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Review Article

Cognitive dysfunction in schizophrenia: An expert group paper on the current state of the art

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ABSTRACT

Cognitive impairment in schizophrenia represents one of the main obstacles to clinical and functional recovery. This expert group paper brings together experts in schizophrenia treatment to discuss scientific progress in the domain of cognitive impairment to address cognitive impairments and their consequences in the most effective way. We report on the onset and course of cognitive deficits, linking them to the alterations in brain function and structure in schizophrenia and discussing their role in predicting the transition to psychosis in people at risk. We then address the assessment tools with reference to functioning and social cognition, examining the role of subjective measures and addressing new methods for measuring functional outcomes including technology based approaches. Finally, we briefly review treatment options for cognitive deficits, focusing on cognitive remediation programs, highlighting their effects on brain activity and conclude with the potential benefit of individualized integrated interventions combing cognitive remediation with other approaches.

1. Introduction

Schizophrenia represents a multifaceted clinical challenge, with significant disability burden. Patients' outcome is still highly heterogeneous and typically poor (McCutcheon et al., 2020). Despite major progress in understanding the biological basis of the disorder and significant advances in management of positive symptoms, other key domains, such as cognition and social cognition, have not yet been adequately addressed. Cognitive impairment, a central feature of the illness is present in over 80% of patients with schizophrenia, is a main determinant of functional disability and the indirect costs of the disease (McEvoy, 2007). Currently available antipsychotics have only limited effects on cognition and side effects may even aggravate some deficits (Kaar et al., 2020). So far, pharmacological options for cognitive deficits in schizophrenia are unsatisfactory due to either limited efficacy or tolerability concerns; at the same time, non-pharmacological interventions consistently suggest potential benefits. Cognitive remediation programs show significant beneficial effects to the point that they are currently considered the best option to improve cognition and are included in clinical guidelines (Keepers et al., 2020; Takahashi et al., 2020). However, even when cognitive remediation is offered, there's still high inter-individual variability in the degree of improvement in cognition and especially in terms of generalization to daily functioning (Deste et al., 2020).

Given the relevance of this topic, an international expert panel of eight international key opinion leaders was organized with the support

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of Angelini Pharma, to discuss scientific progress on cognitive impairment associated with schizophrenia. The panel targeted a range of topics regarding cognitive dysfunction in schizophrenia with the aim to provide a global overview bridging research findings with clinical practice, with a focus on non-pharmacological interventions. This expert group paper, as the main output of the meeting, addresses cognitive dysfunction starting from its onset and course, discussing it considering the neurobiological alterations linked to the disease and highlighting its role prediction of risk for psychosis. It then provides an overview on methods for measuring social cognition and functional outcome, moving toward to examine the available treatment options, with their pros and cons, and their effects also on brain activity.

2. Cognitive impairment: early emergence and course after illness onset

Cognitive abilities have been extensively studied in patients with schizophrenia and there is a clear consensus on the presence of cognitive deficits (Fatouros-Bergman et al., 2014). These deficits encompass general intelligence and a wide array of neurocognitive domains, with an array of severity of impairment. There is also strong evidence that cognitive impairment is detectable before illness onset and may thus represent a useful marker for early detection and intervention. There is still debate, however, on the course of cognitive deficits over time. In this section, we will provide an overview of cognitive trajectories from the premorbid phase to the long-term outcome.

2.1. Premorbid phase

There is a general agreement that some degree of neurocognitive and social cognitive impairment can be detected in the premorbid phase in people who will later develop schizophrenia, as well as in non-affected first-degree relatives. These findings suggest that cognitive anomalies can be considered as markers of altered neurodevelopment and may be an expression of genetic risk and early developmental insults, as well as their interaction (Rapoport et al., 2012). For this reason, a better understanding of the timing of cognitive deficits is crucial, not only for early intervention, but also to provide further inside into brain functioning over the disease course.

Available studies on the premorbid phase show both general and specific cognitive impairment, encompassing IQ, as well as attention, memory, reasoning, executive functions and processing speed (Sheffield et al., 2018; Woodberry et al., 2008). Although assessment of cognition through standardized batteries increases sensitivity and specificity, it is time consuming and may not be suitable for large scale studies addressing the premorbid phase. A more feasible approach for this purpose is the use of data on academic achievement, however variable results have been reported (Dickson et al., 2012). A recent meta-analysis, including follow-back studies, retrospective population cohort studies and birth cohorts, focused on subjects aged 16 years or younger to limit the risk of detecting a decline related to the presence of prodromal symptoms. Results indicate that 16-year old subjects who later develop schizophrenia show significantly poorer general academic and mathematics achievement a number of years prior to illness onset compared to individuals who did not develop schizophrenia, showing at the same time reduced achievement of higher education program compared to the healthy population (Dickson et al., 2020). However, the effect sizes of difference in performance relative to controls are small ($d \sim 0.3$) and more prospective cohort studies are needed in order to consolidate reliable clinical knowledge.

2.2. Prodromal phase

In the past decades, there has been an increasing interest on the assessment and identification of the schizophrenia prodrome. In this view, identifying the trajectory of cognition may help to define optimal early intervention strategies. Despite heterogeneity between studies due to the differences in the definition of prodromal stages (discussed below), overall results show cognitive deficits, although less marked than those seen in patients with first episode (Giuliano et al., 2012). The impairment encompasses main cognitive domains, especially executive functioning and working memory, as well as speed of processing (Simon et al., 2007).

A recent meta-analysis of retrospective studies confirmed poorer cognitive performance in subjects meeting the criteria of Clinical High Risk for Psychosis (CHR—P) in comparison to healthy controls (HC) (Catalan et al., 2021). Specifically, CHR-P showed poorer outcomes in executive functioning, attention, general intelligence level, processing speed, verbal fluency and visual, verbal and working memory. Interestingly, analyzing data from a subset of 22 longitudinal studies assessing transition to psychosis, CHR-P individuals who later developed psychosis showed poorer performance on the same cognitive domains, compared to people who met the same CHR-P criteria but did not go on to develop a psychotic disorder. This finding supports the role of neurocognitive dysfunction as potential marker predicting transition in individuals at CHR-P (Carrión et al., 2016; Seidman et al., 2016).

2.3. First episode psychosis

It is well established that patients with schizophrenia present extensive cognitive deficits at the time of the first episode of psychosis, however it is less explored if there is a gradient of deficit from the prodromal phase to the first episode and if these deficits are associated with antipsychotic treatment and other clinical features.

A pioneering study comparing subjects at first episode of psychosis (FEP) with two groups of patients at different prodromal stages (ultra-high-risk-UHR and basic symptoms-BS) and a patient control group, showed a progressively greater severity of cognitive deficit from prodrome to FEP (Simon et al., 2007). The data collected support the hypothesis that the prodrome is characterized by increasing levels of both positive symptoms and cognitive impairment although these two trajectories are not parallel (Simon et al., 2007).

Most studies addressing cognition in FEP have been conducted on antipsychotic treated patients, with some exceptions (Saykin et al., 1994), raising the concern whether the observed deficits were a manifestation of the illness or, at least partly, a consequence of the antipsychotic drug. Aiming at clarifying this issue, a meta-analysis of 23 studies, including a total of 1106 patients and 1385 examined cognitive abilities in drug-naïve patients with schizophrenia (Fatouros-Bergman et al., 2014). The results confirmed previous findings, showing reduced performance drug-naïve patients compared to healthy controls, with medium to large effect sizes. The severity of impairments deficit and the domains affected: verbal memory, speed of processing and working memory, are comparable to those reported in antipsychotic treated patients.

Another aspect to consider is the specificity of early stage deficits related to schizophrenia. It is recognized that cognitive deficits are present also in other psychiatric conditions, especially bipolar disorder. A meta-analysis comparing healthy controls, first-episode bipolar disorder and first-episode schizophrenia showed that the latter performed significantly worse than patients with first episode bipolar disorder on all cognitive domains (Bora and Pantelis, 2015). Still, performance of patients with bipolar disorder was intermediate between healthy controls and patients with schizophrenia, suggesting that, although less pronounced, neurocognitive alterations are present in bipolar disorder. This suggestion is supported by the data finding cognitive impairments in unaffected first degree relatives as well (Bora, 2017).

2.4. Chronic phase

The trajectory of cognitive deficits after the onset of schizophrenia is still a matter of debate. From the theoretical point of view, two

hypotheses coexist. The first, purely neurodevelopmental, claims that cognitive deficits derive from altered brain development and they represent an impaired acquisition of function, rather than a decline (Zipursky et al., 2013). The second postulates the contribution of a neurodegenerative component, in addition to the first, possibly linked to inflammatory processes, or chronicity of psychotic symptoms, that cause a further deterioration in cognition after the onset (Monji et al., 2013).

Studies attempting to examine longitudinal changes in cognition in patients with schizophrenia faces many methodological issues, including the appropriate duration of follow-up, the comparison group sand the role of confounding factors. Supporting the neurodevelopmental theory, Bora and Murray, in a meta-analysis of longitudinal studies assessing cognition in FEP and UHR subjects, reported an overall improvement of cognitive functions after the onset, except in working memory and verbal fluency (Bora and Murray, 2014). In contrast, a more recent study with about 10 years prospective follow-up of patients with first-episode psychosis, including also healthy controls, found decline in a number of cognitive measures (Zanelli et al., 2019). Specifically, first episode patients who were later diagnosed with schizophrenia showed a progressive decline in IQ and in specific neurocognitive domains, such as verbal knowledge and memory, with variable magnitude of changes. A decline was also observed in patients diagnosed with other psychotic disorders, specifically in measures of memory, while in healthy individuals cognitive abilities were stable. Results thus support the presence of a cognitive decline that progresses after the psychosis onset, however the degree of change is heterogeneous and may vary across cognitive domains. Data from a 20-year follow-up study also reported evidence of decline in cognitive functioning compared to normative standards, with declines also noted in similarly aged participants with histories of psychotic bipolar disorder and major depressive disorder (Fett et al., 2020).

In sum, evidence suggests lower global and domain-specific performance relative to controls from the premorbid phase with a progressive worsening until the first episode of psychosis, while the trajectories after onset are less clear. To obtain more representative data and to clarify the debate of progression of cognitive deficits in further studies, it will be useful (but generally impractical) to conduct larger prospective studies enrolling both patients and controls. In fact, many studies do not include control groups, and use reference dataset rather than prospective evaluations. Finally, many confounding factors may influence the cognitive trajectory beyond the decline caused by the illness itself. For example, a recent meta-analysis in patients with schizophrenia showed that chronic smoking was associated with a more severe impairment in core cognitive domains (Coustals et al., 2020). In this view, it is to note that patients with schizophrenia are frequently burdened by comorbidities such as substances and cigarette misuse, obesity and metabolic syndrome (Strassnig et al., 2017; Zipursky et al., 2013).

3. Cognitive trajectories and brain imaging

In the past century, schizophrenia research has been biased by a focus on positive symptoms. Indeed, prognosis of schizophrenia has not changed substantially since the introduction of first antipsychotic drugs, and some argue it has not meaningfully improved since the illness was first described (Kahn and Keefe, 2013). In the past decades, based on the evidence reported in the previous paragraph, schizophrenia has been increasingly viewed as a primary cognitive disorder instead of a mere psychotic disorder. In parallel, neuroimaging studies reported several diffuse alterations in brain structure and functioning, which are more pronounced in the association cortex and subcortical brain regions (Keshavan et al., 2020). In particular, the focus is on brain development, both in early phases and in adolescence. Here, we discuss the main changes occurring during neurodevelopment in relation to cognitive abilities and the alterations reported in schizophrenia.

Adolescence represents a time of dramatic changes in both body and behavior, principally due to by major changes in the neural systems that subserve higher cognitive functions. According to Shaw et al., in early childhood it is possible to find a negative correlation between intelligence and cortical thickness, contrasting to the positive correlation, which is found in late childhood and beyond. Additionally, children with higher IQ demonstrate a particularly plastic cortex, indicating that the neuroanatomical expression of intelligence in children is dynamic (Shaw et al., 2006). Understanding the quality, quantity and timing of behavioral and brain changes could uncover patterns of potential therapeutic relevance, guiding treatments basing on the different ages (Lee et al., 2014).

In schizophrenia, evidence shows that developmental abnormalities, poor neuromotor function and increased behavioral disorders, often precede the manifestation of schizophrenia and in many cases, the first signs are cognitive symptoms. In a study conducted on monozygotic (MZ) and dizygotic (DZ) twins, lower school performance originated about 7.5 years earlier in subjects who later developed schizophrenia than in control twins, preceding the onset of psychosis by 10 years (Van Oel et al., 2002). This process might suggest that the origins of psychotic disorder involve dynamic developmental processes, at least throughout the first 2 decades of life (Mollon et al., 2018). In line with this, a previous study analyzing several IQ subtests showed that future schizophrenia cases had reduced linear changes than healthy comparison subjects, thus indicating that their growth on tests measuring freedom from distractibility and visual-spatial problem solving skills was slower. On the other hand, developmental lags were less apparent among subjects who later developed recurrent depression (those cases exhibited slower cognitive growth on only the arithmetic subtest) (Reichenberg et al., 2010).

As mentioned above, brain structure progressively changes starting from childhood and later in adolescence, thus translates in increased brain volume and connectivity. Interestingly, it has been shown that changes in brain volumes from childhood to early adolescence are heritable (Van Soelen et al., 2013). The adolescent brain can be considered as a network in progress in which individual differences in maturation relate to level of intellectual functioning (Koenis et al., 2015). A study focusing on healthy subjects with an IQ of over 110 showed both more pronounced thickening of the medial temporal cortex and attenuated thinning of the frontal cortex over time when compared to individuals with average (IQ 90 to 110) and below-average intellectual ability. In this context, intelligence seems genetically represented in a spatially distributed and densely connected network of gray matter regions providing a high capacity infrastructure (Bohlken et al., 2016). In support of this hypothesis, some studies focused on patients with 22q11.2 deletion syndrome (22q11DS), who are known to have an elevated (25%) risk for developing schizophrenia. The results showed that a subgroup of children with 22q11DS display a substantial decline in cognitive abilities, starting at a young age, which were even more significant in those subjects with 22q11DS who developed psychotic disorder, most pronounced in verbal IQ. Importantly, the IQ trajectories in those with and without a psychotic disorder diverge several years before the usual onset of psychosis in 22q11DS (Vorstman et al., 2015).

Schizophrenia is thus characterized by compromised intellectual ability and progressive brain tissue loss (van Haren et al., 2008), and both are heritable traits. The relevance of this association is that brain changes and intelligence are both partly influenced by the same genes (Brans et al., 2010). Comparing patients with schizophrenia to healthy controls subjects across the same age range, over a five-year-interval, cerebral volume loss in patients was mainly characterized by the absence of the normal curved trajectory of volume change with age observed in healthy subjects. Cerebral tissue loss was associated to lateral ventricle increase in schizophrenia, resulting most prominent before the age of 45 years, while white matter volume increased excessively before the age of 32. These findings suggest the most part of brain tissue loss in schizophrenia occurs during the first 10 to 20 years of the illness, while later in life the degree of cerebral volume loss in patients is similar to that observed with normal aging (van Haren et al.,

2008). These changes may be influenced by the stress associated with psychotic relapses and re-treatment as well. In addition, progressive brain tissue loss in schizophrenia was related to relative cognitive decline during the early course of illness. (Kubota et al., 2015). Based on a meta-analysis, which included about 18,000 subjects divided into medicated and medication-naïve patients, brain loss in schizophrenia appears to be related to a combination of (early) neurodevelopmental processes, which reflect in intracranial volume (ICV) reduction, but also to illness progression. In the antipsychotic-naive sample, brain changes reflected those observed in the medicated samples, albeit to a lesser extent (30% less considering total ICV). These data suggest that part of the reduction in brain volume observed in schizophrenia must be present prior to the age when the cranium reaches its final size, which is in early adolescence (at age 13). Interestingly, white matter reduction was similar in the medicated and medication-naïve samples, thus suggesting that the reduction in white matter is present before treatment initiation and progresses little during the subsequent course of the illness, whereas gray matter reduction, although also reduced at treatment onset, does worsen, increasing with illness duration (Haijma et al., 2013).

Overall, brain changes in schizophrenia seem progressive and pronounced, related to both risk and illness and cognitive performance. While early developmental abnormalities are more clearly identified also with respect to their role in cognitive performance, the relation with neurodegeneration needs to be further explored. A final issue for consideration is the interaction between medication discontinuation, relapse, and retreatment, as the studies noted above have found that either more time spent in psychotic episodes or a greater number of hospital readmissions are also cortical with cortical volume changes after the time of the first episode.

4. Prediction of psychosis: where are we?

In the past decades many efforts have been devoted to early detection of psychosis, with the hope that identifying the prepsychotic precursor stages would lead to successful prevention. This field has developed rapidly and determined a significant transition in the clinical characterization of psychotic disorders, as underlined also by the inclusion of the category “attenuated psychosis syndrome” as a condition for further studies in the fifth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).

The construct of a clinical high-risk state for psychosis (HR), also known as the “at-risk mental state” (ARMS), “prodromal,” and “ultra-high-risk” (UHR) state, has evolved to capture the prepsychotic phase, describing manifestations through the prodromal stages up to the early psychosis phase (Fusar-Poli et al., 2013). Two main criteria are currently used to diagnose HR state, namely Ultra High Risk (UHR) (Jackson et al., 1994) and Basic Symptoms (BS) (Klosterkotter et al., 1996) criteria. Importantly, both criteria focus on symptoms and on alterations of cognitive and functional domains. UHR criteria integrate both state and trait features, as well as functioning. They require the presence of either attenuated psychotic symptoms (APS), brief limited intermittent psychotic episode (BLIP) or trait vulnerability alone or in combination. In addition, a marked decline in psychosocial functioning and unspecified prodromal symptoms must be presented. BS criteria consist instead of attenuated sub-clinical disturbances of different domains, including perception, thought, processing, language, and attention subjectively experienced by patients in the absence of overt psychotic symptoms. Intact reality testing and insight into the symptoms is required to meet the criteria. Different specific tools have been developed and are currently used in clinical practice to diagnose the HR state.

The most widely used interviews to assess UHR features are the Comprehensive Assessment of At-Risk Mental State (CAARMS) (Yung et al., 2003), the Structured Interview for Prodromal Symptoms (SIPS) together with the companion Scale of Prodromal Symptoms (SOPS) (Barton et al., 2003), the Early Recognition Inventory for the Retrospective Assessment of the Onset of Schizophrenia (ERIraos) (Häfner et al., 1992), and the Basel Screening Instrument for Psychosis (BSIP) (Riecher-Rössler et al., 2008). For the assessment of BS, the Bonn Scale for the Assessment of Basic Symptoms (BSABS) (Ziermans et al., 2011) and the Schizophrenia Proneness Instrument, adult version (SPI-A) (Schultze-Lutter et al., 2007) and child and youth version (SPI-CY) (Fux et al., 2013) are among the most frequently employed tools. Despite the heterogeneity of the available scales, their prognostic accuracy is high and comparable. A meta-analysis including eleven independent studies with a mean follow-up of 3 years and over 2500 people seeking help, revealed an excellent sensitivity (AUC = 0.90; 95% CI: 0.87–0.93), analogous or even higher that other tests used in preventive medicine. Moreover, the metaregression performed found limited effects depending on the instrument, age, gender, follow-up time, sample size, and quality assessment (Fusar-Poli et al., 2015). However, the specificity of these assessments needs to be improved in order to be cost-effective for implementation in clinical practice.

Accurate assessments of prodromal symptoms can lead to early recognition of UHR subjects who can benefit from pharmacological treatment. This is particularly relevant also for cognition, as clinical remission is one of the main determinant of cognitive trajectories over time. Protracted latency of interventions, thus duration of untreated psychosis, or treatment resistance, as well as ultra treatment resistance (resistance to clozapine) play a major role in determining cognitive impairments (Spangaro et al., 2021).

A key issue, given this fine grained characterization of HR state, is to identify who among HR individuals will progress to full-blown psychosis. A series of predictors, including neurobiological, cognitive, clinical and environmental variables have been explored. In detail, a significant predictive value has been reported for delusions, hallucinations or formal thought disorder in clinical models, for verbal and executive functions in neurocognitive model, for gray matter volume alterations in prefrontal, perisylvian, and subcortical structures in biological models and for measures of urbanity, social-sexual aspects, and social and personal adjustment in environmental models (Montemagni et al., 2020). However, most of these models failed to prove internal validation and evidence suggest that an integrated model combining biological, clinical, cognitive and socio-cognitive variables could reach a better predictive than each model separately (Addington et al., 2019). Concerning cognitive impairments in UHR, they show mild to moderate globally distributed neuropsychological deficits which lie between FEP and healthy subjects. Moreover, cognitive impairments seem greater in patients who will experience full-blown onset of symptoms (Hauser et al., 2017). Notably, despite cognitive deficits are established in UHR subjects, they already exist before the prodromal phase but do not tend to progress unless onset and chronic or sub-chronic illness occurs (Bora and Murray, 2014). These findings further suggest that early interventions are fundamental in preventing the progression of cognitive impairments along the course of the illness.

In sum, important advances have been made in accurate prediction (Fusar-Poli et al., 2015; Montemagni et al., 2020), but not without difficulties and limitations that must be overcome, such as methodological issues in ascertainment, diagnosis, the use of data-driven selection methods and lack of internal and external validation (Addington et al., 2019). Recommendations for the future include more RCTs comparing treatments, as well as more collaborative research programs, and ensuring they are accessible and harmonized with respect to criteria and outcomes (Devoe et al., 2020). Indeed by improving early identification and therefore early interventions, better cognitive trajectories could be obtained in patients who will develop schizophrenia.

5. Cognitive assessment: “are we measuring the right stuff”?

The question raised two decades ago by Green et al. (2000) significantly shaped the landscape of cognitive assessment for schizophrenia in research and clinical settings, extending it beyond the traditional neurocognitive domains with the goal to capture ecological daily

functioning. Tools that we use to evaluate cognitive abilities with the aim of identifying correlations with functional outcome were developed for different purposes. Specifically, Green et al. stated in 2000 that the concept of "learning potential" could be the mediator between basic neurocognition and skill acquisition. Notably, to determine "learning potential", a shift in the assessment from what the individual currently knows to what the individual is capable of learning is required. Nowadays, different tools have been developed to provide a more exhaustive estimate of cognitive abilities effectively used by the patient in everyday life. Here we will focus on measures of functional outcome and social cognition, discussing also the role of subjective assessments.

5.1. Functional outcome

The assessment of everyday functioning in patients with schizophrenia is fundamental in all phases of illness, given the illness related impact on the autonomy and functional performance of patients. In the past, the gold standard to assess treatment response in schizophrenia has been considered positive symptoms, paying less or not at all attention to negative symptoms and cognitive impairment, leaving patients with such symptomatology considering it as the "residual phase" of illness. Fortunately, nowadays there is increasing interest in assessing functional improvement in clinical trials. Co-primary functional outcome measures are often included and are required for studies on cognition to verify to what extent improvements in cognitive performance translate into improvements in global functional capacity (Laughren and Levin, 2011).

However, assessing functional outcome still represents a challenge and there is a debate on what measures should be included. Ideally functioning should be evaluated by "hard" outcomes, such as how many patients have a job or how many have a relationship, but the feasibility within RCTs would be very difficult. Moreover, changes of functioning in everyday life involves many moderating factors, such as the availability of psychosocial rehabilitation, social support networks, local employment rates, and training opportunities which are difficult to control for and make it challenging to evaluate the actual functional benefits of cognition-enhancing effects (Green et al., 2008). Intermediate measures are thus needed and among these, functional capacity, defined as the capability of performing activities in a test situation, proved to be a mediator of the effects of cognition in functioning. In fact, real-world adaptive life skills seem to be predicted mostly by symptoms and functional capacity, while less by neuropsychological performance. Moreover, in some domains, negative and depressive symptoms can directly influence "real-world" performance while not relating to functional capacity or neuropsychological performance (Bowie et al., 2006).

For the assessment of functioning in the community, several instruments are used in clinical practice. The Global Assessment Scale (GAS) (Endicott et al., 1976), the Global Assessment of Functioning (GAF) (Hall, 1995), the Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992), the Personal and Social Performance scale (PSP) (Morosini et al., 2000) and the World Health Organization Disability Assessment Schedule 2.0 (WHODAS) (Üstün et al., 2010), which represents part of the Standard Set of Patient-Reported Outcomes for Psychotic Disorders (McKenzie et al., 2021) are among the most frequently employed, but many other have been developed, including a Work Readiness Questionnaire (Potkin et al., 2016). Most of these classical scales are observer-rated and some of them, such as the GAS, GAF and WRQ include the assessment of psychopathological domains or psychological constructs that may influence functioning. Despite the availability of several scales to evaluate functioning, growing evidence in the field states that these functional assessments do not adequately capture the real world functioning of patients. Response biases and failures in the ability to self-assess functioning are common. In fact, between 50% and 80% of patients with schizophrenia have poor insight of illness and their self-assessment of cognitive impairments and functional abilities is also impaired compared to other information, including scores on performance-based ability measures (Durand et al., 2015; Gould et al., 2013).

In recent years, the advent of alternative and innovative methods such as Ecological Momentary Assessment (EMA), a method based on momentary sampling of what people are actually doing in their daily lives has been increasing used. Real-time assessment of functioning behaviors with vivo data collection techniques with smartphones (Granholm et al., 2020).

Multiple meta-analyses have found very few and minimal correlations between objective indicators of functioning subjective quality of life (QoL), and most studies also find relative minimal impairments reported in subjective QoL (Narvaez et al., 2008). Critical issues have been found, especially when asking about potential, performance on activities done in an undefined period and comparisons with normative standards. In addition, QoL scores commonly relates to mood state (in particular depression) than environmental factors, such as unemployment or reduced residential status. A recent study showed that about 20% of the participants with schizophrenia, assessed 90 times over 30 days with Ecological Momentary Assessment (EMA), reported that they were sad on a single survey. The self-perception of never being sad were associated with overestimated functioning compared to observers and being more commonly home and alone than both participants with schizophrenia who reported occasional sadness and participants with bipolar disorder (Jones et al., 2021). Collecting data with ecological momentary assessment has yielded information that seems less biased and quite congruent with other convergently validating data, including Positive and Negative Syndrome Scale score and GPS mobility as a digital biomarker of self-reported activities (Depp et al., 2019). Momentary assessments have evidence for convergence with clinical ratings and evidence for validity in terms of response biases.

As mentioned above, in the development of cognition-enhancing drugs for schizophrenia, the U.S. Food and Drug Administration (FDA) indicated that significant improvement on a consensus cognitive performance endpoint would be necessary, but not sufficient, for drug approval. In addition, the FDA requires improvements on a functionally meaningful co-primary measure that would theoretically have more validity than cognitive performance measures. The National Institute of Mental Health Measurement and Treatment Research to Improve Cognition in Schizophrenia (NIMH-MATRICS) Initiative identified, through a broad-based multidisciplinary consensus process, standardized instruments (Green et al., 2008). In particular, two measures of functional capacity and two interview-based measures of cognition were selected for their psychometric properties and approved by the FDA, namely the Maryland Assessment of Social Competence (Bellack et al., 1994), the UCSD Performance-Based Skills Assessment (Patterson et al., 2001), the Schizophrenia Cognition Rating Scale (Keefe et al., 2006) and the Clinical Global Impression of Cognition in Schizophrenia (Ventura et al., 2008). However, given the relatively early stage of method development in this area, novel instruments also with different approaches and considering the different dimensions of outcome are expected. Similarly, Virtual reality assessment of functional capacity (VRFCAT) shows promising results in assessing functional capacity. VRFCAT is an immersive VR task simulating activities of daily living in a realistic and interactive virtual environment and it can recognize functionally meaningful improvements in patients' everyday lives (Harvey et al., 2019).

In conclusion, it appears clear that certain features of schizophrenia are not amenable to assessment other than with self-report. However, there are some characteristic response biases, including under reporting disability and mood state severity. For instance, interviews on cognition capacities do not correlate with cognitive performance, suggesting that patients (and also relatives) are disoriented about their (dis)abilities and may not see the relation with cognition deficits (Poletti et al., 2012). It is possible to avoid the most challenging of these biases, by avoiding asking about abilities and referencing normative standards. Moreover, it is useful to avoid asking questions that require substantial aggregation

of data.

5.2. Social cognition

Social cognition represents the cognitive capability to perceive, categorize and interpret social behavior of other people and concerns the various psychological processes that enable individuals to take advantage of being part of a social group. Social cognition is composed by multiple potential domains and multiple tasks can thus be used to measure it. While it is widely acknowledged that social cognition is a major determinant of functioning in schizophrenia with both direct and indirect effect, mediating neurocognition, it is less clear which domain of social cognition most strongly affect outcomes (Bechi and Spangaro, 2019). The Social Cognition Psychometric Evaluation (SCOPE) study (Pinkham et al., 2014) was conducted to identify and improve existing measures of social cognition so they can be suitably applied in large-scale treatment studies. This study surveyed experts, tested tasks, and examined the psychometric properties of existing social cognition measures. The results suggested only a limited set of measures that seemed suitable for use in clinical trials (Pinkham et al., 2018).

Given the challenges with performance based measures, the Observable Social Cognition Rating Scale (OSCARS) was designed, similar to Schizophrenia Cognition Rating Scale (SCoRS), but focused on social cognition abilities (Healey et al., 2015). It is an 8-item assessment scale evaluating subject's Theory of Mind, emotional perception, cognitive rigidity, jumping to conclusions and attributional style. The results showed that OSCARS was able to quantify Social Meta Cognition and that the correlation with functional outcome is stronger than that of performance-based social cognitive tests (Silberstein and Harvey, 2019).

6. Treatment of cognition

6.1. Pharmacological treatment

Current antipsychotic treatments do not satisfactorily address cognitive deficits in schizophrenia. However, there still is a debate if and how any pharmacological treatments could impact on cognitive outcome in schizophrenia, both in specific domains and global performance, as well as about the potential superiority of some drugs compared to others.

While early studies reported some degree of improvement in individuals treated with antipsychotics (mainly second generation agents-SGA), however mainly with small effect sizes that could be secondary to clinical effects or lack of the negative side effects of older medications (Harvey et al., 2001). Despite studies examining first episode and chronic patients, comparing multiple different treatments, results were quite inconsistent (Davidson et al., 2009; Sakurai et al., 2013). A recent systematic review and meta-analysis (Baldez et al., 2021) comparing several antipsychotics, confirmed the negative effects of haloperidol and evaluated differential effects of amisulpride, quetiapine, lurasidone, olanzapine, perphenazine, risperidone, and ziprasidone on specific cognitive domains.

Another element of interest that must be considered, although not exhaustively discussed in this paper, is the augmentation of antipsychotics with pro-cognitive agents, such as stimulants, Modafinil and d-Cycloserine. However, a comprehensive meta-analysis (Sinkeviciute et al., 2018) assessing the efficacy of pharmacological cognitive enhancers in schizophrenia, showed only limited positive effects and lack of evidence on the longer term. Many of these studies were poorly designed (Harvey and Sand, 2017) and better studies, including combining cognitive training and cognitive enhancement therapies, are in process (Harvey et al., 2020).

6.2. Anticholinergic and antihistaminergic effects on cognition

Medications with anticholinergic activity are widely used in clinical practice for the treatment of several organic diseases, but also for the treatment of different mental illnesses. The cumulative effect of these medications, also called anticholinergic burden (AB), has been shown to be associated with adverse outcomes and can lead to functional and cognitive decline (Reinold et al., 2021). AB may cause short term effects, such as confusion and memory loss in older adults, but also long term effects, such as increased risk of cognitive decline (Coupland et al., 2019). These findings are particularly interesting considering that several pharmacological therapies used to treat schizophrenia are characterized by significant anticholinergic properties (Kaar et al., 2020). Data in the literature highlighted that AB was associated with impaired cognitive ability and functioning (Eum et al., 2017, 2021; Joshi et al., 2021) as well as negative impact on the outcome of psychosocial treatment in people with schizophrenia (O'Reilly et al., 2016). In this view, clarifying the impact of cognitive impairment attributable to anticholinergic medication the burden may help optimize cognitive outcomes in psychosis. A study in FEP reported an association between higher daily equivalents of chlorpromazine and lower cognitive performance in verbal memory, processing speed, and global cognition (Ballesteros et al., 2018). Authors also found a deleterious effect on verbal memory caused by all psychiatric treatment with anticholinergic properties. Therefore, it is evident that clinicians should be aware of the potential cognitive impairment associated with antipsychotics also in FEP. Another recent study suggested that AB can have also a direct negative impact on functional capacity in people with schizophrenia (Khan et al., 2021). Thus, reducing AB could improve functional capacity and potentially real-world function in schizophrenia.

For antihistaminergic drugs, it is well known that they can cause several side effects, such as nausea and vomiting, dry mouth, urinary retention, blurred vision, confusion, drowsiness, dizziness, and restlessness. In addition to this, H1- receptors seems to be involved also in the weight gain. In particular, anti-histaminergic activity is the strongest predictor of weight gain with antidepressants (Salvi et al., 2016). These data are important because metabolic syndrome and cognitive deficits are related to each other in a bidirectional way in schizophrenia (Bora et al., 2017; Lindenmayer et al., 2012) and metabolic syndrome has been suggested to negatively influence CR outcome (Bosia et al., 2017). Antipsychotic Drugs with high levels of antihistaminergic activity and sedation, such as quetiapine, cause daytime sleepiness, which leads to impairments in cognitive functioning that are persistent for as long as 6 months (Loebel et al., 2014).

6.3. Cognitive remediation

Cognitive remediation (CR) is a behavioral training–based intervention that aims to improve cognitive processes with the goal of durability and generalization to global functioning. Recently CR has been included in the practice guidelines for schizophrenia. As a matter of fact, the 2019 German clinical practice guidelines emphasized that every person with schizophrenia should be offered CR, which had the highest recommendation grade (i.e., A) (Takahashi et al., 2020). Accordingly, the American Psychiatric Association Practice Guideline for the treatment of patients with schizophrenia suggested in the guidelines published in 2020 that patients with schizophrenia should receive CR (Keepers et al., 2020). The inclusion of CR in treatment recommendation for schizophrenia represents an important turn in the frame of approaching schizophrenia as a cognitive disorder.

Despite the variability across the specific programs used, in the past decades converging evidence was gathered on the positive effects of CR. A recent and comprehensive meta-analysis on 8000 participants evaluating the effects of CR (Vita et al., 2021) found an overall positive impact of CR on global cognition and functioning, strengthening the notion that CR represents a valid and effective treatment. This meta-analysis also took into account the core treatment characteristics, recently identified by an expert working group (Bowie et al., 2020), namely the presence of an active and trained therapist, repeated practice of cognitive exercises,

structured development of cognitive strategies and integration with psychosocial rehabilitation. Results underlined that integration with psychosocial rehabilitation is crucial for transfer of cognitive gains to functional outcome. This confirms previous findings suggesting that improvements in functional domains after CR occur only when other rehabilitative interventions, including standard rehabilitation therapy, are provided in synergy (Bowie et al., 2012; McGurk et al., 2015). Looking at gains in daily functioning, a study suggested that these depend on the achievement of a harmonious and balanced cognitive profile, rather than being related to quantitative changes in specific domains of cognition, supporting the idea that a qualitative leap in cognition is needed in order to gain an advantage in real life activities (Bosia et al., 2017).

Concerning durability, different studies support that CR effects persist at least on the short-medium term not only on cognition, but also in quality of life and reduced use of services (Garrido et al., 2017; Poletti et al., 2010; Vita et al., 2016). Functional gains accruing from combined CCT and vocational interventions appear to continue to accelerate for 18 months or more following the end of the active intervention (McGurk et al., 2015) in the medium-long term. Buonocore et al. (2018) evaluated the persistence of both cognitive and functional effects of a combined CR + standard rehabilitation therapy 5 years after the interventions (Buonocore et al., 2018). Results suggested that cognitive effects persist, while as for functioning, only the extension of the standard rehabilitation following CRT seems to produce a stabilization of the functional gain obtained after CR. These results suggest that prolonging standard rehabilitation could contribute to consolidate the acquired cognitive strategies and thus provide more structural changes, needed for a stable generalization of results to functional outcome. The results are supported by data from studies of healthy older people, where CR benefits were clearly persistent 10 years after treatment (Rebok et al., 2014).

Despite the proven effectiveness of CR, the range of effects sizes on primary outcomes is reported ranging from small to moderate (global cognition: d, 0.29 [95% CI, 0.24–0.34]; global functioning: d, 0.22 [95% CI, 0.16–0.29]) (Vita et al., 2021), highlighting the need to further optimize treatment to reach satisfactory outcome in all patients. In this view, it is of relevance to identify predictors and moderators of CR effectiveness. This would allow to act directly on predictive factors, if they are modifiable, or to adjust CR and even integrate it in the case of unmodifiable factors.

As mentioned above, the cognitive remediation expert working group identified CR core features that can be modifiable, thus providing recommendations for CR design, conduct, reporting, and implementation (Bowie et al., 2020). The identified core treatment characteristics are: 1) the presence of an active and trained therapist, who works with the patients in order to identify barriers, track progress, and adjust short- and long-term goals as needed; 2) repeated and intensive practice of cognitive exercises, whose difficulty level should increase to keep the tasks challenging and engaging; 3) structured development of cognitive strategies, facilitated by clinicians that should suggest potential strategies, if participants struggle to produce them; 4) integration with psychosocial rehabilitation in order to support participation in real world transfer activities. Although several studies suggest that hoe based CCT has similar cognitive efficacy across prodromal, first episode and more chronic patients, those interventions did not provide rehabilitation interventions and were not associated with spontaneous functional gains (Loewy et al., 2016; Ramsay et al., 2020).

Another relevant aspect that should be accounted is the presence of metabolic syndrome (MetS) in schizophrenia. Studies show that MetS influences CR-induced dynamic modulation of cognitive functions hampering the capacity to restore cognitive deficits. Bosia et al. (2018) showed significant cognitive improvement after CR only inpatients without MetS, thus suggesting that the standard CR protocol may not be sufficient and that prior or concomitant interventions targeting MetS should be recommended in these patients (Bosia et al., 2018).

Moreover, literature pointed out some possible unmodifiable predictors that may affect CR outcomes. In particular, current IQ could be a relevant moderator of CR benefits, since the change in IQ after the disease onset seems to affect patients' response to CR (Seccomandi et al., 2021a). Furthermore patients' age seems to be a factor limiting CR benefits in older people, specifically in the domain of executive functions (Seccomandi et al., 2021b). Genetic factors influencing CR response have also been investigated. A recent review on the topic identified polymorphisms in the Catechol-O-Methyltransferase (COMT), Brain-Derived Neurotrophic Factor (BDNF) and Excitatory Amino Acid Transporter-2 (EAAT2) genes as candidate predictors of CR outcomes (Penadés et al., 2020a). In details, the BDNF Met allele seems to inhibit the positive changes in BDNF serum levels after CR, thus hampering CR effects, similarly the COMT Val allele, associated to reduced prefrontal dopamine levels, appears to limit the cognitive improvements. Interestingly, these studies also suggest an interaction between genetic polymorphisms and pharmacological treatment that may affect CR improvements. Indeed, a reduced improvement in the core domain of speed of processing has been reported among COMT Val/Val patients treated with clozapine (Bosia et al., 2014). Lastly, the EAAT2 genotype seems to influence CR outcome, the T/T genotype (higher transporter expression) being associated with greater cognitive improvement after CR in working memory and executive functions. However, the effects of EAAT2 on executive functions were decreased by clozapine treatment (Spangaro et al., 2018).

Finally, there is some evidence of an interplay between CR and specific antipsychotics in determining synergistic effects on cognition. Regarding positive interactions between antipsychotics and CRT, Matsuda et al. reported that association between aripiprazole and neurocognitive rehabilitation seems to enhance the improvement in working memory and motor speed (Matsuda et al., 2014). Moreover combining treatment with lurasidone and CRT, a higher mean cognitive composite score emerged (Kantrowitz et al., 2016). These findings further suggest that combined and tailored therapeutic approaches are needed in order to improve cognition and quality of life in patients affected by schizophrenia (Swerdlow, 2011).

6.4. Potentiation strategies

Given the small to moderate effects of CR, recent studies are focusing on integration with other pharmacological and nonpharmacological strategies that can lead to greater improvement in cognition, symptoms, and functioning.

An element of interest is the augmentation of CR with pro-cognitive agents. Different pharmacological strategies (stimulants or plasticity-inducing agents) may lead to different types of gains when combined with CR. Several plausible mechanisms of action of pharmacological augmentation to CR have been theorized. Pharmacological interventions with stimulants, such as amphetamine and related compounds, could enhance motivation. These compounds are able to increase sensitivity to reward, thus perceived reinforcement, acting on dopamine-mediated reward system. Moreover, pharmacological interventions may increase training efficiency improving attentional performance. In addition, enhancing processing speed, drugs may also induce the consolidation of therapeutic gains making rapid early gains and solidifying motivation to perform (Harvey and Sand, 2017). Swerdlow et al. demonstrated that amphetamine treatment showed benefit on gains during auditory training in schizophrenia. Moreover, differently from placebo group, benefits persisted one week after a single 1-h training session (Swerdlow et al., 2016). The augmentation potential of Modafinil was also examined with conflicting findings. Michalopoulou et al. reported positive effects of combined treatments (Michalopoulou et al., 2015), while a previous study was negative (Gilleen et al., 2014). Psychoplastogens, such as glutamatergic compounds have the potential to induce neuroplasticity after single administration. In particular, d-cycloserine (DCS) has been studied in schizophrenia for its properties of partial antagonism on *N*-methyl-D-aspartate glutamatergic receptors and

the potential to modify the memory consolidation process (Goff et al., 2008). To date the study conducted by Cain et al. is the only proof of effectiveness of d-Cycloserine in augmentation to CRT, stating improvements in memory of a practiced auditory discrimination task compared to placebo. In addition, improvements in negative symptoms were also detected (Cain et al., 2014). An additional study examining the effect of D-serine, a related compound, as augmentation strategy did not find incremental benefits (D'Souza et al., 2013). However, higher dose may be required as suggested by authors. Concerning guanfacine, a norepinephrine alpha-2 agonist licensed for the treatment of ADHD, McClure et al. (2019a) performed a study of augmentation of cognitive remediation and social skills training with guanfacine in patients with schizotypal personality. Participants showed significant improvements in reasoning, problem solving and functional capacity compared to group treated with cognitive remediation, social skills training, and placebo Clearly the data are promising, but too few to draw conclusions. Moreover, all the possible dosing strategies and augmentation possibilities have not been explored making the overall scenario interesting in terms of future research.

Another promising strategy is to combine CR with aerobic exercise. A meta-analysis showed that exercise significantly improves global cognition and the cognitive domains of social cognition, working memory, and attention, especially in those interventions using higher dosages of exercise (Firth et al., 2017). Based on these data, Takahashi et al. (2020) evaluated the combined effects of CR + aerobic exercise, showing a significant increase of cortical thickness in the right entorhinal cortex after 6 weeks of intervention (Takahashi et al., 2020). These results suggest that aerobic exercise exerts structural neuroplastic effects. However, results on the combined effects of CR + exercise occasionally inconsistent. McGurk et al. (2021) evaluated if the increase of brain derived neurotropic factor (BDNF), following exercise may mediate improved cognitive functioning, but results did not show that exercise augments CR, possibly because the cognitive remediation program resulted in strong gains in cognitive functioning (McGurk et al., 2021).

Lastly, another relevant tool that can be integrated in CR protocols is transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique that can promote neural plasticity. A 2021 clinical trial evaluated whether the addition of tDCS to CR can lead to clinically relevant improvements in cognitive and daily functioning (Poppe et al., 2021). Results from this pilot study show that the addition of tDCS to CR seems to have an additive effect, however further studies are needed to explore this aspect.

6.5. Neuroimaging the effects of cognitive remediation

Despite the increasing number of neuroimaging studies in schizophrenia, there is still no consensus on specific neuroimaging markers able to define cognitive in patients. However, there is evidence of a greater involvement of specific networks and brain areas in cognitive processes. Specifically, Fractional Anisotropy (FA) of Corpus Callosum, gray matter (GM) in the salience network and fractional amplitude of low-frequency fluctuation (fALFF) in the Default Mode Network are highly predictive of multiple cognitive domains (Sui et al., 2018). It can thus be hypothesized that with a combined approach, analyzing separate cohorts co-varying multimodal signatures of these circuits, a neuroprognosis can be drawn in terms of cognitive performance.

A promising and growing field is the research of structural and functional brain effects of CR that may lead to a better comprehension of the neurobiological mechanisms underlying cognitive abilities and their dynamic modulation through targeted interventions. Concerning brain morphology and volumes, cognitive improvements achieved through CRT seem to be associated with basal cortical thickness in some regions of the frontal and temporal lobes (Penadés et al., 2016). Protective effects of CR on gray matter of the frontal and temporal lobes have also been suggested (Eack et al., 2010), as patients undergoing CR showed greater preservation of gray matter volume over 2 years. Specifically, patients showed less gray matter loss in the hippocampal region (Eack et al., 2010; Morimoto et al., 2018) and fusiform gyrus and even greater gray matter increases in the left amygdala (Eack et al., 2010; Penadés et al., 2017). On the other hand, CR showed benefits also on white matter (WM). Specifically, increased FA index in the anterior part of the genu of the corpus callosum emerged after CR, highlighting greater integrity of fibers (Penadés et al., 2013). In addition, significantly increased FA values were also described in the posterior lobe of the left cerebellum, along with significantly decreased radial (RD) and mean diffusivity (MD) values (Matsuoka et al., 2019).

Looking at neural activation following cognitive training, evidence suggests that CR induces increased activity in several brain regions, probably depending on the specific training program used. Despite the detection of a widespread involvement of different brain areas, the prefrontal cortex seems to be the most implicated (Mothersill and Donohoe, 2019; Ramsay et al., 2017). Other areas of interest are parietal lobes and temporal regions, such as amygdala and superior temporal gyrus (Mothersill and Donohoe, 2019).

Finally, CR seems to modulate activity and synchronization at the network level. Indeed, patients undergoing CRT showed a reduction in over-activation of the central executive network (CEN) during task-related responses and downregulation of DMN, commonly over-active in schizophrenia, suggesting improved efficiency in both networks (Penadés et al., 2013). Therefore, balanced activity and synchronization between different networks represent a target of therapy. In addition, increased thalamo-temporal connectivity is reported in response to targeted cognitive training in recent onset schizophrenia (Ramsay et al., 2020).The concept of connectivity is closely related to WM and general improvements in functional connectivity (FC) were reported after CR, particularly in frontal and temporal brain regions, implicated in problem solving and emotion processing (Eack et al., 2016). Increased thalamus connectivity was also described (Ramsay et al., 2020), as well as increased connectivity between sensorimotor networks (Penadés et al., 2020b).

Neuroimaging data have also been investigated to identify markers affecting CR response. Among these, as mentioned before a greater baseline thickness in frontal and temporal cortex emerged as a predictor of better cognitive outcome after CRT (Penadés et al., 2016). Moreover, preserved integrity within long-range WM fibers connecting prefrontal-thalamic-sensorimotor areas may be an important determinant for neurocognitive benefits induced by CRT (Subramaniam et al., 2018). Specifically, integrity of the fronto-occipital fasciculus predicted improvements in attention/vigilance, while WM integrity within the right corticospinal tract and bilateral medial lemnisci predicted improvements in executive functioning (Subramaniam et al., 2018). Other findings support the role of fractional anisotropy (FA) in the superior longitudinal fasciculus (SLF) in predicting improvements in visual-spatial working memory and the role of average FA in determining enhancements in social cognition (McClure et al., 2019b).

With respect to prediction of response to antipsychotic treatments, several markers are reported for positive symptoms. Among these, increased ventricular volume and reduction of gray matter, particularly in frontal and medial temporal lobe are associated with decreased response (Bodnar et al., 2012; Jääskeläinen et al., 2014; Lieberman et al., 2001). Increased glutamate levels in prefrontal areas and in the striatum are also associated with refractory positive symptoms (Demjaha et al., 2014; Mouchlianitis et al., 2016). Otherwise, greater activation of prefrontal and striatal areas is reported in treatment responders (Bodnar et al., 2012; Nielsen et al., 2012) as well as increases in FC between these regions. Still, neuroimaging may represent a useful tool to identify underlying substrates and mechanism of action of specific therapies, allowing us to understand the best way to combine pharmacological and nonpharmacological interventions.

7. Conclusions and future directions

Schizophrenia is a major psychiatric disorder that afflicts about 1% of the world's population, falling into the top ten medical disorders causing disability. It is widely acknowledged that such disability is mainly determined by the core cognitive deficits that accompany the illness and still represent a treatment issue. In this view, significant research efforts have been dedicated to both understanding the etiology and course of cognitive impairment, as well as to develop new targeted treatments. However, despite the scientific breakthroughs of recent decades and the undoubtable changes in patients' quality of life from the Kraepelin's era, existing therapeutic strategies have limited effects on neuropsychological performance.

The relation between cognition and schizophrenia is such that it can be approached as a cognitive disorder. Cognitive deficits clearly arise before symptom onset, they are subtle during the premorbid phase and become increasingly pronounced during the prodromal phase up to the first episode of psychosis. This course strongly suggests the presence of neurodevelopmental alterations, which is further supported by neuroimaging findings of early developmental abnormalities with trajectories that are comparable to those of cognitive deficits. Based on this developmental path, cognition gained increasing interest also a possible marker for early detection and prevention of psychosis. Cognitive performance identifies subjects at risk of psychosis, and identified as a predictor of transition to psychosis. Moreover, while the role of pharmacological treatment in the pre-psychotic stage is yet debated in terms of both efficacy and side effects, behavioral interventions targeting cognition appear to be promising strategies for subjects at risk. After the psychotic onset and through the chronicity of the illness, the trajectory of cognitive impairment is still less clear, with early reports of improvement, but more recently, better studies showing worsening performance relative to controls. At this stage, many factors may contribute to the progression of cognitive deficits, including neurodegenerative processes linked both to the disorder itself, as well as to life styles and comorbidities.

Looking at treatments for cognitive deficits in schizophrenia, a crucial aspect to consider is the outcome measure. While a good consensus has been reached on standardized batteries evaluating cognitive deficits in patients with schizophrenia, the picture is less clear for the assessment of functional outcome. Indeed, improvement of cognition has the goal to improve functioning. However, there are still some open issues, concerning both the relation between specific cognitive and functional domains, as well as the assessment scales used. In particular, a growing area is the development of tools assessing functional capacity, an intermediate between cognition and community functioning, as well as interview-based measures of cognition and social cognition.

Considering treatment options, currently available antipsychotics not only do not restore cognitive dysfunction, but they may also aggravate it directly and indirectly, especially through anticholinergic and antihistaminergic activity. On the other hand, current findings show that non-pharmacological approaches based on neuroplasticity stimulation are able to enhance neuropsychological functioning, presenting good feasibility, tolerability, and replicability. Among these, cognitive remediation is being increasingly implemented in clinical practice, showing positive effects on both cognitive deficits and functional outcomes that persist, at least, in the mid-term period. Of note, neuroimaging studies demonstrated detectable effects of CR on brain activity proving its ability to modulate neuroplasticity and suggested a protective effect on gray matter. Cognitive remediation, currently considered the best treatment option for cognitive dysfunction, also contributed to a shift in the overall view of schizophrenia. Indeed, historically cognitive deficits were seen to unavoidably progressive, or, at the best, stable. Contrary to these assumptions, in the past decades growing evidence showed that cognitive remediation can induce significant changes not only at the behavioral, but also at the biological level, leading to a global improvement in neural system dysfunction. However, cognitive remediation is only capable of inducing moderate changes in patients with schizophrenia, with a high outcome variability between subjects. This great heterogeneity of results depends on several modifiable and unmodifiable factors that influence CR effects. These variables should be carefully evaluated to optimize treatment and address all the relevant components jointly.

Finally, combined approaches adding different pharmacological and non-pharmacological strategies to treat cognitive deficits in schizophrenia appear particularly promising, with the potential to significantly increase the effect sizes of improvements and percentage of treatment responders. In this view, neuroimaging represents a useful tool to unravel the underlying neurobiological effects and neuroplasticity mechanisms, as well as to identify biomarkers to predict treatment outcome. This would pave the way to individualize interventions as well, which can also be dynamically modulated through the course of treatment itself, according to the patient's needs.

Declaration of competing interest

Dr. Harvey has received consulting fees or travel reimbursements from Alkermes, Bio Excel, Boehringer Ingelheim, Karuna Pharma, Merck Pharma, Minerva Pharma, SK Pharma, and Sunovion Pharma (DSP/Angelini) during the past year. He receives royalties from the Brief Assessment of Cognition in Schizophrenia (Owned by Verasci, Inc. and contained in the MCCB). He is chief scientific officer of i-Function, Inc.

Dr. Cavallaro has received honoraria as for lectures from Angelini.

Dr. Bosia has received research grants from the Italian Ministry of Education and the Italian Ministry of Health but does not have financial relationship to any pharmaceutical company.

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Dr. Howes is a part-time employee of H. Lundbeck A/S and has received investigator-initiated research funding from and/or participated in advisory/speaker meetings organized by Angellini, Autifony, Biogen, Boehringer-Ingelheim, Eli Lilly, Heptares, Global Medical Education, Invicro, Jansenn, Lundbeck, Neurocrine, Otsuka, Sunovion, Rand, Recordati, Roche and Viatris/Mylan. Neither Dr. Howes or his family have holdings/a financial stake in any pharmaceutical company. Dr. Howes has a patent for the use of dopaminergic imaging.

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Dr.Kahn has no recent biomedical conflicts of interest.

Dr. Vita received, during the past years, directly or indirectly, support for clinical studies or trials, conferences, consultancies, Congress presentations, advisory boards from: Angelini, Boehringer Ingelheim, Innovapharma, Janssen- Cilag, Lundbeck, Otsuka, Pfizer, Recordati, Roche, Rovi Pharma, Takeda.

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