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From "What" to "How": The Effort to Fill the Gaps in Understanding Cognitive Processes Underpinning Remission in Schizophrenia

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Abstract

Introduction: The accumulation of robust evidence culminated in the establishment of the cognitive deficits as a core symptom of Schizophrenia (SCZ). To date, there has been reliable evidence that cognitive deficits are associated with poor symptomatic outcomes in SCZ. Nevertheless, they have not been incorporated in definitions of remission and a systematic understanding of how cognition contributes to remission is still lacking. Although the standardized remission in SCZ criteria proposed in 2005 has encouraged studies to understand the role of cognitive function in symptomatic remission from SCZ, most investigations were cross-sectional and have studied samples of chronically ill patients. The purpose of the present study was to bring together the efforts of recent follow-up studies in early in earlier stages of the disease to fill the gap in the literature on understanding how cognitive impairment is related to remission.

Methods: A comprehensive search of the PsycINFO and MEDLINE/PUBMED databases was conducted.

Results: One study evaluated executive functioning in Early-Onset Schizophrenia (EOS) across stages of illness and suggested that executive impairment is present at the onset of SCZ and persists in attenuated but stable form after the resolution of psychotic symptoms. Studies in first-episode schizophrenia (FES) patients highlighted that despite verbal memory performance is strongly related to clinical remission in FES spectrum, it appears to have not a meaningful contribution to functional recovery. Longitudinal studies in SCZ patients suggested that executive function and higher premorbid Intelligence Quotient (IQ) were the best predictors of remission.

Conclusion: Since were emphasized the need to conduct longitudinal follow-up studies to assess the relation of cognitive performance to the proposed remission criteria, some efforts have been made to fill the gaps in understanding cognitive processes underpinning remission in schizophrenia. Notwithstanding the question regarding how aspects of symptomatic remission affect, and are affected by, aspects of cognitive function, remain not yet clarified, these long-term prospective studies addressing different domains of neurocognition in schizophrenia patients undergoing remission, mainly in early stages of illness, are being very enlightening to guide and encourage new researches.

Keywords: Schizophrenia; Remission; Cognitive function

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Introduction

This disappointment encouraged the search for other factors that could be related to functional improvements [1]. Actually, schizophrenia is characterized by significant heterogeneity in outcome and the last decades have witnessed a significant interest in identifying factors that can moderate or influence clinical and functional outcomes in people diagnosed with schizophrenia and several markers were associated with a poor outcome, which include: Being male, having a younger age of onset, poorer insight,

longer duration of untreated psychosis, poorer premorbid social adjustment, and higher negative symptoms [2]. In this context, cognition emerged as a promising marker, and numerous studies have showed that cognitive functions are strongly correlated and are an important determinant of outcome in SCZ [1].

Recently, disturbed processing in cognition was considered a fundamental symptom of schizophrenia, with mild cognitive deficits appearing well before the onset of psychosis, followed by a sharp decline in functioning, at or near of First-Episode Psychosis (FEP), that remains into chronic stages [2]. Thus, besides the positive and negative symptoms, cognitive impairment is also an important key feature of schizophrenia and often pre-dates the disorder [3]. Cognition must be considered in the future research to overcome the lack of progress in our understanding of schizophrenia and to the development of adequate treatments, which cognitive deficits should be central to any guidelines [4].

Against the background of many advances in the treatment of schizophrenia over the past 50 years, the outcome for many patients remain poor, and the majority of patients still experience persistent incapacitating symptomatology and multiple relapses during the course of the illness [5,6]. In the search for the potential markers of outcome in schizophrenia, the findings have contributed to identify the factors, such as cognition, and to answer the question about "what" is related to outcome, but the question "how" remains unclear.

To date, there has been reliable evidence that cognitive deficits are associated with poor symptomatic outcomes in schizophrenia [7]. Nevertheless, they have not been incorporated in definitions of remission [5]. A systematic understanding of how cognition contributes to remission is still lacking. The purpose of this paper is to review recent research into the relationship between cognitive deficits and symptomatic remission. All selected studies were published after the introduction of the consensus definition for remission in SCZ proposed in 2005 by the Remission in Schizophrenia Working Group (RSWG). According to RSWG, symptomatic remission is achieved when the following criteria is fulfilled: Mild severity (score of 3 or lower) in 8 items of the Positive and Negative Symptoms Scale Positive and Negative Symptoms Scale (PANSS) (e.g., delusions, unusual thought content, hallucinatory behavior, mannerisms/posturing, blunted affect, social withdrawal, lack of spontaneity). There is also a minimum time threshold of 6 months in which the symptoms of severity must be maintained [5,8].

The standardized remission criteria has encouraged studies to understand the role of cognitive function in symptomatic remission from schizophrenia, however most investigations were cross-sectional and have studied samples of chronically ill patients. Taken together, the results from these previous studies there were no clear evidence whether cognitive ability is a contributing factor for achieving remission. Although cognitive performance was identified as a predictor of outcome in schizophrenia [9] was not assessed in follow-up studies in the relation to the proposed remission criteria [8]. Therefore, the nature of how aspects of symptomatic remission affect, and are affected by, aspects of cognitive function remains unclear. More recently, we have witnessed an increase of longitudinal studies in earlier stages of the disease and the present systematic review brings together the efforts of recent studies to fill the gap in the literature on understanding how cognitive impairment is related to remission.

Search Strategy

A comprehensive search of the PsycINFO and MEDLINE/PUBMED databases was conducted. Within the domain of cognitive systems, the following search terms were used: (1) Neurocognition/cognitive function; (2) Attention; (3) Memory; (5) Speed of processing; (4) Executive functions. Within the domain of symptomatic remission, the following terms were used: (1) Symptomatic remission; (2) Symptomatic patients. Search terms for schizophrenia included the following: (1) Early-onset schizophrenia; (2) First-episode schizophrenia/first-episode psychosis; and (3) Chronic schizophrenia.

The results from these searches were assessed for eligibility using the following hierarchical criteria: (1) Studies were peer-reviewed original articles published in English; (2) Participants had a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria or to the International Classification of Diseases (ICD) criteria; (3) Symptom severity was assessed by means of the Positive and Negative Symptoms Scale (PANSS) and to assess remission, the majority of the studies have used the criteria proposed by Andreasen et al. [5], according to which 8 items of PANSS (delusions, unusual thought content, hallucinatory behavior, mannerisms/posturing, blunted affect, social withdrawal, lack of spontaneity) should be scored ≤3 (mild) for at least 6 months; (4) The groups were compared using statistical techniques; (5) The research method used was a longitudinal study; (6) Published after 2010.

Early-Onset Schizophrenia (EOS)

Early-Onset Schizophrenia (EOS) is considered to be the most severe form of the disease, fortunately is extremely rare. Schizophrenia onset before age of 18 years old is strongly associated with higher morbidity and mortality risks for children and adolescents. Because of the interplay between genetic and environmental risk factors, this form of schizophrenia seems to have meaningful neurodevelopmental components which are associated with a correspondent cognitive process development [10].

Remberk et al. [11], evaluated executive functioning, using Wisconsin Card Sorting Test (WCST), in EOS across stages of illness. Hospitalized EOS subjects (aged 13-18) with first episode at the introduction of pharmacotherapy (FES T1) and after the resolution of psychotic symptoms at psychopathological symptoms mean 7 weeks (FES T2) and Stable Outpatients (SO) group (aged 16-19 with diagnosis of early-onset schizophrenia, with at least one previous hospitalization and illness duration of minimum one year) were matched with healthy controls. Severity of symptoms was assessed with Positive and Negative Syndrome Scale (PANSS), total score and positive, negative and general psychopathology subscales scores were analyzed, however any formalized definition of remission was applied. The results showed that patients performed significantly worse in WCST than

healthy controls, however FES T1 presented more pronounced executive impairment and psychopathological symptoms than FES T2 and SO, between which no differences were observed, suggesting that executive impairment is present at the onset of schizophrenia and persists in attenuated but stable form after the resolution of psychotic symptoms.

First-Episode Psychosis/Schizophrenia

Chronic schizophrenia patients have generally long histories of multiple episodes of psychosis and treatment, thus the neurocognition dysfunctions widely observed are likely to be influenced by effects of age, clinical symptoms, illness duration and severity, which emphasizes the need for studies of young and first-episode patients. While most the majority of first-episode schizophrenia patients may be able to achieve and maintain a remission of symptoms, the overall rate of recovery during the early years of the disease is very low: Only one in seven are likely to meet criteria for recovery [6,12].

Torgalsbøen et al. [13], conducted a long-term prospective study of first-episode schizophrenia patients (FES) assessing the relationship between neurocognition and remission in first-episode schizophrenia patients with follow-up points at baseline and after 6 months. Their results showed that more than half of the group of first-episode patients where in remission, neurocognitive baseline measure of attention (from the MATRICS Consensus Cognitive Battery) predicted remission status at follow-up and in the early course of the illness, and remitted patients had significantly higher scores on overall neurocognitive function than those not fulfilling the remission criteria.

Chang et al. [14], also examined the longitudinal relationships between cognitive functioning and symptomatic remission in first-episode schizophrenia patients. The cognitive functions were measured at clinical stabilization and at 12, 24 and 36 months. The findings suggested that verbal memory impairment might be specifically related to attainment of sustained remission in the early stage of the illness.

Based on previous investigations on FEP that have isolated verbal memory as a potential cognitive marker of symptomatic remission, Benoit et al. [15], designed a study aimed to compare verbal, visual and working memory performance between remitted and non-remitted FEP longitudinally. Using the full RSWG criteria to categorized symptomatic remission, cognition was evaluated after 3 and 15 months of treatment. The results suggested that verbal memory might be a specific and stable marker of clinical remission in FEP patients, corroborating the findings of Chang et al. [14].

Considering the relevance of symptomatic remission and cognition for functional outcome, primary goal following treatment of schizophrenia, Jordan et al. [16], organized a longitudinal study to investigate the contribution of cognition, in particular verbal memory, and symptomatic remission to social and occupational functioning in a sample of first-episode schizophrenia subjects. They conclude that verbal memory contributed only slightly to such outcome, while length of remission of negative and positive symptoms made a large contribution at 2 years. These results highlights that despite verbal memory performance is strongly related to clinical remission in first episode of schizophrenia spectrum [14,15], it appears to have not a meaningful contribution to functional recovery.

Bodnar et al. [17], conducted an important study that shown a strong evidence of the parahippocampal cortex as a possible neural marker of early remission among first-episode schizophrenia patients. The results also have showed that non-remitted first-episode schizophrenia patients performed worse in verbal memory domain and there is a positive correlation between bilateral parahippocampal cortex volume and verbal memory performance. These results are in line with Chang et al. [14], and Benoit et al. [15], but are not confirmed by Torgalsbøen et al. [13]. Notwithstanding, Torgalsbøen et al. [13] is an outgoing study, and is recommended to wait for the results from the next follow-up before drawing conclusions. In addition, chronic patients with an average (or higher) verbal intelligence appears to be more likely to reach the status of clinical remission in schizophrenia [3].

Chronic Schizophrenia

Andreou et al. [7], run a longitudinal study aimed to assess the contribution of neuropsychological deficits on the probability of achieving early symptomatic remission after a psychotic episode in schizophrenia patients. The results suggested that patients who achieved remission exhibited a significant better performance on the Trail Making Test Part B (TMT-B), a neuropsychological instrument of choice to measure executive function, and higher premorbid Intelligence Quotient (IQ). According to the findings, TMT-B performances at baseline were the one of the best predictors of remission.

A polish research group [3] investigated the association of cognitive deficits and clinical remission at baseline and after three years. Higher verbal IQ, but not performance intelligence, was related to a greater chance of remission after three years, which suggests that patients with an average (or higher) verbal intelligence, in a non-active phase of the illness are more likely to reach the status of clinical remission in schizophrenia.

Conclusions and Future Directions

Advances in treatments, a novel understanding of the etiology and course of schizophrenia, and earlier attention to diagnosis have led to a shifting on the perspectives surrounding schizophrenia, improving longer-term outcome potential and encouraging an increase in emphasis on functional outcome and overall well-being of schizophrenia patients. Although many improvements have been made since the introduction of the consensus definition for remission in schizophrenia proposed in 2005 by the Remission in Schizophrenia Working Group, this criteria are confined to dimensions of psychopathology and did not address other domains, such as cognition, that are critical to functional recovery [18].

Actually, remission is a more defined and achievable goal, a necessary step but not sufficient toward recovery [19]. The remission criteria, unlike recovery, implies symptoms that do not interfere with function, thus people diagnosed with schizophrenia in remission may continue to be cognitively impaired and

marginalized, most because of a poor social functioning [20]. It has important implications especially for patients, families, direct-to-consumer advertising, insurance companies, governments, and societies, because the term remission might bring the expectation that all explicit signs of the disease are gone and that the individual is now freed from illness, which contrasts with reality, frustrating them all [18].

Cognitive functioning has been found to be improved in recovery [21], and a better cognitive performance was associated with the adequate social/vocational functioning and symptom remission components of recovery [12], strengthening the considerable amount of the evidences that supports the substantial influence of cognition on functional capacity yielding autonomous everyday functioning in schizophrenia patients [22,23].

Lepage et al. [2], have explored neurocognitive function in relation to both clinical and functional outcome, and highlighted that verbal memory appears to be one of the strongest markers of outcome. However, despite verbal memory performance are strongly related to clinical remission in first episode of schizophrenia spectrum [14,15], it appears to have not a meaningful contribution to functional recovery [16]. However, these results differ from some published studies that suggest that verbal memory deficits might reduce one's employment prospects compromising overall functional outcome [24,25].

Remberk et al. [11], bring out that executive impairment is present at the onset of the disease and persists in attenuated but stable form after the resolution of psychotic symptoms. These results are consistent with those of previous literature that have noted decline of cognitive functions at the time of onset of clinical symptoms with partial recovery of cognitive functions during the stabilization phase after first onset [23].

Andreou et al. [7], emphasized that a better executive performance seems to predict early symptomatic remission after a psychotic episode in schizophrenia patients. Some of the earlier cross-sectional studies have found no significant differences in executive functioning of fully remitted patients and healthy controls [26] or of remitted and non-remitted schizophrenia patients [27]. On other hand, some studies revealed marked differences in executive functioning between patients who have met the remission criteria from those who haven´t [25,28]. Taken together, these findings are in line with prior research, which identified a little consistent evidence of differential decline in executive functions in schizophrenia patients [23]. The long-term prospective study referred [7], appears to provide clearer evidence about the impact of executive functions on symptomatic remission after an acute episode in schizophrenia patients.

Since Lambert et al. [8], emphasized the need to conduct longitudinal follow-up studies to assess the relation of cognitive performance to the proposed remission criteria, some efforts have been made to fill the gaps in understanding cognitive processes underpinning remission in schizophrenia. Although the question regarding how aspects of symptomatic remission affect, and are affected by, aspects of cognitive function, remain not yet clarified, these long-term prospective studies addressing different domains of neurocognition in schizophrenia patients undergoing remission, mainly in early stages of illness, are being very enlightening to guide and encourage new researches.

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