrated a significant improvement in several cognitive domains (selective attention, executive functioning, verbal learning and memory and verbal fluency) in partial responders to FGAs antipsychotics who had been switched to olanzapine. Furthermore, Wang et al. [26] reported that olanzapine could significantly improve short-term memory, immediate memory and memory quotient in first-episode schizophrenic patients. Some findings suggest that aripiprazole may offer advantages over olanzapine in improving neurocognitive function [27]. In an independent systematic review, Houthoofd et al. [28] reported positive effects of risperidone on neurocognitive function in patients with schizophrenia and schizoaffective disorder in processing speed, attention/vigilance, verbal and visual learning and memory and in reasoning and problem-solving. However, the effect of risperidone on social cognition in patients with schizophrenia remains controversial due to conflicting results [29]. Amisulpride seems to improve verbal fluency performance, attention and working memory, with particular benefits on this last one when associated to aripiprazole [30]. Clozapine improves significantly attention and verbal fluency, but only modestly executive functioning and delayed recall [24]. Carpenter et al. [31] reported small advantages of SGAs compared to FGAs in terms of cognitive performance. As shown above, the studies that have focused on the possible differential effects of specific SGAs were not conclusive. In this regard, although a meta-analysis on SGAs effect on cognitive functioning in patients with schizophrenia was able to detect some interesting preliminary results, these were mostly controversial, not showing any uniform effect of each SGAs on cognitive profile [32]. Moreover, a recent meta-analysis on the effect of SGAs subcategories on the cognitive profile of patients with schizophrenia, based upon the chemical structure (the *-pines*, and the *-dones*), showed that the cognitive effect of the two SGAs categories was overall comparable (significant, with a small ES), and there were no clear evidences that the pattern of cognitive effects was different between the two SGAs subtype [33].

On the other hand, given that individual SGAs show different pharmacological profiles and that cognitive function consists of different domains, it is possible that the effects on cognitive function may differ among drugs. This is in line with results from a network meta-analysis study that found SGAs different effects on distinct cognitive domains in schizophrenia patients. In particular, quetiapine, risperidone, and olanzapine had better effects on the overall cognitive profile than amisulpride and haloperidol, but when a single cognitive domain was considered, quetiapine, risperidone and olanzapine were better than amisulpride on executive functions, quetiapine was better than other antipsychotics on attention and processing speed, followed by ziprasidone and olanzapine, and ziprasidone was better than amisulpride and haloperidol on memory [34].

In this perspective, a recent and comprehensive meta-analysis of the effects of antipsychotic treatment on cognitive performance found a favorable effects for amisulpride, quetiapine, lurasidone, olanzapine, perphenazine, risperidone, sertindole, and ziprasidone, with small differences between molecules in different cognitive domains [35]. Inferior effects were observed for remoxipride, clozapine and haloperidol, outperformed by placebo in most cognitive domains, as well as in the composite global cognitive score. Another meta-analysis depicting cognitive effects of SGAs compared to placebo underlined a small significant pro-cognitive for these compounds [36]. Lastly, treatment with antipsychotic medication is associated with moderate improvement in cognitive performance in schizophreniform disorder and in FEP patients [34].

Cognitive functioning in schizophrenia: focus on long-acting injectable (LAI) antipsychotics

Several studies observed an improvement in the cognitive functioning switching from oral formulation of antipsychotics to a long acting injectable (LAI) formulation. For example,

switching from oral risperidone to risperidone LAI (R-LAI) seems to improve verbal memory [37], with a significantly greater mean changes from baseline on the STM-COMET memory scanning test and memory filtering test. Switching from oral risperidone to R-LAI may affect motor processing function and attention improvement efficacy by allowing the dosage of anti-Parkinson's medications (such as biperiden, an anticholinergic drug) to be reduced. The benefits about switching from an oral therapy to a LAI one are also shown in another study, where patients who switched from oral risperidone to paliperidone LAI showed greater improvements in attention and processing speed compared to those who continued on risperidone [38]. As for the oral formulation, second-generation LAI appear to be better on the cognitive profile also if compared to the first-generation LAI. For example, comparing haloperidol decanoate with R-LAI, patients whose therapy was switched to second-generation LAI exhibited significant improvement in memory, executive function, motor processing function, and attention. Also in these cases, a possible explanation could be that FGAs determine EPS more often than SGAs and, for this reason, their use can lead to the coadministration of anti-Parkinson's medications; this association is known to result in cognitive dysfunction [39]. These observations seem confirmed also in the comparison between first-generation LAI and other second-generation LAI: for example, switching to aripiprazole LAI seems to be associated to a better cognitive function in verbal memory, working memory, verbal fluency, and executive function [40]. Different results were found in a more recent meta-analysis that compared oral and LAI formulations of antipsychotics on a wide range of outcomes, such as: efficacy, effectiveness, hospitalizations, adverse events, cognition, functioning and quality of life. In particular, while LAI were found to be superior to oral formulations in terms of risk of hospitalizations and relapse, no significant differences were observed regarding cognitive performance [41].

Cognitive functioning in schizophrenia: focus on antidepressants

In major depressive disorder (MDD), antidepressants are generally associated with beneficial effects on cognitive impairment, which may be mediated at least in part by the improvement obtained in affective symptoms, making it a partially indirect effect. Interventions targeting multiple neurochemical systems simultaneously (e.g. serotonin-norepinephrine reuptake inhibitor, SNRIs, such as duloxetine) might be more likely to improve cognitive performance than treatments targeting only a single system (e.g. selective serotonin reuptake inhibitor, SSRIs, such as escitalopram) [42]. Furthermore, vortioxetine seems to improve cognitive symptoms in MDD through its multimodal action, in particular on different serotoninergic receptors which may modulate glutamatergic neurotransmission [43]. For these reasons, several clinical studies have evaluated the effects of antidepressants on cognitive performance in schizophrenia. In preliminary studies, selective serotonin reuptake inhibitors (SSRIs) seem not to have any effects on cognitive functions, while bupropion, a noradrenaline and dopamine reuptake inhibitor, showed an improvement in attention tests [44]. Moreover, mirtazapine seems to improve visual-spatial ability and general mental speed/attentional control and mianserin added to FGAs showed improvements on memory and learning skills [45]. Unfortunately, a meta-analysis which evaluates the effect of antidepressant augmentation of antipsychotics for the treatment of cognitive deficits in schizophrenia, found no clinically meaningful improvement in any cognitive domain or the composite score [46]. In line with these results, a recent meta-analysis [47], considering the effects of adjunctive fluvoxamine, and a Cochrane Collaboration meta-analysis [48], focused on adjunctive mirtazapine, observed no significant pro-cognitive effect of the antidepressant drug. These findings suggest that, in patients with chronic schizophrenia, cognition does not appear to be significantly improved by the enhancement of serotonergic or noradrenergic neurotransmission on top of antipsychotic. However, antidepressants have been found in some studies to significantly reduce negative symptoms, but also depressive symptoms in schizophrenia patients with a comorbid MDD [49].

Cognitive functioning in schizophrenia: focus on new pharmacological targets

The exact mechanism of cognitive dysfunction in schizophrenia is still debated, but the most supported hypotheses are the glutamatergic, cholinergic, GABAergic, and histaminergic ones [50]. Consequently, a number of GABAergic agents have been studied to stimulate cognition in schizophrenia. Precisely, a dysfunction of γ-aminobutyric acid (GABA) interneurons has been suggested in the pathophysiology of schizophrenia, as the result of a reduction of GABA interneuron density in the frontal cortex and, consequently, an imbalance between excitation and inhibition in the cerebral cortex. According to the "GABA hypofunction" theory, a developmental deficit of inhibitory GABA interneurons may underlie neurodegeneration through an excessive activation of glutamatergic neurons [51]. Moreover, an imbalance between excitatory and inhibitory (E-I) activity, induced by low activity of glutamatergic projections and GABA interneurons in the prefrontal cortex, may lead to impaired working memory in schizophrenia [52]. To correct the "E-I imbalance", new compounds has been developed to treat negative symptoms and cognitive deficits, as the agonists of the glycine site of N-methyl-D-aspartate (NMDA) receptor, DA-D1 receptor, metabotropic glutamate receptor and 5-HT1A receptors [53]. Clinical evidence suggests that serotonin 5-HT1A receptor agonists improve cognitive deficits in schizophrenia, through the correction of the E-I imbalance via the suppression of GABA neural function.

Several compounds have been developed to influence GABA activity, but most of these compounds have failed to demonstrate neurocognitive benefits in large clinical trials [54].

The effects of glutamatergic agents on cognitive deficits have also been investigated. Glutamate is the major excitatory neurotransmitter in the central nervous system and its receptors include NMDA and AMPA receptors. NMDA receptor antagonists, such as ketamine and phencyclidine, can produce clinical and cognitive symptoms of schizophrenia in healthy individuals, leading to the hypothesis that the NMDA receptor could be involved in the pathophysiology of psychosis [55]. Several clinical trials have examined the neurocognitive enhancement benefits of a group of amino acids that act as glutamate agonists by binding to the glycine site on NMDA receptors. These NMDA receptor agonists include glycine, D-cycloserine, and D-serine but none of the currently published studies produced evidence about their benefits on neurocognition: in an initial exploratory study, a single dose of D-cycloserine improved performance on a delayed recall task, but later studies were not able to replicate this finding. Conversely, glycine has shown a beneficial effect as an adjunctive agent to antipsychotics for negative and cognitive symptoms.

Cholinergic agents act on the central cholinergic system, which innervates a diverse range of cortical and subcortical structures, interacting through coordinated acetylcholine (ACh) release with nicotinic and muscarinic receptors. The once common practice of co-administering anti-cholinergic and antimuscarinic agents to schizophrenic patients treated with FGAs to reduce EPS side effects, used to determine a worsening in cognitive impairments [56]. In healthy subjects, the acute administration of anti-muscarinic agents can produce cognitive impairments that mimic the deficits observed in schizophrenic patients [57]. Significant reductions in the expression of M1 and M4 receptors have been consistently reported in the post-mortem brains of schizophrenic patients in regions linked to cognitive function, including the hippocampus, frontal and prefrontal cortex, superior temporal gyrus and the anterior and posterior cingulate cortex. Conversely, the expression of M2 and M3 receptors has been reported as unaltered in the brains of patients with schizophrenia across a number of cortical regions [58]. In accordance with this evidence, it has been suggested that a dysfunctional muscarinic system is contributing to the symptoms of schizophrenia and might represent a therapeutic target. In this regard, clozapine was the first atypical antipsychotic to show nootropic attributes inducing mild improvements across a number of cognitive functions, including learning and memory, eventually attributed to its effects on the muscarinic system [59]. Galantamine is a competitive and reversible cholinesterase inhibitor that also acts as a M1 muscarinic acetylcholine receptor agonist or a modulator of at α4 and α7 nicotinic receptors, and has been used primarily in the treatment of early-stage of vascular dementia and Alzheimer's disease: this drug produced neurocognitive benefits in schizophrenic patients [60]. The five muscarinic receptors share considerable orthosteric binding site homogeneity, while they present a secondary allosteric binding site, which is substantial heterogeneous and became the target for most recently developed drugs. Positive allosteric modulators (PAMs) are a class of allosteric agonists that increase the receptor's affinity for ACh at the orthosteric binding site and consequentially potentiate the receptor's response to Ach. BQCA and PQCA [61,62] are strong, highly selective M1 receptor PAM reported to produce pro-cognitive responses, including enhancing memory function and increasing spontaneous prefrontal brain activity in preclinical trials. In addition to antipsychotic-like qualities, the M4 receptor PAM, VU0467154 and VU1052100 have been reported to enhance cognition [63]. However, more investigations are required to determine the suitability of muscarinic PAMs as new treatments against psychotic and cognitive symptoms in schizophrenia patients.

Development strategies of nicotinic agents mostly focused on the α7-subtype of the nicotinic acetylcholine receptor because of a variety of factors: the genetic links between this subunit and schizophrenia, its high expression rates in key cognitive processing areas (e.g., hippocampus, thalamus, and prefrontal cortex) and the evidence of a decreased expression in post-mortem studies on patients' brains [64]. The α7 nicotinic acetylcholine receptors (α7 receptors) have been shown to play an important role in cognition and have potential therapeutic applications in cognitive impairment in schizophrenia as well as in Alzheimer's disease. Encenicline demonstrated clinically meaningful improvements in cognition and functioning in patients with schizophrenia, whereas varenicline, an α7-subtype of the nicotinic acetylcholine receptor agonist originally approved for smoking cessation, and tropisetron, a 5-HT3 receptor antagonist and α7-subtype of the nicotinic Ach receptor partial agonist approved as antiemetic agent, showed the same inconsistent effects on cognition in schizophrenia [65]. Several cognitive enhancers approved for Alzheimer's Disease, such as antidementia agents (donepezil, rivastigmine, galantamine and memantine), have been tested for their potential to improve cognition in schizophrenia. Unfortunately, cognitive deficits in schizophrenia and in Alzheimer's disease are determined by different mechanisms, as recent findings suggest [66]. Studies on the acetylcholinesterase inhibitors, such as donepezil, rivastigmine and galantamine, gave mixed [67] or negative results [68] in schizophrenia patients. Memantine, usually prescribed as neurocognitive enhancer in Alzheimer's disease, has several mechanisms of action. Although memantine may have possible procognitive effects in schizophrenia patients [69], it does not appear to produce any benefit when added to atypical antipsychotic therapy [70].

Oxytocin is a hypothalamic peptide contributing to maternal infant bonding. Several smaller studies

were done evaluating the effects on social cognitive functioning of this molecule administered intranasally in people with schizophrenia. Further testing is needed to explain whether oxytocin has therapeutic potential for social cognitive deficits and/or negative symptoms in schizophrenic patients [71].

Guanfacine, atomoxetine and reboxetine, three noradrenergic compounds, have been evaluated for their hypothetical procognitive benefits in people with schizophrenia; however, in published clinical trials, all of them have demonstrated a lack of efficacy in this population [72].

Some published studies on serotoninergic agents have evaluated tandospirone, buspirone and ondansetron. However, no study has suggested robust procognitive effects of these compounds [73].

Following the hypothesis that inflammation plays a role in the pathogenesis of schizophrenia, several drugs targeting neuroinflammation and oxidative stress were studied. In fact, increased rates of schizophrenia were observed after infectious events, such as maternal exposure to flu and upper respiratory infections. Studies revealed that in pregnant women, an augmented expression of inflammatory cytokines in the second trimester increased the risk of schizophrenia in their offspring [74]. Viral exposure can reduce the density of receptors relevant for neurocognition, such as D1 receptors in the frontal areas and NMDA receptors in the hippocampus, it can decrease protein kinase B expression and impair axonal integrity [75]. Levels of proinflammatory cytokines, such as interleukin IL-6, are elevated in schizophrenia and have been shown to influence specific brain regions, including prefrontal cortex, medial temporal regions and long-term potentiation in the hippocampus [76]. IL-6 increases oxidative stress, which may interfere with the expression of inhibitory GABA interneurons and impact executive functioning: levels of C-reactive protein (CRP), an inflammatory biomarker, are associated with neurocognitive deficits, but not necessarily with symptom severity in people with schizophrenia [77]. Neuroinflammation indirectly slows neurogenesis, synaptogenesis and dendritic growth as it impacts the activity-dependent transport of brain-derived neurotrophic factor (BDNF), a neuroplasticity-regulating protein. Given their impact on neurocognition, neuroinflammation and oxidative stress are potential targets for psychopharmacological enhancement of neurocognition. Minocycline, a broad-spectrum antibiotic, is a long-acting tetracycline traditionally prescribed as treatment of bacterial infections. There has been recent interest about possible anti-inflammatory, anti-oxidative and neuroprotective benefits of minocycline in people with neurodegenerative disorders and in people with schizophrenia [78]. In this context, also acetylsalicylic acid (aspirin), traditionally used as an analgesic and an antipyretic medication, has gained recent interest as an anti-inflammatory agent in schizophrenia [78]. Particular attention has been paid to the anti-inflammatory properties of simvastatin and rosuvastatin; however, evidences are sparse [79].

Also, interest emerged about the possible pro-cognitive effect of modafinil, a stimulant drug marked as a "wakefulness-promoting medication", that has a yet unclear mechanism of action, but it appears to show therapeutic effects by increasing the expression of histamine in the hypothalamus [80]. Modafinil activates glutamatergic circuits while inhibiting GABA and seems to act as a dopamine agonist, inhibiting the reuptake of dopamine by binding to the dopamine reuptake transporter. In some studies, modafinil was shown to improve attention, memory and executive functioning in people with schizophrenia; however, several studies found no benefits of this agent [81,82].

Omega-3 fatty acids are known to be essential for normal cortical expansion and maturation and functional integrity during prenatal and postnatal phases and during adult development. It has been demonstrated that omega-3 fatty acids may be beneficial to decrease the risk of a frank psychotic disorder in ultra-high-risk individuals, suggesting possible neuroprotective effects [83]. However, very few clinical studies on omega-3 fatty acids have examined their neurocognitive benefits.

Some studies demonstrated that the adjunctive use of N-Acetylcysteine, a precursor of glutathione with antioxidant effects, improves negative symptoms of schizophrenia, and appears to have a neuroprotective effects and to regulate glutamatergic pathways by acting on the redox/glutathione sensitive site of the NMDA receptors, D-serine [84], although there was no direct examination of its neurocognitive benefits [85].

Cannabis sativa is the most widely used drug in the world. It contains over 70 different constituents, including delta-9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD). CBD can interfere with the detrimental actions of Δ9-THC in terms of psychotic proneness and cognitive dysfunction [86]. On the other hand, CBD is a particularly interesting target as a novel approach for cognitive improvement in schizophrenia, in part, due to its strong anti-inflammatory properties. CBD has the potential to limit Δ9THC-induced cognitive impairment and to improve cognitive function in different pathological conditions, but there is limited evidence investigating the therapeutic efficacy of CBD as treatment for cognitive deficits in schizophrenia [87]. However, evidences suggesting cognitive improvement in neurological disorders with CBD treatment emerged [88].

Non-pharmacological interventions to improve cognitive functioning in schizophrenia: focus on cognitive remediation

New non-pharmacological interventions to improve cognitive symptoms in schizophrenia are under study, with the ultimate goal to also obtain a better functional outcome [89]. These interventions, including cognitive

remediation (CR) approaches, are enclosed in a positive light and they are grounded in a recovery rather than deficit model [90]. This new interest is based on the factors associated with an improved quality of life, such as the ability to enjoy social and familial interactions, the advance in educational endeavours and performing well at work. The underlying theoretical framework of these improvements comes from the modern neuroscientific knowledge, which supports the idea that brain would be able of changes and development throughout lifespan [91]. According to this perspective, psychosocial interventions base their theoretical principles on the concept of cerebral plasticity and neurogenesis [13]. As stated by different scientific theories, the development of skills can occur at any age and can help to advance or to restore the brain capacity for improving cognitive and social performance [91]. Learning in an appropriately stimulating environment can help the patient to benefit from brain malleability and to improve functioning [92]. In the next paragraph we will present a definition of CR interventions and their general principles and features. Then we will review the main results reported in recent meta-analyses regarding the efficacy of CR treatments in experimental conditions as well as their effectiveness "in the real world", underlining also the potential neurobiological correlates of the effects of CR in patients with schizophrenia. We will also review current evidence of possible benefits deriving from CR in the early course of schizophrenia and in subjects "at risk" of psychosis.

What is cognitive remediation and how does it work?

One of the first definitions of CR was "the therapeutic process of increasing or improving an individual's capacity to process and use incoming information in order to allow increased functioning in everyday life". This includes methods to train and restore cognitive function and compensatory techniques. More recently, during Cognitive Remediation Experts Workshop (CREW), the definition of CR for schizophrenia became "a behavioural training-based intervention that aims to improve cognitive processes (attention, memory, executive functions, social cognition or metacognition) with the goal of durability and generalization" [93]. According to those experts, "the effectiveness of this training is enhanced when provided in a context (formal or informal) that gives support and opportunity for extending everyday functioning" (Florence, April 2010). As mentioned above, CR bases its theoretical principles on the concept of cerebral plasticity and neurogenesis. Sure enough this intervention, when carried out in a stimulating context, seems to facilitate the development of the brain plasticity [92]. CR strategies can be distinguished into two main models: compensatory and restorative [94]. The treatments based on compensatory strategies try to bypass or to eliminate the specific cognitive deficit, using the subject residual cognitive abilities. On the other hand, the restorative methods use the capacity of the brain to develop and repair itself throughout life-time; these strategies are based on knowledge about neuronal plasticity, working with the aim to correct a specific deficit repairing the specific underlying compromised function. Furthermore, restorative remediation strategies utilize two different approaches: bottom-up or top-down [95]. Bottom-up approaches start with the remediation of basic neurocognitive skills (e.g. attention) and advance to more complex skills (e.g. problem solving). Quite the opposite, top-down approaches use more complex skills with the aim to enhance single and specific neurocognitive domains. Therefore, some restorative strategies take advantage of the use of drill and practice exercises in order to restore cognitive functions and, possibly, to improve neuronal plasticity. On the other hand, other techniques are based on the implementation of new strategies and tend to favour the generalization in different contexts through the execution of different tasks that involve the use of similar strategies [94]. In this context, some CR programs focus on a specific cognitive deficit (e.g. attention or ToM), whereas others work on multiple cognitive domains and are more comprehensive. It is undoubtedly possible that all the above mentioned CR strategies would be complementary and synergic and that the potentiation of specific target functions may favour the development of new compensatory strategies of problem solving, which could be applied and could influence the patient's daily life [96,97]. Structure and frequency of sessions and duration of treatment programs can also vary across the different interventions [98]; CR techniques can be advocated as a package that provides a standard set of exercises or it may be personalized only to target deficits identified in the single individual [99]. To reach the established objectives, CR employs several learning strategies: errorless learning, scaffolding, positive reinforcement, massed practice and information processing strategies [100]. Errorless learning inhibits the implicit encoding of errors, which cannot then be differentiated from correct information by explicit recall. Scaffolding is similar to errorless learning in ensuring a high degree of success for the learner and minimising errors, by carefully regulating the complexity of material to be learnt. The trainee is encouraged to use previously established areas of competence, whilst help is provided with new aspects of learning. Massed practice consists in the practice of a repeated exercise (at least 2-3 times per week) in order to encourage the upkeep and application of the skills developed. Information processing strategies involve verbalization, information reduction, breaking and simplifying the task into smaller steps, providing written prompts, chunking, self-monitoring, mnemonic strategies, categorization, organization and planning. These strategies are otherwise applied to various level in different methods of CR, depending on whether they are primarily based on repeated execution of specific tasks or on the implementation of new strategies. A few factors have influence on a positive treatment response for CR training, such as training of the therapist, motivation of the patient,

type and intensity of training and cognitive resources at baseline [96]. In past decades, a number of CR techniques have been developed and adopted in multimodal treatment approaches in schizophrenia: computerized and non-computerized, designed for individual or group settings. The main structured protocols of cognitive training for schizophrenia are described in Table I. At the same time, many authors investigated the efficacy on CR in patients with schizophrenia. In the next paragraph we will analyse the principal results about this topic.

Cognitive remediation: focus on social and non-social cognition

Starting from the definition of CR, we know that one of the aims of these behavioural training-based interventions is to improve cognitive processes, that are recognized as the most important predictors of functional outcome and quality of life in people with schizophrenia [112]. Various published meta-analyses support the efficacy of CR for enhancing cognitive outcomes. Nevertheless, the first results that we can find from the literature are controversial. In two independents reviews, Kurtz et al. [113] and Twamley et al. [114] underlined that CR programmes have effective components that hold promise for improving cognitive performance (with a medium or large ES). On the other hand Pilling et al. [115], in a first review based on few studies, reported that CR had no benefit on attention, verbal memory, visual memory, planning, cognitive flexibility or mental state and concluded that CR did not appear to confer reliable benefits for patients with schizophrenia and could not be recommended for clinical practice. After the earliest reviews, it was developed a rich body of literature that well established that CR is effective in reducing cognitive deficits with long-term benefits in schizophrenia [113,114,116,117]. All these reviews find a moderate ES of CR programmes in improving neurocognitive deficit. The results about cognition acquire robustness when CR is associated with psychiatric rehabilitation: this combination led to significant favourable outcomes for global cognition [118]. One of the most important meta-analyses of the available controlled studies of CR in schizophrenia performed by Wykes et al. [117] including 40 studies and about 2.000 patients, showed a moderate improvement in overall cognitive performance (more effective when patients were clinically stable). Authors declare that no treatment element (remediation approach, duration, computer use, etc.) was associated with cognitive outcome. This work underlined some durability of the effects (ES = 0.43), as shown in follow-up studies [119]. Durability of effects were also underlined in two recent studies performed by Buonocore et al. [120,121], who found out that all cognitive abilities improved with CR, in association with standard rehabilitation, remained stable over time from the end of treatment to evaluation at 5 and 10 years, except for psychomotor speed and coordination that showed a significant decrease. Positive effects of CR on global cognition were found also in a recent metanalytic work, indicating that CR improves cognition across several domains including processing speed, working memory and learning, much more in inpatient settings [122]. Overall, the most recent and comprehensive meta-analysis on the effectiveness of CR for people living with schizophrenia included 130 studies and a total of 8,851 participants, and found a consistent small-to-moderate positive effect of CR on cognitive performance and functioning [11]. Regarding the instrument utilized to administer CR, computer-assisted cognitive remediation (CACR) methods [123] showed significantly improvement especially on the domains of attention and working memory (marginally on other neurocognitive domains). Moreover, a recent meta-analytic study performed by Kambeitz-Ilankovic et al. [124] underlined that the effects of CR on cognitive outcomes are consistently reported both for training administered in a computerized fashion and for training supplemented by human guidance (SHG). Nonetheless, the comparison between CR administered with or without human guidance revealed that the human approach gives largest effects on the cognitive subdomains of working and verbal memory. On the other hand, no difference was reported between individual and group method.

A substantial but controversial body of literature was presented also for social cognition, starting from the first meta-analysis that debates this topic, performed by Grynszpan et al. [125], highlighting the efficacy of CACR particularly in social cognition and ending with some specific reviews that analyse promising results of training specifically developed for social cognition in schizophrenia. As example, a meta-analysis performed by Kurtz and Richardson [126] stressed the greatest effect of social cognitive treatments on facial affect recognition (FAR), with a moderate-to-large ES for affect identification and a large ES for affect discrimination. Authors also reported a moderate ES for ToM and a large impact on measures of observer-rated community and institutional functioning. According to Yeh et al. [127], that more recently conduct a meta-analytic work on CACR and social cognition with particular attention regarding ToM, there are different recent results around this topic. Prikken et al. in fact [123] found no effect of CACR on social cognition, whereas Lindenmayer et al. [128] suggested that CACR could enhance social cognition. Authors highlight that findings are inconsistent also regarding the relationship between ToM deficits and cognitive load in schizophrenia [129]. Hence, they focused their analysis on CACR and ToM in schizophrenia, founding that computerize training did not significantly enhance affective ToM ($p = 0.42$), instead treatments without computerized training were significantly superior in terms of improving cognitive ToM.

Concerning all different methods of interventions (CACR and pen and pencil), two recent systematic reviews [130,131] highlight positive results, emphasizing that targeted interventions produce more significant improvements, particularly in the domains of affect recognition, emotion processing and ToM. Results were less clear for social

Table I. The main structured cognitive remediation protocols in schizophrenia.

Cognitive Training	Target	Duration	Setting (Individual/ Group)	Computer assisted/Not computer assisted	Restorative/ Compensatory	Top-down	Bottom-up	Drill and practice	Strategy Coaching	Individual adjustment
IPT [101]	Cognitive functions, social skills and problem solving	Sessions of 60 minutes, 2-3 times a week (about 12 months)	Group (6-8)	Not computer assisted	Restorative	+	+	+	+	-
NET [102] (Bell et al., 2001)	Cognitive functions and social cognition	Sessions of 45 minutes at least 5 times a week (about 6 months)	Individual/Group	Computer assisted sessions and not computer assisted sessions	Restorative	-	+	+	-	+
NEAR [103]	Cognitive functions and problem solving	Sessions of 60 minutes, twice a week (about 4 months)	Individual/Group (3-10)	Computer assisted sessions and not computer assisted sessions	Restorative	+	-	-	+	+
CRT [97]	Cognitive functions	40 sessions at least 3 times a week, 45-60 minutes each one	Individual	Not computer assisted session	Restorative	+	+	+	+	+
CET [104]	Cognitive functions and social cognition	Biweekly sessions (about 2,5 hours every week) for 24 months	Group (couples and then groups of 3-4 couples)	Computer assisted sessions and not computer assisted sessions	Restorative	+	+	+	+	-
INT [105]	Cognitive functions and social cognition	30 biweekly sessions, 90 minutes each one	Group (6-8)	Computer assisted sessions and not computer assisted sessions	Restorative	+	+	+	+	-
SSANIT [106]	Cognitive functions, social cognition and social skills	NT: biweekly sessions of 1 hour SST: weekly sessions of 2 hours Duration: 6 months	Individual (Group)	NT sessions: computer assisted SST sessions: not computer assisted	Restorative	+	+	+	+	+
TAR [107]	Social cognition	12 sessions twice a week, 45 minutes each one	Small groups of two patients and a psychotherapist	Computer assisted sessions and not computer assisted sessions	Restorative/ compensatory	-	+	+	+	+
SCIT [108]	Social cognition	24 weekly sessions, 50 minutes each one (about 6 months)	Group (6-8)	Computer assisted sessions and not computer assisted group sessions	Restorative	-	+	+	+	-
SCET [68]	Social cognition, ToM	36 sessions of 90 minutes, twice a week (about 6 months)	Group	Not computer assisted	Restorative	-	+	+	+	-
SCST [109]	Social cognition	12 weekly sessions, 60 minutes each one (about 3 months)	Group (6 patients)	Computer assisted sessions and not computer assisted group sessions	Restorative	-	+	+	+	-
Cogpack*	Cognitive functions	Sessions variables in duration and frequency (starting from 2-3 weeks)	Individual	Computer assisted	Restorative	-	+	+	-	+
CIRCUITS [110]	Cognitive functions and metacognition	12 sessions, three times a week, 60 minutes each one (40 sessions)	Individual	Web-based computerised CR therapy with therapist plus independent session	Restorative	+	+	+	+	+
CCT [111]	Cognitve functions	12 two hour- weekly sessions (about 3 months)	Group (4-8 patients)	Group sessions with two facilitators	Compensatory	+	+	+	+	-

CCT: compensatory cognitive training; CET: cognitive enhancement therapy; CRT: cognitive remediation therapy; INT: integrated neurocognitive therapy; IPT: integrated psychological therapy; MCT: metacognitive training; NEAR: neuropsychological educational approach to remediation; NET: neurocognitive enhancement therapy; NT: neurocognitive training; SCET: social cognition enhancement training; SCIT: social cognition and interaction training; SCST: social cognitive skills training; SSANIT: social skills and neurocognitive individualized training; SST: social skills training; TAR: training of affect recognition; ToM: theory of mind.
** Cogpack (www.markersoftware.com) is a typical computer-assisted cognitive remediation (CACR) technique.*

perception, a complex construct that tends to be culturally specific [132], and for attributional bias, domains that appear to be more difficult to measure and train. Such skill in 'cognitive restructuring' is thus more challenging for people with schizophrenia to acquire, compared to emotion perception training which comprises drills and practice to achieve implicit learning and automation [133].

Promising results were found also in a recent meta-analysis performed by Nijman et al. [134] that investigate the efficacy and the durability of different types of social cognition training, with an analysis of moderators of treatment outcome. Authors found that broad-based social cognition training significantly improved emotion perception, social perception, ToM and social functioning. Targeted social cognition training had the largest effect on emotion perception and social perception. These improvements were maintained at follow-up but were generally less than at post-treatment. Regarding treatment variables that significantly moderated outcome, they underlined that individual treatments were more effective for emotion perception, but group treatments worked better to improve social functioning.

In recent years, studies about CR pay their attention on a better understanding of whom is able to benefit from CR: this knowledge would enable clinicians to more effectively refer patients to CR or tailor the intervention to the individual [135]. In particular, the identification of CR response predictors in patients with schizophrenia is still a topic with equivocal findings and only a few studies have looked for the relationship between CR response or resistance and the biological, socio-demographic, clinical, and cognitive features in schizophrenia [136]. In a recent review of literature, Barlati et al. identify some type of predictors, underlining that CR seems to be more effective in schizophrenia patients with the following features: younger age, shorter duration of illness, few disorganized symptoms, greater pre-treatment cognitive reserve, greater improvement after CR and lower dosages antipsychotics in their current treatment. About CR characteristics, a much larger effect of CR on functioning

was found out when a strategic approach was adopted and when CR was offered as part of broader psychosocial rehabilitation interventions. On the other hand, international scientific literature is controversial on the following predictive factors: genetic variability, cognitive and functional impairment at baseline [136]. Moreover, Seccomandi et al. [137] performed a systematic review of the putative factors which may affect CR response, with the aim to identify potential individual factors at baseline, moderators, that may predict treatment outcomes and that may be used to tailor CR and improve its benefits. Authors highlighted five categories of moderators that might influence CR response: demographics, biological, cognitive and functional, psychological and illness-related characteristics. Nonetheless, they underline that there was no high-quality replicated evidence, which identifies reliable moderators of CR response. Recently Vita et collegues, in their meta-analisys, focused on ingredients of effectiveness, moderators of response, as well as barriers and facilitators for implementation in real-world clinical practice of rehabilitation services represent fundamental issues that require further discussion and investigation. No difference in effectiveness was observed regarding pencil-and-paper or computer-delivered interventions, or regarding individual- or group-based programs. On the contrary, the active participation of a trained therapist, the repetition of cognitive exercises, the development of novel cognitive strategies and the presence of activities to facilitate transfers of cognitive gains in the real-world context emerged as core elements of effectiveness [11]. Moreover, factors that have a positive effect on efficacy have also been shown to positively influence treatment acceptability [138].

The growing amount of data on CR refers mostly to adult and chronic patients with schizophrenia, but less it is known about the effectiveness of CR in the early course of the disease and its possible application on the prodromal phase of the illness [139]. Early phases of the illness are considered a crucial period that could potentially influence its course and during which neural plasticity is thought to play a major pathoplastic role [140]. This could justify the theoretical usefulness of interventions targeting cognitive improvement [141]. Revell et al. [142] in their meta-analysis on CR in early schizophrenia underlined that CR in FEP had a positive effect on global cognition; the areas with major results are verbal learning, memory and social cognition (although only in 3 of trials). Improvements nearing uncorrected significance were also seen in processing speed, working memory and in reasoning and problem solving. These results were similar to that reported in the Wykes et al. [117] meta-analysis performed on "chronic" patients, although the ES in FEP review are smaller. The work of Revell et al. [142] reported in conclusion of meta-analytic estimate that CR had a non-significant positive effect on global cognition. Nonetheless, this preliminary non-significant effect, according to Lewandowski [143], underlines that CR is feasible and potentially efficacious in recent-onset and high-risk patients. This recent review highlights that, in recent-onset patients with schizophrenia, most reports show improvements after CR in one or more domains of cognition. With regard to people at high risk of developing psychosis, some studies report similar promising results although findings on efficacy are inconclusive due to small sample sizes and lack of control [144]. Some studies indicate that effects of CR in these populations may be of similar or greater magnitude as those seen in chronic patients [140], suggesting that young patients with greater potential for plasticity may indeed benefit as much or more than patients with presumably reduced plasticity.

In a recent review, Bellani et al. [145] pay their attention on CR-induced structural and functional brain changes in early SCZ. According to the authors, current literature showed a protective effect of CR on some regions of grey matter volume, as in selected medial-temporal (i.e. hippocampus, parahippocampus and amygdala) and thalamic regions. Functional changes acted on dorsolateral prefrontal and insular cortices both associated with improvements in cognitive performance and emotion regulation. Authors conclude that CR appears to be a promising treatment in the approach of cognitive impairment and neural alterations associated with the early phase of schizophrenia, but future research are needed to clarify whether the positive effects of cognitive training persist over time. Overall, preliminary evidence supports the extension of CR in early course and high-risk populations.

Finally, while recent evidence suggest that CR interventions can also be delivered remotely [146], attrition rates appear to be very high, and more research is currently needed to confirm its effectiveness in this format: in-person treatment sessions currently represent the optimal standard [147].

Cognitive remediation: focus on psychosocial functioning

In past decades different outcome measures were recognized as being relevant for effective interventions in schizophrenia such as: quality of life (QoL), obtaining and working competitive jobs, family and quality of and satisfaction with interpersonal relationships, leisure time and other elements of daily living, finances, the ability to solve interpersonal problems and physical and mental health [148]. Some of these key elements compose psychosocial functioning – defined as patients' ability to fulfil their role in society as a member of a family or in a professional career – that should be a priority target for therapeutic interventions in schizophrenia [148]. As we know starting from scientific literature [149], functional outcome is strongly influenced by cognitive impairment. According to some authors, cognitive deficits explain 20-60% of the variance of real-life functioning. Since these premises, it is crucial that CR could generalize its results and could have impact on social functioning of patients. Starting from McGurk et al. meta-analysis [150], that includes 26 studies

(about 1,500 patients), CR programmes demonstrate a small/medium ES for functioning (ES, 0.35). Moreover, CR programs that provided adjunctive psychiatric rehabilitation had significantly stronger effects on improving functional outcomes (ES, 0.47) than programs that did not (ES, 0.05). McGurk et al. found that CR intervention, that included strategy coaching, had stronger effects on functioning than programs that focused only on drill and practice technique. According to the authors, this effect is accordant with previous researches showing that cognitive impairment reduces response to psychiatric rehabilitation [151] and suggests that improved cognitive performance may empower some patients to benefit more from rehabilitation. Also in a previous meta-analysis on CR in schizophrenia, Twamley et al. [114] underlined that all the different types of approaches, whether computer assisted or not, have effective components that are promising for improving everyday functioning. Similar results were found at a later time in Wykes et al. meta-analysis [117], in which CR was associated with a small/medium ES for functioning (ES, 0.35) with a significant heterogeneity in the ES. Stronger ES for improved psychosocial functioning were found by authors in studies that provided adjunctive psychiatric rehabilitation and use of drill and practice plus strategy coaching (ES, 0.62), compared to drill and practice only. This moderator of response could justify the significant heterogeneity in the ES. These findings are also in line with the results of a meta-analysis of integrated psychological therapy (IPT) [101], in which the strongest effects on functioning were found in programs that integrated CR and social skills training rather than programs that provided either intervention alone [116,152].

Furthermore, in 2019 Van Duin et colleagues performed a meta-analysis in order to investigate whether a combination of psychiatric rehabilitation (PR) and CR reinforces the effect of a stand-alone PR or CR intervention on separate domains of functioning. They analysed three areas: vocational, social and community functioning. Regarding vocational functioning, the combination of CR and PR led to significant favourable outcomes for employment rate, hours worked, job duration and quality of performance in work or education compared with a single PR intervention. Similar results were found in social functioning, in which the combination of CR and PR had significant favourable outcomes for social skills if compared with a single PR intervention. Quite the opposite, no significant beneficial effects were found in community functioning (independent and daily-living skills, role adjustment and performance and social and occupational functioning) when it was compared with a single PR intervention. Results on social and work outcomes were confirmed also by Kambeitz-Ilankovic et al. [124] that found a small, significant effect of CR on functional outcomes. Also the more recent and comprenshive meta-analisys carried-out by Vita et al. [11] underline that the integration of CR into a structured psychiatric rehabilitation program or its association with other evidence-based psychosocial interventions produced better improvements in both cognition and functioning.

With respect to the persistence of the effects on daily functioning, patients treated with the 6 months CRT showed a significant decrease in functional performance after 5 years, compared to the end of treatment. On the contrary, no differences between the end of CR intervention and 5 years later were observed within group that received further standard rehabilitation for a year [120]. Finally, a study performed by the same research group confirmed that functional improvement of cognitive remediation interventions together with standard rehabilitation interventions is still conserved 10 years after the end of the treatments [121].

Results on functioning were controversial regarding meta-analyses focused only on CACR methods, that seem to be effective in some areas of functioning. On one hand, according to Prikken et al. [123], in patients receiving computerized cognitive drill and practice training compared to a control condition, significant effects on global functional outcomes were absent. On the other, Chan et al. [153], who performed a review on CACR and productivity outcomes, found that CACR can enhance productivity outcomes for patients with severe mental illness (SMI), including higher employment rate, longer duration of work and higher income, improving also quality of life in this population.

Examining results derived from social cognitive training (SCT), we can observe that the first systematic review, that debates this topic [131], concludes that there is also a need for more studies to measure intervention effects on real-world social functioning and that there is potential in including learning strategies (i.e errorless learning) and harnessing technology (i.e virtual reality and home-based online training) in order to improve distal outcomes of social competence and social functioning. More promising results derive from following studies: Grant et al. [154] found a positive effect on functional outcomes used both broad-based and focused studies. The majority of included studies which found an improvement in functioning also reported an improvement in ToM and in social perception. These data support the idea that improvement in ToM may benefit more directly functional outcomes [155], because ToM seems to be relevant in everyday social interactions [156] and because social perception requires the ability to decode social interactions that is strongly associated with functioning improvement. Also, Nijman et al. [134] found that broad-based SCT (with and without CRT) had a significantly larger effect on social functioning, that persists at follow-up. In this meta-analysis the group treatment was the only variable that significantly moderated outcome. Concerning CR in in-patients, a recent meta-analysis of Cella et al. [122] showed that there was a positive but no statistically significant effect in favour of CR compared to treatment as usual (TAU) or TAU plus additional interventions. Authors supposed that assessing social and vocational outcomes in in-patient settings may be

difficult because patients may have limited opportunities to practice and take part in activities assessed as part of functional assessment measures.
Significant positive effects of CR were seen on functioning also in FEP [142], with a significantly larger effect in treatments, which employed CR with adjunctive psychiatric rehabilitation (e.g. psychoeducation and training to develop social, vocational and daily living skills), replicating the findings of the Wykes et al. meta-analysis performed on adult / chronic patients. These results could indicate that targeting cognitive impairments early in the course of the disorder can result not only in cognitive improvement per se, but also in significant functional benefits in such critical domains as employment, social functioning, and major role functioning [8,139]. In addition, the results could include CR as part of continuing rehabilitation, that may be able to translate cognitive gains directly to better function.

Cognitive remediation: focus on clinical symptoms

Some small but encouraging results, that infer by CR techniques, were found also in schizophrenia symptoms: as we know from scientific literature, there is a better prognosis in individuals with psychosis, in terms of functioning and symptoms remission, for those with better cognitive performance [157]. Recently it become established the idea that CR has a direct effect on symptoms. Since the first meta-analytic study performed on this topic [114], CR (both computer-assisted and not) demonstrated its positive effects on symptoms, with the unknown possibility if these effects were sustainable. Also, two meaningful meta-analytic works agreed with these preliminary results, finding a small significant ES for symptoms, that however disappeared at follow-up assessment [117]. A more recent work conducted by Kambeitz-Ilankovic et al. [124], underlines similar effects, finding a small, significant ES of CR on clinical outcomes, particularly in two subdomains: negative and depressive/anxious symptoms. The same results were found in a meta-analysis about CACR training [123], with some small differences: CACR methods showed small/moderate, but only marginally significant effects on negative symptoms and total symptoms, whereas the analysis including all CR methods shows no significant effects on positive, general, and total symptoms, nor on clinical global scores. According to Wykes et al. [117], also Kambeitz-Ilankovic et al. [124] showed no differential response between human guidance of treatment and computerized CR. These results suggest that computerized training programmes, that have the potential to be performed independently by patients, are effective [123]. Regarding integrated interventions (for example, IPT), whether they yielded some significant immediate and long-term effects in more proximal outcomes, small effects were found in symptoms [116]. Similar, significant positive effects of CR were seen also in FEP patients on global symptoms: in more detail, CR had a significantly smaller effect on symptoms both when it was delivered one to one with a therapist, as well as when it was delivered in groups [142].
Other specific trainings, for example social cognitive training programmes do not report significant effects on positive and negative symptoms of schizophrenia [126]. According to the authors, the limited effects of social cognitive training on positive and negative symptoms may reflect the multi-determined nature of these disease domains, including emotionally charged family relationships. These interventions produced moderate size effects on general symptoms, suggesting that social cognitive training may be more effective in influencing general psychiatric symptoms such as depression and anxiety.
Furthermore, some studies gave specific attention on CR effect on negative symptoms [158]. Authors underline that negative symptoms are not traditionally considered a primary target for CR, but their results demonstrate a small to moderate effect of CR on negative symptoms at post-therapy, with this effect being maintained at follow-up. These findings highlight that CR may have similar ES to other available pharmacological and behavioural interventions designed to tackle negative symptoms directly [159]. Authors suggest that future researches should explore in detail the relationship between cognitive and negative symptoms in schizophrenia. This suggestion was conducted in a recent study exploring the effect of integrated neurocognitive treatment (INT) on relapse rates, which were significantly lower in the INT condition compared with TAU both during therapy and at one-year follow-up. This analysis points out that the relapse rate after therapy was associated with significant reductions in negative and general symptoms, improvements in functional outcome and overall cognition. Authors underline that out of these variables, negative symptoms were identified to show the strongest association with relapses after therapy [160].

Conclusions and future directions

Cognition in schizophrenia is an important target of intervention due to its relationship to outcomes and recovery. In patients with schizophrenia, both social and non-social cognitive deficits are related to outcomes and can limit recovery even when other support has been provided [93]. Different pharmacological and non-pharmacological approaches were developed to restore these deficits, although these interventions are still under study and discussed. Some of these treatments, such as SGAs and CR, demonstrate their efficacy also through neuroimaging studies, that underline their neurobiological effects [20,161]. Furthermore, for each intervention we know that some individuals show little benefit and other much more. This difference leads to an increasing interest in investigating potential moderators, mediators and predictors of treatment, with the aim to make each treatment tailored for each patient. Despite there are still some future perspective to observe, different studies support

the idea that an integrated approach is required in order to increase everyday functioning and to decrease disability in schizophrenia [89]. To sum up, as recently pointed out by expert group consensus on cognition in schizophrenia [162], pharmacological and non-pharmacological approaches moderate both functional improvements and recovery.

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