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Cognitive dysfunctions in psychiatric disorders: recognition and treatment

Guest Editor: Antonio Vita



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People suffering from psychosis, in particular from schizophrenia and bipolar disorder, but also from depression, present various disorders of cognitive functions, both in the context of neurocognition and of social cognition. These deficits have a significant negative impact on patient's functioning in the real life and contrast the clinical remission and functional recovery of the patient. The evaluation of these deficits and their treatment are therefore an essential objective of an effective management of subjects with psychiatric disorders in the perspective of recovery and psychosocial reintegration.

The 1st National Conference promoted by the Italian Group for the study and treatment of Cognition in Psychiatry (GICoPsi), held in Naples on 31.5.2017, has addressed the issues of the characteristics of neurocognitive dysfunctions and social cognition in severe mental disorders and their functional impact, that of the use of tools for the assessment of cognition and functioning that are both valid but also easily applicable in clinical practice, as well as that of the possible treatments of cognitive deficits. The role of drugs available today and that of targeted cognitive rehabilitation interventions applied to the main psychiatric disorders have also been reviewed. Finally, some qualified experiences of implementation of cognitive rehabilitation techniques within the Mental Health Services of our Country were presented and compared.

This Special Issue of the Journal of Psychopathology collects the speakers' contributions to the Congress, the inaugural moment at the national level of the Group.

The Italian Group for the Study and Treatment of Cognition in Psychiatry (GICoPsi) is an Association established with the aim of promoting the study and scientific research in the areas of characterization, assessment and treatment of cognitive dysfunctions in the main psychiatric disorders. In particular, objectives of the Association are:

- a) to promote initiatives aimed at developing, among psychiatrists and mental health workers, the study of alterations of cognitive functions in the main psychiatric disorders and their treatment;
- b) to sensitize the public opinion and public structures on the need to develop and support this branch of psychiatry;
- c) to promote the organization of conferences, congresses, courses and seminars, for the purposes referred to in the previous points;
- d) to collaborate with authorities, bodies and associations for the development of initiatives that are part of its aims;
- e) to promote and encourage scientific studies and publications, collect data and news, also at the international level, and carry out research projects in the field of characterization, assessment and treatment of cognitive dysfunctions in the main psychiatric disorders;
- f) to encourage the development of initiatives related to the educational and professional updating of associates.

Silvana Galderisi
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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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Assessing cognition and real-world functioning in schizophrenia

Summary

With the new focus on functional recovery in schizophrenia, factors limiting function in schizophrenia are receiving increasing attention.

Neurocognitive (NC) impairment accounts for 20-60% of the variance in real-world outcome. The effect sizes of the associations between NC and functional outcome tend to be medium for specific domains and larger for summary scores. Mapping NC deficits often requires the use of extensive test batteries that are lengthy and costly and require advanced training in assessment to score and utilize the results. The currently available NC assessment instruments differ widely in the population intended for use, administration time, interpretation of results, and the assessment of certain NC domains.

Social cognition (SC) contributes to functional outcomes beyond the influence of NC and may have a greater impact than NC on social outcomes. In addition, SC may mediate the relationship between NC and social functions in both chronic and first-episode patients. The degree of the relationship between SC and functioning varies, depending on the SC domain and the type of functional outcome assessed. In the past, there has been controversy over what SC processes should cover. Moreover, the most critical issue is that there is no consensus in the field as to which measures best assess each SC domain. As a result, a heterogeneous group of tasks have been administered with significant conceptual overlap and questionable psychometric properties across studies. This problem is present across all SC domains and contributes to the inconsistency of the reported findings.

The assessment of real-life functioning in schizophrenia presents complex challenges from variability in the operational definition of functional outcome to problems in identifying optimum information sources. In this context, there are still few satisfactorily reliable instruments for the assessment of functional outcomes that are practical in terms of time involved, and most real-life functional outcome scales seem to be largely redundant with each other when utilized simultaneously.

This update describes the main NC and social cognition (SC) batteries and real-world assessments used in schizophrenia and discuss their advantages and disadvantages.

Key words

Schizophrenia • Neurocognition • Social cognition • Real-world functioning • Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) • Specific Levels of Functioning (SLOF)

Introduction

During the last two decades, the field of psychiatry has moved toward the goals of remission and recovery rather than mere symptom improvement¹. Recovery refers to patients being able to function normally at work or school, in the community, and at home. It may occur even if patients are still experiencing some ongoing symptoms. Recovery can also involve a host of subjective experiences including attaining a self-appraised acceptable quality of life or reasonable sense of social rank and recapturing a cohesive sense of oneself as a valuable person in the world. Recovery requires that the person diagnosed with schizophrenia be an active agent in that process². It has been suggested that only 13.7% of subjects in their first episode of schizophrenia or schizoaffective disorder met full recovery criteria for 2 years or longer³.

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A key focus of current research is to identify factors limiting function in schizophrenia.

Neurocognitive (NC) impairment has long been recognized as a core component of schizophrenia and is closely linked to social and occupational outcome⁴. This association between NC and outcome is robust – it was replicated and extended in many countries, using many different types of assessments, in different patient groups across phase of illness, including prodromal⁵. NC impairment accounts for 20-60% of the variance in real-world outcome⁴ and has been shown to predict social outcomes more closely than do psychotic symptoms⁶. However, effect sizes of the associations between NC and functional outcome tend to be medium for specific domains and larger for summary scores.

Thus, the questions have shifted from whether NC is related to outcome to how NC is related to outcome. Further, not all types of NC are equally important when it comes to navigating the real world.

In a 1996 review, Green⁷ has shown that several NC domains were associated with specific functional outcomes in schizophrenia. The strongest evidence showed that verbal memory was associated with all measures of functional outcomes; moreover other correlations were found between vigilance and both social problem solving and skill acquisition, and between card sorting and community functioning.

This growing realization that NC deficits are central to outcomes have directed attention at the assessment of these important aspects of the disorders.

This update describes the main NC and social cognition (SC) batteries and real-world assessments used in schizophrenia and discuss their advantages and disadvantages.

Cognitive assessment

NC deficits often precede the manifestation of psychosis and might be the first signs of schizophrenia in at-risk patients⁸, they are orthogonal to positive and negative symptoms⁹, are relatively stable over time, continue to be present after remission of psychosis, and are relatively unaffected by antipsychotic treatment¹⁰.

Moreover, although NC assessment does not represent a clear diagnostic marker, as a clear profile on neuropsychological tests has not been defined, it can offer an understanding of NC deficits and guide treatment targets and recommendations. Several investigators have emphasized different area of cognition. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative¹¹, sponsored by the United States National Institute of Mental Health (NIMH), identified seven distinct, separable cognitive domains as commonly deficient in schizophrenia: attention/vigilance, working memory, reasoning and problem solving,

processing speed, visual learning and memory, verbal learning and memory, and social cognition. The seventh domain, SC, was included because it was viewed as an ecologically important domain of cognitive deficit in schizophrenia that shows promise as a mediator of NC effects on functional outcome. Some NC domains were not included in this list, i.e., verbal comprehension was not included in the cognitive battery as it was considered resistant to change¹².

A growing body of the literature suggests that many of these deficits can be traced to a generalized cognitive impairment¹³. Patients with schizophrenia have been shown to perform below the level of their peers by over one standard deviation (SD) and have a unique profile of impairment of cognitive domains¹⁴.

Thus, the evaluation of a patient with schizophrenia should begin with a general assessment to evaluate the patient's average cognitive functioning, investigating the school or works performances, any developmental delays or change in overall functioning, and the ability to solve problems in daily lives. Proverb interpretation brings out unusual thought content and deficits in executive function.

Tests for measuring cognition

Many instruments are available for the assessment of cognitive functioning in patients with schizophrenia. These instruments differ widely in the population intended for use, administration time, interpretation of results, and the assessment of certain cognitive domains, and little guidance is available for selection among these instruments for clinical trials.

Mapping cognitive deficits often requires the use of extensive test batteries that are lengthy¹⁵ and costly and require advanced training in assessment to score and utilize the results. In particular, due to the nature of deficits in schizophrenia, it is reasonable to suggest the need for an affordable, easy to administer test that identifies deficits in cognitive skills in order to recommend an intervention for addressing these deficits.

Useful tests for clinical practice are described below.

Wechsler Adult Intelligence Scale

Abbreviated versions of the Wechsler Adult Intelligence Scale (WAIS)¹⁶ have been developed as pragmatic timesaving devices that balance the length of assessment with accurate estimates of the overall level of general intellectual functioning. Two main types of abbreviations of the WAIS have been proposed¹⁷: “select-subtest” and “select-item”. Selected subtests abbreviations reduce the amount of time spent on test assessment by only administering selected subtests to obtain estimated cognitive functioning scores¹⁸. This selection can vary from seven to as few as two subtests, in which,

for example, only the subtests Vocabulary and Block Design are being administered. Select-item abbreviations involve the administration of previously selected items from all subtests. The Satz-Mogel short form¹⁹ is frequently used as a “select-item” abbreviation and has shown to be an accurate measure of general intellectual ability when compared with the full WAIS²⁰. In the Satz-Mogel method, the item selection concerns the administration of every second (or third) item in WAIS subtests (e.g., Information, Block Design) that take a long time to administer.

The proposed 15-minute version of the WAIS by Verlhof and colleagues²¹, that includes only select items from three subtests, may serve as a useful screening device for general intellectual ability in research or clinical settings, and is recommended when a quick and accurate IQ estimate is desired.

Repeatable Battery for the Assessment of Neuropsychological status

The Repeatable Battery for the Assessment of Neuropsychological status (RBANS) is a standardized screening instrument designed to assess global neuropsychological functioning in a brief administration. Several studies have supported the psychometric properties of the RBANS²², with past research reporting acceptable test-retest reliability, internal consistency, and concurrent validity²³. The RBANS has been found to be a valid measure of the cognitive decline associated with various neurological conditions including stroke, Alzheimer's disease, multiple sclerosis, Parkinson's disease, and Huntington's disease. This instrument measures several cognitive domains of interest in schizophrenia – immediate memory, visuospatial/constructional ability, language, attention, and delayed memory – and provides a global measure, the total scale score. In addition, the RBANS offers two alternate forms to reduce the potential influence of practice effects in serial test administration. Wilk and colleagues²⁴ found that RBANS was reliable and sensitive enough to differentiate between patients with schizophrenia and healthy subjects and was suited for repeated measures.

Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)²⁵ was designed by the NIMH to support the development of pharmacological agents for improving the neurocognitive impairments in schizophrenia. It has been recommended by the United States Food and Drug Administration (FDA) to assess cognitive impairment as the primary outcome measure in registry trials of schizophrenia²⁵. An initial MATRICS consensus conference involving more than 130 scientists

from academia, government, and the pharmaceutical industry led to agreement on seven cognitive domains for the battery and on five criteria for test selection. The criteria emphasized characteristics required for cognitive measures in the context of clinical trials: test-retest reliability; utility as a repeated measure; relationship to functional status; potential changeability in response to pharmacological agents; and practicality for clinical trials and tolerability for patients. Cognitive function was measured according to the 7 cognitive domains of the MCCB derived from scores on 10 cognitive measures: speed of processing (Trail Making Test Part A; Brief Assessment of Cognition in Schizophrenia: Symbol coding; Category fluency test, animal naming), attention/vigilance (Continuous Performance Test: Identical Pairs), working memory (Wechsler Memory Scale, spatial span subset; Letter Number Span test), verbal learning (refers to immediate verbal memory, Hopkins Verbal Learning Test (HVLT)-Revised, immediate recall), visual learning (refers to immediate visual memory, Brief Visuospatial Memory Test-Revised), reasoning and problem solving (Neuropsychological Assessment Battery (NAB), mazes subtest), and social cognition (Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT): managing emotions branch). The MCCB can be administered in 1 to 1.5 hours.

After substantial use in the testing ground of multisite clinical trials, the MCCB has demonstrated impressive psychometrics. It has shown sensitivity to improvement from interventions, most notably for cognitive training interventions so far. The MCCB also tracks with key biomarkers, which is an important feature as efforts are made to apply experimental medicine principles, such as target engagement, to psychiatric treatment trials. Two limitations of the MCCB should be pointed out. First, the MCCB was developed to facilitate drug approval from the U.S. FDA. Because clinical trials are often international, it soon became obvious that a key limitation of the MCCB was that it was available only in English. Hence, the MCCB has now been professionally translated and is commercially available in over 20 languages (see www.matricsinc.org for a listing). With the help of an industry-academic-government consortium (MATRICS-CT), representative normative data were collected in key countries and these norms were used to create international scoring programs. Recently, Mucci et al.²⁶ have reported the normative Italian data. A second change reflects the growing awareness that NC and SC are separable dimensions. It is possible that a treatment will affect SC and NC differently, and that is assumed for specific interventions, that are focused on one area or the other. To allow trial investigators to examine NC only, the MCCB scoring program now provides an option for a “neurocognitive composite” that

does not include SC. A limitation of the MCCB is that it does not have an option for a SC composite, because there is only one test in that domain.

Brief Assessment of Cognition in Schizophrenia

The Brief Assessment of Cognition in Schizophrenia (BACS)²⁷ is a portable pen-and-paper, concise tool designed to evaluate five different domains of cognitive function with six tests (impairment of verbal memory, working memory, motor speed, verbal fluency, attention and processing speed, and executive function), assessing the aspects of cognition found to be most impaired and most strongly correlated with outcome in patients with schizophrenia.

The BACS is easily performed in clinical settings and can be administered by medical professionals in 30–35 minutes. It yields a high completion rate in these patients, and has high reliability. The BACS was found to be as sensitive to cognitive impairment in patients with schizophrenia as a standard battery of tests that required over 2 h to administer.

The way used to create the BACS and the RBANS was to create a new group of tests that assess all or many of the key domains of neuropsychological functioning in less time than the comprehensive batteries traditionally used. With this approach, one can create tests that are specifically sensitive to the deficits in schizophrenia patients and likely to be amenable to change with atypical antipsychotics. Assessment batteries such as these require the collection of large amounts of data to establish population norms, reliability, and validity. These psychometric properties make the BACS a promising tool for assessing cognition repeatedly in patients with schizophrenia, especially in clinical trials of cognitive enhancement.

Brief cognitive assessment

The Brief cognitive assessment (BCA) consists of three standard tests selected from among those commonly included in comprehensive cognitive batteries administered to patients with schizophrenia: Verbal Fluency (letters and categories), Trails A and B, and the Hopkins Verbal Learning Test.

The way used to create the BCA was to select a small number of standardized tests widely used in clinical neuropsychology, that examine a variety of cognitive domains in a very limited fashion. With this approach, normative data and information regarding the sensitivity, reliability and validity of the individual tests included in the battery are already available.

The creation of the BCA was guided by several principles. First, the battery had to be very brief (maximum 15 min), including time for set-up, administration, and scoring. Second, tests in the BCA had to be easy to administer and score and the results had to be understandable to clinicians who were not neuropsycholo-

gists. Third, the battery had assess aspects of each of the cognitive domains known to be impaired in patients with schizophrenia, including executive functions, memory, attention, and processing speed. Fourth, the tests selected had to have been found to be sensitive to improvements with atypical antipsychotics. Finally, the tests had to have been found to be related to measures of functional outcome in schizophrenia patients.

Schizophrenia Cognition Rating Scale

The Schizophrenia Cognition Rating Scale (SCoRS)²⁸ assesses the following cognitive domains: memory, working memory, attention, reasoning and problem solving, language and motor skills. The SCoRS has several advantages including brief administration time, approximately 15 min per interview, association to real-world functioning, good test-retest reliability, and correlations with performance-based measures of cognition²⁸. Moreover, its rating is based on information from three separate sources including patient, informant of the patient who has regular contact with patient and interviewer.

The SCoRS has shown good reliability, validity, and sensitivity to cognitive impairment in schizophrenia, with the advantage of brief administration and scoring time. The SCoRS was developed to measure cognitive functions through questions about cognitions related to daily life events²⁸. It consists of 20 items. Each item is rated on a scale ranging from 1 to 4 with higher scores reflecting a greater degree of impairment. Every item is given anchor points based on the degree of their daily problems. Two studies have demonstrated significant correlations between SCoRS ratings with NC functions as well as psychosocial functioning, in Singaporean, and Italian schizophrenia patients^{29,30}.

Social cognition assessment

SC impairments may precede onset of the schizophrenia^{31–33} and are present early in the illness³⁴. Such SC deficits have been consistently linked to a variety of real-world outcomes, such as social competence, community functioning, and quality of life³⁵. The extent of overlap between SC and NC has been an area of debate within the literature. SC contributes to functional outcomes beyond the influence of NC and may have a greater impact than NC on social outcomes^{36–38}. In addition, SC may mediate the relationship between NC and social functions in both chronic^{39–41} and first-episode patients⁴². Moreover, treating SC deficits leads to improvements in real-world social outcomes, including social adjustment, social functioning, social relationships, aggressive incidents, and social skills⁴³.

The degree of the relationship between SC and functioning varies, depending on the SC domain and the type of functional outcome assessed.

Even if the study of SC is quite robust, its study is in some ways less developed than that of NC. In the past, there has been controversy over what SC processes should cover.

Moreover, the most critical issue is that there is no consensus in the field as to which measures best assess each SC domain. As a result, a heterogeneous group of tasks have been administered with significant conceptual overlap and questionable psychometric properties across studies. This problem is present across all SC domains and contributes to the inconsistency of the reported findings ⁴⁴.

The Social Cognition Psychometric Evaluation (SCOPE) ⁴⁵ study was designed to address these challenges: first, to achieve a consensus on the crucial SC domains in schizophrenia; second, to evaluate the psychometric properties of existing measures and their suitability for clinical trials.

Using methods similar to other NIMH measurement initiatives (eg, MATRICS, MATRICS-CT, and VALERO), the panel of experts in the schizophrenia-spectrum research field identified and supported the value of four key domains, including emotion processing (EP; the ability to perceive and appropriately use emotions), theory of mind (ToM; the ability to infer one's own and others' mental states), social perception (SP; ability to decode and interpret social cues in others), and attributional style (AS; ability to explain the causes or make sense of social interactions and events). Two additional domains, social metacognition and social reciprocity, however suggest avenues for expansion of SC research.

Using RAND consensus ratings, the expert survey of SC produced 108 different outcomes measures, with many of these domains and measures being very closely related to each other. The panelists lastly selected the following measures for further evaluation: Ambiguous Intentions Hostility Questionnaire, Bell Lysaker Emotion Recognition Task, Penn Emotion Recognition Test, Relationships Across Domains, Reading the Mind in the Eyes Test, The Awareness of Social Inferences Test, Hinting Task, and Trustworthiness Task. However, the similarity of many of these measures to each other has led to challenges in direct comparisons of their usefulness, as many of these assessments have overlapping content. Moreover, only a limited amount of psychometric information is currently available for the candidate measures, which underscores the need for well-validated and standardized measures in this area.

In the context of a multicenter study of the Italian Network for Research on Psychoses (NIRP), the assessment of SC included a test contained in the MCCB: the Mayer-Salovey-Caruso Emotional Intelligence Test (MS-CEIT) ⁴⁶, managing emotion section, which examines

the regulation of emotions in oneself and in one's relationships with others by presenting vignettes of various situations, along with ways to cope with the emotions depicted in these vignettes. It was integrated by the Facial Emotion Identification Test (FEIT) ⁴⁷, which examines emotion perception, and The Awareness of Social Inference Test (TASIT) ⁴⁸, which is a TOM test consisting of 7 scales (positive emotions, negative emotions, sincere, simple sarcasm, paradoxical sarcasm, sarcasm enriched, lie), organized into three sections: Emotion recognition; Social Inference (minimal); Social Inference (enriched). The manual of the TASIT was translated into Italian by a psychiatrist of the Department of Psychiatry of the University of Naples SUN. The videotaped vignettes of the TASIT were dubbed in Italian at the Fono Roma Studios (www.fonoroma.com). As to the FEIT, the adaptation of the Italian version required the translations of the six emotions reported on the screen above the stimuli.

Real-world functioning assessment

The assessment of real-life functioning presents complex challenges from variability in the operational definition of functional outcome to problems in identifying optimum information sources ⁴⁹. Indeed, many different strategies have been proposed to assess real-life functioning, including self-report interviews, proxy reports, informant interviews ⁴⁹, direct observations by trained clinicians ⁵⁰, and performance-based measures, which assess functional capacity ("what a person is able to do under optimal conditions") ⁵¹. However, reports of real-life outcomes vary across informants and contain elements of error or shortcomings ⁴⁹. It has been suggested that self-reports should be accepted at face value even if they reflect patients' delusional beliefs ⁵² and have limitations such as inaccurate estimations ⁵³. Other investigators have highlighted the potential for psychotic symptoms, mood states, disorganized thinking, lack of insight, and NC deficits to limit the usefulness of the self-report methodology in severely ill schizophrenia patients. Furthermore, it has been suggested that these measures may not adequately reflect the effects of various interventions ⁵⁴. However, studies have shown that patient self-reports of everyday functioning in schizophrenia often do not converge with objective evidence or the reports of others ^{55 56}. Self-reports of functioning therefore appear problematic, and alternative assessment methods may be required. However, many patients have no caregivers to provide information, and variance in their reports can be influenced by the amount of contact with the subject and situation specificity of the observation. High contact clinicians appear to generate ratings of everyday functioning that are more closely linked to patients' ability scores

than friends or relative informants⁵⁷. Both types of direct assessment (direct observation versus analogue assessment) have advantages and limitations. Real-life observations are necessarily individualized and non-standardized as well as costly and potentially reactive (presence of an observer may alter the environment and resulting behaviors). To this end, performance-based measures of functional capacity have been developed. However, they are valid to the extent that they measure the relevant skills accurately, but other factors may influence real-life outcomes, such as financial resources, motivation and symptoms of the illness may limit the extent to which skills that are present in the behavioral repertoire are actually performed in real-life settings⁵⁸.

Overview of everyday real-life outcomes

In this context, research efforts are increasingly turning to the design, evaluation and improvement of relatively economical real-life measurement⁵⁹⁻⁶¹. Moreover, given concerns about length and ease of administration, as well as burden to the subject for assessment batteries, a practical measure must be both cost efficient and require a modest amount of time to administer⁵⁹. However, there are still few satisfactorily reliable instruments for the assessment of functional outcomes that are practical in terms of time involved, and most real-life functional outcome scales seem to be largely redundant with each other when utilized simultaneously. One upshot of this situation is the Validation of Everyday Real-World Outcomes in schizophrenia (VALERO Expert panel) initiative. The goal of this initiative was to identify the functional rating scale or scales (or subscales from existing scales) (self-report and informant-based reports) most strongly related to performance-based measures of cognition and everyday living skills through a comprehensive evaluation of existing instruments⁴⁹. The outcomes may include social, vocational, independent living, self-care or any combination of these. The scale characteristics, which were rated by the panelists and were similar to those deemed important in the MATRICS process, were: reliability (test-retest and inter-rater), convergence with performance-based measures of functional capacity and neurocognitive performance, sensitivity to treatment effects, usefulness for multiple informants (e.g., self, friend or relative, case manager, or prescriber), relationships with symptom measures, practicality and tolerability for people with low education levels, and convergence with other measures of real-life functional outcomes (including either other rating scales or achievement milestones). Among the 59 measures nominated, the investigators selected the 11 scales that were the most highly nominated, had the most published validity data regarding their psychometric qualities and best represented the domains of inter-

est (social functioning, everyday living skills, or both these areas -"hybrid" scales). Scales were rated on a 9-point (1-9) scale, where scores of 1-3 were poor, 4-6 were fair to good and 7-9 were very good to superb. The two scales that scored highest across the various criteria for each of the classes of scales (hybrid, social functioning, and everyday living skills) were selected for use in the first substudy of VALERO⁴⁹. The scales selected were the Quality-of-Life Scale, Specific Levels of Functioning Scale, Social Behavior Schedule, Social Functioning Scale, Independent Living Skills Schedule, and Life Skills Profile. The overall results of this first substudy of VALERO show that all examined scales can be considered as somewhat useful in their current versions. Moreover, many of these scales lack critical data regarding reliability across investigators and relationship with neuropsychiatric and functional capacity performance. Ratings for usefulness across multiple raters were also quite low, partly because many of these scales do not have alternate forms that attempt to capture the differing perspectives of different raters. As an entirely effective measure of the real-life outcomes component of the functional outcomes construct has not yet been identified, some measures are likely to be suitable in the interim. Thus, comprehensive real-life functioning assessment, using self-report, informant report and interviewer best judgment across six different real-life functioning rating scales may be required to capture the complexity of functional outcome in schizophrenia⁵⁸. The Specific Levels of Functioning (SLOF) Scale⁶² is a 43-item multidimensional behavioral survey administered in person to the caseworker or caregiver, selected on the basis of his/her familiarity with that person or a patient-administered scale completed with verbal instructions from the examiner to rate its own performance. The scale does not include items relevant to psychiatric symptomatology or cognitive dysfunctions, but assesses the patient's current functioning and observable behavior, as opposed to inferred mental or emotional states, and focuses on a person's skills, assets, and abilities rather than deficits that once served as the central paradigm guiding assessment and intervention for persons with disabilities. It comprises six subscales: (1) physical functioning, (2) personal care skills, (3) interpersonal relationships, (4) social acceptability, (5) activities of community living and (6) work skills. The work skills domain comprises behaviors important for vocational performance, but is not a rating of behavior during employment. The latter would not be feasible, since the majority of patients with schizophrenia are unemployed; therefore, the proxy measure of work skills from the SLOF is used. Lastly, the SLOF also includes an open-ended question asking the informant if there are any other areas of functioning not covered

by the instrument that may be important in assessing functioning in this patient. Each of the questions in the above domains is rated on a 5-point Likert scale. Scores on the instrument range from 43 to 215. The higher the total score, the better the overall functioning of the patient. According to the original version of the SLOF, the time frame covered by the survey is the past week. Each informant is asked to rank how well they know the patient on a 5-point Likert scale ranging from “not well at all” to “very well.” Ratings on individual items of the SLOF may be used to capture the current state of overall functioning while showing specific areas of therapeutic and rehabilitative need, i.e. to identify goals in planning treatment for clients, to develop special intervention or skill-training programs, or to assign clients with similar or complementary strengths and needs to existing programs. An adaptation of the SLOF is to allow patients to rate themselves on each item, while staff make independent judgments. Patients and staff then

share their ratings, discuss discrepancies and negotiate a mutually acceptable set of functionally oriented goals for the plan. This process also could serve as a form of quality assurance, allowing patients and staff to obtain potentially valuable feedback about the patients’ self-perceptions and help staff to gauge better the accuracy of their judgments⁶². Lastly, the SLOF has direct applications in research on patient outcome and program evaluation.

The SLOF was found to be a reliable and valid scale, with a good construct validity and internal consistency, as well as a stable factor structure. In the context of the NIRP, the instrument was translated in Italian⁶³ and its construct validity, internal consistency and factor structure as explored⁶⁴.

Conflict of Interest

None.

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Cognitive remediation – where are we now and what should we do next?

Summary

Although we have evidence that cognitive remediation is effective we have not yet persuaded service providers to adopt it into their treatment packages. This paper outlines the cognitive remediation literature that has sculpted the field. It is not a systematic review but an expert's opinion of the research required to influence treatment decisions so that our patients are offered the best options for fulfilling their goals. The gaps in research include defining the benefits in terms of those that service providers and service users value. These include costs against the effects of treatment and fulfilling individual recovery goals. These are not rocket science and only require extra and least burdensome (on participants) measures to be added to studies. We also need to use data we already possess to carry out further analyses to indicate how different therapies work and to compare across studies in large individual participant level databases.

Key words

Cognitive remediation therapy • Schizophrenia • Cognitive deficits

Cognition has always been thought to be important in a diagnosis of schizophrenia and particularly the effect that cognition has on perceptions, comprehension and in the development of acute symptoms such as hallucinations and delusions. Even 50 years ago individuals with a diagnosis of schizophrenia interviewed in pioneering studies of service user experiences described how their cognitive difficulties interfered with everyday cognition and mentioned, memory, sustained and divided attention as well as their overall concentration¹. Following these studies further research highlighted cognition as a “stable vulnerability” factor after noting that cognition was poor even between episodes but was worse in an acute episode of the disorder. Further studies, including my own²⁻⁴ then demonstrated that cognition predicted the limits of rehabilitation with those with poorer cognition having much less independence in their recovery. This research provided an essentially pessimistic view which suggested that cognition was intimately linked to psychosis and that the effects were widespread. Medical treatments seemed to have no impact. Then cognitive remediation appeared. Twenty odd years after the first studies there is now a growing and optimistic view of the potential for cognitive remediation to provide real benefits in terms of boosting recovery goals. The field is thriving. In a search of studies of cognitive remediation between 2014 and 2017 there were 76 trial reports in schizophrenia and 113 in non-schizophrenia disorders. But what exactly have we learnt and should we be paying more attention not just to trial quality but to factors such as the moderators and mediators of outcome.

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Is cognitive remediation useful?

Here I am quoting from the Cognitive Remediation Experts Workshop which in 2012 defined it as “is an intervention targeting cognitive deficit

using scientific principles of learning with the ultimate goal of improving functional outcomes. Its effectiveness is enhanced when provided in a context (formal or informal) that provides support and opportunity for extending everyday functioning". The key words are that we use scientific learning principles derived from psychological and educational research. People with the diagnosis also value improvements in cognition but we also need to be mindful that their expressed goals are often about functioning, and hence the addition of the goal of improving functioning outcomes. Figure 1 shows the outcomes from a meta-analysis ⁵ showing that the cognition effect size is 0.45 and that this effect is not changed when considering only studies that had high quality methods. This meta-analysis also concluded that there was a benefit to functioning that was durable. Treatment guidance depends on empirical data showing benefit so most scientists would assume that this treatment would be in the guidance. However, there is disagreement on whether enough evidence exists, with differing views around the world. Some countries and US states mandate the treatment whereas others have been more reticent despite the current evidence. There is even a difference within the UK with Scotland including cognitive remediation and the English guidance excluding it. What is clear is that it is not just the evidence base that affects treatment acceptance but also market forces particularly in the area of so-called "brain training" programmes. Apart from a fine for false advertising by the Federal Trade Commission (FTC) there have also been two open letters and a review, all from academics, arguing the case for and against the effectiveness of brain training mostly in the healthy population. There is complete agreement with the FTC that there has been an over-selling of training benefits in the healthy population and some grudging acceptance that there may be some benefit in clinical populations. This public disagreement will make service providers wary of adopting a good psychological treatment because they think it may be a leisure activity. There have also been two well publicised negative studies of cognitive remediation in schizophrenia ^{6,7}. These studies rather than negating the current evidence are important in providing a context in which benefits can disappear. Both are similar in adopting a novel software programme with little prior information on benefit. In fact the Gomar study used a programme that had been used in dementia and autism with little effect. So there is the possibility that the programmes were not effective in any context. But the programmes look similar to those used in many other studies. The main difference in both studies was the inclusion of participants who were much older than those recruited to many of the other cognitive remediation studies. There is some evidence that age does reduce

the effect size ^{8,9} and this factor alone may have accounted for the disappointing effects.

The gold standard for measuring the likelihood of benefit is dependent on the meta-analyses of individual trials. There are now 19 in the literature following the 2011 Wykes meta-analysis ⁵. Of these only two did not find a cognitive and/or functioning benefit and four did not find a symptom improvement. The evidence now appears to be overwhelming and what is required is not proof that there is any benefit but advice on how to personalise or tailor treatment so that there is the best chance for an individual to show an improvement.

Is there evidence on boosting cognitive remediation benefits?

The Wykes et al. (2011) study ⁵ found no specific differences between therapies or studies that would indicate better cognition outcome. We do know that improving motivation might show effects ¹⁰, and that learning potential might influence cognitive outcomes ¹¹ but all these effects need further replication. The Wykes meta-analysis also showed that teaching information processing strategies rather than just practising tasks benefited functional outcomes. Studies such as those of McGurk and colleagues and Bell and colleagues ^{12,13} demonstrate that adding cognitive remediation to other rehabilitation programmes such as supported employment differentially improved outcomes. In fact, in the McGurk study people who had failed to get a job, despite wanting one, were randomised to receive either supported employment or supported employment plus cognitive remediation. Over a 24-month period those receiving the additional therapy were more likely to be competitively employed and to have been in employment for longer. In another study Chris Bowie ¹⁴ provided individuals with skills training alone, cognitive remediation alone or a combined group. He found cognitive improvements only when cognitive remediation was provided and few improvements when only skills training was provided even in skills training. The most benefit was produced when the two therapies were provided together.

It seems that cognitive remediation has an effect on cognition and the assumption is that this then has a knock on effect on skills training. But the analyses of whether the effects are linked are only just being carried out. For instance, Wykes et al. ¹⁵ tested whether cognitive benefits were linked to functional benefits in a study of supported, voluntary and competitive employment. Despite there being reasonable benefits to memory, flexibility and planning, only the planning measure was predictive of improved quality of work (the primary outcome). The improvement in planning only accounted for 15% of the variance leaving a hefty 85% to be accounted for in the direct effect of

cognitive remediation on outcome. So we are still unclear which cognitive domains should be targeted to improve particular functional outcomes. The obvious way to make a choice has been to look for correlations between cognition and functional outcomes but as we have seen in the previous study those correlations do not necessarily predict the right target. In fact, Reeder et al.¹⁶ showed in a trial that although there were correlations between memory and social functioning, changes in memory did not benefit social functioning. It was a change in an uncorrelated variable that seemed to have a large effect.

Do we know how to tailor treatment?

We do possess some knowledge of personal characteristics that could enable us to understand the beneficial effects. In terms of sociodemographic and non-clinical factors we have some evidence that older people provided with cognitive remediation for a similar amount of time as younger individuals show smaller benefits in terms of cognition^{8,9,17} We also know that some individuals show little benefit in terms of functional outcomes. For instance, a follow-up of a supported employment and cognitive remediation study¹⁸ two years after cognitive remediation, found there was no overall benefit in terms of employment status. However, if the group was divided into those with poor or better functioning at baseline a clear difference emerged. Those who had poor functioning at baseline showed a benefit from therapy two years later, but those whose functioning was higher did not seem to need the boost provided by cognitive remediation. In terms of treatment attributes, we know that pairing cognitive remediation with other rehabilitation services improves functioning and that providing a cognitive remediation programme which provides strategic teaching improves functioning. However, we do not know which cognitive domain we should target as many are reduced in those with a diagnosis of schizophrenia and that those same domain deficits are shown in both early and more chronic stages¹⁹. Targeting the domain that is most problematic has also not shown benefits as there was no difference in a targeted therapy and a more general approach in a large trial in France²⁰. So there is a lot we do not know. We do not, for instance, know if maintaining therapy gains by repeating sessions after the main therapy has ended will maintain benefits over longer periods of time, or whether increasing the number of sessions for those who are more chronic will boost therapy gains. It is likely that a more general rather than a focussed approach would be appropriate at this stage, as it is unclear whether there is only a benefit for cognitive domains that are problematic or whether functional improvements are gained with a strengthening of domains where performance is not so reduced. The main obstacle for all tailoring is an understanding of the mechanisms of change. There was hope that brain

imaging might help to unravel these complex mechanisms. Despite having evidence that cognitive remediation affects brain activation²¹⁻²⁴ the modulation of activation and connectivity^{25,26}, structural integrity²⁷ and the prediction of outcome²⁸ we still do not know if these effects are replicable and they do not provide much information on how to change therapy ingredients or choose the individuals who will receive a benefit. In particular, there are individual differences in the way that tasks are approached that entirely explain the brain imaging results (e.g.²¹). The causal gap in neuroscience has recently and cogently been described by Etkin²⁹. Until we have better data these studies although interesting do not offer much information to direct research in cognitive remediation.

Currently there is little rigorous evidence on which to make decisions on who to exclude from therapy or how to provide therapies. Personalisation of therapy will therefore still depend on a clear case formulation where individual goals are set and an appropriate cognitive remediation programme is provided. It is unlikely that any identified variable can offer much benefit in terms of personalisation as the list has neither been replicated nor been tested for its predictive properties across different therapies and different populations. That should be one of the tasks for the next period of research.

What is the goal of cognitive remediation therapy?

Cognition

What individuals with a diagnosis of schizophrenia want is to attain their recovery goals and ensure that the benefits last a long time. One of the issues is to understand how we measure outcome. Some time ago Wykes and Huddy³⁰ pointed out that the choice of cognition measures affects whether there is a significant effect. For instance, if two people differ in their performance on an outcome then it will be easier to show an improvement in the person who has poorer performance than one whose performance is average. This is a particular concern when performance is measured on a very narrow measure such as those produced by the CNTRICS consortium³¹. This allows very specific information to be extracted on the effects on particular cognitive domains. However, more general, sometimes called “dirty”, measures which rely on several cognitive domains to achieve good performance, will provide a clearer view of efficacy for a large number of people and it could be argued that this approach delivers stronger evidence for treatment implementation decisions. We also may be taking a “shoot yourself in the foot” approach to measuring some cognitive outcomes. Performance in planning tests is often determined by time-dependent measures. If a person is taught to plan, they are likely

to slow down and therefore not complete as many tasks within the allotted time or the time taken is longer although errors are reduced. In these situations, the speed-error trade-off is likely to leave individuals with the same score or an even lower score despite learning to plan more efficiently. This feature is more likely to occur in treatments emphasising strategy learning but has happened in studies where attention was trained. In one study despite finding no effect of training on cognitive measures there was an effect on functioning ³².

Functioning

Although people with schizophrenia notice and value improvements in cognition ³³, it is functional benefits that feature as recovery goals. Life skills, employment, relationships as well as housing have all featured in reports of goals ³⁴. Here too we have problems in what would be the correct measure to use. Cognitive improvements might impinge on many different areas of functioning and these are also affected by the opportunity to practice new skills. This lack of opportunity has spurred researchers to adopt interim measures such as functional capacity measures. Although these provide some information on new learning often studies do not find close relationships between these capacity measures and actual performance. It is also actual performance that drives treatment implementation. So despite the extra efforts required to collect data from informants or in the field and the length of follow-up to determine change, the balance between the quick fix capacity measure and actual performance still favours measuring outcomes of value to individuals with the disorder.

We know that we can boost functional outcomes but are these benefits maintained. Certainly my own experience which has mainly been without being paired with other rehabilitation, has shown that maintenance of treatment effects on functioning without some extra rehabilitation is hard to achieve ^{35 36}. One recent Italian study suggested that cognitive remediation did boost the outcome from standard rehabilitation but although cognitive outcomes were stable over time, the treatment arm that maintained functional improvements was one where cognitive remediation was paired with standard rehabilitation which was provided for an extended period of 12 months ³⁷. Those in the study arm which provided less standard rehabilitation did not see those benefits.

Treatment implementation

The variation in implementation around the world is not just dependent on clear outcomes. It is also driven by a lack of information on the cost-effectiveness of treatment. All clinical services need to make decisions about how to spend their resources and if the choice is to spend it on cognitive remediation or not then there needs to be a good case made as there is an opportunity cost attached to this decision. We know that those individuals

with cognitive problems are more highly dependent on psychiatric and residential services ³⁵ and that cognitive difficulties are related to these costs, i.e. those with more cognitive problems use more and higher cost services ³⁸. Cognitive remediation provides value in terms of improving the outcomes of supported employment and reducing failure, especially for those with poor functioning at baseline. This is a cost saving which has not so far been calculated. A novel study linking cognitive remediation with cognitive behaviour therapy (CBTp) ³⁹ discovered that those receiving supportive therapy or cognitive remediation prior to CBTp were no different in their levels of symptoms at the end of the trial. However, those who had received cognitive remediation achieved this level in fewer sessions. As CBTp requires more expensive therapists with a longer training programme this study suggests that there might be a potential cost saving. A few other studies have contributed to the evidence base on costs. The first of these studies was by Reeder et al. ⁴⁰ demonstrated a saving in both residential and day care services at follow-up which was related to cognitive improvements after cognitive remediation. More recently, Vita et al. ⁴¹ in Italy has shown a reduction in the number and length of admissions and Garrido et al. ⁴² in Spain have shown reductions in both emergency and admission costs. The evidence base for the benefits in terms of costs is therefore growing and should be part of new trial outcomes.

Conclusions

Cognitive remediation does provide positive outcomes. We need to investigate the benefits of individual therapies against each other in order to understand their different benefits and costs. Some of these analyses can be carried out within large participant level databases and the National Institute for Mental Health has developed such a platform called the Database of Cognitive Training and Remediation Studies which has uploaded randomised trials of cognitive remediation at the participant level ⁴³. These data will provide more data to test mechanisms as well as allowing between-therapy comparisons of potential predictors of outcome and therefore allow us to develop a set of variables for tailoring treatments. But if we are to implement therapy we need to persuade both service users and providers of the benefits. For this we need real outcomes valued by our clients which include recovery goals and the cost-effectiveness of treatment. Both are of interest as cognitive remediation requires commitment from providers and users who may well consider other therapies of more benefit.

Conflict of Interest

None.

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Psychopharmacological treatment of cognitive deficits in Schizophrenia and mood disorders

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Summary

Objectives

Cognitive dysfunction is a core feature and a transdiagnostic domain of psychiatric disorders, such as Schizophrenia, Bipolar Disorder and Depression. The study of these disorders may contribute to the development of novel drugs and to the repurposing of existing agents for the treatment of cognitive impairment. This manuscript will review the literature regarding the effects of pharmacological treatment of cognitive deficits in psychiatric disorders.

Methods

PubMed was used for the search including the following terms: Schizophrenia, Major Depressive Disorder, Bipolar Disorder, pharmacological treatment, antipsychotics, antidepressants, lithium and anticonvulsant medications.

Results

The treatment of Schizophrenia with First Generation Antipsychotics (FGAs) has relatively little influence on cognitive symptoms. It has been indicated that Second Generation Antipsychotics (SGAs) may partially improve cognitive dysfunction, due to their relatively high affinity for serotonin 5HT_{2A} receptors. Dysfunction of γ -aminobutyric acid (GABA) led to the "GABA hypofunction" theory and to the development of novel compounds to treat cognitive deficits. The effects of glutamatergic agents indicated benefits on cognition of a group of amino acids that act as glutamate agonists by binding to the glycine site on NMDA receptors. It was discovered that the administration of muscarinic antagonists potentiated the cognitive impairments, and the α 7 nicotinic acetylcholine receptors have been shown to play an important role in cognition with potential therapeutic applications in Schizophrenia. A number of studies regarding drugs targeting neuroinflammation and oxidative stress to improve cognitive deficits emerged.

Regarding Major Depressive Disorder (MDD), conventional antidepressants are generally associated with beneficial effects on cognitive impairment in individuals with MDD, which may be mediated at least in part by the improvement obtained in affective symptoms, suggesting a partially indirect effect. Furthermore, it has been hypothesized that vortioxetine may improve the cognitive symptoms of MDD through its effects on serotonergic receptors which may modulate glutamatergic neurotransmission, exerting its antidepressant and beneficial effect on cognitive function via a distinct mechanism.

The literature findings regarding the effects of lithium on cognition in Bipolar Disorder are inconclusive, while anticonvulsant medications, such as valproic acid, lamotrigine and carbamazepine, showed well-established mood stabilizing and cognitive enhancing properties.

Conclusions

Cognitive dysfunction in Schizophrenia, Major Depressive Disorder and Bipolar Disorder is a relevant determinant of patient clinical and functional outcomes. Clinical studies evaluated several compounds to estimate their positive impact and their efficacy profiles on cognitive domains.

Key words

Cognition • Psychopharmacology • Schizophrenia • Major Depressive Disorder • Bipolar Disorder

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Introduction: cognitive impairment and actual pharmacological target

Cognitive dysfunction is a relevant dimension of psychiatric disorders, such as Schizophrenia, Bipolar Disorder and Depression. Cognitive impairment is associated with different genetic, epigenetic, developmental and environmental factors. Although some of these factors may be compensated, others are not reversible, so prevention and early treatment are crucial ¹.

As regards Schizophrenia, cognitive impairment represents a core feature of the disorder ². A considerable proportion of patients with Schizophrenia performs an average of 1.0 to 2.0 standard deviations below the population norms on standardized psychometric tests ³. Neurocognitive impairment is detectable before the first episode of psychosis ⁴ and it has been reported to be one of the strongest predictors of functional outcome in Schizophrenia ⁵; this form of deficit is not only present in patients, but also in their first degree relatives ⁶. Most patients with Schizophrenia show deficits in at least one cognitive domain, including working memory, attention, processing speed, reasoning and problem solving, social cognition, visual learning and memory ⁷, with a significant impact on functioning ⁸, quality of life ⁹, success in psychosocial rehabilitation programs and employment ¹⁰. Understanding of cognitive deficits' neural bases is limited. Since the discovery of chlorpromazine's antipsychotic properties in 1952, treatments to date have mainly targeted the dopamine type 2 receptor, mostly via direct antagonism of the receptor. Although this mechanism is relatively effective on positive symptoms, both first and second-generation antipsychotic drugs minimally impact negative and cognitive aspects. The use of already-approved drugs and already-available complementary medications to enhance cognition has been proposed ¹¹. Also, several agents have been developed and tested to improve neurocognition in Schizophrenia. It is possible that the heterogeneity of mechanisms responsible for cognitive deficits in Schizophrenia may be at the heart of the lack of success of any single pharmacological approach. Promising results obtained with cognitive remediation have suggested that promotion of neuroplasticity could be an effective approach. Although most efforts have focused on dopaminergic, cholinergic, glutamatergic, noradrenergic, GABAergic and serotonergic mechanisms, the impact of neuroinflammation and oxidative stress and their downstream effects on neuroplasticity and D1 and NMDA receptors suggest that they may be treatment targets for neurocognition in Schizophrenia ¹². Similarly, regarding Major Depressive Disorder (MDD), cognitive deficits are considered core symptoms of the disorder, and appear to be broadly associated with functional outcome. Until now, they have been gener-

ally considered a direct consequence of depressive symptoms ¹³, but it is still debated whether they are independent of mood. In fact, cognitive symptoms have been demonstrated not only during depressive episodes, but also during remission. Studies investigating cognitive functioning in MDD have focused on patients with a history of more than one Major Depressive Episode (MDE) ¹⁴. Deficits have been identified in the areas of psychomotor speed, attention, learning and memory, executive functioning, cold cognition, hot cognition and social cognition. In addition, brain abnormalities in regions related to these functions have been demonstrated ¹⁵ even during the early stages of the illness.

To date, although inconsistent but positive effects of conventional treatments on cognitive impairment are observed, no single antidepressant agent has received approval for the treatment of cognitive symptoms associated with MDD. Data across new agents are preliminary and are promising for EPO, SAME, insulin, NAC and antidiabetic agents ¹⁶. Several mechanisms may contribute to cognitive dysfunction in MDD, including, but not limited to, over-activation of the hypothalamic-pituitary-adrenal axis, oxidative and nitrosative stress, imbalances in pathways involved in cell survival and death and immune activation. These pathways may offer a basis for the development of novel drugs and/or the repurposing of existing agents for the treatment of cognitive impairment in Depression ¹⁷.

Regarding the cognitive profile of patients with Bipolar Disorder (BD), the existence of cognitive impairment has been well demonstrated by several studies ¹⁸, with impairment in psychomotor speed, declarative memory, executive function, visual memory and attention ¹⁹. These deficits are present during all phases of BD ²⁰, including euthymia ²¹, with significant consequences on functioning and quality of life ²². BD has a substantial genetic component, with estimated heritability ranging from 70% to 80% ²³. Unaffected relatives and offspring of BD patients exhibit mild deficits in memory, visuospatial and executive function domains. A meta-analysis revealed executive functions and verbal memory deficits of small effect size in first-degree relatives of BD patients ²⁴. Despite the negative impact of cognitive deficits on the functional status of BD patients, there is no specific pharmacological agent for the management of cognitive symptoms among bipolar patients. The variability of available findings suggests that medications might be of marginal benefit in the treatment of this impairment, and it is still unclear which deficits are more likely to respond to therapeutic interventions.

Psychopharmacological treatment to improve cognitive deficits in Schizophrenia

Treatment of Schizophrenia is often limited to the reduction of positive symptoms, while negative symptoms

and cognitive impairment may persist throughout life, in spite of treatment with antipsychotics²⁵. First Generation Antipsychotics (FGAs) have relatively little influence on cognitive and negative symptoms and may cause adverse side effects, such as extrapyramidal motor symptoms, tardive dyskinesia, weight gain and sedation²⁶. Recently, second-generation antipsychotics drugs (SGAs) have been used as first-line medications to treat patients with Schizophrenia. It has been indicated that SGAs may partially improve cognitive dysfunction, which may be related to their relatively high affinity for serotonin 5HT_{2A} receptors compared with D₂ receptors²⁷. The apparent cognitive enhancement may be related to one or more of the following effects of atypical antipsychotics agents, not shared by typicals: increased release of dopamine (DA) and acetylcholine (ACh) in the prefrontal cortex and hippocampus²⁸; antagonism of 5-HT_{2A}, 5-HT_{2C} or 5-HT₆ receptors²⁹ and stimulation of 5-HT_{1A} receptors³⁰. An increased release of DA may particularly lead to stimulation of D₁ and D₃ receptors, which might have a beneficial effect on cognition, assuming that these receptors are understimulated in Schizophrenia. An increased release of ACh might lead to enhancement of M₁, M₄, or $\alpha 7$ nicotinic acid post-synaptic receptors, all of which have been indicated as potentially involved in cognitive impairment in Schizophrenia³¹.

However, several investigators have speculated that the cognitive improvements observed with SGAs may reflect an avoidance of potentially deleterious effects associated with FGAs rather than a specific enhancement of cognition³². A meta-analysis by Woodward et al. demonstrated that SGAs improved overall cognitive function to a greater extent than FGAs³³. McGurk et al. demonstrated a significant improvement in several cognitive domains (selective attention, executive functioning, verbal learning and memory and verbal fluency) in partial responders to typicals antipsychotics who had been switched to olanzapine³⁴. Furthermore, Wang et al. reported that olanzapine could significantly improve short-term memory, immediate memory and memory quotient in first-episode schizophrenic patients³⁵. Some findings suggest that aripiprazole may offer advantages over olanzapine in improving neurocognitive function³⁶. Furthermore, a systematic review of eleven comparative studies revealed that paliperidone resulted in significantly greater improvements in social functioning compared to those achieved with comparative antipsychotics, including risperidone, olanzapine and aripiprazole³⁷.

In an independent systematic review, Houthoofd et al. reported positive effects of risperidone on neurocognitive function in patients with Schizophrenia and Schizoaffective Disorder in processing speed, attention/

vigilance, verbal and visual learning and memory and in reasoning and problem-solving³⁸. However, the effect of risperidone on social cognition in patients with Schizophrenia remains controversial due to conflicting results³⁹. Regarding long acting injection (LAIs) treatments, patients who switched from risperidone to paliperidone long acting showed greater improvements in attention and processing speed compared to those who continued on risperidone⁴⁰. Davidson et al. reported small advantages of SGAs compared to FGAs in terms of cognitive performance⁴¹. In conclusion, the studies that have focused on the possible differential effects of specific SGAs were not conclusive. Given that individual SGAs show different pharmacological profiles and that cognitive function consists of different domains, it is possible that the effects on cognitive function may differ among drugs. Treatment with antipsychotic medication is associated with moderate improvement in cognitive performance among patients with Schizophrenic form Disorder or at first episode of Schizophrenia.

To stimulate cognition in Schizophrenia, a number of GABAergic agents have been studied. Dysfunction of γ -aminobutyric acid (GABA) interneurons has been suggested in the pathophysiology of Schizophrenia, as the result of an imbalance between excitation and inhibition in the cerebral cortex. There is histological evidence of the reduction of GABA interneuron density in the frontal cortex⁴² and it has been suggested that a developmental deficit of inhibitory GABA interneurons may underlie neurodegeneration through the exaggerated activation of glutamatergic neurons⁴³. In this context, an imbalance between excitatory and inhibitory (E-I) activity, induced by low activity of glutamatergic projections and GABA interneurons in the prefrontal cortex, may lead to impaired working memory in Schizophrenia⁴⁴. These observations led to the "GABA hypofunction" theory⁴⁵ and to the development of novel compounds to treat negative symptoms and cognitive deficits, correcting the "E-I imbalance"⁴⁶, including agonists of the glycine site of NMDA receptor, DA-D₁ receptor, metabotropic glutamate receptor and 5-HT_{1A} receptors⁴⁷. Clinical evidence suggests that serotonin 5-HT_{1A} receptor agonists improve cognitive deficits in Schizophrenia, through the correction of the E-I imbalance via the suppression of GABA neural function⁴⁸. Several compounds have been developed to influence GABA activity, but most of these compounds have failed to demonstrate neurocognitive benefits in large clinical trials⁴⁹. The effects of glutamatergic agents on cognitive deficits were also investigated. Glutamate is the major excitatory neurotransmitter in the central nervous system. Glutamate receptors include NMDA and AMPA receptors, which are G-protein coupled receptors that trigger second-messenger cascades upon glutamate

binding. NMDA receptor antagonists, such as ketamine and phencyclidine, can produce clinical and cognitive symptoms of Schizophrenia in healthy individuals, leading to the hypothesis that the NMDA receptor could be involved in the pathophysiology of psychosis. This hypothesis has gained traction based on findings of altered glutamate levels in cerebrospinal fluid and cortex of patients with Schizophrenia and of genetic risk factors in genes for the NMDA receptor. Drugs can modulate the NMDA receptor through different mechanisms, such as binding the NMDA glycine co-agonist site, increasing glycine concentration (glycine transporter inhibitors) and influencing the NMDA receptor via glutathione, the major anti-inflammatory molecule in the central nervous system⁵⁰. Several clinical trials have examined the neurocognitive enhancement benefits of a group of amino acids that act as glutamate agonists by binding to the glycine site on NMDA receptors. These NMDA receptor agonists include glycine, D-cycloserine, and D-serine but none of the currently published studies produced evidence that the adjunctive use of these compounds improves neurocognition. D-cycloserine, currently approved for treatment of Tuberculosis, binds to the glycine site and acts as a partial agonist of the NMDA receptor. In an initial exploratory study, a single dose of D-cycloserine improved performance on a delayed recall task, but later studies were not able to replicate this initial finding of improved cognition. Glycine has shown a beneficial effect as an adjunctive agent to antipsychotics for negative and cognitive symptoms.

Cholinergic agents act on the central cholinergic system. This innervates a diverse range of cortical and sub-cortical structures, interacting with two structurally diverse families of receptors, the nicotinic and muscarinic receptors, through coordinated acetylcholine (ACh) release⁵¹. The administration of anti-cholinergic and anti-muscarinic agents was once common practice among schizophrenic patients due to the capacity of these drugs to alleviate extrapyramidal side effects commonly caused by typical antipsychotic medications. Besides worsening the severity of positive symptoms, it was discovered that the administration of muscarinic antagonists potentiated the cognitive impairments prevalent amongst patients⁵². With the advent of atypical antipsychotic medications, the concurrent administration of anti-muscarinic drugs ceased. In healthy subjects, the acute administration of anti-muscarinic agents can produce cognitive impairments that mimic the deficits observed in schizophrenic patients⁵³. Significant reductions in the expression of M1 and M4 receptors have been consistently reported in the postmortem brains of schizophrenic patients in regions linked to cognitive function, including the hippocampus, frontal and pre-frontal cortex, superior temporal gyrus and the anterior

and posterior cingulate cortex⁵⁴. Conversely, the expression of M2 and M3 receptors has been reported as unaltered in the brains of patients with Schizophrenia across a number of cortical regions⁵⁵. In accordance with this evidence, it is apparent that a dysfunctional muscarinic system is contributing to the symptoms of Schizophrenia and thus this system might thus represent a therapeutic target⁵⁶. In this regard, clozapine was the first atypical medication to show nootropic attributes inducing mild improvements across a number of cognitive functions, including learning and memory⁵⁷, eventually attributed to its effects on the muscarinic system. Galantamine is a competitive and reversible cholinesterase inhibitor that also acts as a M1 muscarinic acetylcholine receptor agonist or a modulator of $\alpha 4$ and $\alpha 7$ nicotinic receptors, and has been used primarily in the treatment of early-stage of Vascular Dementia and Alzheimer's Disease⁵⁸: this drug produced neurocognitive benefits in schizophrenic patients^{59 60}.

The five muscarinic receptors share considerable orthosteric binding site homogeneity. As a consequence, it is very difficult to target a specific muscarinic receptor at this site without manipulating any of the remaining four receptors and producing unwanted side-effects and/or receptor down-regulation/drug desensitization. Fortunately, it has been discovered that M1, M2, M3, M4 and M5 receptors all exhibit a secondary, allosteric binding site. Unlike the orthosteric binding sites, the allosteric binding sites demonstrate substantial heterogeneity across the five muscarinic receptors, thus becoming the target for most recently developed drugs. Positive allosteric modulators (PAMs) are a class of allosteric agonist that do not directly activate the receptor. By binding to the allosteric site, muscarinic PAMs increase the receptor's affinity for ACh at the orthosteric binding site and consequentially potentiate the receptor's response to ACh⁶¹. BQCA⁶² and PQCA⁶³ are potent, highly selective M1 receptor PAM reported to produce pro-cognitive responses, including enhancing memory function and increasing spontaneous prefrontal brain activity in pre-clinical trials. In addition to antipsychotic like qualities, the M4 receptor PAM, VU0467154⁶⁴ and VU1052100⁶⁵ have been reported to enhance cognition. Although more detailed investigations are required to determine the suitability of muscarinic PAMs as novel treatments against psychotic and cognitive symptoms of Schizophrenia, the already available evidence is promising. Regarding nicotinic agents, the hypothesis that nicotine might improve cognition derived from the observation that smoking rates in patients, whether taking an antipsychotic or not, are significantly higher (40-90%) compared to general population (15-25%)⁶⁶. Drug development strategies mostly focused on the $\alpha 7$ -subtype of the nicotinic acetylcholine receptor. Interest in this re-

ceptor subtype is based on genetic links between this subunit and Schizophrenia, on its high expression rates in key cognitive processing areas (e.g., hippocampus, thalamus, and prefrontal cortex) and on the evidence of a decreased expression in post-mortem studies on patients' brains. The $\alpha 7$ nicotinic acetylcholine receptors ($\alpha 7$ receptors) have been shown to play an important role in cognition and have potential therapeutic applications in cognitive impairment in Schizophrenia as well as in Alzheimer's Disease ⁶⁷.

Encenicline demonstrated clinically meaningful improvements in cognition and functioning in patients with Schizophrenia ⁶⁸. Varenicline, an $\alpha 7$ -subtype of the nicotinic acetylcholine receptor agonist originally approved for smoking cessation, and tropisetron, a 5-HT₃ receptor antagonist and $\alpha 7$ -subtype of the nicotinic Ach receptor partial agonist, approved as antiemetic agent, showed the same inconsistent effects on cognition in Schizophrenia. Several cognitive enhancers approved for Alzheimer's Disease such as antidementia agents including donepezil, rivastigmine, galantamine and memantine, have been tested for their potential to improve cognition in Schizophrenia. Since they have always been the only cognition-enhancing agents available on the market their potential effects on cognition in Schizophrenia were obviously examined. Findings, however, have painted a different picture, suggesting that cognitive deficits in Schizophrenia most likely arise from different mechanisms, if compared to the ones involved in Alzheimer's Disease. Studies on the acetylcholinesterase inhibitors, donepezil, rivastigmine and galantamine have been mixed ⁶⁹ or negative ⁷⁰. Memantine, typically prescribed to enhance neurocognition in Alzheimer's Disease, has several mechanisms of action. Studies on the possible procognitive benefits of memantine in Schizophrenia are available ⁷¹, but Authors found that adjunctive memantine (in patients with atypical APDs therapy) did not produce any benefits on neurocognition in Schizophrenia ⁷².

Oxytocin is a hypothalamic peptide contributing to maternal infant bonding. There have been several smaller studies on the effects of intranasal oxytocin on social cognitive functioning in people with Schizophrenia. Further testing is needed to explain whether oxytocin has therapeutic potential for social cognitive deficits and/or negative symptoms in people affected by Schizophrenia. Three noradrenergic compounds have been evaluated for their putative procognitive benefits in people with Schizophrenia; however, in published clinical trials, all three compounds (guanfacine ⁷³, atomoxetine ⁷⁴ and reboxetine ⁷⁵) have demonstrated no sign of possible efficacy in schizophrenic patients.

Some published studies on serotonergic agents have evaluated tandospirone ⁷⁶, buspirone ⁷⁷ and ondansetron ⁷⁸.

However, no study has suggested robust procognitive effects of these compounds. Also, interest emerged about the possible procognitive effects of histaminergic agents. Modafinil, a wakefulness-promoting medication, has a yet unclear mechanism of action. Modafinil appears to show therapeutic effects by increasing the expression of histamine in the hypothalamus ⁷⁹ and seems to act as a dopamine agonist, inhibiting the reuptake of dopamine by the dopamine transporter ⁸⁰. In some studies, modafinil was shown to improve attention, memory and executive functioning in people with Schizophrenia; however, several studies found no benefits of modafinil.

Authors studied several drugs targeting neuroinflammation and oxidative stress, following the hypothesis that inflammation plays a role in the pathogenesis of Schizophrenia. In fact, increased rates of Schizophrenia were observed after infectious events, such as maternal exposure to influenza and upper respiratory infections. Studies revealed that in pregnant women, an augmented expression of inflammatory cytokines in the second trimester increased the risk of Schizophrenia in their offspring ⁸¹. Viral exposure can reduce the density of receptors relevant for neurocognition, such as D1 receptors in the frontal areas and NMDA receptors in the hippocampus, it can decrease protein kinase B expression and impair axonal integrity ⁸². Levels of proinflammatory cytokines, such as interleukin IL-6, are elevated in Schizophrenia ⁸³ and have been shown to influence specific brain regions, including prefrontal cortex, medial temporal regions and long-term potentiation in the hippocampus ⁸⁴. IL-6 increases oxidative stress, which may interfere with the expression of inhibitory GABA interneurons and impact executive functioning ⁸⁵; levels of C-reactive protein (CRP), an inflammatory biomarker, are associated with neurocognitive deficits, but not necessarily with symptom severity in people with Schizophrenia ⁸⁶. Neuroinflammation impacts the activity-dependent transport of brain-derived neurotrophic factor (BDNF), a neuroplasticity-regulating protein that promotes neurogenesis, synaptogenesis and dendritic growth ⁸⁷. Given their impact on neurocognition, neuroinflammation and oxidative stress are potential targets for psychopharmacological enhancement of neurocognition. Minocycline, a broad-spectrum antibiotic, is a long-acting tetracycline traditionally prescribed as treatment of bacterial infections.

There has been recent interest about possible anti-inflammatory, anti-oxidative and neuroprotective benefits of minocycline in people with neurodegenerative disorders and in people with Schizophrenia. Acetylsalicylic acid (aspirin), traditionally used as an analgesic and an antipyretic medication, has gained recent interest as an anti-inflammatory agent. Particular atten-

tion has been paid to the anti-inflammatory properties of simvastatin and rosuvastatin; however, evidences are sparse⁸⁸. Omega-3 fatty acids are known to be essential for normal cortical expansion and maturation and functional integrity during prenatal and postnatal phases and during adult development⁸⁹. It has been demonstrated that omega-3 fatty acids may be beneficial to decrease the risk of a frank psychotic disorder in ultra high-risk individuals, suggesting possible neuroprotective effects⁹⁰. However, very few clinical studies on omega-3 fatty acids have examined their neurocognitive benefits. Some studies demonstrated that the adjunctive use of N-Acetylcysteine, a precursor of glutathione with antioxidant effects, improved the negative symptoms of Schizophrenia, although there was no direct examination of its neurocognitive benefits⁹¹. Cannabis sativa is the most widely used drug in the world. It contains over 70 different constituents, including delta-9-tetrahydrocannabinol (Δ 9-THC) and cannabidiol (CBD)⁹². CBD can interfere with the detrimental actions of Δ 9-THC in terms of psychotic proneness and cognitive dysfunction⁹³. On the other hand, CBD is a particularly interesting target as a novel approach for cognitive improvement in Schizophrenia, in part, due to its strong anti-inflammatory properties⁹⁴. CBD has the potential to limit Δ 9THC-induced cognitive impairment and to improve cognitive function in different pathological conditions, but there is limited evidence investigating the therapeutic efficacy of CBD as treatment for cognitive deficits in Schizophrenia. However, evidences suggesting cognitive improvement in neurological disorders with CBD treatment emerged⁹⁵.

Psychopharmacological treatment to improve cognitive deficits in major depressive disorder

Several clinical studies have primarily evaluated the effects of conventional antidepressants on cognitive performance in individuals with MDD. Conventional antidepressants are generally associated with beneficial effects on cognitive impairment in individuals with MDD, which may be mediated at least in part by the improvement obtained in affective symptoms, making it a partially indirect effect. For example, it was reported that SSRI treatment led to a significant improvement in memory performance in individuals with MDD⁹⁶. Studies showed that treatment with sertraline is associated with significant improvements in psychomotor speed and executive functions⁹⁷. On the other hand, other findings indicated that sertraline, citalopram or paroxetine were not associated with significant changes in cognitive performance in patients with Major Depression, whereas a beneficial effect was observed in pa-

tients with Minor Depression⁹⁸. Interventions targeting multiple neurochemical systems simultaneously (e.g. SNRIs) might be more likely to improve cognitive performance than treatments targeting only a single system (e.g. SSRIs)⁹⁹. For instance, a trial including adults with MDD treated with escitalopram or duloxetine showed that SNRIs were superior to SSRIs in ameliorating memory performance. Despite both escitalopram and duloxetine improved measures of working memory, attention, executive functions processing speed and motor performance, the improvement induced by duloxetine was greater than the one induced by escitalopram in episodic and working memory¹⁰⁰. However, duloxetine did not differ from placebo in several assessed cognitive domains in a study on elderly individuals with MDD¹⁰¹. A recent meta-analysis further indicates that standard antidepressant drugs may ameliorate certain cognitive domains in patients with MDD, namely psychomotor speed and delayed recall. However, the evidence base remains limited, and the effect sizes derived from this meta-analysis were small in magnitude (standard mean difference was 0.16 for psychomotor speed and 0.24 for delayed recall, respectively)¹⁰². These results might be encouraging; however, the extrapolation of a class effect on cognition based on results from a single medication within that class should be a very cautious operation. Long-term therapy with certain antidepressants may also be linked to cognitive side effects in adult subjects with MDD. For instance, in depressed individuals reaching partial or full remission, the treatment with antidepressants has been associated with increased cognitive deficits, such as apathy, inattentiveness, forgetfulness, word-finding difficulty and mental slowing¹⁰³. Vortioxetine is an antidepressant agent that acts as an antagonist of the 5-HT₃ and 5-HT₇ serotonin receptors, as a partial agonist of the 5-HT_{1B} serotonin receptor, as an agonist of the 5-HT_{1A} receptor, and that inhibits the serotonin transporter¹⁰⁴. Vortioxetine may influence learning and memory processes by improving hippocampal synaptic plasticity and increasing the output of pyramidal cells¹⁰⁵. Furthermore, it has been postulated that vortioxetine may improve the cognitive symptoms of MDD through its effects on cognate serotonergic receptors which may modulate glutamatergic neurotransmission¹⁰⁶. McIntyre et al. evaluated the efficacy of vortioxetine on cognitive function (executive functions, processing speed, attention, learning and memory) and depression in adults with recurrent moderate-to-severe Major Depressive Disorder (MDD). In terms of primary endpoint, Vortioxetine significantly improves cognitive functions. Analyses indicate that the beneficial effect of vortioxetine on cognition is largely a direct effect of the treatment. Vortioxetine significantly improved objective and subjective measures of cognitive function in adults

with recurrent MDD and these effects were largely independent from the improvement of depressive symptoms. The clinical relevance of the significant effect of vortioxetine on objective neuropsychological test scores was supported by the magnitude of the standardized effect sizes, which ranged from 0.23 to 0.52 [Cohen's *d*] ¹⁰⁷. The 5-HT system not only plays a critical role in the regulation of mood, but it is also intimately involved in the regulation of cognitive function, as evidenced by preclinical and clinical studies ¹⁰⁸. Vortioxetine activates cortical networks associated with cognitive processes; 5-HT_{1A} receptor agonism and 5-HT₃ and 5-HT₇ receptor antagonism contribute to these activating effects of vortioxetine ¹⁰⁹. Furthermore, vortioxetine is associated with the disinhibition of GABA interneurons ¹¹⁰ that plays an important role in the activation of the cortical and hippocampal networks involved in cognitive processes and with 5-HT₃ receptor antagonism ¹¹¹. In addition, vortioxetine exerts its antidepressant and beneficial effect on cognitive function via a distinct mechanism. There is evidence that cognitive function may vary independently of mood state in MDD. In particular, improvements in cognitive performance do not necessarily follow improvement in mood symptoms, which may reflect the distinct neural basis of cognitive control and emotion regulation related to depression ¹¹².

To date it is a high priority to identify new compounds to develop an effective treatment for Major Depressive Disorder. Lisdexamfetamine dimesylate (LDX) is a pharmacologically inactive pro-drug of D-amphetamine approved for ADHD. Augmentation therapy with LDX administration seems to be effective in reducing depressive symptoms ¹¹³ and improving the executive functions ¹¹⁴. Erythropoietin (EPO) exerts antidepressant-like and neuroprotective effects, enhancing hippocampus-dependent memory and neuroplasticity ¹¹⁵. Clinical evidence suggests that EPO may have cognitive-enhancing effects in MDD. Minocycline, as in Schizophrenia, has been proposed to play a role in the neuroprogressive nature of MDD and there is some evidence that pro-inflammatory status may also correlate with poor neurocognitive performance. Results obtained from preclinical ¹¹⁶ and clinical ¹¹⁷ studies have supported the potential of intranasal insulin in improving memory performance and executive functions. SAME is obtained from the essential amino acid methionine and from adenosine triphosphate. SAME is a major methyl donor required for the synthesis of several neurotransmitters and serves as a precursor molecule to the transsulfuration pathway, leading to the synthesis of glutathione ¹¹⁸. The procognitive potential of SAME was preliminarily documented in SSRI-resistant outpatients with MDD ¹¹⁹. Authors described inconsistent results about Acetyl-L-carnitine ¹²⁰, omega-3 polyunsaturated fatty acids ¹²¹,

melatonin ¹²², modafinil ¹²³, galantamine ¹²⁴, scopolamine ¹²⁵, N-acetylcysteine ¹²⁶, curcumin ¹²⁷, statins ¹²⁸ and coenzyme Q10 ¹²⁹.

Psychopharmacological treatment to improve cognitive deficits in bipolar disorder

The literature findings regarding the effects of lithium on cognition are equivocal. Although some studies reported cognitive deficits in attention and memory ¹³⁰, others failed to detect any impact of lithium treatment on cognitive performance ¹³¹. Furthermore, studies did not find any cognitive difference between bipolar patients treated with different agents (including lithium) and drug-naïve BD subjects ¹³². The cognitive impairment associated with medications appears to be present in BD patients who did not receive monotherapy with lithium. Therefore, the results might suggest that lithium only has minor side effects on cognition, at least in a clinically stable subgroup of BD patients. BD patients taking anticonvulsants as mood stabilizers other than lithium also showed deterioration in several cognitive domains. Furthermore, several cognitive functions are compromised in BD. In particular processing speed, sustained attention and emotion recognition are impaired in all BD patients regardless of the prescribed medication ¹³³.

Anticonvulsant medications, such as valproic acid, lamotrigine and carbamazepine, have well-established mood stabilizing and cognitive enhancing properties. A follow-up study found that lamotrigine-treated BD patients obtained better scores on verbal fluency and verbal memory compared with patients treated with valproic acid and carbamazepine ¹³⁴. Little is known about the neurocognitive effects of valproic acid and carbamazepine in BD, but studies in healthy volunteers and epileptic patients have shown that anticonvulsants generally lead to psychomotor retardation and memory and attentional decline ¹³⁵.

Compared to lithium and anticonvulsants, findings on the cognitive effects of second-generation antipsychotics in the treatment of BD are limited. Quetiapine and risperidone in euthymic BD patients showed adverse effects on cognitive domains ¹³⁶. Further analyses revealed that quetiapine, olanzapine and risperidone had no robust evidence regarding their beneficial properties ¹³⁶ on cognitive aspects. Recently, Yatham et al. indicated some preliminary evidence about the efficacy of lurasidone in improving cognition in euthymic patients with Bipolar I Disorder. Overall, the evidence supporting a possible role of cholinesterase inhibitors in the treatment of BD-related cognitive impairment is very limited. In conclusion, the pathophysiological mechanisms involved in the cognitive deficits found among bipolar patients may result from disruption in noncho-

linergic neurotransmitter systems. If confirmed by future studies, this hypothesis would explain the reason why BD patients are less likely to respond to this class of medications.

Mifepristone is a glucocorticoid receptor antagonist; authors observed significant improvements in spatial working memory, spatial recognition memory and verbal fluency in bipolar patients receiving mifepristone¹³⁶; however, the side-effect profile of this medication restricts its clinical routine use in the clinical setting.

Growing evidence points to a possible role of insulin on neuroplasticity regulation and the presence of insulin receptors in the hippocampus suggests that insulin may be involved in processes associated with memory consolidation¹³⁷.

Authors evaluated several compounds to estimate their

positive impact on cognitive domains. Studies were conducted to examine pramipexole^{138 139}, N-acetyl cysteine¹⁴⁰, omega-3 polyunsaturated fatty acids¹⁴¹, L-carnosine¹⁴² and erythropoietin¹⁴³. To date, no study has suggested robust procognitive effects of these compounds. Finally, growing evidence points to the role of inflammatory processes in the pathophysiology of BD and some studies have evaluated the correlations between inflammatory cytokines and cognitive impairment in BP. Therefore, the possible role of antiinflammatory agents in the treatment of cognitive impairment in BP seems to be a promising target for future studies¹⁴⁴.

Conflict of Interest

None.

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Neuroeconomic models: applications in psychiatry

Summary

Neuroeconomics is a discipline aimed at investigating the neural substrate of decision-making using, along an interdisciplinary way, research methods and information deriving from economics, cognitive and social psychology, and neuroscience. The combination of economic game theory and neuroscience has the potential to better describe the interactions of social, psychological and neural factors that may underlie mental illnesses. These concepts will allow a description of psychopathological disorders as deviation from optimal functioning. Neuroeconomic models can lead to identify quantitative phenotypes that will allow for further investigations in individuals with mental disorders. In this paper evidences from the interaction between neuroeconomics and psychiatry are reported, supporting the utility of economic concepts such as under ambiguity/risk and social decision making to psychiatric research, in order to improve diagnostic classification and therapy eventually.

Key words:

Neuroeconomics • Decision making • Game theory • Psychiatric disorders • Social cognition • Social decision-making

Introduction

In October 2017 Richard Thaler was awarded with the Nobel Prize for Economics for its contribution in integrating the economic and psychological analysis of the individual decision-making process. This award has sealed, if ever there was a need, the importance of the neuroeconomics, as a relevant field of interest in which economists as well as psychologists and psychiatrists focused their studies. The aim of neuroeconomics is the understanding of human decision making (DM) using, along an interdisciplinary way, research methods and information deriving from economics, cognitive and social psychology, neuroscience.

Alterations of DM processes have been studied not only in the human 'behaviour', investigating how neuroeconomic models, i.e. the study of how the economic behaviour can drive the person to do "the best for himself" and the best way to utilize resources, but also in psychiatric disorders.

Neuroeconomy and decision making

The neuroeconomic perspective focuses and explain the needs derived from adaptation and survival. Deployment and utilization of the resources in order to obtain the maximum reward and the best probability of survival is an economical question eventually. This perspective possesses therefore an evolutionary computational connotation in terms of adapting energy expenditure in the environmental economy so that the probability of survival can be maximized. Although it could seem complex, everyone in its everyday life operates decisions, quite automatically, without apparent mental effort.

DM implies complex processes involving higher-order cognitive functions, as executive functions are, focused to the choice and regulation of the

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possible action that lead to the optimal outcomes. It modulates reward and punishment perception so that advantageous choices can be made.

DM processing by the central nervous system depends from three temporally and functionally distinct, although partially, processes: assessment and formation of preferences among the possible options; selection and execution of an action; experience or evaluation of an outcome ¹.

Being DM so pervasive and necessary for human, both in physiological and in pathological cognition such as in mental disorders, necessity to obtain information to understand choice mechanisms and their link to neurobiological substrates is warranted. To do so, application of game theoretic probes (i.e. economic games) as quantitative ways to investigate subjects' choices that match or deviate from optimal has been productive.

Economic games, far from being an object of amusement, are approaches to understand the features of strategic interactions, a decision problem with structure, so that the player's payoffs can depend on its motivated choices under some input. These games reflect the investment of the limited energetic resources of an organism to pursue prey or food resource in the presence of uncertainty: choices therefore that are of biological value under selective pressure. They permit to explore the limitations in capacity to estimate probabilities, calculate the likelihoods of payoffs and the risks involved, and, as the game progresses, the player capacity to adequate its behaviour.

Several research paradigms have been elaborated to investigate and compute these real-life DM processes, likely the most utilized is the Iowa Gambling Task (IGT) ². It was developed for the evaluation of the orbitofrontal cortex (OFC) functioning associated with uncertainty, reward, and punishment processing.

This task permits to investigate the degree to which a subject selects small immediate gains, but associated with long-term gains (advantageous option), over large immediate gains associated with long-term losses (disadvantageous option). It also measures two kinds of decisions under uncertainty, i.e. risk and ambiguity. Decisions under ambiguity have to be performed in the first trials, while choice under risk in the last trials of the task as the game progresses.

The distinction between these two kind of uncertainty is based on the probabilities assigned to the outcomes. A choice under risk is linked to a foreseeable probability of possible outcomes and their associated payoffs, i.e. the player has some possibility to estimate the probability of the outcome. A choice under ambiguity instead possesses little or no evidence for having confidence in the assignment, with the unclear possibility to forecast the outcome. Evaluation of sensitivity to risk and ambiguity

is important in the investigation of cognitive processing of persons with mental disorders for which impulsivity valuation and the DM can be perturbed ³. The risky condition, in which an outcome probability prediction could be reliably estimated is more frequent in everyday life. However, the outcome of choices under ambiguity is inevitable and necessary eventually, to compute the risk of future decisions based on probability knowledge.

Recent studies using gambling games reported abnormal DM performance in several mental disorders. From a clinical perspective, this impairment can be considered a transnosographic trait that may influence the therapeutic response, determinate interpersonal difficulties, be related to suicidal risk and aggressive acts. It can be a feature of a wide range of *impulsive spectrum* disorders. The personality trait of impulsivity has been frequently suggested to be associated with DM impairment: subjects with impulse control problems display a decreased reasoning on the consequences of their choices. This can be the case, for instance, of disorders such as addiction and schizophrenia ⁴.

Estimation of the impulsivity often expressed by addicts, utilized DM games in order to determinate temporal discounting behaviours. Drug addicts by definition make poor decisions, such as continued drug abuse in the face of adverse consequences (i.e. a kind of 'myopia for the future'); gambling tasks can identify quantifiable neurobehavioural hallmark of addiction. Persons with alcohol dependence have been found to operate more disadvantageous choices leading to lower scores in their IGT performance, significantly related to impulsivity evaluation. These data suggest that DM impairment is related to impulsive dimension, an important feature in subjects with alcohol dependence likely with a role in increasing the proneness to a chronic relapsing course ^{5,6}.

Studies using DM games, particularly IGT, on patients with schizophrenia showed conflicting results. Some of these did not find differences from healthy controls ⁷, while other ones showed instead impairment ⁸. Researches examining the association between DM performance and symptoms of schizophrenia suggest that OFC dysfunction is associated with social behaviour impairment and possibly negative symptoms ⁹. Moreover, imaging studies examining neural correlates of IGT revealed that subcortical areas, other than OFC, were highly involved in DM processing ¹⁰. These subcortical areas can be associated with different symptoms. Some studies reported a positive association between IGT impairment and negative symptoms ⁹, although an association with positive symptomatology was also found ¹¹. Interestingly, recent reports show that individuals with schizophrenia are particularly impaired during the last IGT trials ^{11,12}. As a matter of fact, after an initial strategy

in facing choices under ambiguity similar to that of controls, patients did not modify their DM behaviour when the choices are under risk, operating disadvantageous choices because they continue their behaviour as they cannot forecast probabilities.

Motivational difficulties might have further accentuated the differences in DM performance¹³. These observations support a problematic lack of shifting behaviour using DM strategies that may lead the subjects to poor functioning suggesting this impairment as a relevant cognitive underpinning of functional outcomes.

The capacity of neuroeconomic games to capture real life DM, possessing highly recognized ecological validity more than most laboratory tasks, leads them to be suitable instruments to explore the relationship between decision making and community functioning outcomes¹⁴. This association has been found in both in individuals with a substance abuse diagnosis¹⁵ and subjects with schizophrenia¹⁶.

These observations could support the hypothesis of dopamine (DA) as a *wind blowing* on the decision making impairment¹⁷. If so DA can be considered as a key neural substrate for tracking the value of stimuli and actions and modulating decision-making within a neuroeconomic perspective. DA abnormalities have been implicated in regulation of energy expenditure, characteristic across disorders, such as addiction and schizophrenia, as well as depression and attention-deficit hyperactivity disorder, all showing a common dysfunction in the brain allocation of energy and resources in economic DM.

Social decision making

The human brain is essentially 'designed' to be social¹⁸. If so the social exchange and interactions necessitate the capacity to assign or refuse credit for shared outcomes in order to act appropriately. In social exchanges, computation of assignment of credit for an outcome is essential. Breakdown of assignment of social agency is a feature of several mental illnesses such as schizophrenia and autism spectrum disorders. Social agency computations are the basic models of other's mental states comprehension, i.e. the so called theory-of-mind^{19,20}.

The gap between decision-making in real life, where the influences of the social context are relevant, and the decision-making process evaluated in the laboratory often intentionally without any social influences, is wide.

The combination of Game Theory tasks with the neuroeconomic paradigms in the study of social DM, can allow greater understanding on how decisions are made in an interactive environment. This is the case of the games of bargaining and competition, in which the brain system of reward and the ability in the strategic game is linked to the evaluations of the intentions of the other²¹.

In other words, the thoughts and actions of an 'agent' depend on the variation of the actions and mental states of other social 'agents'²².

Decision making in complex social interactions needs to interpret intentions and the development of a Theory of the Mind (ToM) of others; this capacity is mediated by the medial prefrontal cortex function²³. An extended neural network contributes to the evaluation of the costs and benefits of social and socioeconomic exchange of the decision-making process, including cooperation and altruistic punishment.

The literature on game theory can provide guidance on solving problems related to social exchange. The cooperation and sanctioning of non-cooperative behaviour (i.e. the altruistic punishment) is regulated by cognitive and emotional mechanisms that have evolved in human beings in response to the need for mutual cooperation in complex social groups. The ToM, the prediction of reward, and the appreciation of social norms, are necessary, although sometimes not sufficient, mechanisms involved in social exchange and functioning.

Economic exchange games represent a relevant quantitative research paradigm to evaluate the social exchange, in terms of the subject's internal norms assessment for the fairness in an exchange, and they require that each subject models their partner's mental state.

There are several games, computationally well-defined, widely used as experimental probes in social DM research: the most known are the prisoner's dilemma, the dictator game, the ultimatum game, the trust game. These games have been proven valuable in clinical populations.

The most known and used is likely the 'ultimatum game' that offers a good example to the comprehension of cooperation or altruistic punishment behaviours. It can be also defined as a game 'take-it-or-leave-it': it involves two players, a proposer and a responder. The proposer possesses a given resource, e.g. 100 euros, that have to split with a responder. For instance, the proposer offers 20 euros to the responder, maintaining for itself the remaining budget. If the responder accepts the split, both 'take' the money, otherwise neither one gets anything (i.e. 'leave'). Theoretically the proposer should give the minimum possible to the responder, while this latter should accept all non-zero offers. This is not instead the case, where the modal offer is 40/100 and in 50% of the cases the responders refuse the 80/20 split proposal. This is a behaviour observed across different cultural and experimental settings and provides the detection of the usual response to fairness deviations²⁴.

This is however a so called 'one-shot game', a kind of game that does not provide the possibility of observing the result of the social signal offered to the partner, as well as the response, i.e. the consequent learning. The

social signal is indeed devoted to the expectation of adjusting the future partner's behaviour in the interaction. This opportunity can be seen in games involving cooperation by repeated interactions (relationships) with possibility to modulate the relationship in a more ecological setting, such as by multi-round fairness games. Neuroeconomic paradigm using this approach is the iterated 'Trust Game'. Similarly to the ultimatum Game it is based on a shared sense of fairness that lead to a mutually satisfying exchange²⁵. The 'player' has the role of 'investor' that send some money to a social partner, the 'trustee'. The sum sent arrives automatically tripled to the 'trustee' that has the possibility to choose the sum to repay the 'investor'. *Trust* can be therefore quantified as the amount of money one person sends to the other one. If both players in this game share and act upon a common social norm, for example they share the winnings of a game equally, an optimal shared strategy is used: e.g. the 'investor' sends its entire endowment to the social partner and this 'trustee' sends back half of the tripled investment. If so, a shared norm and cooperative strategy mutually benefit both players. If the investor instead considers the payment from the trustee too poor, he can refuse it and both the players don't receive nothing. Again, as in 'one shot' game, the 'investor' should accept all non-zero offers, giving instead the 'trustee' the minimum possible. Differently from this basic theory, the modal observed behaviours show a rejection of less than 20% of the total amount, showing a tendency to altruistic punishment that can modulate the subsequent responses to fairer exchanges. The game therefore is really based on trust: if the 'investor' and the 'trustee' respect trust reciprocating money, both players end up with higher payoff.

These neuroeconomic quantitative/computational paradigms have been used to study social interaction in mental disorders, such as borderline personality disorder (BPD), externalizing behaviour problems, depression, social anxiety, psychosis²⁶.

Studies of BPD with iterated Trust task showed failure in cooperation, associated with an insensitivity of anterior insular cortex^{27,28}. In a study on adolescents with externalizing behaviour problems a reduced reciprocity during social reasoning independent from ToM functioning was shown²⁹. Monterosso et al.³⁰ provided similar evidences in the addiction area. Ernst³¹ examined reward-related and goal-directed processing in relation to symptoms of depression supporting connection of the DM processing to neural dysfunction. Diminished activity for social than to non-social partners (i.e. a computer) in a region of the medial prefrontal cortex implicated in ToM was found in patients with social anxiety. Patients with psychosis showed lower baseline levels of trust compared to healthy controls at Trust Game³².

These results demonstrated a validity of neuroeconomics tasks to investigate and discriminate psychiatric disorders.

Future directions

Although the social neuroeconomic tasks used are of relatively good ecological value, they present however some pitfalls. As a matter of fact, the conceptualization of 'social cognition' is limited because these tests are typically 'off-line', i.e. are related to hypothetical scenarios in which the participants 'do not interact' and the event does not happen in real time, does not represent a real social interaction, does not elicit full emotional and behavioural involvement.

An alternative paradigm is the integration of a computer-aided task by which the subject experience a real social neuroeconomic interaction, i.e. the interchange is 'on line' with a 'Trustee' that responds in real time to the investment proposal of the subject. The subject, moreover knows some essential characteristics of the partner, such as name, sex, age (Fig. 1). Preliminary data using this paradigm show association of the neuroeconomic indexes, such as invested and gained money with daily life functionality (Riccardi et al., in preparation).

Conclusions

These studies suggest that fairness games through the neuroeconomic computations they provide can identify quantitative phenotypes in individuals with mental disorders.

Social exchange is common to all humans. When the biological substrates implementing these models are damaged or altered, abnormal behaviour is expressed. Economic games are beginning to provide new ways to capture and quantify this behaviour and the associated neural correlates, and may produce new biomarkers of mental diseases³³.

DM impairment can be considered a transnosographic trait that influences the symptomatology of many disorders and modulates the therapeutic response. Its definition allows a reformulation of those conditions that are described with various terms such as "impulsivity", "disinhibition" and "risk taking behaviour". All these generic descriptive terms can be interpreted in the light of knowledge about DM processes; their evaluation can offer useful information in the psychopathological, clinical and rehabilitation fields.

DM processes, particularly those relating to decisions under risk conditions, are associated with the functional deficit and social cognition constructs in people with mental disorders, such as schizophrenia.

The study of the diagnostic and predictive utility of neuroeconomic approaches in understanding these conditions is at the moment at the beginning. The possibility however that the DM processing investigated by fair-

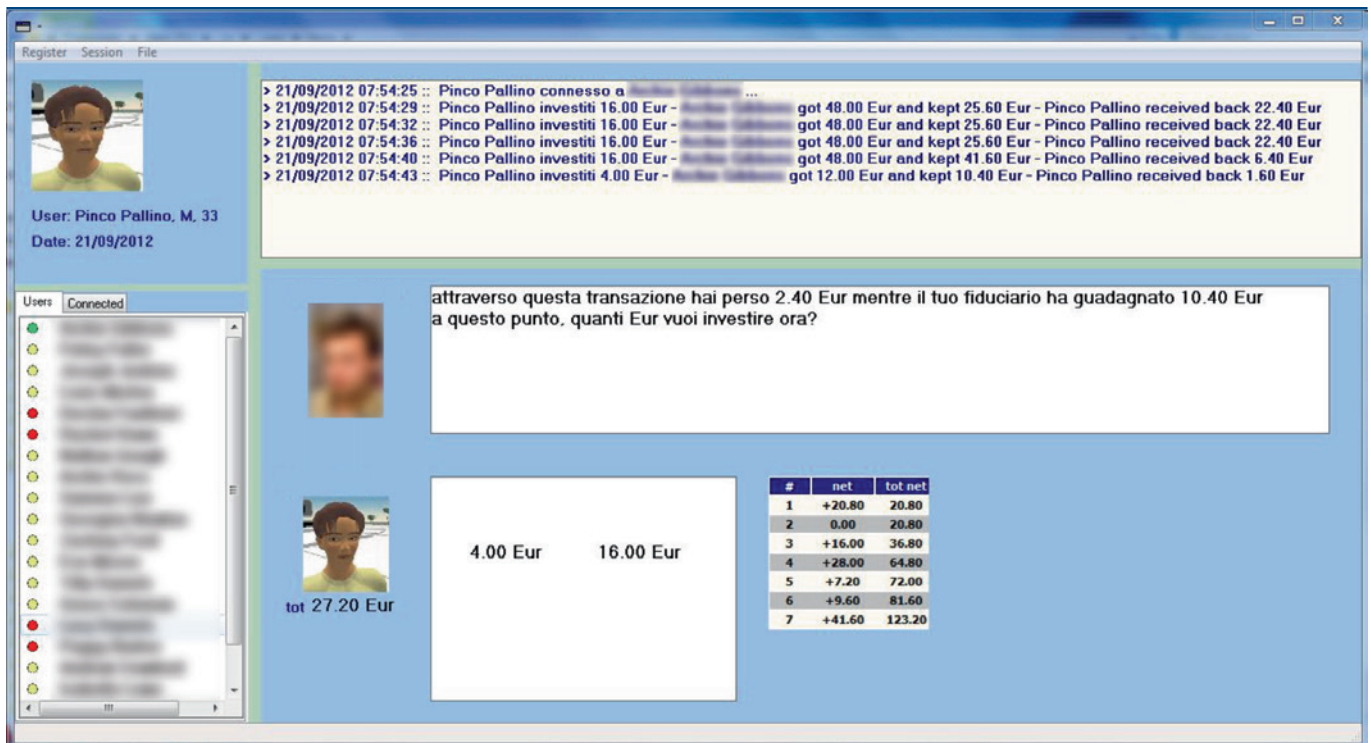


FIGURE 1. Trust game 'on line': example of an ongoing economic transaction.

ness games could be sensible to modulation by pharmacological (e.g. serotonergic or oxytocin modulation) or other kind of interventions (e.g. cognitive remediation) is exiting ⁴.

Once that the concept of DM will reach an adequate definition in pathophysiological, neuropsychological

and neurochemical terms, there will be real possibilities for the elaboration of a rational intervention for people presenting such clinical manifestations.

Conflict of Interest

None.

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Implementing cognitive rehabilitation interventions for schizophrenia patients in mental health services: focus on Integrated Psychological Therapy (IPT)

Summary

Objectives

Integrated Psychological Therapy (IPT) is a group-based cognitive-behavior therapy program for schizophrenia that integrates cognitive and social cognitive remediation with psychosocial rehabilitation. IPT is based on the underlying assumption that basic deficits in cognitive functioning have a pervasive effect on higher levels of behavioral organization, including social skills and social and independent functioning. Meta-analytic studies underlined that IPT is an evidence-based rehabilitation approach for schizophrenia patients. The aim of this review was to discuss the feasibility and effectiveness in implementing IPT in everyday clinical practice in an Italian mental health service, among patients with schizophrenia and to identify the promoting strategies and the barriers against IPT implementation.

Methods

For these purpose, five studies published from 2011 to 2016 were included in the review, investigating the IPT cost-effectiveness ratio, compared with treatment as usual (TAU) in people with schizophrenia in a real-world psychiatric rehabilitative setting at the University Department of Mental Health of the Spedali Civili Hospital in Brescia (Italy).

Results

IPT was accepted by the majority proportion of schizophrenia patients and findings have shown promising improvement in clinical, cognitive and psychosocial functioning, persisting over time, after IPT intervention, with a favorable cost-effectiveness ratio.

Conclusions

In summary, our experience demonstrated that IPT could be effectively implemented as an integral component of psychosocial interventions and that it was accepted by a significant proportion of people with schizophrenia admitted to a medium-length-of-stay psychiatric rehabilitation setting. Participants who completed the cognitive training were observed to have significantly improved cognition and psychosocial functioning, whereas the groups who did not participate or discontinued the training did not demonstrate similar gains. Although these promising and encouraging results on IPT efficacy in real-world psychiatric rehabilitative setting, there is need for further translational research evaluating the effectiveness and applicability of cognitive remediation in everyday clinical practice.

Key words

Schizophrenia • Cognitive remediation • Integrated Psychological Therapy • Evidence-based practice • Recovery

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Introduction

Schizophrenia has a heterogeneous range of outcomes and end states, from severe cases requiring repeated or continuous hospitalization, to cases in which a single psychotic episode is followed by complete remission and recovery¹. In past decades, it became evident that interventions focused only on schizophrenia symptoms do not result in a treatment success covering all areas of life and are not sufficient for a successful oc-

occupational performance and for good interpersonal relationships². Antipsychotics are a fundamental element of schizophrenia treatment, although the available antipsychotics have significant limitations³. Antipsychotics can assure a period of stability and facilitate the introduction of additional treatments such as psychosocial interventions, which play an important role in improving functional outcomes and promoting recovery in schizophrenia⁴. Psychosocial interventions are supported by substantial evidence of efficacy and effectiveness in several outcome measures in schizophrenia⁵. In a recent systematic review on rehabilitation interventions to promote recovery, Morin and Franck⁶ highlighted the efficacy of cognitive remediation (CR) in reducing the impact of cognitive impairment on functioning, of social skills training (SST) in learning a variety of skills and to a lesser extent in reducing negative symptoms, of psychoeducation in improving adherence to treatment and reducing relapses, and of cognitive-behavior therapy (CBT) in reducing the intensity of positive symptoms. An appropriate treatment targeting cognition, social cognition, negative symptoms and functional capacity, and integrative interventions combining different psychosocial therapies need to be instituted taking into account the specific needs of each patient.

Cognitive impairment in schizophrenia

Cognitive functioning is moderately to severely impaired in patients with schizophrenia. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project has identified seven distinct cognitive domains that are impaired in patients with schizophrenia: speed of processing, attention/vigilance, working memory, verbal and visual learning, reasoning and problem solving, and social cognition⁷. Social cognitive deficits include impairments in facial affect recognition, in perceiving and interpreting social cues, theory of mind (ToM), and the ability to make appropriate causal attributions for events⁸. Both cognitive and social cognitive deficits are thought to underlie the severe functional disabilities associated with schizophrenia, and several studies have shown that cognitive deficits are related to social deficits and poorer outcomes in different functional domains⁹. With this more detailed knowledge about the role and meaning of cognitive deficits in schizophrenia, improvement in cognitive functions has become a relevant target in the care and clinical management of the illness. Although pharmacological treatment has been shown to be effective in reducing psychotic, particularly positive symptoms, cognitive impairment has mostly been found to be poorly affected by such treatments¹⁰. Major initiatives are under way to find new non-pharmacological treatments for cognitive impairment in schizophrenia with the aim of improving also patients' functional outcomes.

Cognitive remediation in schizophrenia

Newer psychosocial interventions and cognitive rehabilitation programs are grounded in a recovery rather than deficit model. The underlying theoretical framework comes from a developmental neuroscience perspective, which supports the idea that the brain is capable of changes and development throughout the lifespan. Most cognitive interventions are based, in principle, on the large literature supporting the concept of brain plasticity and neurogenesis¹¹. CR for schizophrenia has been defined as "a behavioural training based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goal of durability and generalization" (Cognitive Remediation Experts Workshop (CREW), Florence, April 2010). In recent decades, a number of CR techniques, computerized and non-computerized, designed for individual or group settings, have been developed and adopted in multimodal treatment approaches in schizophrenia^{12,13}. To date, various published meta-analyses support the efficacy of CR in reducing cognitive deficits and in improving functional outcome with long-term benefits in schizophrenia. The results of these meta-analyses highlighted that the most significant effects on social functioning can be demonstrated when cognitive training is administered together with other psychosocial rehabilitation programs, and when a strategy coaching approach based on learning strategies is adopted¹⁴.

Cognitive remediation in schizophrenia: focus on Integrated Psychological Therapy

Evidence-based integrated approaches combining CR with social skills therapy have been demonstrated to be effective in achieving functional recovery in schizophrenia patients¹⁵. In this perspective, Integrated Psychological Therapy (IPT) combines cognitive remediation with training in social cognition, social skills, and problem solving¹⁶. IPT is a group-based CBT program for schizophrenia that integrates cognitive and social CR with psychosocial rehabilitation. IPT is based on the underlying assumption that basic deficits in cognitive functioning have a pervasive effect on higher levels of behavioral organization, including social skills and social and independent functioning. Based on this theory, successful psychosocial rehabilitation requires remediation of both underlying cognitive impairments and related social cognitive deficits, as well as building social, self-care, and vocational skills. IPT integrates cognitive and psychosocial rehabilitation in a manualized and standardized intervention with the goal of improving social competence in patients with schizophrenia. IPT is organized into 5 sequentially subprograms, beginning with cognition and social cognition, and followed by communication and social skills, and then problem-

solving skills. The cognitive differentiation subprogram aims to improve specific basic and more complex cognitive functions such as attention (selective attention and sustained attention), memory, conceptualization abilities (e.g., abstraction, concept discrimination, categorization) and cognitive flexibility; The social perception subprogram addresses deficits in social cognition (e.g., social and emotional perception, focusing on the improvement of skills pertaining to discrimination between relevant and irrelevant stimuli, between objective and emotional stimuli, and interpretation of social cues). Cognitive and social subprograms of IPT might work in a synergistic manner, thereby enhancing durability of therapy effects and improving functional recovery. The third subprogram serves as a bridge between the first 2 and last 2 subprograms by focusing on cognitive skills that directly impact on interpersonal communication, such as verbal fluency and executive functioning. The fourth and fifth subprograms focus on building patients' social competence through practice of interpersonal skills (eg, role plays) and group-based problem solving exercises. The two meta-analysis performed by Roder et al.^{17 18} have shown that IPT is an effective rehabilitation approach for schizophrenia. Patients undergoing IPT showed significantly greater improvement in all outcome variables (cognition, social cognition, psychosocial functioning, and negative symptoms) than those in the control groups (placebo-attention conditions and standard care), maintaining their mean positive effects during an average follow-up period of 8.1 months.

Implementation strategies in mental health services: focus on evidence-based psychosocial rehabilitation

During the past few decades, several psychosocial rehabilitation techniques have demonstrated their efficacy and effectiveness^{5 10}. However, under ordinary circumstances these evidence-based interventions are not easily translated into practice, as access to and use of the evidence-base are not straight forward for most healthcare providers in most countries of the world. As a consequence, a huge gap between the production of evidence (what is known) and its uptake in practice settings (what is actually done) has been repeatedly highlighted and described in different countries and in different healthcare systems. It is interesting to note that although the pathway from evidence generation to evidence synthesis and guideline development is highly developed and quite sophisticated, the pathway from evidence-based guidelines to evidence-based practice is much less developed¹⁹. For health system stakeholders, the challenge today has become less about identifying best practices but rather implementing a continuum of available, effective practices and ensuring that these are both accessible and sustainable²⁰. When seeking to implement psychosocial rehabilitation

interventions, stakeholders must consider a wide range of issues arising at different levels of influence (intervention, individual, organizational, and system) and stages of the implementation process (planning, engagement, execution, and evaluation)²¹. The Consolidated Framework for Implementation Research (CFIR) identifies 5 domains that regroup constructs theorized to play a role in the implementation process: *i*) the characteristics of the intervention (for example, evidence, complexity, adaptability, and cost); *ii*) the characteristics of the individuals involved (for example, knowledge, skills, attitudes, values, and identity); *iii*) the inner setting / organizations (for example, culture, leadership, resources, and access to expertise and support); *iv*) the outer setting (for example, community needs, policies, and incentives), and *v*) the implementation process (for example, collaboration and support of stakeholders, quality monitoring and evaluation)^{22 23}. The key issues are: *i*) whether guidelines may have any impact on healthcare provider performance, and thus on patient outcomes; and *ii*) how implementation should be conducted to maximize benefit²⁴. Current knowledge on how implementation programs should be developed is very scant. Implementation methods range from simple interventions, to more complex and multifaceted interventions, but it remains unclear which elements of the implementation strategies adopted in each initiative were critical to producing positive or negative implementation outcomes and how these may link to different service user outcomes²⁵. Consideration of the factors that contribute to implementation success or failure is important to reduce gaps in services and ensure the availability of a continuum of effective and sustainable mental health services.

Objectives

The aim of this review was to discuss the feasibility and effectiveness in implementing an integrated CR interventions – IPT – in everyday clinical practice of an Italian mental health service, among patients with schizophrenia. In the original articles we wanted to examine the following hypothesis: *i*) IPT shows better improvement in cognitive functions in comparison to treatment as usual (TAU); *ii*) IPT obtains superior effects in symptom reduction and in psychosocial functioning in comparison to TAU.

Materials and methods

Five studies published from 2011 to 2016 were included in the review. All the studies taken into account had the same inclusion and exclusion criteria and applied the same assessment tools. Patients enrolled were recruited and followed in the setting of two rehabilitative centers at the University Department of Mental Health of the Spedali

Civili Hospital in Brescia (Italy). They fulfilled DSM-IV TR criteria²⁶ for schizophrenia and were aged between 18 and 50 years. Exclusion criteria were: *i*) a concomitant DSM-IV TR diagnosis of mental retardation (as revealed by a Wechsler Adult Intelligence Scale-Revised (WAIS-R)²⁷ total IQ lower than 70) or of substance use disorder; *ii*) severe positive symptoms or impulsive behavior requiring a higher security setting; *iii*) significant changes in psychopathologic status (requiring hospitalization or major change in pharmacologic treatment) in the last 3 months. All patients not presenting these exclusion criteria entered the recruitment phase independent from other clinical or anamnestic variables, including that of previous abuse or present substance misuse. These are the same patients exclusion criteria in the rehabilitative centers where the study was conducted, according to the admission/discharge criteria for day centers and rehabilitation centers in the Lombardia Region, Italy, so that no further selection of patients among those treated in these centers was done.

Assessment

The following evaluations were completed at baseline, at the end of treatment and at 1-year follow-up by raters who were independent from those involved in the CR treatment of the patients.

Psychopathology

Psychopathologic assessment was made by means of the Positive and Negative Syndrome Scale (PANSS)²⁸.

Neurocognitive assessment

Patients received a comprehensive battery of neuropsychological measures to assess general intelligence, attention, verbal memory, working memory and executive functions. The battery comprised the WAIS-R²⁷, adopted at study entry as an inclusion criterion measure; the Trail Making Test A (TMT-A) and the Trail Making Test B (TMT-B)²⁹; the Wisconsin Card Sorting Test (WCST)³⁰; the Self-Ordered Pointing Task (SOPT) and the Visual Conditional Associative Learning Task (VCALT)³¹; and the California Verbal Learning Test (CVLT)³².

Functioning

The following scales were adopted to evaluate psychosocial functioning: the Global Assessment of Functioning (GAF) scale²⁶, the Health of the Nation Outcome Scale (HoNOS)³³ and the Personal Social Functioning Scale (FPS)³⁴.

Neuropsychological tasks were administered by trained personnel external to the treatment teams who did not know individual patients and their treatment allocation. On the other hand, the functional outcome measures were completed by the multidisciplinary team taking care of the patients in the rehabilitative centers, who

were trained in the use of these instruments and used them routinely in these centers. This team, which did not comprise the personnel specifically involved in the experimental treatment for the individual patients, completed the evaluations with team consensus, using all the useful informative sources (clinical records, patient interview, information obtained from close relatives and the case manager). The assessments were checked by one independent research assistant at each center, who was unaware of the treatment received by each patient, and interviewed the psychiatrists and the rehabilitation team about assessments. In the few cases of disagreement between the research assistant and the rehabilitation team, the rating was reassessed and a final agreement was reached. Finally, psychopathology was assessed by the psychiatrists in the psychiatric units following each patient, not directly implicated in the rehabilitative interventions.

Cognitive remediation interventions

In the studies, patients were administered the first two subprograms (cognitive differentiation and social perception) of IPT (IPT-cog). The cognitive components of IPT represent a practical compromise between a rigorously targeted cognitive approach, as commonly used in laboratory studies, and a more comprehensive and ecologically meaningful clinical approach. The IPT-cog group attended group therapy sessions twice a week, 45 minutes each session, for 24 weeks. The IPT-cog group was conducted by one trained psychiatrist or psychologist and another professional who administered the two cognitive subprograms following the IPT manual. The original manual was translated into Italian and adapted for Italian language and culture³⁵. In one study IPT effectiveness was compared with computer-assisted cognitive remediation (CACR) techniques³⁶. The CACR used the Cogpack program (www.marker-software.com). Cogpack was administered individually twice a week, in 45-min sessions, for 24 weeks. Finally, the TAU comparison group participated in non-cognitive-oriented group psychosocial interventions, consisting of different types of activities, such as expressive groups, physical training, or occupational therapies. TAU modality was designed to match IPT-cog and/or Cogpack with respect to group size, length and frequency of therapy sessions and, in general, amount of treatment received. In addition to participating in the IPT-cog, Cogpack or TAU program, patients continued with standard psychiatric care provided by a multidisciplinary mental health team (psychiatrists, nurses, occupational therapists, social workers, and psychologists), including other rehabilitative interventions (not cognitive-oriented) aimed at improving social skills, social relationships or work abilities, individually tailored in relation to clinical needs and personal preferences and

delivered in a balanced way between the groups. This allowed good comparability of the groups on treatments received and time spent in the outpatient services and rehabilitative centers of the psychiatric units involved in their treatment. The allocation of patients followed a centralized stratified randomization according to a complete block design generated by the project coordinators of the study outside the centers themselves so that the staff at the centers were not in a position to decide whether to include an individual patient in a specific treatment modality or not.

Table I summarizes CR implementation strategies applied in the Department of Mental Health of Brescia and IPT feasibility and effectiveness among patients with schizophrenia.

Results

In a first study we analyzed the effectiveness of the IPT-cog training compared with a similar amount of standard, non-cognitive-targeted, rehabilitative interventions in patients with schizophrenia within a psychiatric and psychosocial treatment regimen representative of the usual setting and modality of care in Italian psychiatric rehabilitative centers³⁷. Thirty-two patients (26 men; mean age 37.1 ± 7.8 years; mean duration of illness 13.7 ± 10.1 years; mean years of education 10.4 ± 3.3 years) fulfilling the study inclusion criteria were randomly assigned to the IPT-cog ($n = 8$ per center) or comparison ($n = 8$ per center) groups. The IPT-cog had a significant effect on specific clinical (negative and total symptom severity), neuropsychological (verbal and working memory function), and psychosocial outcome variables. This is consistent with the results of the two meta-analysis of IPT treatment, which revealed significant effect sizes of the treatment method on clinical, neuropsychological and functional outcome measures^{17 18}. It is possible to hypothesize that the significant effects on functional outcome found in our study may have been influenced by the naturalistic setting in which IPT-cog was offered and the integrated multimodal approach in which it was developed. In fact, there is evidence that CR has much more marked effects on outcome when embedded within a more general rehabilitation treatment framework^{14 15}. In a second step, we compared the effectiveness of two different CR modalities – IPT-cog and Cogpack – with respect to a similar amount of standard, non-cognitive-targeted, rehabilitative interventions in patients with schizophrenia³⁶. After 6 months of treatment, patients undergoing CR interventions demonstrated significantly greater improvements in psychopathologic, cognitive and functional outcome measures with respect to patients following the usual setting of psychiatric and psychosocial treatment. Both IPT-cog and Cogpack interventions had a significantly

larger effect on negative, positive and total symptom severity than usual care. IPT-cog showed a significantly better effect on processing speed and working memory variables, on which Cogpack had smaller, trend effects; both cognitive treatments had somewhat larger effects on some functional (GAF) measures, but only the Cogpack group showed a better effect on psychosocial functioning as revealed by the HoNOS scale. Overall, the study demonstrates the effectiveness of IPT-cog and Cogpack in schizophrenia when applied within a psychiatric and psychosocial treatment regimen representative of the usual setting and modality of care, with no evident superiority of any of the methods.

Then, we were interested in determining which factors contribute to a positive outcome after cognitive rehabilitation and whether different factors are associated with different degrees of improvement in both cognitive and real-world functioning in individual patients after CR. For this purpose, we examined 56 patients with schizophrenia who had completed a 6-month CR intervention and showed different cognitive and functional outcomes³⁸. Measures of cognitive and functional amelioration after CR were analyzed in relation to patients' clinical, neuropsychological and functional variables at baseline using logistic regression analysis. We found that a substantial number of patients showed cognitive and functional improvement (46.2% and 41.8%, respectively) and/or cognitive and functional normalization (32.4% and 23.6%, respectively) after CR. The main predicting findings were the following: *i*) a lower antipsychotic intake at baseline predicted cognitive improvement; whereas *ii*) lower antipsychotic intake, severity of specific symptoms, and higher cognitive functioning (particularly executive functions and verbal memory) at baseline were associated with cognitive normalization after remediation treatment; *iii*) functional improvement was predicted by lower patient age and type of CR intervention; whereas *iv*) functional normalization was related to lower baseline antipsychotic intake and, at a trend level, to higher executive functioning and type of CR intervention. Therefore, according to our data, CR could be more effective in younger, less disorganized, and cognitively less impaired patients, who take a smaller amount of antipsychotics. The predictive role of lower antipsychotic dosage on cognitive and functional outcome after remediation suggests either that patients with less severe illness could gain better advantage from CR interventions or that high dose or complex antipsychotic therapy may limit the effectiveness of such interventions³⁸.

In another study patients treated with CR or TAU for 6 months were reassessed with the same neuropsychological, clinical, and functional measures 1-year after completion of the randomized CR or TAU intervention³⁹.

TABLE I. Implementation strategies, feasibility and effectiveness of Integrated Psychological Therapy among patients with schizophrenia.

CR intervention	Setting and duration of CR	Patients characteristics	Type of studies	Assessment	Integration with other interventions
IPT (a manualized group-based CBT program for SCZ, integrating cognitive and social CR with psychosocial rehabilitation)	Group (6-8 patients) Sessions of 45 minutes, 2 times a week, for 6 months Real-world psychiatric rehabilitative setting (day centers and rehabilitation centers)	SCZ patients n = 84 Gender 58 (male) Mean age (years) 39.00 ± 9.90 Age at onset (years) 23.50 ± 6.95 Duration of illness (years) 15.89 ± 9.73	Two- / three-arm prospective controlled study in a real-world setting (IPT; Cogpack; TAU)	Cognitive, functioning and symptoms assessment at baseline and at discharge (6 months) and at 1-year follow-up after discharge	CR was administered together with other rehabilitative interventions (not cognitive-oriented) aimed at improving social skills, social relationships or work abilities, individually tailored in relation to clinical needs and personal preferences

CR: cognitive remediation; CBT: cognitive-behavior therapy; IPT: Integrated Psychological Therapy; SCZ: Schizophrenia; TAU: treatment as usual.

* TR11 is an innovative territorial project on integrated CR interventions in patients with schizophrenia and their impact on functional outcome.

During the follow-up, patients with schizophrenia were treated naturalistically in the outpatient facilities of the centers involved in the study and received pharmacological treatment and non-structured psychosocial interventions. The aim of this study was to further analyze whether the cognitive and functional effects of CR in patients with schizophrenia persist beyond the time of application of the remediation method in a naturalistic setting of care. At the 1-year follow-up, the advantages of CR remained significant for clinical variables and specific cognitive domains. Functional measures showed increasing improvement at follow-up. Overall, study results support the hypothesis that improvements observed after CR are largely stable after 1-year follow-up, which is compatible with the assumption that CR therapies may provide persistent modification of core aspects of the illness by implementing cognitive strategies and providing more structural metacognitive changes. These results may be clinically relevant, because the resources required for implementing CR interventions may be repaid in the long run by showing their relevant and stable effects in the real world. In this perspective, we performed a study with the aim to assess possible changes in the use of psychiatric services and pattern of care in patients with schizophrenia treated with CR or TAU⁴⁰. The use of inpatient and outpatient psychiatric services was assessed in the 12 months before and after a CR intervention or TAU in a sample of 84 patients with

schizophrenia. Data collected in the 12 months before the administration of CR or TAU interventions and those collected in the 12 months after completion of such interventions were analyzed. This study indicated that CR may have a significant impact on the use of psychiatric services and pattern of care of schizophrenia patients in the 12 months after CR intervention, compared with those patients who received TAU. We found a reduction in acute psychiatric hospitalizations, with a smaller number and shorter duration of hospitalizations in acute wards, an increase in outpatient service use and more frequent access to advanced and more complex forms of psychosocial rehabilitation, with higher total number of outpatient and rehabilitative interventions, as well as a more constant, intensive and articulated rehabilitation in the CR group. Overall, we can affirm that CR may modify the use of psychiatric services and the patterns of care of patients with schizophrenia, with a favorable cost-benefit ratio⁴⁰.

Discussion and conclusions

In different setting of care of the Department of Mental Health of Brescia, IPT was accepted by a sizable proportion of people with schizophrenia. Our data have shown promising improvement in clinical, cognitive and psychosocial functioning, persisting over time, with a favorable cost-effectiveness ratio, after IPT interven-

Main findings	Staff working on project	Staff training program	Barriers	Funding
CR improves symptom severity, neuropsychological and psychosocial functioning at discharge and at 1-year follow-up. CR could be more effective in younger, less disorganized, and cognitively less impaired patients, who take a smaller amount of antipsychotics. CR may modify the use of psychiatric services and patterns of care in SCZ patients, with a favorable cost-benefit ratio.	6 new psychologists; 2 new rehabilitation technicians Multidisciplinary mental health team: psychiatrists, nurses, professional educators	Five days of accredited skills training, for two editions, for a total of 48 training hours on: cognition in SCZ; clinical, cognitive and functional assessment; CR techniques, IPT; group practical exercises	IPT evidence-based efficacy and effectiveness; resistance to change; workload; costs	Funding for implementation strategies was provided by the Health Authority of the Lombardia Region (project TR11*)

tion^{36 37 39}. IPT is one of the earliest broad-based treatment providing training in cognition and involve other activities such as social cognitive remediation, cognitive behavioral therapy, and symptom management skills. This category of interventions results in a large number of activities that usually assume that training on basic cognitive activities (attention, memory, executive functions) and social cognition must be conducted before more complex social and interpersonal skills can develop. Integrated approaches, like IPT, may provide opportunities to learn and practice strategies and skills relevant for functional recovery in a supportive environment and to tightly link the (re)gained cognitive abilities to everyday life activities^{14 15}. Future research should clarify which are the active elements of integrated interventions and the crucial factors for the translation of cognitive change into broader concepts of real life and their underlying neural mechanisms. Only an integrated and multifaceted approach involving pharmacotherapy, psychosocial interventions, and attention to environmental circumstances can improve functional outcome in schizophrenia¹. Clinical services focusing on early detection, treatment, and recovery need continuous funding to be proactive in implementing guidelines and closing the gap between what is possible and what actually occurs¹. Development of rehabilitation plans requires a juxtaposition of individual factors with community factors. Assessment informs patients and rehabili-

tation provider of available opportunities and resources in the community, as well as available services in local rehabilitation programs. Rehabilitation services have a bidirectional mandate, in which providers need to help people learn skills to accomplish goals toward their disability and also need to address community barriers that undermine goals¹. Modern mental health systems are currently attempting to reduce gaps that exist between what is known to be effective and what the services really deliver in routine care. This task involves developing a strong understanding of the implementation process as well as the roles that actors at different levels must play to effectively bring about practice changes. Future efforts to implement evidence-based psychosocial interventions, like CR, should engage all key stakeholders and adopt a systems perspective to reduce inequities in care and make accessible the broadest range of evidence-based services²³. Moreover, mental health services committed to delivering evidenced-based psychosis care need to attend to the challenges of enhancing the skills of staff and maintaining the range of skills required to deliver interventions to address the cognitive deficits of psychosis. In this perspective, a multi-level training, accessible supervision and organizational processes, such as ongoing fidelity monitoring, are key to workforce development and program maintenance⁴¹. In summary, IPT was effectively implemented as an integral component of psychoso-

cial interventions and it was accepted by a significant proportion of people with schizophrenia admitted to a medium-length-of-stay psychiatric rehabilitation setting. Participants who completed the cognitive training were observed to have significantly improved cognition and psychosocial functioning, whereas the groups who did not participate or discontinued the training did not demonstrate similar gains. Although these promising

and encouraging results on IPT efficacy in real-world psychiatric rehabilitative setting, there is need for further translational research evaluating the effectiveness and applicability of cognitive remediation in everyday clinical practice.

Conflict of interest

None.

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Targeting social cognition to improve functional outcome of patients with schizophrenia: clinical evidences

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Summary

Social cognitive deficit is a key feature of schizophrenia, highly contributing to determine the functional impairment associated to the disease. Given the absence of effective pharmacological treatments, over the years several rehabilitative interventions targeting social cognition have been developed, with positive effects on patients' daily functioning and quality of life. In this Manuscript we will discuss rehabilitative interventions adopted and designed at IRCCS San Raffaele Turro (Milan), with a specific focus on training targeting social cognition. Clinical evidences indicate that combined rehabilitation of both social cognition and neurocognition in schizophrenia deficit is able to lead to better improvements of the two components of cognition and functional outcome. The identification of all factors influencing functioning and outcome of rehabilitation, and the personalization of rehabilitative programs according to patient's cognitive and clinical profile will allow to maximize interventions' efficacy and to promote functional remission, which represents the ultimate goal of the treatment of schizophrenia.

Key words

Schizophrenia • Social cognition • Rehabilitation • Cognitive deficit

Introduction

Functional impairment represents one of the main features in schizophrenia, determined by both neurocognitive and social cognitive deficits ¹. Patients often exhibit a low level of community functioning even prior to the onset of the first psychotic episode, generally worsening over the course of the illness.

Functional disruption is a treatment-refractory area of dysfunction in patients affected by schizophrenia ². Impairments in functioning manifest premorbidly and persist in remitted patients, often detectable in first-degree relatives of patients diagnosed with schizophrenia as well. Indeed, functional disability has been reported to be only marginally related to positive and negative symptomatology ³. Cognitive functions, such as verbal and visual learning and memory, working memory, speed of processing and attention, are strongly associated with daily functioning and are considered the most reliable predictors of functional outcome ⁴. However, taken together neurocognitive abilities are able to explain just the 20-30% of functional variability of patients with schizophrenia, suggesting that other elements may be involved ⁵.

In this context, social cognition has been proposed as the main mediator between neurocognition and daily functioning ^{6,7}. Social cognition represents the interface between emotional and cognitive processing, a multifactorial construct including the ability of individuals to understand themselves and others in the context of social interactions, such as others' thoughts, feelings and intentions ⁸.

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Different studies showed that social cognition is associated with patients' quality of life and employment rate, considered indicators of "real-world" functioning⁹. Particularly, Theory of Mind (ToM), defined as the ability to infer other's mental states, and emotion recognition are two main components of social cognition and are highly correlated with functional domains and quality of life¹⁰. Studies including both neurocognition and social cognition reported a relationship between the two domains, also evidencing a stronger association of social cognition with functioning⁹. Social cognition is considered a more complex domain, requiring intact neurocognition as a 'necessary but not sufficient' condition².

As previously mentioned, social cognition has thus been proposed as the mediator between neurocognition and functioning¹¹. Different studies confirmed this hypothesis, although the specific interplay between the two components of cognition is not yet completely clarified¹².

Given the relationship between social and neurocognition and their impact on functional outcome, in recent years several integrated rehabilitative interventions have been developed¹³⁻¹⁵, showing that combined rehabilitation programs have a greater effect on functioning than single interventions¹⁶⁻¹⁸.

Rehabilitative interventions for patients with schizophrenia and related disorders at San Raffaele University Scientific Hospital, Milan

Rehabilitation of patients with schizophrenia and related disorders represents one of the main clinical and research fields of the Disease Unit for Psychotic Disorders at San Raffaele University Scientific Institute Hospital. Over the years, the synergy between clinical and research activity allowed to integrate and develop different new rehabilitative interventions, in order to offer increasingly effective and tailored rehabilitative programs. Rehabilitative programs are designed for both inpatients and outpatients, with differences between the interventions related to the different duration of the treatments, which are much longer for the latter. Rehabilitative programs for inpatients, with a mean duration of 1 month, usually consist in Standard Rehabilitation Therapy (described below) added to a short-term intensive (daily) Cognitive Rehabilitation Therapy (4 weeks). For clinically stabilized outpatients with schizophrenia the center offers clinical and psychological assistance, as well as complex individualized rehabilitative programs encompassing different interventions which are selected according to patient's clinical, neurocognitive, social cognitive and functional features.

Indeed, entering into rehabilitation programs requires careful and extensive evaluation through different

scales such as the Positive and Negative Syndrome Scale (PANSS), the Brief Assessment of Cognition in Schizophrenia, Wisconsin card sorting test, Quality of Life Scale, Theory of Mind Picture Sequencing Task and other more specific instruments for special research purposes.

A brief description of the different rehabilitative interventions adopted at San Raffaele Turro is listed below.

Standard rehabilitation program (SRT)

The SRT represents the start point of rehabilitation program. The intervention is focused on main community goals of social abilities, work, and autonomy, including subprograms from Integrated Psychological therapy (IPT Verbal Communication, Social Skill Training and Problem Solving), social skills training programs for residential, vocational, and recreational functioning, and psychoeducation.

Cognitive Remediation Therapy (CRT)

CRT consists in a Computer-aided training employing the Cogpack Software® (Marker, 1987-2007). This software includes different neurocognitive exercises that can be divided into domain-specific exercises, aimed at training specific cognitive areas known to be impaired in schizophrenia (verbal memory, verbal fluency, psychomotor speed and coordination, executive function, working memory, attention). Moreover, it also includes non-domain-specific exercises, which do not focus on one specific function but require the use of several functions at a time and engage functions such as culture, language and simple calculation skills. Most exercises are adaptive and the computer sets the level of difficulty, based on patients' performances during the session. The software records the performance of each patient for every session, giving the chance to receive feedback on both performance during the session and over the course of treatment, and allowing therapists to obtain a course profile of each patient. Usually CRT has a duration of 12 weeks (two 1-hour session/week). Neurocognitive improvements of CRT lead to moderate improvement of general functioning, however we observed that the improvements in daily functioning depend on the achievement of a cognitive profile as much as possible "normal", harmonious and balanced, supporting the idea that a qualitative leap in cognition is needed in order to gain an advantage in real life activities¹⁹. In a recent study we investigated the persistence of both cognitive and functional effects of combined cognitive remediation plus standard rehabilitation interventions, 5 years after completion of the intervention, also comparing different durations of the standard rehabilitation. Surprisingly, Results showed that cognitive abilities remained stable after 5 years in both groups, while functional performance significantly decreased in

patients treated with the 6 months intervention only. Data thus suggest that cognitive effects persist even after 5 years, while a longer standard rehabilitation following the cognitive remediation program may be needed to achieve a stable functional gain ²⁰.

Social cognitive interventions

Social Cognitive Training (SCT)

SCT, designed and developed in our center, targets two different social cognitive abilities such as Emotion Processing (EP) and Theory of Mind (ToM). SCT is conducted by a trained psychologist over 12 weeks (one 1-hour session/week) on groups of about five members and made use of short videos selected from international cinema movies depicting human social interactions. In each session, two or three clips are showed and could be viewed several times, according patients' requests. Patients are then asked to become "social detectives", collecting every concrete and meaningful piece of information they notice and hypothesize interpretations of the scenes based on expressed emotions, relationships between characters, implicit motivations and mental states.

The efficacy of this training was confirmed in a recent study conducted by our team ²¹ where patients included in SCT group were compared with both a cognitive remediation therapy plus standard rehabilitation (CRT) and an outpatients no treatment group (NT). All patients were assessed before and after treatment with a ToM, EP, and a neurocognitive evaluation. Results showed an improvement of ToM abilities in SCT group compared with CRT and NT, but no in EP. We observed also a smaller improvement of ToM ability among patients in control condition who participated to CRT, this result suggesting us that progresses showed by the SCT group are not only related to an unspecific effect of rehabilitation or to neurocognitive enhancement therapy but mainly to the SCT's effect.

Theory of Mind Intervention (ToMI)

ToMI, designed and developed in our center, is conducted by trained psychotherapists over five modules divided into 18 sessions (one 1-hour session twice a week) on groups of about 5 members using comic strips and cartoons depicting human social interactions. The modules are executed in ascending order of complexity, with the first three modules regarding cognitive ToM and the last two concerning affective ToM. Patients are then trained to recognize the relevant details, to collect every concrete and meaningful information, to read the verbal part of comic strips and to identify literal meaning. Patients have also to interpret hidden meaning using all the information collected and to hypothesize interpretations of scenes on

the basis of expressed emotions, relationships between characters, implicit motivations and mental states. Eventually, answers written by the patients are read aloud and discussed within the group. In a recent study we proved the efficacy of ToMI training compared to an active control group (newspaper discussion group, ACG) ²². Before intervention, psychopathological, neuropsychological, functional and ToM assessments were conducted (baseline evaluation). Performances of interest (ToM) were re-evaluated after 3 months. Results showed an improvement of ToM abilities in ToMI. This improvement observed is not related to intellectual functioning or daily functioning of patients, although these variables correlate with basal ToM values.

In a further study ¹⁶ we compared the effect of both ToMI and SCT versus NT on ToM abilities, confirming the efficacy of both training and observing no differences between groups.

Moreover in a recent study conducted by our group ²³ we analyzed ToM improvement after treatment and clinical and demographic influencing factors on work abilities in a sample of patients attending to a work therapy group (WTG). WTG is designed for patients who previously had a job or are trying to obtain a new employment. WTG is conducted by rehabilitative therapists and is made up of 10 modules divided into: 1. Job/Work motivation; 2. Knowledge of previous working experiences and organization of curriculum vitae; 3. Assessment of patient's expectancies; 4. Assessment of residual resources; 5. Planning of interests and future possibilities; 6. Job interview strategies; 7. Possible problems in employment reality; 8. Substantial relationship problems managed with role-playing; 9. Submission of curriculum vitae and management of anxiety related to job wait; 10. Administration of bureaucracy related to job's contract and work reality. Interestingly, we reported that work outcome resulted significantly predicted by age at onset, neurocognitive abilities and the degree of ToM improvement after ToMI, thus further indicating the importance of an integrated rehabilitation program for patients with schizophrenia.

Emotion processing training

Deficits in emotion processing (EP) represent a target of rehabilitation in schizophrenia, as they have been related to poor personal and social functioning. We developed two treatments targeting EP, 1-hour sessions/week on groups of about five subjects ²⁴. The emotion recognition by video group (ERV) training used short videos depicting human social interactions, selected from The Awareness of Social Inference Test (TASIT; McDonald, Flanagan, Rollins, & Kinch, 2003). We chose to use only the first part, the Emotion Evaluation Test, as training material, because it is designed to train interpretation

of naturalistic emotional display including facial movement, tone of voice and gestures (Fear, Anger, Sadness, Disgust, Surprise, Happiness and Neutral state). Before watching the video, patients were invited to pay attention to the signals listed above. A guided discussion about recognition of emotion expressed by the professional actors followed, with the goals to recognize: (1) which emotion was expressed by the actors, and (2) which elements facilitated understanding of the emotion (facial gesture, interaction among actors). If none of the participants chose the right emotion, the psychotherapist pointed out the emotional signals expressed in the video. In the emotion recognition by audio group (ERA) we used the same materials as those of the ERV training (TASIT part 1) but played only the audio, as suggested by the TASIT manual. Patients spent the first session identifying how emotions could be expressed in a dialogue listening to voices only, without seeing images. A guided discussion about recognition of emotion expressed by the professional actors followed, and the goals were to identify: (1) which emotion was expressed by actors, and (2) which elements facilitated understanding of the emotion (tone of voice, interaction among actors, topics and subjects discussed in the speech). If none reached the correct emotion, the psychotherapist pointed out the emotional signals expressed in the speech. Results showed a significant improvement in EP through the specific channel trained for both groups, with an extended effect also on vocal stimuli for the visual training group. Positive correlations were found between working memory, social functioning and EP. Our findings help to shed light on the possible different involvement of perceptual channels in schizophrenia, as well as supporting previous evidence that emotion recognition may be inter-related but does not overlap with neurocognition and can be specifically trained.

Metacognitive Training (MCT)

MCT, developed by Mortiz and colleagues, addresses several cognitive biases, including bias against disconfirmatory evidence (BADE), Jumping to Conclusion,

ToM and Overconfidence in Memory. The primary target of MCT is to modify the cognitive infrastructure of delusional ideation, improving patients' awareness of both the presence and dysfunctionality of cognitive distortions. MCT is conducted by trained psychotherapists on groups of 5 members. It is composed of eight modules, lasting 16 weeks (1 session/week). The modules deal with monocausal and unbalanced attributions, jumping to conclusions, belief in flexibility, deficits in theory of mind and social cognition, memory (overconfidence in errors), depression and low self-esteem. Interestingly, we reported that combining MCT with CRT can lead to greater improvements on BADE²⁵.

Conclusions

This overview on rehabilitative interventions strongly supports the importance and the need of integrated programs targeting both neurocognition and social cognition. Indeed, as we recently reported, psychosocial interventions targeting social cognition allows to achieve higher rates of recovery, that represents the ultimate treatment goal in schizophrenia²⁶.

Moreover, offering a broad range of different interventions allows personalizing rehabilitative programs according to patient's profile, thus maximizing treatments efficacy and promoting functional remission.

Beside cognitive functioning and psychopathology, other variables such as premorbid adjustment, genetic variability and pharmacological treatment are known to influence outcome of rehabilitation among patients with schizophrenia^{27,28}. The challenge of future research is to identify all factors influencing functioning and outcome of rehabilitation, and then to develop new integrated interventions. This would pave the way to higher rates of functional recovery of patients with schizophrenia, eventually reducing the psychosocial burden of the disease.

Conflict of Interest

None.

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Implementation of cognitive rehabilitation in psychiatric services: integration of cognitive remediation and psychosocial rehabilitation

Summary

Objectives

A critical review of Cognitive Remediation, applied to schizophrenic beginnings or stages of disease, has shown that cognitive remedies are more effective when applied at an early stage of the disease. Here is presented an experience conducted at the Center for the psychotic beginnings of the Department of Mental Health of the ASL "Salerno".

Methodology

The study evaluates the outcomes of a CogPack computerized cognitive training, for a period of 12 months, on 47 patients divided into three groups of young people diagnosed with the schizophrenic syndromic spectrum. The rehabilitated functions were sustained and selective attention, verbal memory, executive functions, coordination and psychomotor speed. The following areas were assessed: Clinical (PANSS, MMPI-2) Neuropsychological (WAIS-R, BACs, WCST), functional and psychosocial (HoNOS, VADO).

Results

The neuropsychological functions affected by the intervention showed a significant improvement only in the first two groups, to which the "Cogpack" method was administered.

Conclusions

The positive outcomes in the patients who followed the CogPack cognitive training, remained stable in the 12 months following the end of the treatment. These first data confirm that the outcomes for those treatments of Cognitive Remedy appear more satisfactory in the context of a psychosocial rehabilitation program oriented to broader skills, as for the training of meta cognition and social competence.

Key words

Cognitive Remediation • Psychosocial interventions • Metacognition • Psychotic onset

Introduction

People with schizophrenia present with an impairment of their cognitive abilities with varying degrees of severity, in particular when it comes to their abilities such as information processing speed, sustained attention, working memory, verbal learning, executive functions and social cognition.

The cognitive deficit specifically is considered a marker of susceptibility to schizophrenia and is a negative predictor of the social and professional functioning of the individual, which furthermore limits the efficacy of rehabilitation treatments.

The insights offered by genetics, neuroimaging and neuropsychology have made it possible to re-assess in a complex though integrated manner, what was once considered an epi-phenomenon rather than a variable of schizophrenia progression.

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Nowadays it has been established in no uncertain way that an impairment of cognitive function is evident as early as the neurodevelopmental phase.

To-date drug therapy alone has failed to show its efficacy in any meaningful way in enhancing cognitive function, which is why in the last few decades, targeted treatment regimens have been developed in order to improve cognitive performance and as well as obtain rather ambitiously, a better clinical and functional outcome of patients with schizophrenia, albeit indirectly ¹.

A wealth of published studies prove in fact the efficacy of said methods in modifying neurocognitive tests and the potential they show to positively affect attention, executive functions and social cognition.

A further positive effect has been shown on social functioning of the individual, in both the overall psychopathological aspect and negative symptoms.

Cognitive remediation as psychosocial rehabilitation strategy

Current methodologies for cognitive rehabilitation include *inter alia* a range of different treatments, both computerized and non-computerized, 1 to 1 and group therapies, which make use of specific strategies and techniques ¹.

Most recent strategies rely on the model of *recovery* rather than the one based on *deficit* ².

Cognitive remediation treatments can be classified based on two main models: compensatory and reparatory/restorative.

Compensatory treatments aim at eliminating or bypassing cognitive deficit by relying on residual cognitive abilities and/or on environmental resources ³.

The goal therefore is to facilitate learning of new skills or encourage the use of the residual ones with the aim of achieving a specific objective by affecting also the environment, thus modifying and adapting the situation in which patients live to help them overcome their disabilities. The objective of this treatment type is above all to improve functioning rather than neuropsychological performance ^{4,5}.

The objective of reparative/restorative treatments is on the other hand to improve and correct cognitive deficits directly by using exercises based on repetition of tasks learned or to develop new learning strategies, and are based on the insights gained in the field of neuroscience, neuroplasticity in particular, namely the possibility to actually 'repair' impaired neuro-processes.

The programs that so evidently rely on neuroscience, prescribe learning and the repetition of tasks relating to relatively isolated cognitive abilities, with the aim of reinforcing and restoring neuroanatomical connections relating to key neuropsychological abilities ^{6,7}.

A meta-analysis of McGurk et al. ⁸ has proved how cognitive remediation programs entailing learning techniques based on development of strategies (re-learning) and task repetition (re-training) as well as problem-solving techniques, based on learning strategy coaching to be applied to everyday life, are more effective on functioning than those focused only on learning and practicing of skills.

A second and more recent meta-analysis by Wykes et al. ⁹ reached the same conclusion on the role of an approach based on strategy coaching.

The authors say in fact that the most marked and significant effects on social functioning are clear when cognitive remediation therapy is administered alongside other psychosocial rehabilitation programs and when the approach used is based on strategy coaching.

Cognitive remediation (CR) is best used within programs aimed at rehabilitation, in such a way that allows for the combination of the objectives of CR with those of psychiatric rehabilitation.

It has been observed in fact that a treatment combining both CR and psychiatric rehabilitation is more effective than either treatment alone.

The indication therefore is to provide both treatments simultaneously, side by side and in an integrated fashion. Cognitive remediation is a cognitive-behavioural treatment for subjects who present with a cognitive impairment that interferes with their day to day normal functioning.

The goal is to help individuals develop and/or reinforce deficient cognitive abilities.

At present software programs and integrated systems useful for remedial cognition are largely available.

Some of these software programs, developed from programs initially developed for the rehabilitation due to neurological lesions, are based on repeated stimulation of specific cognitive functions, via the execution of tasks involving specific abilities.

The majority of these software programs make use of positive reinforcement as motivational tool, as well as allowing for adjustments in the duration and complexity of the tasks assigned and the possibility to adapt the treatment type to the patient's specific characteristics.

One of the most widely used computerized cognitive training programs is the Cogpack method (The Cogpack package).

The CogPack is made of 30 sub-programs that involve the cognitive and functional areas listed below: selective and sustained attention, verbal memory, visual-spatial memory, working memory, reaction time, numerical skills, problem solving.

Exercises are assigned randomly and they have a level of difficulty that can be automatically adapted to the patient's abilities, thus avoiding both the execution of too easy a task than the frustration arising from tasks that are too complex.

CogPack has proved effective in improving executive functions, information processing speed, learning and verbal fluency¹⁰ and, when administered together with an ordinary psychosocial rehabilitation program, has been effective in functional outcome scores too. The efficacy of CogPack on clinical, neuropsychological and functional scores, has been further confirmed by studies carried out in our country¹¹⁻¹³.

Cognitive treatment and psychotic onset

Cognitive deficits have an early onset, often prior to the onset of the full-blown condition, thus indicating a predisposition to the development of the pathology. Most recent research-based data and the guidelines on schizophrenia suggest that an early and timely intervention on patients at the onset of the psychoses may not only reduce the severity and counteract biological, psychological and social consequences of the disease, but it can furthermore play a role in fighting deterioration into social functioning, which is already present when the psychoses is yet to manifest.

From a neuropsychological standpoint, some studies highlight the correlation between early onset and severity of cognitive deficits observed.

This result is even more relevant in view of the fact that cognitive deficits are not only the “core” of the condition but are furthermore the most significant predictor of the outcome. Rajji et al.¹⁴ in a meta-analysis have compared the neuropsychological profile of patients with early onset schizophrenia (under 18), patients with onset in early adulthood (by age 40) and patients with onset in late adulthood (older than 40).

Patients with early onset have shown when compared with the other two groups, more severe cognitive deficits in all functions assessed (IQ, executive functions, information processing speed, visual memory, working memory). A few randomized studies on patients with disease onset in adulthood have shown the efficacy of “Cognitive Remediation Therapy” in terms of cognitive function¹⁵⁻¹⁷, but also in the reduction of psychiatric symptoms¹⁸ and improvement in overall functioning^{18,19}. As it is often the case however, despite the numerous research programs carried out on adult patients, there is little data available on the efficacy of cognitive treatment on patients with early or very early disease onset. This in spite of the fact that early cognitive deficits that typically precede the onset of schizophrenia in patients with early or very early disease onset, have been widely recognized¹⁴.

It is therefore clear that these initial signs significantly impair the performance at school and the day-to-day normal functioning of patients with early or very early disease onset and that the prognosis for this patient type is bad.

A major review of Cognitive Remediation, applied at disease onset or during the prodromal (?) phases of the disease^{20,21} has shown how cognitive therapeutic remediation is more effective when used in the early stages of the disease.

This evidence suggests that taking on patients and the combination of drug and psychosocial treatments with proven efficacy may improve the quality of life of patients and their family and reduce at the same time the high material and social costs of schizophrenia.

This highlights the need for a therapeutic approach that is as integrated as possible and one that has as its main objective the treatment as early as reasonably possible of psychotic symptoms thus reducing, or even preventing altogether, the psychosocial deterioration associated to this disorder.

The experience of the Mental Health Department in Salerno.

Early treatment and recovery: from cognitive remediation to integrated neurocognitive therapy

Method

The study assesses the outcome of a computerized cognitive training “CogPack” on 47 patients divided in three groups who have had a diagnosis of schizophrenia (F20-F24 ICD X) with an *average age of 20.88* (17/29 year old) (Fig. 1), *Height M 82.89* and an average duration of the disease of *13 months since disease onset*.

The neuropsychological functions object of the intervention were: *sustained and selective attention, verbal memory, executive functions, coordination and psychomotor speed*.

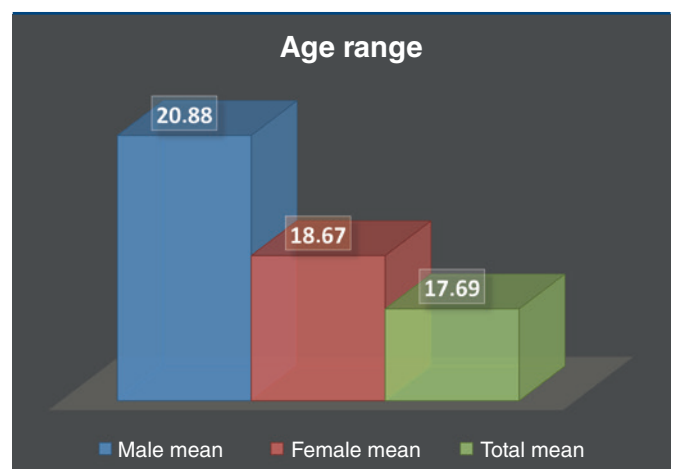


FIGURE 1. Distribution by age groups.

The first group is composed of 20 young people treated with Cogpack in combination with other psychosocial interventions (individual, family psychotherapy, expressive group, art therapy, occupational therapy, etc.) (Fig. 2).

The second group was made of six young patients treated exclusively with CogPack (Fig. 3).

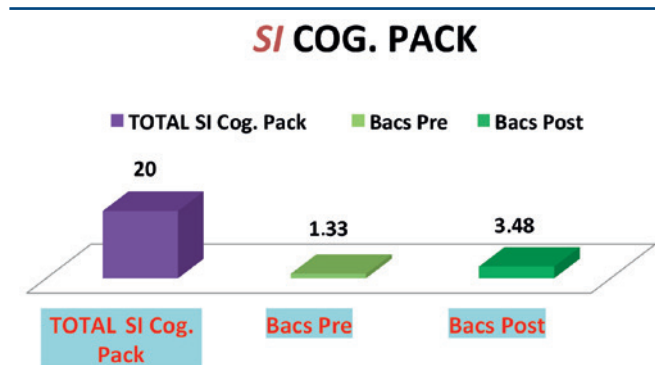


FIGURE 2. Patients treated with the “Cogpack” method.

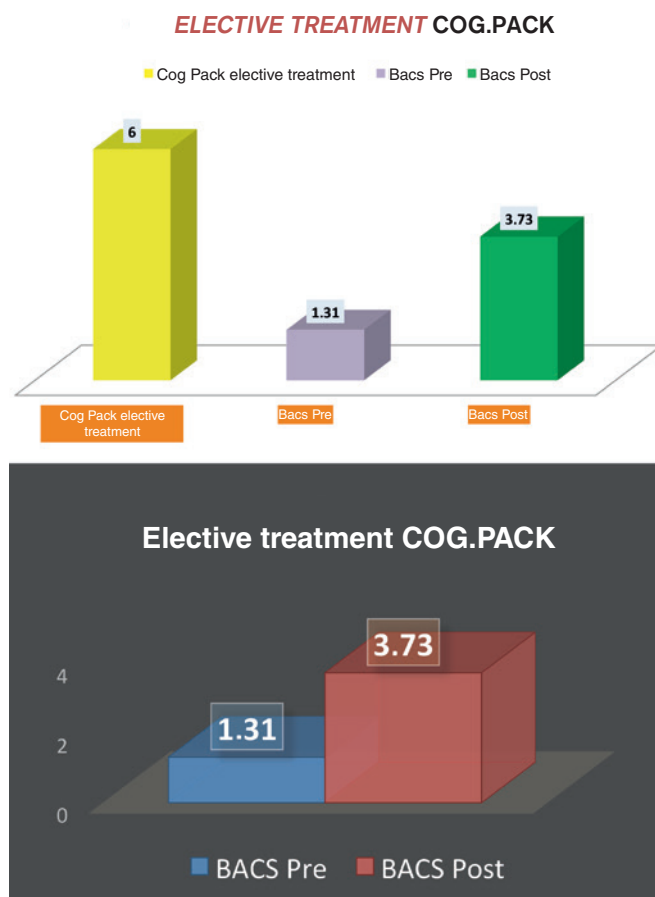
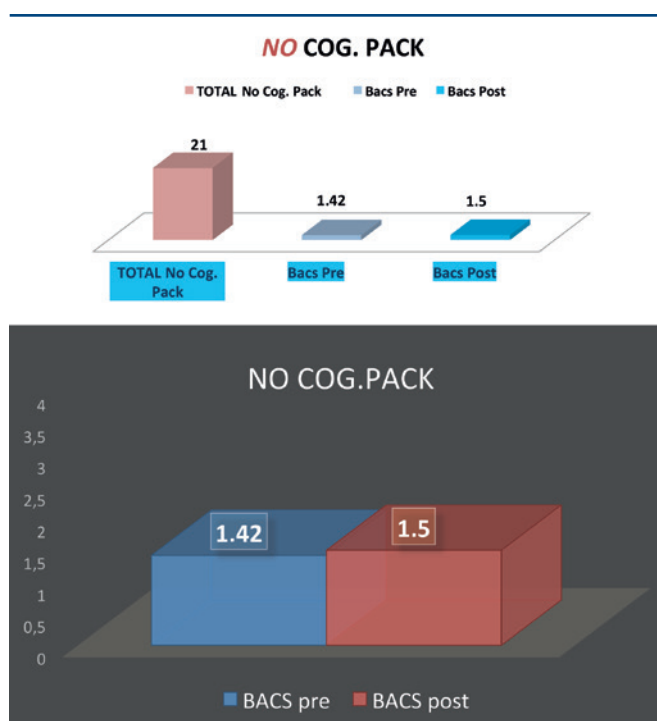


FIGURE 3. Patients in elective treatment “Cogpack”



FIGURES 4. Patients who have followed a psychosocial naturalistic treatment.

The third group was made of 21 young patients treated with psychosocial therapies without CogPack (Fig. 4).

Evaluation

The evaluation involved four specific areas for which we used the following tools: Clinical (PANSS, MMPI-2) Neuropsychological (WAIS-R, BACs, WCST), functional and psychosocial (HoNOS, VADO).

Results: the treatment duration was 12 months. The results have been evaluated by comparing the scores obtained in the BACs (pre- and post-treatment and at follow-up, 12 months since the end of treatment).

The neuropsychological functions involved in the intervention showed a significant improvement only in the groups that received the “Cogpack” method (CogPack/CCogpack plus other therapies), there were no significant changes in the third group who had not been treated with CogPack and only received other therapies.

Conclusions: The results indicate that Cogpack cognitive training can be effective for the cognitive functions most involved in schizophrenic disorders. The positive effects in patients who have followed the Cogpack cognitive training (48 sessions) in combination with other therapies, were sustained in the 12 months following end of treatment. The improvement of cognitive mentioned areas is related to the clinical insight, the social cognition and therefore functional outcome.

Patients who followed the Cogpack Treatment have also started an Integrated Neurocognitive Therapy (INT), at 6 months after the end of treatment and are currently still in treatment.

There was a significant motivation and a high level of satisfaction in all patients enrolled, no drop-out during the observation period. The number of patients that showed an improvement in functioning in social activities is significant. These first data confirm that the outcomes for those treatments of Cognitive Remedy ap-

pear more satisfactory in the context of a psychosocial rehabilitation program oriented to broader skills, as for the training of metacognition and social competence. The need to implement these interventions in care pathways on the early signs of pathology "pre-beginning" appears to be confirmed.

Conflict of Interest

None.

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The implementation of cognitive remediation interventions in Campania

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Summary

Cognitive impairment is considered a core aspect of schizophrenia and an important therapeutic target for its negative impact on real-life functioning of affected people. Psychotropic drugs commonly used in the treatment of schizophrenia do not improve and might even worsen cognitive dysfunctions. In contrast, cognitive remediation (CR) was found to improve cognitive deficits and real-life functioning of subjects with schizophrenia. The present paper aims to provide a brief review of the theoretical basis of different CR programs and to illustrate the implementation of two such programs in Campania. In particular, the Social Skills And Neurocognitive Individualized Training (SSANIT) and the Computerized Interactive Remediation of Cognition - Training for Schizophrenia (CIRCuiTS) will be illustrated. SSANIT is an integrated program, including individualized computerized CR and social skills trainings.

CIRCuiTS is a stand-alone computerized CR program targeting the development of metacognitive skills. Factors informing the choice of a specific CR program for individual subjects are also illustrated.

Key words

Cognitive remediation • Social Skills And Neurocognitive Individualized Training (SSANIT) • Computerized Interactive Remediation of Cognition Training for Schizophrenia (CIRCuiTS)

Introduction

Cognitive impairment has been considered a nuclear aspect of schizophrenia since the earliest descriptions of the syndrome. However, for several decades the evaluation and treatment of cognitive dysfunctions have not been the focus of research in this area. In a few research centers, the evaluation of cognitive functions was mainly focused to the characterization of pathophysiological mechanisms of the syndrome^{1,2}. Over the past decade, a broad consensus has been achieved on the definition of cognitive dysfunction as an important target of clinical research³.

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project identified seven distinct cognitive domains compromised in schizophrenia patients: processing speed, attention/concentration, working memory, spatial memory, verbal memory, problem solving and social cognition⁴. These cognitive deficits are present, in attenuated form, even before a full blown psychotic episode and in non-affected first-degree relatives, suggesting that cognitive deficits can be biological markers of the disorder^{5,6}. In addition, cognitive deficits predict functional capacity (i.e., the ability to perform tasks of everyday life in a controlled environment, e.g. write a check to pay a bill or reschedule an appointment with a doctor), considered a mediator of the impact of cognitive deficits on real-life functioning^{5,6}. In the light of these data, the impairment of cognitive functions is considered a central aspect of treatment and clinical management of the disorder. The available pharmacological treatments do not have a proven efficacy on cognitive deficits in patients with schizophrenia⁹. Therefore, several cognitive re-

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mediation techniques (“Cognitive Remediation”, CR) were developed.

The purpose of this article is to provide a brief review of the principles on which the different interventions of CR are based and to illustrate the programs implemented in Campania by our Department.

Cognitive remediation in schizophrenia: rationale and techniques

CR is defined a “behavioral training-based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goal of durability and generalisation” (cognitive remediation experts Workshop [CREW], Florence, April 2010). It is widely recognized that CR techniques, unlike pharmacological treatments, represent an effective method for the improvement of cognitive functions in schizophrenia¹⁰. The hypothesis that the training of cognitive abilities might improve these functions is corroborated by the most recent neuroscientific evidence of brain plasticity during the whole life span in relation to the quantity and quality of the received stimuli¹¹ and by data showing neurobiological changes, i.e., an increase in gray matter, following CR¹¹. Two different theoretical CR models have been elaborated: the compensatory and the restorative ones. The “compensatory” model tries to eliminate or overcome specific cognitive deficits, using the residual cognitive abilities of the subject and/or environmental resources. The “restorative” model is based on the neuroscience findings, such as neuronal plasticity, and aims to correct specific deficits by trying to repair the underlying impaired functions¹². The restorative method uses two different strategies called “bottom-up” and “top-down”. The bottom-up approach begins with the training of basic neurocognitive skills, such as attention, and then remediate more complex functions, such as problem solving. In contrast, top-down approaches starts from more complex skills, targeting the development of metacognitive skills, such as self-control and strategies for learning and for the application of cognitive skills. The latter approach might facilitate the transfer of the improved cognitive skills to real-life situations¹³.

CR uses several learning strategies, such as errorless learning, scaffolding, massed practice, positive reinforcement and information processing strategies¹³. In recent years, numerous cognitive computerized and non-computerized techniques have been implemented, designed as training programs for individual or group settings¹⁴.

CR has been offered to subjects with schizophrenia as stand-alone programs (targeted interventions), or within an integrated rehabilitation program, in association with a psychosocial rehabilitation intervention (e.g., social skills training or supported work).

Targeted and integrated interventions

Targeted CR interventions hypothesize that training the

basic cognitive deficits leads to an improvement of more complex functions, such as functional capacity and real-world functioning. Integrated interventions (CR + psychosocial interventions) aim to provide a context in which to actively practice the new skills acquired with CR.

To date, some meta-analyses confirm the efficacy of CR techniques^{10 15-17}. Specifically, these interventions improve the cognitive performance of the patients (both on trained and untrained cognitive tasks) and have a moderate effect on the real-life functioning^{10 15-16}. Although both targeted and integrated training programs demonstrated effectiveness in improving cognitive functioning, generalization to the real-life functioning is greater with integrated programs. Targeted interventions, however, present some advantages: 1) impose a limited number of sessions; 2) do not require multiple skills of the therapists; 3) do not require the availability of funds to implement complex psychosocial interventions.

In order to select the most appropriate CR program, it is of utmost importance to consider the clinical needs of the individual patient. A person with impairment only in some cognitive domains, which has a limited impact on real-life functioning, could be the ideal candidate for targeted intervention. Conversely, a subjects with pervasive cognitive deficits and severe impairment of real-life functioning might benefit more from an integrated intervention.

An important task of future research in the field is to clarify whether targeted, top-down interventions, including a specific metacognitive training might improve real-life functioning, overcoming the need to integrate CR with psychosocial interventions.

Implementation of CR interventions in Campania

Starting from the theoretical assumptions and findings reviewed above, the Department of Psychiatry of the University of Campania “Luigi Vanvitelli” has implemented two different rehabilitative interventions: an integrated intervention, the Social Skills And Neurocognitive Individualized Training (SSANIT), and a targeted “top-down” intervention, including a metacognitive training.

Implementation of an integrated rehabilitative intervention: the Social Skills And Neurocognitive Individualized Training (SSANIT)

The Social Skills And Neurocognitive Individualized Training (SSANIT) was developed by our research group, integrating and modifying two already available interventions, the Social Skills Training and a computerized CR training developed for neurological patients. Particular attention was devoted to the individualization of both interventions, and to the development of strategies to make the skills learned applicable in real life contexts to favor generalization¹⁸. The psychosocial intervention of SSANIT (Social

Skills Individualized Training, SSIT) consists in a rehabilitative training for interpersonal skills. The SSIT includes different phases: (1) establishing a rationale for learning the skill; (2) discussing the component steps of the skill; (3) modeling the skill in a role play and reviewing the role play with the patients; (4) engaging a patient in a role play; (5) providing positive feedback; (6) providing corrective feedback; (7) engaging the patient in a second role play of the same situation; (8) providing additional feedback and (9) assigning homework¹⁹. The focus of this part of the SSANIT is to improve people's social competence for areas which are important to function effectively in real life contexts. The learned skills can make the individual able to deal with his/her social network. A better social network would allow the subject to have more opportunities to request help during stressful life events. Furthermore, a greater sense of social autonomy would have a positive effect on the subject's self-esteem. The psychosocial intervention lasts a total of 6 months, with weekly group sessions, of 2 hours each.

The neurocognitive component (Neurocognitive Individualized Training, NIT) of the SSANIT is based on a computerized CR program, RehaCom, developed by HASOMED GmbH (Inc., Ltd) in Magdeburg, Germany²⁰. The subject works with RehaCom on a personal computer with a special keyboard with simple, large and light keys. RehaCom is a very flexible software that gives to the therapist the possibility to individualize the intervention. In fact, the therapist can choose different exercises for the training of different cognitive functions, and can set the level of difficulty for each starting session and each domain. Thus, motivation is improved and frustration is avoided. All the training results are automatically saved in RehaCom and a new session starts where the last one ended; therefore, it is possible to check the course of therapy at any time, adjusting the parameters when necessary. For the implementation of the NIT the following RehaCom modules were used: "Attention and concentration", "Verbal memory", "Memory for faces", "Logical thinking", "Shopping" and "Day planning". Two one-hour weekly sessions are provided for a six-month total duration.

The implementation of these interventions involved the working groups of the coordinating center and the Day Care Centers of Campania Mental Health Departments (Avellino 1, Benevento 1, Puglianello and Bucciano), and was divided into the phases illustrated below. During the first phase, personnel for the management of the interventions was identified and trained. For each Day Care Center the équipe included two nurses, a psychologist, and a social worker or psychiatric rehabilitation technician. The 3-month training involved attending held 10 2-hour lessons on the theoretical and practical aspects of the integrated intervention, held by a psychiatrist with specific expertise in CR and SST. In the second phase, psychiatrists

and residents in psychiatry in the University Department were trained for psychopathological, cognitive, and real-life functioning assessments. The University Department personnel was only involved in the assessments and not in treatment.

In the third phase, 60 patients with a diagnosis of schizophrenia or schizoaffective disorder were assessed at baseline and then randomized to the SSANIT program or to structured leisure activities (SLA). The fourth phase of the study consisted in the post intervention assessment of psychopathological, cognitive, social and personal functioning.

Figure 1 illustrates the procedure followed to implement the SSANIT program.

At the end of the integrated intervention, 11 patients dropped (3 in the SSANIT and 8 in the SLA group). The results showed an improvement in social and personal functioning in SSANIT patients, compared to the control group. No significant group effects were observed on psychopathological variables and cognitive indices. Patients who participated to NIT showed, however, an improvement in the performance at RehaCom, achieving a satisfying performance at the most difficult levels, for all the trained domains, with the exception of the day planning module. In conclusion, the low number of dropouts and the results obtained confirmed the effectiveness of an integrated rehabilitation treatment compared to SLA.

Implementation of a targeted cognitive remediation: "Computerized Interactive Remediation of Cognition Training for Schizophrenia" (CIRCuiTS)

In 2010 the research group coordinated by Prof. Wykes developed a new-generation metacognitive computer-based rehabilitation program: The Computerized Interactive Remediation of Cognition - Training for Schizophrenia (CIRCuiTS)²¹. The intervention was designed to improve cognitive skills such as long-term memory, working memory, attention, problem solving, processing speed, comprehension, flexibility and planning, in people with schizophrenia or schizoaffective disorder. Specifically, CIRCuiTS aims to improve metacognitive knowledge (knowledge of one's cognitive skills) and metacognitive regulation (the ability to monitor and control the application of the same skills).

The program is set in a virtual "village" and the activities take place in the relevant buildings. There are 27 tasks, each with 12-15 levels of difficulty, adjusted according to the patient's abilities. Two types of tasks are included: "abstract" and "complex". Abstract activities have a "neutral" content (such as numbers or geometric shapes) and are designed to train specific simple cognitive functions. Abstract, simple tasks are predominant in the first phase of the program, gradually become less frequent and are replaced by more "complex" tasks, which are more "ecological", i.e., similar to everyday life activities (e.g. planning

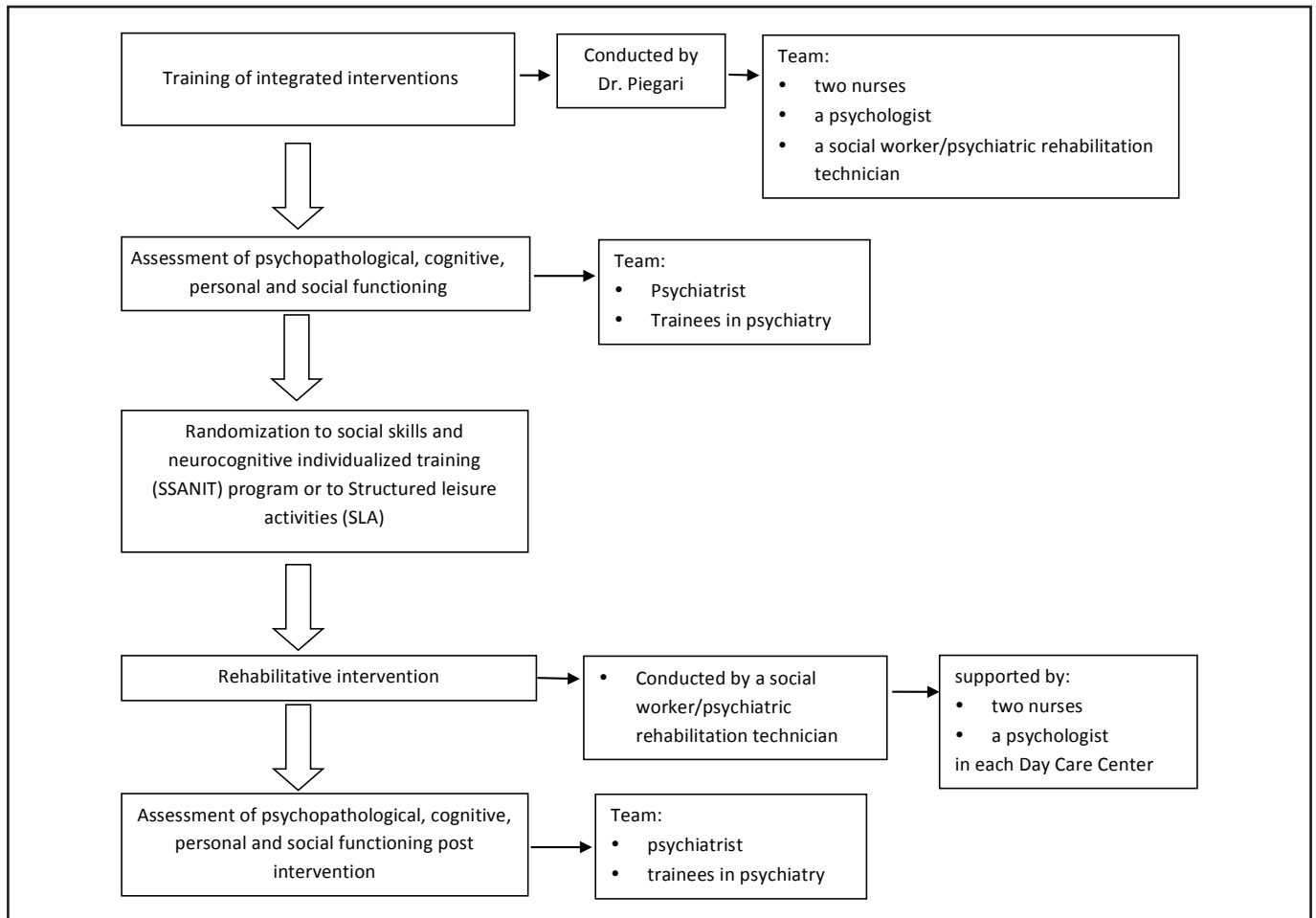


FIGURE 1. *SSANIT implementation procedure.*

a trip, making or recalling a shopping list). The different tasks belong to 5 categories: work, social situations, cooking, shopping and travelling.

Metacognitive regulation is encouraged by asking participants to develop a plan, to estimate the difficulty before beginning a task, than monitor and finally review task performance. After the task, participants review their scores and rate how difficult they found the task and how useful they found the selected strategy. In addition, the program includes specific strategies to encourage the user to draw parallels between activities within the session and everyday life and to apply the new skills learned in real-life situations.

CIRCuiTS includes a maximum of 40 sessions, with a frequency of 3 sessions per week, including, if possible, one patient's home session. Each session lasts about one hour, but duration is adjusted to participants' attentional capacity (being shorter at the beginning and then gradually increasing to match subject's improvement in attention).

The Department of Psychiatry of the University of Campania "Luigi Vanvitelli" has developed a study with the aim to provide data on the feasibility and acceptability of the Italian version of the program in a sample of outpatients of the University Mental Health Department. Before starting the research project, a psychiatrist from the University of Campania followed a two-month training at King's College, taking part in the translation to Italian and adaptation of CIRCuiTS to the Italian cultural context. After this period two psychiatric rehabilitation technicians were trained by the same psychiatrist and conducted the rehabilitation intervention with 4 patients each (8 patients in total). The rehabilitation project was structured in three main phases. During the first phase, a psychiatrist and a psychologist performed the basic cognitive and psychopathological evaluations. During the second phase the intervention was carried out, with two weekly sessions supervised by the psychiatric rehabilitation technicians and a third weekly session conducted autonomously at home by the patient.

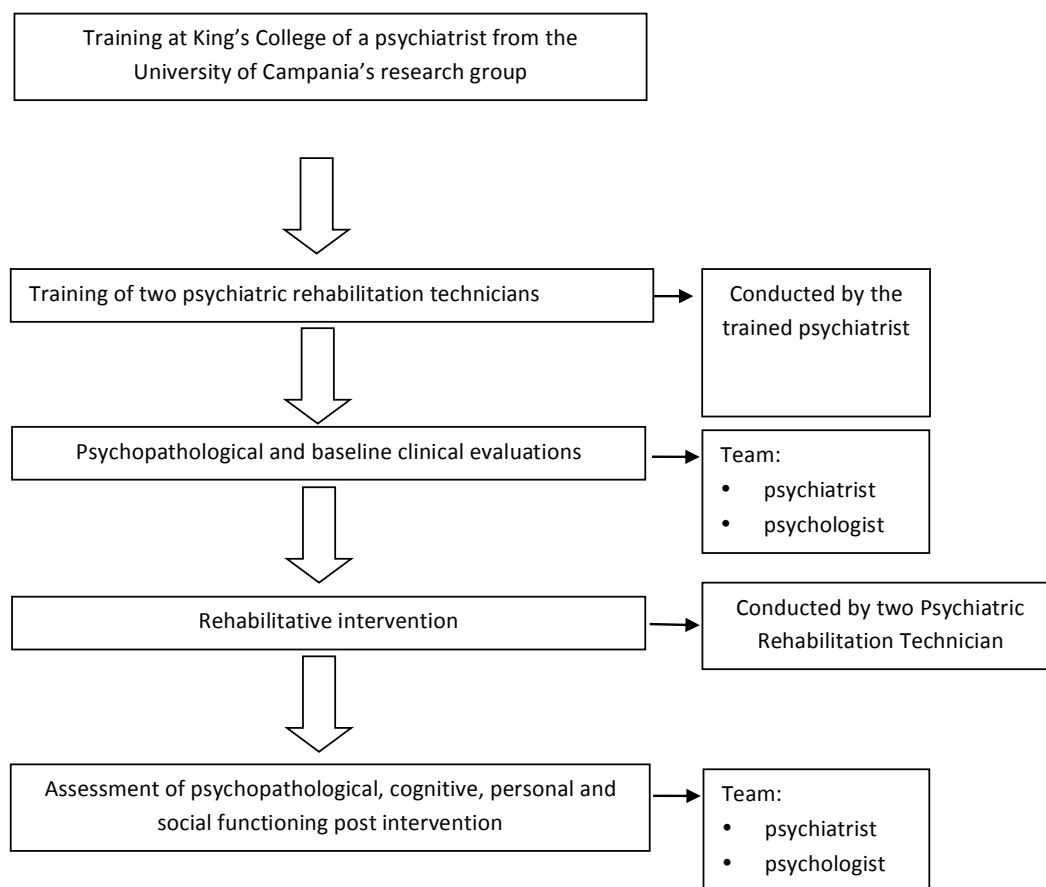


FIGURE 2. *CIRCuiTS implementation procedure.*

In our center, the home sessions were started after at least 3 weeks of training with the supervision of the therapist. During the last phase, post-treatment cognitive assessments and psychopathological evaluations were carried out.

Figure 2 illustrates the procedure for the implementation of CIRCuiTS program.

No patient dropped from the intervention, confirming that the program has a high acceptability and feasibility. Post-intervention evaluation showed a significant improvement in cognitive indices and real-life functioning. The results of our study are still preliminary, but other studies on CIRCuiTS have already demonstrated the effectiveness of the program^{22,23}.

Conclusions

Our experience confirms that the implementation of targeted or integrated CR interventions is feasible both at University Departments and in Day Care Centers of Mental Health Departments. After a first and more complex phase consisting in the implementation of the intervention (in par-

ticular in the identification and training of the personnel), these programs are found to be feasible and acceptable for both patients and involved personnel. The low percentage of dropouts can be a reliable indicator of the quality of the implementation.

The patients benefit from CR interventions: 1) by improving their cognitive skills; 2) by increasing awareness of their cognitive dysfunctions and of the impact on daily life of the same deficits; and 3) learning strategies to cope with their deficits.

The therapeutic team therefore has an additional tool to improve a nuclear aspect of the schizophrenic syndrome, the impairment of cognitive functions, which has a negative impact on real-life functioning and on effective participation to more complex rehabilitation programs, such as supported work.

To implement a successful intervention, the duration and modality of the intervention must be agreed with the patient and adapted to his/her specific needs (for example, reduced motivation for intensive schedule with several weekly sessions).

In our opinion, to individualize the intervention, patient's clinical and logistic problems, for example the lack of social competence, the presence of residual psychotic symptoms, and logistic difficulties (for example, the distance between the residence of the patient and the Department) should be taken into account. For example, an individual CR intervention can be preferred if the subject has difficulties in engaging in group therapy, due to its reduced social competence or social anxiety; moreover, the possibility of home CR sessions, followed via internet by the rehabilitation technician, can open new perspectives for users who have logistic problems.

Assessment is a critical aspect in the process of therapy individualization. Several psychometric batteries and interviews for the assessment of cognitive functioning have been validated for this purpose. Psychometric tests have the advantage of being more precise, but more complex to

administer. These test batteries generally take more than one hour for a complete evaluation. Interviews for cognitive assessment are less precise but easier to administer. Only after an accurate assessment of cognitive functioning is it possible to identify the right intervention for the individual subject. Italian standardization of test batteries and clinical interviews, in subjects with schizophrenia, has opened the road to the systematic assessment of cognitive dysfunctions in clinical settings.

In conclusion, our experience with several CR programs is positive and has permitted a fruitful collaboration between Academic and non-Academic Mental Health Departments.

Conflict of Interest

None.

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Illness duration effect on Computer-Assisted Cognitive Remediation (CACR) efficacy in Schizophrenia: a preliminary report

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Summary

Computer-Assisted Cognitive Remediation (CACR) interventions are reliable and efficacious to improve the cognitive deficit in people with a diagnosis of schizophrenia (PSZ). Aim of this study was to investigate the illness duration effect on CACR efficacy. We divided a sample of 32 PSZ in those with a Short Duration of Disease (SDD; n = 12) and those with a Long Duration of Disease (LDD; n = 20). In the whole sample of 32 PSZ, cognitive, insight and functioning indices improved at the end of CACR intervention, as well as 3 and 6 month after the end of CACR program. No significant difference of cognitive, insight and functioning indices emerged between SDD and LDD during the 6-month follow-up period. Findings from this preliminary report revealed that CACR is an efficacious strategy to improve cognition, and consequently insight and functioning, in PSZ both in early-stage and chronic disorder.

Key words

CACR • Cognitive remediation • Schizophrenia • Cognition • Functioning • Insight • Psychosis

Introduction

Schizophrenia is widely believed a cognitive illness¹, despite to make a diagnosis of schizophrenia specific criteria describing cognitive deficits are absent in the current diagnostic classification systems. Cognitive impairment in people with a diagnosis of schizophrenia (PSZ) is present early in the course of illness, frequently preceding the onset of the full psychosis of several years. Moreover, deficits in PSZ's cognition have been clearly recognized to influence the everyday functioning and to determine the outcome in the "real-world"².

In rehabilitation setting of schizophrenia, cognitive remediation provides powerful and efficacious learning strategies (including errorless learning, scaffolding, massed practice, positive reinforcement and information processing strategies) to improve PSZ's cognition^{3,4}. Computer-assisted cognitive remediation (CACR) offers a set of cognitive remediation tools through cognitive exercises with different difficulty levels customized on subjects' performance. CACR programs are commonly implemented in cognitive remediation setting for schizophrenia³. Meta-analytic evidence of cognitive remediation techniques (comprising CACR too) shows a significant improvement in cognition (including general and specific cognitive domains), as well as an overall effect on functioning and functional outcome⁵⁻⁸.

Despite how PSZ's cognition becomes different during the course of illness is still under debate¹, brain structural and functional modifications are observed during the course of schizophrenia², sometimes differentiating specific stages of illness duration⁹. The influence of schizophrenic illness duration on CACR is not well investigated¹⁰. Aim of this preliminary study was to investigate the results of CACR intervention on PSZ's cognition, insight and functioning at different stages of illness duration.

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Methods

Subjects

People with a diagnosis of schizophrenia (PSZ) from an outpatient program for cognitive rehabilitation of “Tor Vergata” University Psychiatry Clinic were considered for the study. The inclusion criteria were: a diagnosis of schizophrenia according to DSM-IV, confirmed with the MINI-Plus ¹¹; an age between 18 and 50 years; a stable clinical and pharmacological condition from at least three months. The exclusion criteria were: history of head trauma; history of perinatal trauma; mental retardation; major neurological illness, included epilepsy; history in the last six months of alcohol and / or substance abuse. Thirty-two PSZ constituted the sample enrolled for the present study (12 women and 20 men; age: mean 33.09 and SD 7.22; education, in years: mean 12.84 and SD 2.69). In order to study the illness duration effect PSZ were divided in those with short disease duration (SDD; lower than 5 years from the first psychotic episode) and those with long disease duration (LDD; higher than 5 years from the first psychotic episode). The Positive and Negative Syndrome Scale ¹² was used to assess the severity of psychopathology. In the week preceding the beginning the CACR intervention, psychiatrists, who followed each patient up in the outpatient clinical program but were not directly involved in the rehabilitation intervention, calculated the PANSS total score following a semi-structured interview and referring to the patient's clinical condition during the week before.

Assessments

Raters, not directly involved in the patients' CACR intervention, performed neurocognitive, insight and functioning evaluations (below described) during the week preceding the beginning (“pre”) and during the week succeeding the end (“post”) of the CACR intervention, as well as three and six months after the CACR end (respectively, “3m post” and “6m post”).

Neurocognitive assessments

The neurocognitive battery was built to measure the cognitive domains mainly impaired in schizophrenia and that could improve with cognitive rehabilitation ⁵: verbal learning and memory, speed of processing, working memory and executive functions. The neurocognitive tests were: the immediate and delayed Rey Auditory Verbal Learning Test (RAVLT), the Trail Making Test A (TMT-A), Trail Making Test B (TMT-B) and the derived index TMT-B minus TMT-A; letter fluency and category fluency; digit forward span and digit backward span. For each test, trained raters carried out the validated Italian version to PSZ. We decided to summarize the results of each test in a single, global cognitive index. For each time of assessment, we calculated the z-score for each test and then we averaged each single z-score obtaining, at the end of

this process, an average z-score, named “cognitive composite z-score”. In order to obtain z-scores, the reference values of means and SDs for cognitive test were derived from a convenience sample of twenty subjects without a personal and familiar history of psychiatric disorders. Additional inclusion criteria were: an age between 18 and 50 years; the absence of a history of head trauma, perinatal trauma, mental retardation and a major neurological illness, included epilepsy. The MINI-Plus was also used to confirm the absence of psychiatric diagnosis in the healthy control subjects (HCS). Enrolled HCS group did not differ respect to PSZ in gender (8 women and 12 men; $\chi^2_1 = 0.033$, $p = 1.000$), age (mean 35.00 and SD 7.83; $t_{30} = -0.896$, $p = 0.374$) and education (mean 12.50 and SD 2.76; $t_{30} = 0.444$, $p = 0.659$).

The Schizophrenia Cognition Rating Scale ¹³⁻¹⁵ was also used as a measure of general cognitive function in PSZ. SCoRS has shown to be a reliable and valid tool for assessing cognitive performance of the “real world” of PSZ, particularly evident by the observations of SCoRS correlations with several measures of functioning.

Insight assessment

The total score of Schedule for the Assessment of Insight ¹⁶ was used to have a general index about the insight and its change after CACR intervention.

Functioning assessment

The evaluation of patient's functioning was carried out with the total score of Life Skill Profile ¹⁷ and Personal Social Functioning Scale ^{18 19}.

CACR intervention

The CACR was performed by the application of COGPACK® program (Marker Software®; www.markersoftware.com) ²⁰, one of most used software packages among those programs available for CACR ^{21 22}. The COGPACK® has different neurocognitive exercises: domain-specific exercises, useful for training specific cognitive domains (particularly among those known to be impaired in schizophrenia: verbal memory, verbal fluency, psychomotor speed and coordination, executive function, working memory, attention); non-domain-specific exercises, that involve, at the same time, the use of various functions and involve culture, language and calculation skills. Most exercises are adaptive and, based on the patient's performance during the session course, the computer sets the level of exercise difficulty. In each session, the program archives the patient's performance, giving patients the opportunity to have, at the end of each session, a feedback on their performance in that session and, eventually, on their progress through the CACR sessions. Each patient received, by a trained cognitive rehabilitation expert, an individual COGPACK® session, administered twice a week, in 45-

55 min sessions, for 18 weeks. After the end of CACR treatment phase, PSZ did not receive any type of structured rehabilitation program, following scheduled clinical visits of outpatient program.

Ethics

Following a standard clinical procedure, all participants were informed about the CACR intervention and provided written informed consent. The current observational study was approved by the “Tor Vergata” University Hospital ethics committee and carried out in accordance with “Ethical Principles for Medical Research Involving Human Subjects” (Declaration of Helsinki, 1964).

Statistical analysis

We performed t-tests for independent samples (with two-tailed p-value) to test the differences between the means for the SDD and LDD groups, and chi-square statistics (with Fisher's exact test for a two-tailed p-value) were performed to test for significance of the association between grouping variables.

A general linear model approach was used to analyze the “between factor” $\times$ “within factor” interaction effect (between or grouping factor: SDD vs LDD; within factor, treatment time: “pre” vs “post” vs “3m post” vs “6m post”) on cognitive, insight and functioning indices. To investigate the “treatment time” effect and “grouping $\times$ treatment time” interaction effect, separate models of repeated measures analysis of variance (rm-ANOVA) was employed (dependent variables in the separate models were: cognitive composite z-score, SCoRS, SAI, LSP and FPS). Univariate results were examined only if Wilks' Lambda multivariate significance criterion was satisfied. The sphericity of the covariance matrix was tested with Mauchly's test of sphericity; in the case of violation of the sphericity assumption, Greenhouse-Geisser epsilon (ϵ) adjustment was used. *Post-hoc* tests were performed to define which variables contributed to the measured effects using Bonferroni's confidence interval adjustment for multiple comparisons. Statistical significance was set at $p < 0.05$.

Results

Among 32 PSZ included in the study, those with a SSD were 12 whereas those with LDD were 20. Descriptive and univariate statistics of socio-demographic and clinical characteristics of the two groups are summarized in Table I. As expected SDD and LDD differed in age (younger age of the SDD group) and illness duration (longer by definition for the LDD group). It is interesting to note that cognitive, insight and functioning indices did not differ between SDD and LDD at pretreatment assessment.

In all rm-ANOVA models, the multivariate test showed a significant “treatment time” effect on cognitive (cognitive composite z-score: Wilks' Lambda = 0.086, $F_{3,28} = 99.322$,

$p < 0.0001$; SCoRS: Wilks' Lambda = 0.183, $F_{3,28} = 41.658$, $p < 0.0001$), insight (SAI: Wilks' Lambda = 0.319, $F_{3,28} = 19.884$, $p < 0.0001$) and functioning indices (LSP: Wilks' Lambda = 0.169, $F_{3,28} = 45.754$, $p < 0.0001$; FPS: Wilks' Lambda = 0.114, $F_{3,28} = 72.297$, $p < 0.0001$). Also the univariate tests for repeated measure adjusted for the violation of the sphericity confirmed these results (cognitive composite z-score: $F_{3,90} = 159.579$, $\epsilon = 0.667$, $p < 0.0001$; SCoRS: $F_{3,90} = 104.744$, $\epsilon = 0.506$, $p < 0.0001$; SAI: $F_{3,90} = 27.996$, $\epsilon = 0.733$, $p < 0.0001$; LSP: $F_{3,90} = 87.114$, $\epsilon = 0.691$, $p < 0.0001$; FPS: $F_{3,90} = 86.009$, $\epsilon = 0.735$, $p < 0.0001$). *Post-hoc* tests showed that, for all indices, the pairwise comparisons “post vs pre”, “3m post vs pre” and “6m post vs pre” were highly significant different with p-values consistently < 0.0001 (cognitive composite z-score, Figure 1A; SCoRS, Figure 1C; SAI, Figure 1E; LSP, Figure 1G; FPS, Figure 1I).

The multivariate test of rm-ANOVA models of cognitive composite z-score, SCoRS and LSP showed a significant “grouping $\times$ treatment time” interaction effect (cognitive composite z-score: Wilks' Lambda = 0.436, $F_{3,28} = 12.099$, $p < 0.0001$; SCoRS: Wilks' Lambda = 0.508, $F_{3,28} = 9.042$, $p = 0.0002$; LSP: Wilks' Lambda = 0.733, $F_{3,28} = 3.396$, $p = 0.032$). For SAI and FPS rm-ANOVA models, the “grouping $\times$ treatment time” interaction effect was not significant at the multivariate test (SAI: Wilks' Lambda = 0.838, $F_{3,28} = 1.801$, $p = 0.170$; FPS: Wilks' Lambda = 0.897, $F_{3,28} = 1.073$, $p = 0.376$). The univariate tests for repeated measure adjusted for the violation of the sphericity did not confirmed the significant “grouping $\times$ treatment time” interaction effect (cognitive composite z-score: $F_{3,90} = 2.403$, $\epsilon = 0.667$, $p = 0.099$; SCoRS: $F_{3,90} = 2.377$, $\epsilon = 0.506$, $p = 0.117$; LSP: $F_{3,90} = 2.097$, $\epsilon = 0.691$, $p = 0.130$), hence revealing no significant difference between SDD and LDD at the end of CACR intervention as well as at 3 and 6 month after the CACR end also for cognitive composite z-score, SCoRS and LSP. *Post-hoc* tests showed in fact that, for all indices in both SDD and LDD, the pairwise comparisons “post vs pre”, “3m post vs pre” and “6m post vs pre” were highly significant different with p-values consistently < 0.0001 (cognitive composite z-score, Figure 1B; SCoRS, Figure 1D; SAI, Figure 1F; LSP, Figure 1H; FPS, Figure 1L). To note that, despite the presence of mean differences for cognitive composite z-score and SCoRS during the follow-up, particularly evident at “6m post” time, pairwise comparison *post-hoc* tests between SDD and LDD at “post”, at “3m post” and “6m post” were not significant for cognitive, insight and functioning indices.

Discussion

Findings from this preliminary report show CACR intervention determines, over a six month period, a stable improvement in general cognition, insight and functioning

TABLE I. Descriptive and univariate statistics of sociodemographic and clinical characteristics of sample.

	SDD (n = 12)	LDD (n = 20)	Statistics
Gender (w/m)	5/7	7/13	$\chi^2_1 = 0.142$ $p = 0.724$
Age (years)	25.83 (3.42)	37.60 (4.62)	$t_{30} = -7.802$ $p < 0.0001$
Education (years)	13.42 (2.58)	12.50 (2.76)	$t_{30} = 0.932$ $p = 0.359$
Onset age (years)	22.58 (2.64)	21.50 (2.61)	$t_{30} = 1.132$ $p = 0.266$
Illness duration (years)	3.00 (1.41)	16.10 (4.99)	$t_{30} = -8.825$ $p < 0.0001$
PANSS total score	72.42 (10.27)	73.60 (15.75)	$t_{30} = -0.232$ $p = 0.818$
Antipsychotics (FGA/SGA)	2/10	7/13	$\chi^2_1 = 1.247$ $p = 0.422$
Chlorpromazine equivalent	241.67 (79.30)	240.00 (109.55)	$t_{30} = 0.046$ $p = 0.964$
Cognitive composite z-score	-0.99 (0.46)	-1.29 (0.61)	$t_{30} = 1.456$ $p = 0.156$
SCoRS	35.33 (6.79)	37.25 (7.02)	$t_{30} = -0.757$ $p = 0.455$
SAI	6.25 (2.09)	6.60 (2.56)	$t_{30} = -0.399$ $p = 0.693$
LSP	123.75 (10.82)	121.70 (15.04)	$t_{30} = 0.411$ $p = 0.684$
FPS	58.33 (11.45)	55.30 (16.07)	$t_{30} = 0.046$ $p = 0.964$

LDD: people affected by schizophrenia with long duration of disease; SDD: people affected by schizophrenia with short duration of disease; FGA: first generation of antipsychotics; SGA: second generation of antipsychotics; SCoRS: Schizophrenia Cognition Rating Scale; SAI: Schedule for the Assessment of Insight; LSP: Life Skills Profile; FPS: Personal Social Functioning Scale. Data are frequencies and means (SDs).

both in early and chronic stages of schizophrenia. These results confirm evidence of cognitive remediation strategies in PSZ with a LDD5 as well as in PSZ with SSD^{7,23}. Despite our CACR sessions and follow-up duration were different from other studies, including the absence of any type of other structured rehabilitation programs during the six month follow-up period after CACR end, improvement in PSZ's cognition and functioning reported in current preliminary study are in line with those results described by others using COGPACK® program²⁴⁻²⁷. We may explain these findings with the high level of efficacy generated by this CACR intervention, mainly based on (re)learning practical cognitive strategies through the high flexibility and adaptation of exercises in several cognitive domains based on PSZ's performances. Our results are similar to those recently reported by Corbera et al.¹⁰. Within a randomized control trial design, these authors studied the effect of a computerized cog-

nitive training program (sequence of computerized cognitive exercises) in PSZ with an early illness phase and in PSZ with a chronic illness phase, distinguishing an early-chronic group (corresponding to chronic phase group of our study) and a late-chronic group. Despite the methodological differences present in these two researches (mainly for a different type of CACR intervention and PSZ involved) both studies revealed PSZ with early and chronic (named early-chronic in Corbera et al.) stages of schizophrenia has an improvement in cognition after CACR.

Future perspectives in our CACR program of rehabilitation setting for schizophrenia might be: (a) a longer follow-up duration^{26,27}, that could give the opportunity to observe the effect of the single CACR intervention on cognition and functioning in schizophrenia, as well as on insight and psychopathology²⁸; (b) more sophisticated cognitive and functioning assessments (as, for

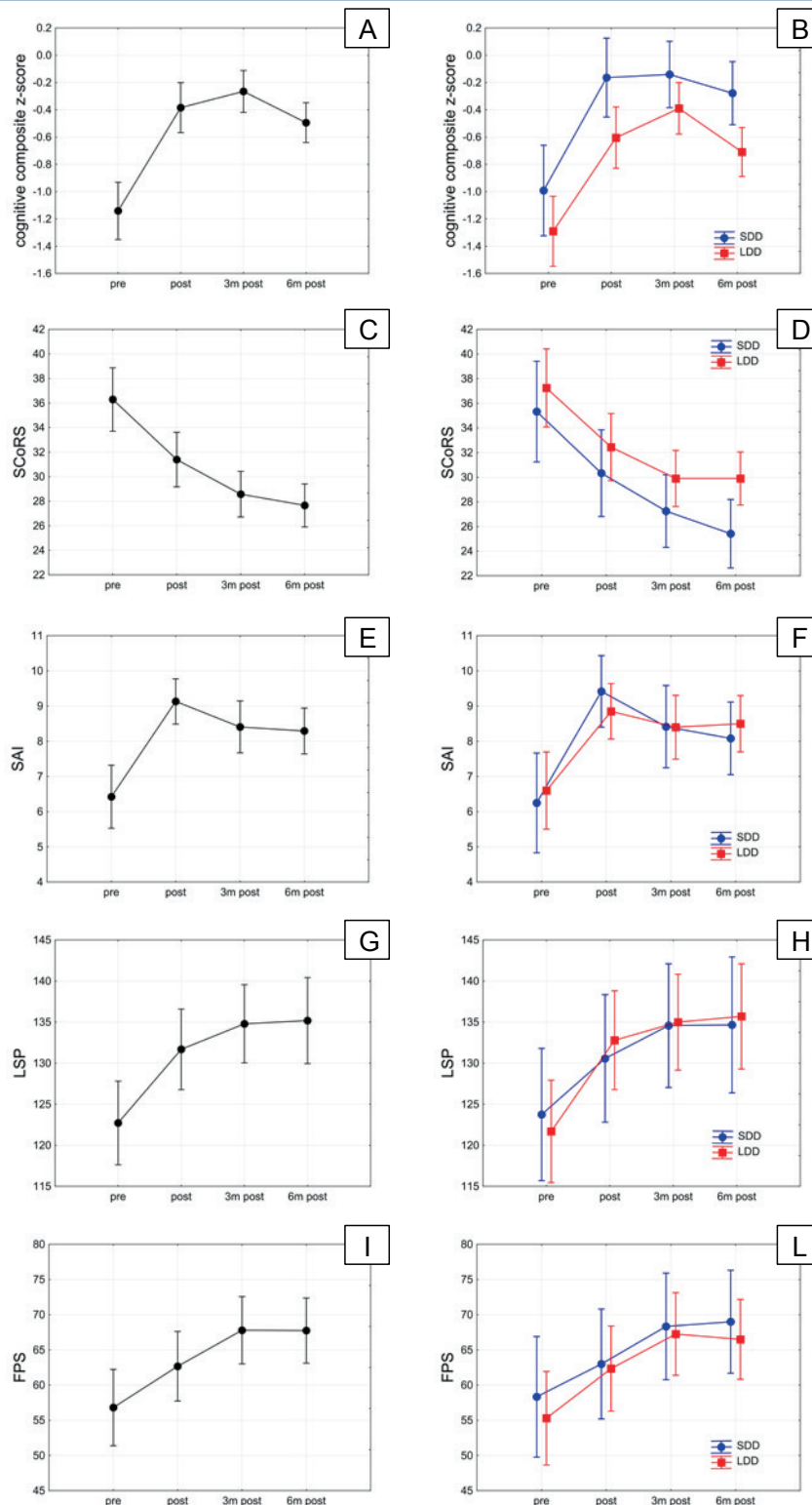


FIGURE 1. Means (circles and squares) and 95% Confidence Intervals (vertical bars) of the cognitive composite z-score, SCoRS, SAI, LSP and FPS during the week preceding the CACR beginning ("pre"), during the week succeeding the CACR end ("post"), as well as three and six months after the CACR end (respectively, "3m post" and "6m post"), in the whole group (left side of the panel) and in SDD and LDD (right side of the panel). LDD: people affected by schizophrenia with long duration of disease; SDD: people affected by schizophrenia with short duration of disease; SCoRS: Schizophrenia Cognition Rating Scale; SAI: Schedule for the Assessment of Insight; LSP: Life Skills Profile; FPS: Personal Social Functioning Scale.

example, the implementation of UPSA-B and SLOF)²⁹⁻³¹; (c) an integration with different rehabilitation techniques during or after the CACR intervention³². In conclusion, according to the current findings from this preliminary report, subjects affected by schizophrenia, independently from stage of illness, may improve in cognition and everyday functioning capacity for several months after a single intervention with a computer-assisted cognitive rehabilitation strategy.

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Conflict of Interest

None.

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