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Neuropsychological correlates of remission in chronic schizophrenia subjects: The role of general and task-specific executive processes

Thais Rabanea-Souza [a,*], Henrique T. Akiba [b], Arthur A. Berberian [a], Rodrigo A. Bressan [a], Álvaro M. Dias [a], Acioly L.T. Lacerda [a]

[a] Laboratory of Interdisciplinary Clinical Neurosciences, Department of Psychiatry, Federal University of Sao Paulo, Sao Paulo, Brazil
[b] Experimental Psychology Program, University of Sao Paulo, Sao Paulo, Brazil

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ABSTRACT

Background: Although cognitive deficits have consistently been characterized as core features of schizophrenia, they have not been incorporated into definitions of remission. Furthermore, just a few studies have examined the relationship between cognitive deficits and symptomatic remission. The main aim of the present study is to evaluate the executive functioning of nonremitted schizophrenia patients.
Methods: 72 remitted and 42 nonremitted schizophrenia patients, and 119 healthy controls were examined. Subjects were tested with a comprehensive battery of cognitive tests, including a measure to assess the general components of executive functioning and individual tasks to tap the three specific executive dimensions assessed in the present study, namely updating, shifting and inhibition.
Results: Schizophrenia subjects performed poorly on general executive functioning and shifting tasks in comparison to healthy controls. Remitted subjects performed better than nonremitted on inhibition and updating tasks. Whereas being a male and showing decreases in updating increase the chances of being in the nonremitted schizophrenia subjects group, increases in shifting and updating enhance the odds of being in the healthy control group.
Conclusion: The present findings suggest that executive function deficits are present in chronic schizophrenic patients. In addition, specific executive processes might be associated to symptom remission. Future studies examining prospectively first-episode, drug naive patients diagnosed with schizophrenia may be especially elucidative.

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Introduction

Schizophrenia (SCZ) is a chronic, disabling neuropsychiatric disease that affects 0.3% to 1.6% of the general population (Jablensky, 2000; Tandon et al., 2008). Notwithstanding the refinement of knowledge regarding its clinical course and advances in pharmacological and nonpharmacological interventions, the majority of individuals with schizophrenia still experience persistent incapacitating symptomatology and multiple relapses (Kane and Correll, 2010).

Different studies have found that remission, which is estimated to be achieved in only one-third of schizophrenia subjects (Lasser et al., 2007), is a good predictor of functional outcome (Andreasen et al., 2005; Emsley et al., 2013; Helldin et al., 2007). In order to provide a greater clarity about treatment goals and an improved framework for designing trials and test its effectiveness, the Remission in Schizophrenia Working Group (RSWG) has proposed consensual and operational criteria for remission in schizophrenia. According to

RSWG, remission is defined as a state in which individuals with schizophrenia have experienced an improvement in core signs and symptoms considering that any remaining symptoms are of such low intensity that they no longer interfere significantly with behavior and are below the threshold typically used for establishing diagnose (Andreasen et al., 2005). The proposed symptom-based criteria include the seven diagnostically relevant items from the DSM-IV, which are cross-matched with eight items from the Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1987). These eight items must score within a symptom level ≤3 points (mild or better severity) and include: delusions, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerisms/posturing, blunted affect, passive/apathetic social withdrawal, lack of spontaneity and flow of conversation. There is also a minimum period of six months in which the symptoms severity must be maintained (Andreasen et al., 2005; Lambert et al., 2010).

Although clinical subtypes have been used in psychiatric nosology as a conceptual framework for understanding schizophrenia in past century, they have not proved useful for prognostic purposes (Braff et al., 2013). More recently, studies investigating different biomarkers have also reported disappointing findings

(Asor and Ben-Shachar, 2012). Cognitive impairments have consistently been considered as core features of schizophrenia (Green and Harvey, 2014). They are present prior to onset of psychosis, are correlated with measurable brain dysfunction more than any clinical manifestation of the illness, are significantly associated with functioning in areas such as work performance, social relationships and independent living, and are increasingly considered as an important target for treatment (Green et al., 2000; Keef, 2008; Lewis, 2004; Palmer et al., 2009). *Given the importance of reentering individuals with schizophrenia to community the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative of the U.S. National Institute of Mental Health (NIMH) set the development of a consensus cognitive battery (MCCB) for measuring cognition in schizophrenia, aiming to guide the design of clinical trials for cognition enhancing agents and encouraging new researches* (Green and Nuechterlein, 2004).

It is noteworthy that cognitive impairments have not been incorporated into instrumental concepts of remission in schizophrenia, despite their clinical relevance (Andreasen et al., 2005; Helldin et al., 2006). Many studies have shown that schizophrenia subjects exhibit executive deficits, which are related to treatment refractoriness and poor functional outcomes and are likely to contribute to other cognitive deficits (Kerns et al., 2008). In addition, frontal lobe functioning measures have also been associated with recovery (Kopelowics et al., 2005). Executive functioning is a multidimensional process that covers a wide range of skills, which are used to guide behavior toward goals and to adapt to novel situations. It is considered the most sophisticated dimension of human behavior necessary for appropriate, socially responsible, independent and productive adult conduct. Executive processes are mediated by prefrontal regions and are associated with the ability to perform high-level tasks involving planning, organizing, initiating, monitoring and adapting behavior (Banish, 2009; Jurado and Rosselli, 2007; Lezak et al., 2004; Wilson et al., 2003).

The heterogeneity of the dysexecutive syndrome in schizophrenia, based on the theoretical model of Miyake et al. (2000), which postulates the notion, originally proposed by Teuber (1972), that different aspects of executive functioning correlate with one another, thus tapping some common underlying ability (unity), but also show some separability (diversity), has been emphasized in studies with chronic schizophrenia patients (Raffard and Bayard, 2012). Previous findings have suggested a specific impairment in the ability to update working memory in schizophrenia, and that this is associated with poor engagement with the environment (Galletly et al., 2006). Few studies have examined the relationship between cognitive deficits and symptomatic remission, and there were no clear evidence whether increased cognitive abilities, more specifically executive function, are a contributing factor for achieving remission. Some of these studies have found no significant differences in executive processes of fully remitted patients and healthy controls (Braw et al., 2012) or of remitted versus nonremitted schizophrenic patients (Brissos et al., 2011). On the other hand, some studies revealed marked differences in executive functioning between patients who have met the remission criteria and those who haven't (Helldin et al., 2006; Hofer et al., 2011). At least part of this apparent inconsistency might be explained by methodological issues. Executive function tests differ in their complexity, specificity of the required specific executive abilities and even non-executive processes (Wood et al., 2009).

None of the previous studies systematically administered multiple executive tasks to understand the heterogeneity of the executive function impairments during symptomatic remission in schizophrenia patients. Therefore, the nature of how specific aspects of symptomatic remission affect, and are affected by, specific aspects of executive processes remains unclear.

The main aim of present study is to examine specific aspects of executive function of both remitted and nonremitted subjects, comparing with healthy controls. We hypothesized that both remitted and nonremitted subjects have executive function deficits in comparison to matched control group and that severity of deficits is greater in nonremitted subjects

Materials and methods

Subjects

A total of 114 subjects with DSM-IV schizophrenia were enrolled. Seventy-two *(44 males; age = 35.98 ± 9.02 years and 28 females; age = 40.11 ± 11.57 years)* patients were classified as remitted and 42 *(36 males; age = 35.86 ± 9.39 years and 6 females; age = 32.33 ± 9.48 years)* as nonremitted. 119 healthy controls (70 males; age = 33.56 ± 9.85 years and 49 females; age = 34.71 ± 11.28 years) were included in a cross-sectional study. *Subjects who were not able to read and/or understand instructions of cognitive tests were excluded.* Patients were recruited from an outpatient unit for treatment of schizophrenia, The Schizophrenia Program, Federal University of Sao Paulo (PROESQ). All participants provided written informed consent and the local ethics committee approved the study.

Diagnosis was assessed by using The Structured Clinical Interview for DSM-IV (SCID-I). Symptom severity was assessed by means of the Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1987). Trained psychiatrists conducted all interviews.

To assess remission, the criteria proposed by Andreasen et al. (2005) were used, according to which 8 items of PANSS (delusions, *conceptual disorganization*, unusual thought content, hallucinatory behavior, mannerisms/posturing, blunted affect, social withdrawal *and* lack of spontaneity) should be scored ≤ 3 (mild). Yet, symptomatic remission criteria should be present for at least 6 months. *Finally, the mean score on each group by gender was 69.72 ± 11.60 and 78.67 ± 2.25 for male and female individuals of nonremitted schizophrenia group and 49.8 ± 10.68 and 50.07 ± 11.18 for male and female individuals of remitted schizophrenia group, respectively.*

Instruments

Nonverbal Intelligence Task (R-1)

This scale was created to allow measures of intelligence in low literacy populations. This test highly correlates with the Raven's Colored Progressive Matrices Test (r = 0.76, p = 0.001), and was chosen for the high frequency of low literacy found in the Brazilian schizophrenia population (Oliveira, 2002).

Computerized Stroop Test

The computerized Stroop Test (Capovilla et al., 2009) was used as a measure of inhibition. This test was composed of three parts of 24 stimuli each. In the first part, the subject was asked to read the word that appears in the computer display and the stimuli are names of four colors (yellow, blue, green and red) written in capital black font. The objective of this part was to evaluate the automation of reading, which was essential for the expected effect. The second part comprises 24 colored circles, six drawn in each of the four colors. Each circle was displayed for 40 ms and the participant had to name the color of the circle as fast as he/she can. The objective of this part was to provide a baseline measure for reaction time. In the third part of the test the subject had to read the color name but the stimuli were divergent; the