

Cognitive deficits in psychotic disorders and their impact on social functioning

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Summary

A large body of evidence demonstrated the presence of cognitive deficits in schizophrenia and schizophrenia-spectrum disorders. Such dysfunctions are also reported in mood disorders, although the results are conflicting as to the severity of the impairment and the involved cognitive domains. Only a few studies compared the profile and severity of cognitive deficits in psychotic and mood disorders, especially during phases of clinical stability. In subjects with schizophrenia, as compared to those with other syndromes, cognitive deficits are more frequent, severe and stable over time; furthermore, they present a lower association with symptoms, clinical phase and drug treatment. Several studies reported that cognitive deficits have a greater impact on real-life functioning than symptoms. Furthermore, there are evidences that cognitive impairment interferes with the outcome of psychosocial rehabilitation programs. Therefore, cognitive deficits are considered an important target for the development of new pharmacological treatments and for rehabilitation programs for patients with schizophrenia and other severe psychiatric conditions. This paper provides a review of the most recent research on cognitive impairment in schizophrenia and schizophrenia-spectrum disorders, and on its association with functional outcome.

Key words

Schizophrenia • Schizophrenia-spectrum disorders • Cognitive deficits • Functional outcome

Introduction

A large body of evidence demonstrated the presence of cognitive deficits in schizophrenia and schizophrenia-spectrum disorders. The cognitive domains mostly impaired are general cognitive abilities, attention, executive functions, working memory, speed of processing, verbal and semantic memory¹⁻⁵. In schizophrenia, compared to other syndromes, including major depressive and bipolar disorder, these deficits are more frequent and severe, show a greater stability over time and are less correlated to symptoms, clinical stage and pharmacological treatment^{6,7}.

The research interest for cognitive impairment in subjects with schizophrenia or other primary psychotic disorders has been limited for a long time. In the last twenty years, the increasing acknowledgement of etiopathogenetic models of these disorders as neurodevelopmental disorders has renewed the interest for detection and treatment of cognitive deficits. These models indicate that subjects at high risk for psychosis demonstrate increasing neurodevelopmental anomalies, with detrimental effects on neural plasticity, related to both genetic and environmental factors^{8,9}. Recent evidences support the hypothesis that genetic influence is not directly related to psychotic disorders, but to specific endophenotypes associated with them, i.e. pathological traits (for example, cognitive deficits) predisposing to the onset of the disease and influencing its course and outcome¹⁰. For these evidences and for the major impact of cognitive impairment on psychosocial functioning, the treatment of cogni-

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tive deficits has become an important therapeutic target in psychotic disorders.

Cognitive deficits in schizophrenia patients

Several studies have contributed to the shift of the research focus on schizophrenia from clinical symptoms to cognitive impairment, providing evidence that the latter predicts functional outcome. It has been widely demonstrated that these deficits have a greater impact on patients' global functioning, and therefore on the outcome of the disorder, compared to positive symptoms, negative symptoms and disorganization¹¹⁻¹⁶. A large study, carried out in 921 subjects with schizophrenia and on their first-degree relatives by the Italian Network for Research on Psychoses (NIRP), has analysed the impact on real life functioning of illness-related variables, such as psychopathology and cognitive deficits, environmental factors and personal resources. Using very sophisticated statistical analysis, the study demonstrated that psychotic symptoms have a limited impact on real-life functioning¹⁴⁻¹⁶, while cognitive deficits explain most of the variance of real life functioning of these subjects^{14 16}.

A large body of evidence suggests that cognitive impairment represents a nuclear aspect of schizophrenia: first, the presence of these deficits during the first episode of psychosis, with characteristics similar to those observed in chronic patients^{5 6 18 19}; second, their role as a vulnerability factor suggested by their presence before the onset of the syndrome^{20 21} and in unaffected first-degree relatives of subjects with schizophrenia^{22 23} and, finally, their persistence after symptom remission²⁴.

A study conducted within the European First Episode Schizophrenia Trial (EUFEST), in a large sample of patients during their first episode of a schizophrenia spectrum disorder (schizophrenia, schizoaffective disorder, schizophreniform disorder), showed that a mild/severe impairment of some cognitive domains is already detectable during early stages of the disorder (speed of processing, attention, verbal memory and cognitive flexibility)^{6 19}. The study also reported that cognitive dysfunction is substantially independent from clinical symptoms, is comparable in drug-naïve subjects and those exposed to a limited amount of antipsychotic treatment and, finally, that it is not associated with the duration of untreated psychosis⁶. These results have been confirmed by a recent metanalysis supporting the existence of cognitive impairment in the earliest stages of the disease in drug-naïve subjects¹⁸, and showing a pattern of cognitive dysfunction (verbal and visual memory, executive functions and attention) similar to that observed in subjects on pharmacological treatment^{25 19}. The study further demonstrated that antipsy-

chotic drugs do not substantially improve the cognitive impairment of these subjects¹⁹.

The hypothesis that cognitive deficits might represent a vulnerability marker has been further confirmed by studies that have reported the presence of these deficits in children that later developed schizophrenia, in comparison with healthy children and children that later developed a mood disorder^{8 24}.

It has been reported that the risk of developing schizophrenia or a psychotic disorder is higher in subjects with reduced general cognitive abilities, as reflected by a lower intelligence quotient (IQ)⁸.

A meta-analysis²⁴ reported that subjects with schizophrenia showed premorbid IQ 1,5 standard deviations below the reference population. Furthermore, it showed that IQ is significantly lower during the first episode of the disease than in the premorbid stage, and it is further reduced in chronic stages. Some authors have reported a specific longitudinal course of the cognitive impairment, during the lifetime of each individual with schizophrenia, with an overall stability in between two periods in which a deterioration is observed: before the psychotic onset and around age 65²⁵.

The mechanism through which a low IQ might contribute or predict the onset of schizophrenia remains unclear. A first hypothesis is that a low IQ might represent a marker of neuroanatomical alterations increasing illness vulnerability; a second hypothesis is that it might predispose to the development of schizophrenia by exposing subjects to a greater psychosocial stress, as cognitive impairment is associated to reduced coping abilities and resilience; a further hypothesis is that low IQ and schizophrenia might share one or more etiologic factors (for example, the genetic asset)²⁶.

Some studies indicate that IQ impairment might be present only in a subgroup of subjects with schizophrenia, characterized by a worse premorbid adjustment^{2 5 8 26} and might predispose to a greater cognitive deterioration at least during the years immediately preceding the onset². In this subgroup, cognitive dysfunction is more severe, often associated with a prevalence of negative symptoms and is more separated and distinct with respect to subjects with bipolar disorder^{5 26}.

Overall the reviewed studies confirmed the presence and substantial stability, after the onset of the disease, of cognitive impairment in most subjects with schizophrenia and that they are outcome predictors.

As a consequence, some authors believe that cognitive deficits should be integrated in the diagnostic criteria of this syndrome^{27 28}. However, it is still unclear if the inclusion of cognitive deficits in the diagnostic criteria of schizophrenia might help in better discriminate the syndrome from other psychiatric disorders, such as mood disorders, that share with schizophrenia the genetic

susceptibility, as well as epidemiological and clinical aspects.

Cognitive deficits in mood disorders

Cognitive impairment is detectable in subjects with bipolar disorder before and at the onset of the disease and they persist even during stages of clinical remission, as reported in schizophrenia^{29 30}. Moreover, a study conducted by Bonnin et al.³¹, demonstrated that subthreshold depressive symptoms along with verbal memory deficits and executive dysfunctions represent an important long-term outcome predictor even in euthymic bipolar patients. Similar results have been reported in subjects with major depressive disorder, in whom cognitive deficits have an impact on real life functioning, especially on work skills^{32 33}.

Two cross-sectional studies have compared the neurocognitive deficits of subjects with schizophrenia and those with a diagnosis of a mood disorder (manic or major depressive disorder) with psychotic features^{34 35}. The results showed that the difference between subjects with schizophrenia and those with a mood disorder was quantitative and not qualitative, since the same pattern of impairments is observed, but the deficits are more severe in schizophrenia. Since these differences are mostly quantitative, it is not possible to exclude that they simply reflect the different levels of severity of these disorders.

Some studies reported that subjects with a mood disorder without psychotic features show a neurocognitive profile closer to that of healthy controls¹. These results seem to support the hypothesis that cognitive functioning is much more related to psychosis, as a dimension, rather than to a specific diagnostic category.

A study conducted by Hochberger et al.³⁶ compared subjects diagnosed with schizophrenia, schizoaffective disorder or bipolar disorder with their first-degree relatives. Cognitive deficits were detectable in each group of patients, but their severity increased from bipolar disorders to schizoaffective disorder and to schizophrenia. The study reported that the most important determinant of cognitive impairment was the presence of psychotic symptoms³⁶.

A few studies have described qualitative differences in the cognitive functioning of patients diagnosed with schizophrenia or mood disorders, reporting only in the first group an impairment of general cognitive abilities (IQ) and/or of some aspects of attention, memory and executive functions^{37 38}.

Based on the evidence analysed so far, as also suggested by the meta-analysis by Heinrichs and Zakzanis³, it is not possible to draw conclusions on whether cognitive deficits might represent a distinctive and specific aspect of schizophrenia.

Social cognition and schizophrenia

Social cognition is a construct including a wide set of social and emotional skills and knowledge, evolving during the development of each individual, which allows subjects to modulate their behaviour according to the specific social environment they belong to. It includes emotion processing (perception and modulation of emotions), social perception (i.e., understanding key aspects of social situations and interactions); social knowledge (i.e., insight concerning social roles and rules characterizing social situations); theory of mind (i.e., the ability to understand and attribute internal states, such as desires and beliefs, and to predict own and others' behaviour based on those mental states); and attributional style, i.e. the ability to understand the causes of particular negative and positive events^{39 40}.

The aspects of social cognition that are most impaired in schizophrenia include: emotion processing, social perception and knowledge, theory of mind (ToM) and attribution style^{39 40}. These deficits are considered nuclear aspects of schizophrenia, as are neurocognitive ones, because an impairment of several social cognition aspects is already detectable before the onset of the disease, in subjects with a high risk of developing the disorder, and after symptom remission^{41 42}. The NIRP study, cited above, demonstrated that healthy first-degree relatives of schizophrenia patients do not show a social cognition impairment, using the test included in the MCCB²². Discrepant findings have been reported in first-degree relatives of subjects with schizophrenia, ranging from no deficit to a mild impairment^{44 45}. These conflicting results are probably due to the heterogeneity of the measures used to assess social cognition in the different trials, some of which might tap domains of social cognition that are not impaired even in subjects with schizophrenia. Another study on the NIRP cohort has demonstrated that the subdomains of social cognition are not all equally impaired in subjects with schizophrenia, with ToM deficits showing the greater discriminative ability among clusters of subjects with no deficit, mild deficit or severe deficit⁴⁶.

Several studies have reported that social cognition, and specifically ToM, is strongly associated to social functioning⁴⁶⁻⁴⁸. The relationship among neurocognition, social cognition and functioning has been modelled, in the NIRP study, using structural equation modelling (SEM^{14 16}). The results showed that the impact of neurocognitive deficits on global functioning¹⁶ and on two specific domains of real-life functioning, i.e. interpersonal relationships and work skills, is partially mediated by social cognition impairment, both in patients and in their unaffected first-degree relatives¹⁴.

These data highlight that an adequate assessment of social cognition impairment is necessary to implement

individualised, targeted rehabilitation interventions for people with schizophrenia.

Cognitive deficits and real-life functioning

Despite the remarkable progress of both pharmacological and psychosocial treatments, schizophrenia remains one of the most disabling diseases in the world⁴⁹. Deficits in everyday life, work and interpersonal skills, as well as failure in participation in and improvement with rehabilitation programs represent the major determinants of disability in subjects with schizophrenia and cognitive deficits have a significant impact on all of them⁵⁰. Several studies, in fact, reported that cognitive deficits are related to poor psychosocial functioning and poor compliance to psychosocial rehabilitation programs^{11-17 50-53}. Cognitive impairment predicts functional outcome at the same level or even better than positive and negative symptoms^{15 16 52} and is associated with disability even in phases of clinical remission⁵⁰.

In a review of longitudinal studies, with at least 6-month follow-up, cognitive measures found to predict social and community functioning in subjects with schizophrenia included secondary verbal memory, verbal fluency and cognitive flexibility⁵¹. Measures of IQ, executive functioning, vigilance, attention and working memory also showed significant associations with poor functional and clinical outcomes⁵². In a comprehensive literature review, Green et al.⁵² highlighted that different cognitive deficits might have an impact on specific areas of psychosocial functioning. In particular, verbal memory and attention are predictive of everyday life abilities, social problem solving and the ability to learn new skills; while deficits of working memory and executive functioning might be linked to occupational functioning deficits. According to these results, Bowie et al.¹⁷, using SEM, reported that attention and working memory deficits were not directly related to everyday life abilities, but were strong predictors of functional and social competence, which mediated an effect on that specific functional outcome. The same cognitive deficits were directly related to work skills, interpersonal functioning and social behaviour, independently of their indirect impact on everyday life abilities. As reported by some authors⁵³, not all functional deficits might be related to cognitive impairment. Therefore, the positive impact that cognitive remediation programs have on cognition do not always translate into an improvement of functional outcome and everyday life skills⁵⁴. Cognitive deficits explain 20-60% of the variance of real-life functioning; consequently, 40-80% of the variance is related to other factors^{51 55}. Some authors underline the role of mediating variables that might help redefine the causal link between cognitive functioning and functional outcome, although how these interdependent variables might have an impact on

the quality of life of schizophrenia patients is still controversial. One of the most widely accepted model was proposed by Harvey et al.⁵⁶ that distinguished between “capacity or competence” (“what can be done”, i.e. the performance in optimal conditions) and “performance” (“what is done”, i.e. real-life functioning). Based on this model, the study conducted by Bowie et al.¹⁷ showed that cognitive deficits do not have a direct impact on real-life functioning, while strongly predicting subjects’ “functional capacity”, which in its turn correlated with several functional outcomes, such as interpersonal abilities, community activities and work skills. These results have been later confirmed by the NIRP study, as said before, in which it has been demonstrated that neurocognitive deficits have an indirect impact on real-life functioning, through functional capacity and social cognition^{14 16}. However, SEM analysis, used to assess the corresponding role of predictors or mediators of the impact of several variables on functioning, are theory-driven and are influenced by the theoretical model that is applied. Using the innovative “network analysis”, a data-driven approach, Galderisi et al.¹⁵ demonstrated that both neurocognitive deficits and social cognition deficits are associated with functional capacity and, through this variable, with everyday life abilities; they are then strongly associated with work skills and interpersonal functioning. These results have important therapeutic implications for rehabilitation interventions: the primary goal of cognitive remediation in schizophrenia patients might be the improvement of the individual functional capacity and of everyday life abilities. “Recovery-oriented” strategies, focusing on the development of independent life skills and social inclusion of the subjects more than just symptom control, are supported by these data. Since real-life functioning was found to be related also to other factors, such as negative symptoms¹⁴⁻¹⁷, there is a strong need for individualised rehabilitation programs. In the last few years, consisting evidences suggest that negative symptoms and social cognition might be significant predictors of some functional domains, specifically of interpersonal functioning. A literature review⁵⁷ has shown an association among negative symptoms, cognitive functions and functional outcome. Using a test which is far from being ideal, this meta-analysis provided support to a mediation role of negative symptoms for the impact of cognitive deficits on functional outcome. However, other studies¹²⁻¹⁷ did not confirm a mediation role of negative symptoms. Some authors reported that negative symptoms and several cognitive domains have both direct and indirect effects on functional outcome; nonetheless, the individual contribution of these variables are relatively modest, while cognitive variables along with clinical symptoms explain 20-35% of the variance of outcome measures^{12-14 16}. These data suggest the complexity of

the relationships among several factors involved in the functional outcome of schizophrenia^{14 58}.

Several studies reported that social cognition deficits have a greater impact on functioning, compared to the traditional neurocognitive measures and to psychopathology¹³. In fact, a recent meta-analysis, assessing the association of neurocognitive and social cognition deficits with global functioning, using data collected from 2692 patients, confirmed that social cognition, and particularly ToM deficits, are stronger predictors of social functioning than neurocognitive deficits⁵⁵. As already reported in the previous paragraphs, several studies have reported that social cognition partially mediates the impacts of neurocognitive deficits on real-life functioning¹¹⁻¹⁶.

Therefore, social cognition now represents a promising target of interventions aimed at achieving a better social functioning⁵⁹.

In conclusion, only an adequate and comprehensive assessment of cognitive deficits and the individualization of rehabilitation interventions can achieve an improvement of real-life functioning and of the patients' quality of life.

Conclusions

Cognitive deficits are a core aspect of schizophrenia, representing a risk factor for the onset of the disease and influencing its course and outcome. Thus they represent an important aspect to be assessed in schizophrenia and psychotic disorders and a strategic target

of pharmacological and rehabilitative treatments, both in primary and in secondary prevention.

The standardization of assessment of cognitive deficits in schizophrenia has progressed more than in other psychotic disorders⁶⁰. However, neuropsychological test batteries specifically developed for schizophrenia-spectrum disorders, as well as most of the individual neuropsychological tests included in these batteries, can be applied in the cognitive assessment of patients diagnosed with other psychiatric disorders. The systematic assessment of cognitive deficits in all severe psychiatric disorders needs to be considered one of the main goals of research and clinical practice.

The increasing number of studies on symptoms remission^{61 62} and evidence of modest association with improved real-life functioning and quality of life^{62 63} suggest the importance of an integrated treatment, in which pharmacological and rehabilitation interventions target different aspects of the multifaceted clinical picture of schizophrenia.

Literature findings on the relationships of cognitive deficits with functional outcomes have also highlighted the role of mediating variables such as functional and social competence, that need to be addressed in the development of focused and individualised treatments^{15 62 63}.

Conflict of Interest

None.

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