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Working memory as a predictor of negative symptoms and functional outcome in first episode psychosis

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ABSTRACT

The relationship of neurocognitive course with clinical and functional outcomes in psychosis is not well known, especially in the long term. The aim of the study was to examine the clinical and neuropsychological course of first-episode psychosis patients at 5-year follow-up and analyze the relationship of cognitive performance with clinical and functional outcome. The 5-year follow-up was conducted with 26 first-episode psychosis patients. Psychotic symptoms were measured by the Positive and Negative Syndrome Scale, manic and depressive symptoms by the Young Mania Rating Scale and Hamilton Depression Rating Scale respectively, and psychosocial functioning by the Functioning Assessment Short Test. The cognitive domains were assessed by the Wechsler Adult Intelligence Scale, the Wisconsin Card Sorting Test, the Trail Making Test, the Verbal Fluency Test, the Stroop Colour–Word Test and the Wechsler Memory Scale. Patients showed symptomatic improvement in the follow-up except in negative psychotic symptoms. There was also improvement in most cognitive domains except in working memory and processing speed in the follow-up. Working memory impairment was associated to negative psychotic symptoms and poor functional outcomes. Negative symptoms mediated the relationship between working memory and outcome. Therefore, negative symptoms should be a primary target of treatment to improve functional outcomes.

1. Introduction

Neurocognitive deficits seem to be present early in the course of psychosis. Numerous neuropsychological studies have found that cognitive impairment in first psychotic episodes manifests across multiple cognitive domains, including working memory, executive functions, attention, processing speed, and learning and memory (Becker et al., 2010; González-Blanch et al., 2010; Keefe et al., 2006; Mesholam-Gately et al., 2009; Zabala et al., 2010). Similar neuropsychological deficits have been described in chronic schizophrenia (Bonner-Jackson et al., 2010; Gold et al., 2009; Shah et al., 2012; Szöke et al., 2008) and bipolar disorder (Arts et al., 2011; Goodwin et al., 2008; Kurtz and Gerraty, 2009; Solé et al., 2012), being more marked in schizophrenia patients than in other psychotic disorders (Reichenberg et al., 2009; Schretlen et al., 2007). Despite the evidence of cognitive dysfunction in patients with first psychotic episodes, the course of neurocognitive functioning in psychosis is not well known, especially in the long term. Moreover, longitudinal neuropsychological studies performed in first-episode psychosis patients have shown inconsistent results. Some studies have suggested that cognitive functioning deteriorates over time according to the neurodegenerative model, which postulates a pattern of progressive cognitive decline in schizophrenia after the first psychotic episode. In particular, this hypothesis was based on longitudinal magnetic resonance imaging studies that showed substantial structural brain changes during the first years after the onset of illness (Arango et al., 2012; Hulshoff Pol and Kahn, 2008; Whitford et al., 2006; Zipparo et al., 2008). However, other studies support the neurodevelopmental model, indicating that the cognitive impairment is not progressive, but rather it is relatively stable and even improves in the follow-up (de Mello Ayres et al., 2010; Leeson et al., 2009; Rodríguez-Sánchez et al., 2008; Rund et al., 2007). According to this hypothesis, it has been suggested

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that cognitive deficits may even predate the onset of illness, before the presence of psychotic symptoms (Frommann et al., 2011; Schubert and McNeil, 2007). Currently, there is general support for the neurodevelopmental model of schizophrenia, although it remains unclear whether after first-episode psychosis certain domains of cognition decline or improve over the course of the illness.

A major concern of clinicians is to identify the most severely affected cognitive domains, the evolution of cognitive impairment in these domains and its relationship with clinical and functional outcomes which could help to resolve the controversies over the neurodegenerative vs. neurodevelopmental hypotheses, explaining the pathogenesis of the illness and its treatments. However, the knowledge on the course of cognitive impairment and its relationship to clinical and functional outcomes remains to be determined. Cognitive deficits have been related to poor clinical and functional outcomes in first-episode psychosis (Brekke et al., 2005; Harvey et al., 2005). On the other hand, some studies have not found this association (Kravariti et al., 2003; Stirling et al., 2003). Further, it has been suggested that neurocognitive dysfunction is not state-related and cannot be considered to be directly caused by, or secondary to, the same underlying pathological process that causes the clinical symptoms (González-Blanch et al., 2008). A relationship between clinical symptoms and neurocognitive functioning has been found, with negative symptoms being the clinical variable most strongly associated with cognitive functioning in the follow-up (Addington et al., 2005; Carlsson et al., 2006; Leeson et al., 2009, 2011). Cognitive dysfunction is also associated with poor psychosocial functioning (Leeson et al., 2009, 2011; Ventura et al., 2009), and it has been suggested that negative symptoms might mediate the relationship between neurocognition and outcome, neurocognition and negative symptoms both being predictors of functional outcome (Ventura et al., 2009).

Despite the evidence for a relationship of neurocognitive deficits with both negative symptoms and functional outcome, most studies have analyzed these associations separately and used a cross-sectional methodology. Little is known about the influence of cognitive deficits on long-term outcomes and longitudinal studies conducted in this area are rare. As far as we know, no longitudinal study has systematically examined whether negative symptoms mediate the associations between neurocognitive performance and functional outcome in psychosis. The aim of the study was, therefore, to examine the clinical and neuropsychological course of patients with first-episode psychosis at 5 years of follow-up and analyse the relationship of neurocognitive functioning with both clinical and functional outcomes. Specifically, we studied the relationship between cognitive domains, negative symptoms and functional outcomes in this long-term follow-up. In addition, we examined whether the relationship between neurocognitive functioning and functional outcome is mediated by negative symptoms.

2. Methods

2.1. Subjects

The study was conducted on patients admitted to Santiago Hospital in 2004 because of experiencing first episode psychosis. The first psychotic episode was defined as the first time that a patient displayed positive psychotic symptoms consisting of delusions and/or hallucinations. All patients who met diagnostic criteria and provided informed consent were included in the study. The sample consisted of subjects of 16–45 years of age who met diagnostic criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) for one of the following disorders: schizophreniform disorder; schizoaffective disorder; schizophrenia; delusional disorder; brief psychotic disorder; atypical psychosis; bipolar I/II disorder; or major depressive disorder with psychotic symptoms. All patients included in the study had less than 6 months of duration of untreated psychosis (DUP). Subjects with mental retardation or organic brain disorders were excluded.

At baseline 45 patients were recruited and met the inclusion criteria to participate in the study. However, of these, 12 patients withdrew from the study during the follow-up and seven did not meet the inclusion criteria for neuropsychological assessment due to acute clinical symptoms (relapses of their disease or rehospitalizations). Therefore, the 5-year follow-up assessment was conducted with 26 patients (58% of the initial sample) and this group constitutes the total study sample.

The mean age of patients was 25.77 ($\pm$7.46) years and 11 (42.3%) were women. Sixty-five per cent of the sample had a secondary school educational level. At baseline, 17 (26.9%) patients abused alcohol, 14 (53.8%) cannabis and 8 (30.7%) other drugs. The main socio-demographic and clinical characteristics of the sample at baseline are listed in Table 1.

There were no significant differences at baseline between patients followed-up for 5 years and those lost to follow-up with respect to the socioedemographic and clinical variables.

2.2. Procedure

All patients were informed about the purpose of the study and provided written informed consent to participate. Subjects were assessed clinically at baseline and the neuropsychological assessment was performed at 6 months after hospitalization, to ensure greater psychopathological stability of participants and avoid the interference of psychopathology with cognitive performance. Criteria for neuropsychological assessment were determined by evaluating psychotic symptom severity from the scores on the Positive and Negative Syndrome Scale (PANSS) positive symptom subscale (less than 4 on any item of the scale). All the patients were followed up for 5 years and were assessed with the same clinical and neuropsychological battery. Follow-up clinical assessment was conducted at 6-months and at 1 and 5-years from baseline, while neuropsychological assessment was performed at 5 year follow-up. Clinical assessment was performed in three stages during follow-up, while neuropsychological assessment was performed in two stages to identify changes over time in cognitive performance, because the cognitive variables are more stable measures than the clinical variables are.

Trained psychologists carried out the assessments of patients and the administration of the tests. In the first phase of the study, assessments were performed by psychologists of the Psychiatry Research Unit of Santiago Hospital and at the 5-year follow-up by clinical psychology residents of the same hospital.

2.3. Measures

All subjects were assessed with an extensive protocol that included clinical and neuropsychological variables.

2.3.1. Clinical and functional assessment

Patients were diagnosed according to the DSM-IV-TR diagnostic criteria using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-Axis I Disorders) (SCID-I) (First et al., 1997). These interviews were carried out independently by two experienced clinicians. The data on interrater reliability obtained with these interviews were satisfactory

Table 1
Socio-demographic and clinical characteristics of the sample.

	(*N*=26)	%
Educational level		
Primary school	4	15.38
Secondary school	17	65.38
College	5	19.23
Diagnosis		
Schizophrenia	12	46.2
Bipolar disorder	9	34.6
Unspecified psychosis	4	15.14
Other psychosis	1	3.80
Pharmacological treatment		
Atypical antipsychotics	16	61.53
Mood stabilizers	9	34.61
No treatment	2	7.69
	Mean	**SD**
Number of admissions	1.65	0.80
Number of episodes	1.70	0.60