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Research Paper

Cognitive Performance associated to functional outcomes in stable outpatients with schizophrenia

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ABSTRACT

Background–objective: Prevalence data of cognitive impairment in Schizophrenia based on large population samples are scarce. Our goal is to relate cognition and functional outcomes, and estimate prevalence of cognitive impairment in a large sample of schizophrenia outpatients treated with second-generation antipsychotics.
Method: A cross-sectional outpatient evaluation conducted during follow-up visits. Selection criteria included six-months stable treatment. The brief battery, EPICOG-SCH, covered four cognitive domains related to functional outcomes: *working memory* (WAIS-III-Letter-Number-Sequencing), *executive function* (Category Fluency Test; CFT), *verbal memory* (WMS-III-Logical-Memory), and *information processing speed* (Digit-Symbol-Coding and CFT). Clinical severity and functional impairment were assessed with CGI-SCH and WHO DAS-S. Impairment prevalence was calculated at ≤1.5 SD.
Results: Among patients recruited ($n = 848$) in 234 participating centers, 672 were under 6-month treatment. 61.5% ($n = 413$) reported cognitive impairment according to CGI-SCH *Cognitive Subscale*. Estimated prevalences were 85.9% (95% CI 85.6–86.2%) CFT-Fruits; 68.3% (95% CI 67.8–68.8%) CFT-*Animals*; 38.1% (95% CI 37.5–38.3%) Digit-Symbol-Coding; 24.8% (95% CI 24.1–25.5%) *Verbal Memory-Units*; 20.9% (95% CI 20.2–21.6%) Letter-Number Sequencing; 11.7% (95% CI 11.0–12.4%) Verbal Memory-Items. Negative and Depressive symptoms, Deficit Syndrome, and functional disability were related to poor performance. Functional disability was predicted by CGI-SCH-Overall severity (OR = 1.34635, $p < 0.0001$), CGI-SCH-Negative Symptoms (OR = 0.75540, $p < 0.0001$), *working memory* (Letter-Number-Sequencing) (OR = −0.16442, $p = 0.0004$) and the time-course (OR = 0.05083, $p = 0.0094$), explaining 47% of the observed variability.
Conclusion: Most prevalent impairments were on *executive function* and *processing speed* domains; however, *working memory* showed the strongest relationship to functional disability. Monitoring cognitive function during follow up is critical to understand patient's everyday functional capacity.

1. Introduction

One of the primary features of schizophrenia is cognitive impairment; in past decades, this has been associated with patient functioning in daily life (Bowie and Harvey, 2006; Bowie et al., 2008; Green, 1996; Green et al., 2000, 2004a; Velligan et al., 1997; Harvey et al., 2006a,b) and greatly influences functional outcome on nearly the same level as negative symptoms (Hofer et al., 2005). Although the characteristics of cognitive impairment of schizophrenia have been extensively described, there are wide variability and heterogeneity in the domains that are affected and their degree of involvement (Fioravanti et al., 2012). A large proportion of schizophrenia patients – but not all – may develop significant, moderate-to-severe cognitive impairment (Montgomery and van Zwieten-Boot, 2007), but also it has been reported that 20–25% of patients may have normal scores on neuropsychological tests (Palmer et al., 2009; Wexler et al., 2009). Existing studies on cognitive deficits, have focused primarily on two methods of comparison: most studies compared patients' deficits with deficits in control groups, while other have compared patients' cognitive performance to that of the general population using normative data (Keefe et al., 2006). In one of the first published meta-analyses, the average patient performance on 22 psychological tests was described to be between 0.46 and 1.41 standard deviations below controls (Heinrichs and Zakzanis, 1998), and later on it was showed that deficit severity can be as great as 2–3 standard deviations below the mean (Keefe et al., 2006).

Drug therapy also plays a role in the patient's cognitive health, and cognitive symptoms' responses following treatment with second-

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generation antipsychotic agents are highly variable (Harvey et al., 2006a; Keefe et al., 1999). Contrary to what one might expect, international surveys on the use of neuropsychological assessments in psychiatric clinical practice have shown that cognitive assessment is not usually included in routine clinical practice (Belgaied et al., 2014; Green et al., 2005).

Schizophrenia's characteristic cognitive deficits have led to various attempts to generate specific batteries (Gold et al., 1999; Hurford et al., 2011; Keefe et al., 2004; Nuechterlein et al., 2008; Pietrzak et al., 2009; Velligan et al., 2004) (for a review of the available measurement tools, see Fagerlund, 2004 and Pino et al, 2008) (Pino et al., 2008), some of which aim to meet time constraints of clinical settings and also result in a composite score representative of the overall deficit. Also, the NIH initiative, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), promoted cognitive assessment in pharmacological research on schizophrenia, following a pre-defined methodology aiming to build a battery addressed to specific goals (Buchanan et al., 2005; Green et al., 2004a; Green and Nuechterlein, 2004).

In clinical practice, determining patient's cognitive abilities conveys specific challenges i.e. not only the efficiency to initially define the existence and degree of impairment and to estimate patients' cognitive strengths and weaknesses, but also to predict its related impact on clinical and functional outcomes, to monitor the effect of clinical changes on cognition and to determine the effect of adjustments/changes on drug treatments (Fagerlund, 2004) or the impact of rehabilitation programs.

After decades of research, the relationship between cognition and function in schizophrenia is now well recognized but not fully described; little is known about this interrelationship over time, about how other variables may influence the role of cognition in shaping functional outcomes (Rajji et al., 2014) or how changes induced in patients' cognitive functioning impact on functional outcomes (Green and Nuechterlein, 2004; Matza et al., 2006; Ventura et al., 2013).

In this Epidemiological Study of Cognitive Impairment in Schizophrenia (EPICOG-SCH) we evaluated the performance of patients on specific cognitive domains associated with patients' functional status according to review works published elsewhere, and we estimated the prevalence of cognitive impairment in those domains using published normative data.

This study is based on a large sample of clinically stable schizophrenia outpatients treated with second-generation antipsychotic drugs as their primary therapy. To this end, the EPICOG-SCH brief battery was built using cognitive tests validated in Spain and with available normative data from the general population. In addition, we aimed to describe the observed relationship between cognitive, clinical variables and patients' functional disability. Functional disability was assessed by the World Health Organization Short Disability Assessment Schedule (WHO DAS-S) (Janca et al., 1996) in which clinicians assesses the patient's difficulties in different functional areas due to his or her mental illness.

This study will provide useful information for clinicians to better understand the complex interaction between cognitive, clinical and functional factors in stable schizophrenia outpatient and, as well as, will provide reference data on the prevalence of cognitive impairment based on a large population, as reference for future studies.

2. Materials and methods

We conducted a cross-sectional epidemiological study with a sample of schizophrenia outpatients on maintenance treatment with second-generation antipsychotic drugs. The patients visited a clinic for a routine control visit at one of the community-based mental-health service centers in Spain, within of the National Public Health System including all 17 Autonomous Communities in the country.

2.1. Participants

Inclusion criteria were at least 18 years of age, having an established diagnosis of schizophrenia according to DSM-IV-TR criteria (American Psychiatric Association, 2002), on maintenance treatment with at least one second-generation antipsychotic drug and treatment remaining stable during the previous six months, and completion of informed consent to participate in the study. Exclusion criteria were not having a clinical history of at least one year at the participating center, suffering an acute depressive episode at the time of selection, at least 2 months elapsed since the most recent neuropsychological or cognitive assessment and presenting severe or uncorrected auditory or visual sensory dysfunctions or psychomotor disturbances that would prevent the completion of cognitive tasks.

The study was approved by the Clinical Research Ethics Committee of one of the participating centers, and this approval extended to all the other participating centers in the country.

2.2. Cognitive assessment battery

For the selection of the domains to be included, the MATRICS-RAND review work was taken into account regarding documented relationship of subtests to functional outcomes (Nuechterlein et al., 2008; Green et al., 2004b). Subtests were selected also considering available versions validated at local level and with published local normative data based on general population. Four domains were identified as relevant in schizophrenia including executive function (although not considered initially within the MATRICS review model); the selected tests composing the final EPICOG-SCH battery were; Letter-Number Sequencing (WAIS-III) (Weschler, 2001; Gold et al., 1997) (*working memory*), Logical Memory (WMS-III-Text A) (Weschler, 2001) (*verbal memory*), Category Fluency Test (3 categories: animals, fruits, cities–villages) (Benton and Hamscher, 1978) (*executive functioning and information processing speed*), and Digit-Symbol Coding (WAIS-III) (Weschler, 2001) (*information processing speed*). For Category Fluency Test the category "*vegetables*" was substituted by "*cities–villages*" due to issues observed in Spanish languages with the original one (Pascual et al., 2000; Buriel et al., 2004). Category Fluency Test was selected as measure of *executive function* as described widely in the literature (Lezack et al., 2004; Heilman and Valenstein, 2003) but also as a measure of *information processing speed*.

2.3. Procedure

Data were collected from a clinical patient interview, including sociodemographic and clinical data and details about both antipsychotic treatments and other concomitant treatments, especially treatments using anticholinergic agents. In addition, socio-occupational status, functional status in different aspects of life and a history of cognitive difficulties symptoms were assessed.

Data on the clinical psychiatric diagnosis included the date of the first schizophrenic episode and the type of schizophrenia according to the DSM-IV-TR (American Psychiatric Association, 2002). The presence of the Deficit Syndrome was recorded (Kirkpatrick et al., 2000; Arango et al., 1998, 2004), and the severity of the disorder was determined based on the week before the visit by the Clinical Global Impression-Schizophrenia (CGI-SCH) Severity Scale (Haro et al., 2003a,b) which includes aspects of the disease in addition to *overall severity*, such as *positive*, *negative*, *depressive* and *cognitive symptoms*.