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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*.

2.3.1. Functional variables

Socio-occupational information about the patients' competitive employment working activity was recorded (Knudsen et al., 2000). The impact of the patient's overall mental health on daily function was assessed using the WHO DAS-S (Janca et al., 1996; Sartorius et al., 1986). This assessment tool is a semi-structured interview designed to assess disability from mental disorders and includes the following dimensions: *personal care*, *occupational* and *family functioning*, *functioning in the wider social context* and an *overall score*.

2.3.2. Cognitive test

Before administering the battery, patients were asked about the existence of cognitive difficulties using an open question and asking about previously conducted testing. Cognitive battery was composed of four subtests with an estimated mean administration time between 20 and 30 min; the sequence of administration was set in the way to avoid administering consecutively tests with verbal material stimuli. Investigators were selected provided they had demonstrable experience administering cognitive tests. Procedures to administer the battery were standardized using the instructions provided in the relevant manuals (Buriel et al., 2004; Wechsler, 2001; Weschler, 2001). Raters were asked to register all patients' responses into the forms and to obtain subtest scores.

2.4. Data analysis

All forms were centrally collected and scores for cognitive tests were centrally monitored to check accuracy and consistency among raters. After reviewing cognitive tests of 40% of the patients, observed discrepancies on scoring criteria were discussed in a meeting to reach consensus. Discrepancies were found mainly on the Category Fluency tests in the way raters scored language/country specificities on the produced names and also on Logical Memory when accepting synonyms as correct answers, among others. Resolution criteria were then applied to all data. Raw scores were transformed into standardized scores (scalar or centile depending on the test) based on published local normative data (Buriel et al., 2004; Wechsler, 2001; Weschler, 2001). For standardization age was the only stratification variable that was available for all age ranges for all subtests with the exception of Category Fluency Cities–Villages. For the WHO-DAS-S, the sum of the scores was considered the measure of overall patient functional disability.

Disability based on the cognitive tests results was identified as equal to or less than 1.5 standard deviations (SD) from the mean of standardized scores (i.e., a 1.5 SD cut-off or 10th centile) i.e., corresponding to a score <5.5 for scalar ratings and <10 for centiles. The prevalence of impairment was defined as the percentage of patients with scores below the cut-off mentioned; prevalence estimates are given with the 95% CI. Raw and adjusted prevalence, according to the estimated total number of patients with schizophrenia in Spain, was estimated. For adjusted prevalence, weights were derived from 2004 population data provided by the National Statistics Institute (Instituto Nacional de Estadística, 2006) and considering a prevalence of schizophrenia of a constant 1% in all constituted communities. In addition, we also provided the prevalence estimates for the cut-off of 1.0 and 2.0 SD below the mean, corresponding to the *lower limit of normal cognitive performance* and to *severe impairment*, respectively (Harvey et al., 2006a; Taylor and Heaton, 2001); these cut-offs correspond to scores between <7 and <4 for scalar scores and between <25 and <5 for centile scores, respectively. The prevalence of impairment for each domain was established when all of the tests administered associated with that domain were below the cut-off. Criterion validity of the battery was based on its relationship with actual patient's clinical and functional status. Wilcoxon test was used to describe differences on performance among clinical subgroups; Spearman correlations were used to describe the association between cognitive performance and, clinical severity and functional disability results.

For exploratory purposes, we constructed two regression models to study the association between cognitive performance and the overall level of functional disability. Both the scores (raw and standardized) of all of the tests and the clinical variables were considered. All of the statistical tests were performed with the significance level set at 5%. The data were analyzed using SAS software release 8.02 (SAS Institute, Cary, NC).

3. Results

3.1. Description of patients and subgroups

Eight hundred and forty-eight (848) patients from 234 centers were evaluated between June and December 2006, from which 176 cases with protocol deviations were observed (20.8%) primarily due to an insufficient duration of maintenance treatment or due to documented changes on the prescribed drugs within the period or not enough data to confirm treatment duration. Ultimately, 672 patients with no changes on their drug therapy regimen were included in the group of analyzed patients. Table 1 shows the patients' sociodemographic and clinical characteristics. The sample consisted of patients with mild to moderate degrees of disease severity according to the CGI-SCH scale (Haro et al., 2003a,b) showing a wide variability in disease duration and overall adherent to prescribed drug treatment. Occupationally active patients comprised 18.9% ($n = 122$) of the cases; 33.6% ($n = 226$) had some type of government-recognized disability. Table 1 shows the results obtained in each functional area evaluated by the WHO-DAS-S; the mean of overall disability was 8 out of 20, with greater disability observed in the subscales of *occupational functioning* and *functioning in the wider social context*.

A total of 67.4% of patients ($n = 453$) met the criteria for the Deficit Syndrome (Arango et al., 1998; Kirkpatrick et al., 2000) and 64.3% ($n = 429$) showed some degree of depression according to the CGI-SCH scale (Haro et al., 2003a,b). Nine hundred and forty-six antipsychotic treatments were recorded, either as primary or as secondary treatment for schizophrenia, and 15.6% of patients had prescribed anticholinergic agents as concomitant treatment ($n = 105$). In total, 42.6% ($n = 286$ cases) were being treated simultaneously with several antipsychotic agents. Among the registered treatments there were Amisulpride (40.8%, $n = 274$), Risperidone (35.7%, $n = 240$), Olanzapine (22.9%, $n = 154$) and Quetiapine (11.8%, $n = 79$), and other agents at lower percentages.

A few patients had a previous cognitive assessment (12.5%, $n = 83$ cases), with a mean time of 28.5 months from the previous test. According to clinical criteria, a large number of patients had cognitive impairment (CGI-SCH ≥ 2 minimal = 91.2%, $n = 613$; and CGI-SCH ≥ 3 moderate = 61.5%, $n = 413$). Additionally, in response to the open question, most patients reported having or suffering cognitive difficulties in their daily lives (78%, $n = 524$), including difficulties in concentration, remembering, maintaining attention when reading, planning capacity, keeping on track during conversations, following instructions or a combination of these, among others.

3.2. Performance and cognitive impairment

The domains with the lowest results were *executive function* (Category Fluency Test) and *information processing speed* (Digit-Symbol Coding and Category Fluency Test), whereas the best results were obtained in the *verbal memory* domain, specifically, in the immediate recall of items (*see* Table 2).

Table 1
Sociodemographic, clinical and functional characteristics of the patients.

Variable	Total Sample ($N = 672$)	
	Mean	*SD*
Age (*years*)	39.0	*10.5*
Time course of the disorder (*years*)	14.4	*9.9*
	n	%
Schizophrenia subtypes		
Paranoid (295.30)	500	*75.3*
Undifferentiated (295.90)	71	*10.7*
Residual (295.60)	59	*8.9*
Disorganized (295.10)	32	*4.8*
Catatonic (295.90)	2	*0.3*
Gender		
Man	447	*67.2*
Woman	218	*32.8*
Educational level completed		
No education completed	66	*9.8*
Primary	312	*46.4*
High School	226	*33.6*
University	60	*8.9*
Unknown	8	*1.2*
Psychiatric Comorbidities[a]		
Substance Use	165	*24.6*
Mood disorders	74	*11.1*
Anxiety disorders	51	*7.6*
Personality disorders	28	*4.2*
Family History[b]		
Depressive disorder	171	*25.5*
Psychotic disorder	133	*19.6*
Substance abuse	94	*14.0*
Bipolar Disorder	23	*3.4*
Treatment Adherence		
Yes	542	*80.7*
No	103	*15.3*
	Mean	*SD*
Mental Health Care Records (Past Year)		
Number visits to the specialist	7.6	*5.9*
Number relapses[c]	0.7	*2.5*
Elapsed time since last relapse (*months*)	25.5	*33.9*
Number of hospital admissions[c]	0.4	*1.1*
Mean length of hospital admissions (*days*)	6.5	*13.7*
	n	%
Governmental disability/handicap		
Officially awarded	226	*33.6*
	Mean	*SD*
Percentage of disability acknowledged (%)[d]	64.4	*10.9*
	n	%
Patients with long term labor incapacity *(disability awarded officially)*		
Temporal labor incapacity	26	*3.9*
Permanent labor incapacity	338	*50.3*
Absolute *(for any type of work)*	197	*62.3*
Total *(for the usual activity)*	101	*32.0*
Partial	17	*5.4*
Great incapacity	1	*0.3*
Under evaluation	52	*7.7*
Unknown	86	*31.1*
Occupational status each		
Retired	241	*35.6*
Unemployed	176	*26.2*
Active work	122	*18.9*
Housework	48	*7.2*
Student	34	*5.1*
Unknown	51	*3.4*
Type of work		
Not working or unknown	472	*70.2*

(continued on next page)

Table 1 *(continued)*

Variable	Total Sample ($N = 672$)	
	Mean	*SD*
Worker in a factory	81	*12.5*
Qualified worker	44	*6.5*
Services/Retails	40	*6.0*
Secretary/Receptionist	10	*1.5*
Associated professional	9	*1.3*
Professional	12	*1.8*
Manager-Business Administrator	4	*0.6*
Currently studying	80	*11.9*
Principal income source		
Pension-subsidy	264	*39.3*
Family support	139	*20.7*
Salary or unemployement benefit	134	*19.9*
Various income sources	43	*6.4*
Not specified	58	*8.6*
Social interaction: frequency of interaction with family		
On a daily basis or almost daily	267	*39.7*
Once or twice per week	140	*20.8*
Once or twice per month	119	*17.7*
Every several month	64	*9.5*
Rarely	65	*9.7*
Never	10	*1.5*
Unknown	7	*1.0*
Social interaction: frequency of interaction with friends		
On a daily basis or almost daily	252	*37.5*
Once or twice per week	201	*29.9*
Once or twice per month	83	*12.4*
Every several month	20	*3.0*
Rarely	78	*11.6*
Never	26	*3.9*
Unknown	12	*1.8*
	Mean	*SD*
WHO DAS-S[e]		
Total Score	8.0	*4,1*
Personal Care	1.1	*1.1*
Occupational Functioning	2.5	*1.4*
Familiar Functioning	1.9	*1.2*
Broad Social Context Functioning	2.6	*1.3*

WHO DAS-S, World Health Organization Disability Scale-Short Version (Janca et al., 1996; Sartorius et al., 1986).
WHO-DAS-S subscales also showed association with their corresponding registered sociodemographic data. In this way *Occupational functioning* was related to patient's actual Work Status ($Chi2 = 172.7626$, $gl = 25$, $p < 0.0001$) and Principal Source of Incomes ($Chi2 = 164.9863$, $gl = 20$, $p < 0.0001$). *Broad social context functioning* was associated both with Frequency of Social Interactions with Family ($Chi2 = 84.6947$, $gl = 25$, $p < 0.0001$) and with Friends ($Chi2 = 218.8328$, $gl = 25$, $p < 0.0001$). *Familiar Functioning* was associated to Frequency of Social Interaction with Family ($Chi2 = 73.2496$, $gl = 25$, $p < 0.0001$). No complementary information was recorded to analyze the association to Personal Care subscale.

[a] Psychiatric conditions were reported in 45.5% (n = 305) of the patients as associated to the diagnosis of schizophrenia; eating disorders, sleep disorders, sexual disorders, and obsessive–compulsive disorders were reported at lower rates.

[b] 50% (n = 337) of the patients reported family history of psychiatric disorders; intellectual disability, anxiety disorders, dementia, obsessive–compulsive disorder, eating disorder, and personality disorder were reported at lower rates.

[c] Related to all patients, including those without relapses or admissions during the specified period.

[d] Established in percentages and ranging in the study from 15% to 100%. Governmental classification system with anchor percentages; 0% means a permanent handicap proof by objective measures not involving disability; from 1% to 24% corresponds to permanent handicap resulting in a mild disability; from 25% to 49% corresponds to permanent handicap resulting in a moderate disability; from 50% to 70% corresponds to permanent handicap resulting in a severe disability; from 70% onwards corresponds to permanent disability producing high severe handicap with a dependent status to carer for daily living activities.

[e] Total score is in a range from 0 to 20 and subscales from ranging from 0 to 5. Higher score means higher disability. For each subscale few patients showed Functioning with Help i.e. Personal Care 6.9% (n = 46), Occupational Functioning 8.4% (n = 56), Familiar Functioning 7% (n = 47), and Broad Social Context Functioning 7.9% (n = 53).

On most of the tests, a higher percentage than expected was observed in the 1.5 SD cut-off compared to a normal reference distribution (i.e., 9.06%) except for the test of verbal memory for items (see Table 2).

Impairment prevalence estimates with 95% CIs for each cognitive tests were, from low to high, *verbal memory* (items), 11.7% (95% CI 11.0–12.4%); *working memory* (Letter-Number Sequencing), 20.9% (95% CI 20.2–21.6); and *verbal memory* (units), 24.8% (95% CI 24.1–25.5%). The most prevalent impairments were in *executive function* and *processing speed* (Category Fluency Test and Digit-Symbol Coding), with Digit-Symbol Coding percentages of 38.1% (95% CI 37.5–38.3%); Category Fluency Test-Animals 68.3% (95% CI 67.8–68.8%); and Category Fluency Test-Fruits 85.9% (95% CI 85.6–86.2%). The population-adjusted prevalence was very similar (results are included as *supplementary material*, see Supplementary Table 1).

As expected, marked heterogeneity was observed in overall cognitive performance. Most of the patients had cognitive impairment in one or two of the assessed cognitive domains i.e. 41% ($n = 220$ cases) had cognitive impairment in one, and 30.6% ($n = 164$) had cognitive impairment in two domains. Impairement for three or four domains were lower: 12% ($n = 67$) and 9.3% ($n = 50$), respectively. A small number of patients had normal performance in all assessed areas (6%, $n = 35$).

Table 2
Results obtained from the EPICOG-SCH cognitive battery and prevalence of cognitive impairment.

Cognitive Subtest	Raw Score					Standardized Score					Percentage of patients with Cognitive Impairment		
	n	Mean	*SD*	Min	*Max*	n	Mean	*SD*	Min	*Max*	Cut off scores for Scalar Scores		
											≤1 *SD* (Score ≤ 7)	≤1.5 *SD* (Score ≤ 5.5)	≤2 *SD* (Score ≤ 4)
Letter-Number Sequencing (WAIS-III)[a]	670	8.5	*3.9*	0	*21*	647	8.9	*3.9*	0	*19*	37.7	20.9	12.8
Digit-Symbol Coding (WAIS-III)[a]	671	43.6	*21.5*	0	*133*	648	6.3	*3.4*	1	*19*	63.4	38.1	27.9
Logical Memory (WMS-III-Text A)[a]													
Units	672	10.4	*4.6*	0	*23*	641	8.4	*3.4*	1	*19*	38.0	24.8	12.2
Issues	672	4.6	*1.7*	0	*7*	649	9.4	*2.8*	2	*15*	25.4	11.7	6.0
											Cut off scores for Centile Scores		
											Centile_25	Centile_10	Centile_5
Category Fluency Test (total score)[b]	672	39.4	*15.6*	0	*148*	–	–	–	–	–	–	–	–
Animals	672	14.0	*5.6*	0	*39*	539	3.0	*2.6*	1	*13*	85.9	68.3	59.9
Fruits	672	10.0	*3.6*	0	*31*	539	1.9	*1.7*	1	*14*	97.6	85.9	76.9
Cities–Villages[c]	672	15.5	*8.1*	0	*78*	–	–	–	–	–	–	–	–

SD, Standard Deviation.
Observed percentages of patients showing cognitive impairment for all subtests are higher than the expected percentages in a normal distribution i.e. 15.7% for ≤ 1 SD and 2.3% for ≤ 2 SD.
When interpreting the estimated prevalences, the similarities and differences between the study sample and normative sample need to be taken into account. In this sense, some differences on sociodemographic factors were observed: participants on the normative samples for WAIS-III and WMS-III were older than the patients in the study sample ($p = 0.000014$ and $p = 0.0001$ respectively) and also the normative sample was composed of a lower percentage of men than the study sample ($p = 0.0001$ for both WAIS-III and WMS-III). Regarding education, patients on the normative sample for WAIS-III had a lower percentage of patients with primary school completed ($p < 0.0001$) compared to the study sample that showed a higher level of education. Information about education was not available for WMS-III normative sample.
With regards Category Fluency normative sample was older ($p < 0.0001$) and with a higher level of education ($p < 0.0001$). Years of education have a clear impact on the performance of this subtest (Buriel et al., 2004).
[a] Standardized as scalar scores (mean 10 SD 3) (Weschler, 2001).
[b] Standardized as centile score. Available normative data only for patients aged 20 to 49 years old (Buriel et al., 2004).
[c] No available normative data in Spain. The category "vegetables" was substituted with "cities–villages" due to the issues related to the category "vegetables" in Spanish language, as noted in past published research (Buriel et al., 2004). The category "cities" is one of the categories included in the Set-Test of Isaac measuring category fluency validated in Spain (Pascual et al., 2000).

On all of the cognitive tests administered, performance was inversely and moderately associated with the level of functional disability assessed by the WHO DAS-S; higher performance was related to less disability (see Table 3).

Patients who were actively employed at the time of participation in the study or who were in training programs performed better on all tests (see Table 4).

3.3. Cognitive performance and clinical profile

With respect to criterion validity, the relationship between performance on cognitive tests and the patient's overall clinical status according to the clinical impression was moderate and statistically significant. Therefore, the more clinically severe patients, according to the CGI-SCH-*Overall severity* and *Cognitive scales*, performed more poorly on cognitive tests (see Table 5). In both cases, performance in the *working memory* domain (Letter-Number Sequencing) had the highest correlation with the clinical impression of severity as assessed by the clinician´s CGI-SCH subscale.

For the remaining evaluated clinical aspects, such as *negative symptoms*, *depressive symptoms* and the presence of the Deficit Syndrome, the results are shown in Figs. 1 and 2 and Table 5. In all cases, the severity of the associated symptoms showed a statistically significant inverse relationship to cognitive performance

Table 3
Relationship between clinical impression, disability and cognitive results.

Cognitive test ($N = 672$)	ICG- SCH[a]		WHO-DAS-S Dimensions[b]				
	General Subscale	Cognitive Subscale	Personal Care	Family and household	Occupational Functioning	Functioning in Broader Social Context	WHO-DAS-S Total Score
Letter-number sequencing-WAIS-III	-0.33^{***}	-0.35^{***}	-0.37^{***}	-0.30^{***}	-0.30^{***}	-0.31^{***}	-0.39^{***}
Digit-symbol coding-WAIS-III	-0.23^{***}	-0.28^{***}	-0.31^{***}	-0.25^{***}	-0.27^{***}	-0.27^{***}	-0.33^{***}
Category Fluency Test (total score)	–	–	-0.30^{***}	-0.25^{***}	-0.27^{***}	-0.28^{***}	-0.33^{***}
Animals	-0.19^{***}	-0.25^{***}	-0.27^{**}	-0.23^{***}	-0.27^{***}	-0.24^{***}	-0.31^{***}
Fruits	-0.20^{***}	-0.23^{***}	-0.30^{***}	-0.22^{***}	-0.24^{***}	-0.24^{***}	-0.29^{***}
Cities/Villages	–	–	-0.27^{***}	-0.23^{***}	-0.23^{***}	-0.27^{***}	-0.30^{***}
Logical Memory*-WMS-III-Text-A							
Units	-0.26^{***}	-0.29^{***}	-0.24^{***}	-0.23^{***}	-0.21^{***}	-0.25^{***}	-0.28^{***}
Issues	-0.21^{***}	-0.20^{***}	-0.15^{***}	-0.19^{***}	-0.14^{***}	-0.19^{***}	-0.21^{***}

Statistical Significance: ** $p < 0.001$ *** $p < 0.0001$.
CGI-SCH-SCH, The Clinical Global Impression-Schizophrenia scale (Haro et al., 2003a,b).
WHO DAS-S World Health Organization Disability Assessment Scale Short Version (Janca et al., 1996; Sartorius et al., 1986).
[a] Correlation coefficients using standardized scores for cognitive subtests.
[b] Correlation coefficients using raw scores for cognitive subtests.

Table 4
Results on cognitive tests on EPICOG-SCH battery according to occupational status.

Cognitive Test	Occupational Status[a]						
	Active Status ($n = 204$)		Non Active Status ($n = 417$)			95% IC of Difference	
	Mean	*SD*	Mean	SD	Sign.	Low	High
Letter-number sequencing-WAIS-III	9.3	*4.0*	8.3	*3.9*	$p = 0.0023^{**}$	0.3	1.6
Digit-symbol coding-WAIS-III	49.5	*20.1*	40.7	*20.5*	$p < 0.0001^{***}$	5.4	12.2
Fluency Test (Total)	43.1	*16.6*	38.3	*15.0*	$p = 0.0014^{**}$	2.2	7.4
Animals	15.2	*6.0*	13.5	*5.6*	$p = 0.022^{*}$	0.7	2.7
Fruits	10.7	*3.6*	9.8	*3.5*	$p = 0.0091^{**}$	0.3	1.5
Cities/Villages	17.2	*8.8*	15.1	*7.8*	$p = 0.0026^{**}$	0.8	3.6
Verbal Memory-WMS-III*							
Units	11.8	*4.6*	9.9	*4.6*	$p < 0.0001^{***}$	1.1	2.7
Issues	5.1	*1.5*	4.4	*1.7*	$p < 0.0001^{***}$	0.4	1.0

95% IC, Confidence Interval; Statistical Significance: *p < 0.05, **p < 0.01,***p < 0.001, ****p < 0.0001.
Patients in an active situation showed better results in all cognitive tests in the EPICOG-SCH battery compared with those in a non-active situation.
[a] Active Status included active workers, students and patients in charge of housework while non-active included unemployed and retire patients.

across all assessed domains. For depressive symptoms, this relationship was also true, except in the *verbal memory* domain, where patients with depressive symptoms showed similar results to those with no such current symptoms. Finally, the subgroup of patients with the Deficit Syndrome performed poorly on all tests (see Table 5).

The first multiple linear regression model was constructed using only the results of cognitive tests (standardized scores) and explained 12.13% of the variability of functional disability, with significant coefficients only for the subtests of Letter-Number Sequencing (OR = −0.32, P < 0.0001) and Category fluency Test-Fruits (OR = −0.35, p =0.0006). A second regression model was constructed, by adding clinical variables such as *clinical impression of severity (CGI-SCH)* and *course of the disease* (as the number of relapses in the previous year, number of admissions and the time course of the condition) to the scores of the cognitive tests (standardized). The resulting model isolated four factors that explained 47% of the observed variability of functional disability: 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 of the disorder (OR = 0.05083, p = 0.0094).

Table 5
Results on cognitive tests on the EPICOG-SCH battery and functional disability according to patient's clinical profile.

	Deficit Syndrome[a]					Depressive Symptoms[b]					Anticholinergic Treatment[c]				
	Meet Criteria ($n = 453$)		Not Meet ($n = 209$)			Present ($n = 429$)		Absent ($n = 238$)			Yes ($n = 105$)		No ($n = 567$)		
	Mean	*SD*	Mean	*SD*	*p-value*	Mean	*SD*	Mean	*SD*	*p-value*	Mean	*SD*	Mean	*SD*	*p-value*
Cognitive Tests															
Letter-number sequencing-WAIS-III[d]	8.3	*3.7*	10.1	*3.9*	$<0.0001^{****}$	8.7	*3.9*	9.3	*3.8*	0.0193^{*}	8.2	*4.1*	9.0	*3.8*	0.0179^{*}
Digit-symbol coding-WAIS-III[d]	6.0	*3.3*	7	*3.3*	$<0.0002^{***}$	6.1	*3.3*	6.8	*3.6*	0.0368^{*}	5.9	*3.5*	6.3	*3.3*	0.1467
Category Fluency Test (Total)[d]	36.9	*14.7*	44.8	*16.3*	$<0.0001^{****}$	38.2	*15.9*	38.2	*15.9*	0.0098^{**}	37.0	*14.4*	39.9	*15.8*	0.0525
Animals	13.2	*5.6*	15.6	*5.7*	$<0.0001^{****}$	13.5	*5.8*	14.8	*5.7*	0.0104^{*}	13.5	*5.5*	14.1	*5.8*	0.3333
Fruits	9.5	*3.5*	11.1	*3.6*	$<0.0001^{****}$	9.7	*3.6*	10.5	*3.5*	0.0068^{**}	9.6	*3.26*	10.1	*3.6*	0.2291
Cities/Villages	14.2	*7.5*	18.1	*8.8*	$<0.0001^{****}$	15.1	8.5	16.2	*7.5*	0.0328^{*}	13.9	*7.6*	15.6	*8.2*	0.0223^{*}
Verbal Memory -WMS-III-Text-A[e]															
Units	7.9	*3.2*	9.5	*3.6*	$<0.0001^{****}$	8.4	*3.5*	8.4	*3.1*	0.5726 ns	7.1	*3.4*	8.6	*3.3*	$<.0001^{****}$
Issues	9.2	*2.8*	10.1	*2.7*	$<0.0001^{****}$	9.4	*2.9*	9.6	*2.3*	0.4159 ns	8.3	*2.9*	9.7	*2.8*	$<.0001^{****}$
WHO-DAS-S Subscales															
Personal Care	1.3	*1.1*	0.6	*0.9*	$<0.0001^{****}$	1.2	*1.1*	0.8	*1.0*	<0.0001	–	–	–	–	–
Occupational Functioning	2.8	*1.3*	1.7	*1.3*	$<0.0001^{****}$	2.6	*1.4*	2.2	*1.5*	<0.0002	–	–	–	–	–
Family and Household	2.2	*1.1*	1.4	*1.1*	$<0.0001^{****}$	2.0	*1.1*	1.7	*1.2*	<0.0003	–	–	–	–	–
Functioning on Broader Social Context	3.0	*1.2*	1.8	*1.2*	$<0.0001^{****}$	2.7	*1.2*	2.3	*1.4*	<0.0001	–	–	–	–	–

WHO DAS-S, World Health Organization Disability Scale-Short Version (Janca et al., 1996; Sartorius et al., 1986).
Statistical Significance: *p < 0.05, **p < 0.01,***p < 0.001, ****p < 0.0001.
[a] According to specific criteria for Deficit Syndrome (Arango et al., 1998, 2004; Kirkpatrick et al., 2000). Deficit Syndrome was significantly related to functional disability in all areas i.e. Personal Care, Chi2 = 54.6915, gl = 5, p < 0.0001; Occupational Functioning. Chi2 = 102.9530, gl = 5, p < 0.0001; Familiar Functioning, Chi2 = 67.8735, gl = 5, p < 0.0001; Functioning in Broader Social Context Chi2 = 125.4340, gl = 5, p < 0.0001).
[b] According to Depression Subscale of CGI-SCH (Haro et al., 2003a,b). Depressive symptoms were significantly related to functional disability in all areas evaluated i.e. Personal Care, Chi2 = 27.2771, gl = 5, p < 0.0001; Occupational Functioning, Chi2 = 22.1539, gl = 5, p = 0.0005; Familiar Functioning, Chi2 = 24.7892, gl = 5, p = 0.0002; Functioning in Broader Social Context, Chi2 = 29.0690, gl = 5, p < 0.0001).
[c] Subgroup of patients treated with anticholinergic agents was similar to other patients regarding socio-demographic variables i.e. age, gender and years of education. This subgroup had a higher percentage of patients at higher severity scores on the ICG-General Subscale (p = 0.0054).
[d] Raw scores.
[e] Standardized scores.

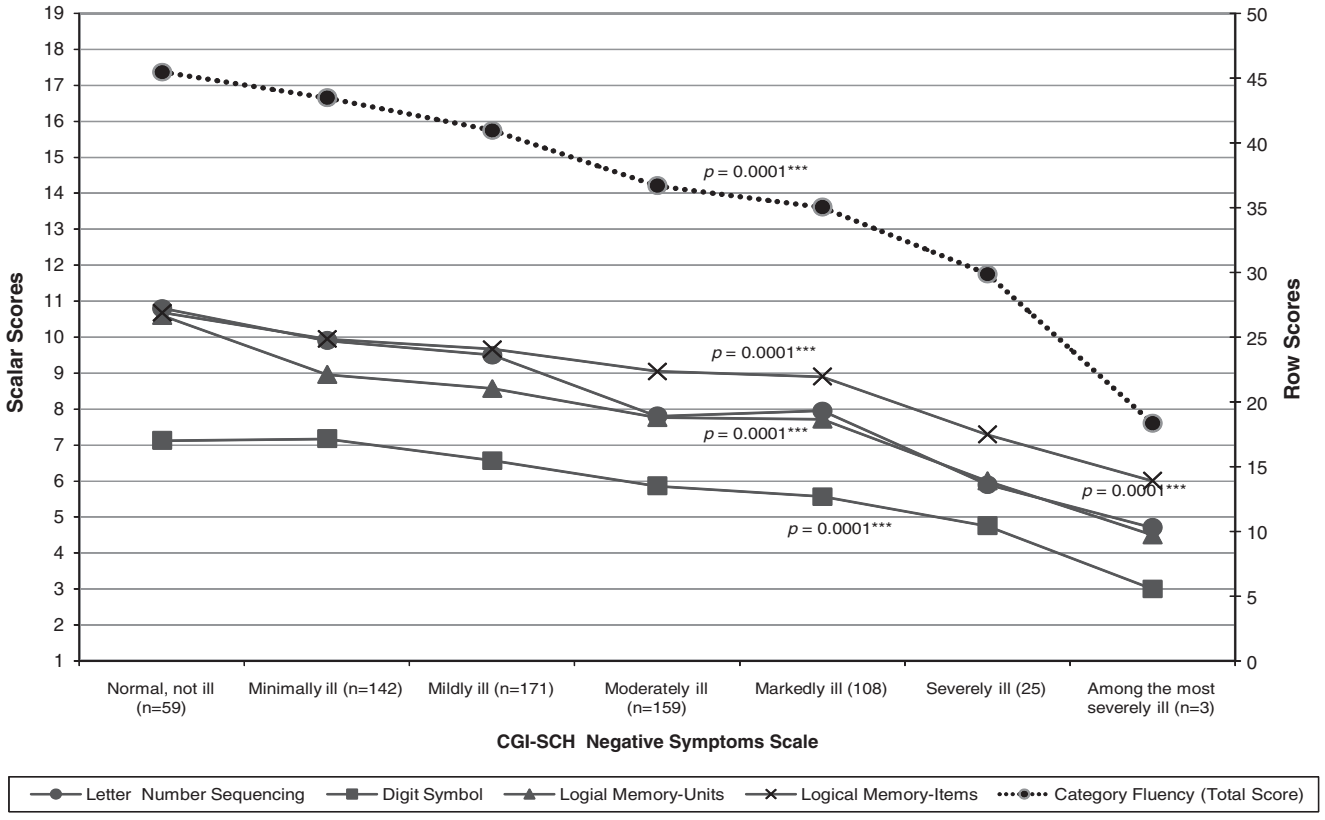

Fig. 1. Patients showing negative symptoms (e.g. affective flattening, avolition or anhedonia) obtained lower results in all cognitive tests.

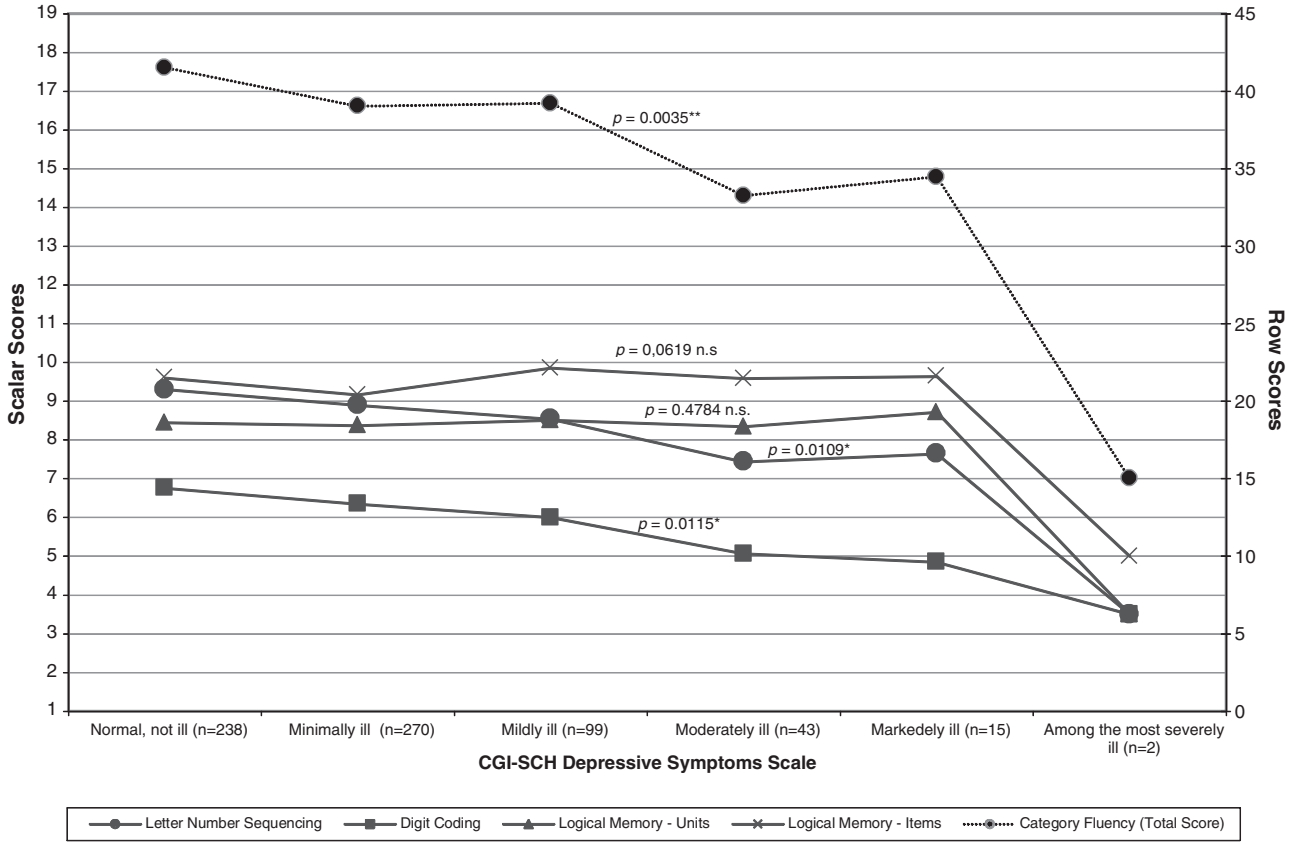

Fig. 2. Patients with depressive symptoms (e.g. sadness, depressed mood or hopelessness) showed lower performance on Category Fluency, Letter Sequencing and Digit Coding tests.

Thus, the overall functional disability recorded in the sample of schizophrenic outpatients studied was associated with both clinical and cognitive variables and with the evolution of the disorder; the cognitive domain of *working memory* showed the highest relationship to the patient's overall functional disability.

4. Discussion

In this study, we describe the cognitive performance of the EPICOG-SCH battery subtests on a large sample of schizophrenia patients receiving stable treatment from second-generation antipsychotic drugs. The lowest performance was obtained in tests assessing *executive function* and *speed of information processing*, followed by tests of *working memory* and *verbal memory*, where the results obtained were below the normative reference population. The cognitive impairment with the higher prevalence (<1.5 SD below the mean) was found for the *executive function* domain (between 70 and 80% of the sample according to the subtest) and *information processing speed*, which had a prevalence of nearly 40%.

However, along with other clinical factors, the domain that had the highest association with overall patient functional disability was the *working memory*.

This result is consistent with previous studies conducted with clinically stable patients, which reported similar results in *working memory* and occupational functioning (Hofer et al., 2005) and between patients with and without cognitive deficits according to their state of competitive employment or vocational functioning using a cut-off of <2 SD (Holthausen et al., 2007). In other studies, *working memory*, along with other domains, such as *processing speed* and *attention*, was also associated with functional outcomes in social and functional skills (Bowie et al., 2008). In addition, in our study, *working memory* was the domain that had the highest correlation with the clinical criteria of cognitive impairment according to the CGI-SCH Cognitive Subscale.

Various studies have identified subtests, such as symbol coding and fluencies, along with tests that have components such as *processing speed*, to be valid and efficient indicators of overall cognitive functioning using different patient groups (Hurford et al., 2011; Wong et al., 2013). With regard to functional outcome, recently Fervaha et al. (2014) using data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, concluded that the subtests of *working memory* and *information processing speed* (Letter Sequencing and Digit-Symbol Coding, respectively) were a valid estimate of overall cognitive status and had a similar relationship to clinical and functional outcomes, as in this administration of the full EPICOG-SCH battery.

The relationship between overall functional status and the cognitive status of patients has been widely discussed and is not as direct as it was believed to have been in the past. In our study, this relationship was mediated by other factors. In the sample of patients studied, patient functioning was related not only to cognitive status and to other clinical factors, such as overall severity and associated negative symptoms, but also to the course of the disease as the time of the disorder's evolution. Our model explained 47% of the variability in this large sample of clinically stable patients monitored on an outpatient basis. The relevance of the time of evolution on cognitive status was highlighted in a meta-analysis study that included 113 different studies. In this study, time of evolution of the disease was a large source of variation contributing to the heterogeneity observed in studies of cognitive impairment in schizophrenia (Fioravanti et al., 2005, 2012).

The contribution of cognition to patient functional status has been examined in several studies, with percentages of the explained variability in functional status accounted for by performance on cognitive tests in the range of 10–40% (Velligan et al., 1997); this range is due to different factors, such as the social context and type of patients studied. With increasing experience and information on this subject, understanding the interaction between cognition and the functioning of patients in the community has become more complex (Green, 2007).

With respect to the factors associated with cognitive outcome, the association between **negative symptoms** and cognitive status has also been reviewed and described in multiple previous studies using more specific tools (Bowie et al., 2008; Harvey et al., 2006b; Hurford et al., 2011; Keefe et al., 2006; Milev et al., 2005; Palmer et al., 2009; Velligan et al., 2004; Villalta-Gil et al., 2006), where negative symptoms have been associated with functional areas of work, education and social functioning (Shamsi et al., 2011; Lin et al., 2013). In contrast, the influence of **depressive symptoms** on cognition in schizophrenia has produced conflicting results in the past (Stip and Mancini-Marie, 2004; Holthausen et al., 2007). In our study, although the presence of symptoms of depression did not seem to affect performance in *verbal memory-immediate recall*, it did negatively influence performance in the remaining tests, which confirmed previous findings that this factor could have a different impact depending on the domain being assessed (Bowie et al., 2008). In the subgroup with depressive symptoms, women were predominating and, although their ages and educational level were similar to the cases without depressive symptoms, they obtained higher clinical severity scores on the CGI-SCH scale, which may partially explain the observed results.

Finally, patients who met the criteria for the Deficit Syndrome (Arango et al., 1998, 2004; Kirkpatrick et al., 2000) obtained lower scores on the cognitive tests compared to the scores of patients who did not meet the criteria. This group consisted of older patients with less education and greater clinical severity assessed by the CGI-SCH overall severity scale, factors that in turn may have influenced cognitive outcomes. These results should be viewed with caution due to the limitations involved in evaluating symptoms using clinical impression scales. Future studies should include specific validated scales in schizophrenia and train raters on the administration of tests.

With respect to limitations, it should be noted that the patients studied were clinically stable and had mild to moderate degrees of severity, thus compromising the external validity of the results in other populations of outpatients with more severe schizophrenia. In addition, cross-sectional studies do not allow for the establishment of causal relationships among the factors studied, and prospective studies are required to confirm any causal links. Also, due to time constrains at clinical settings, the number of subtests included in the resulting battery is not comprehensive enough to provide a complete picture of patient cognitive status and this is important to take into account when considering our results. Lastly, for this project raters were not trained to administer the cognitive or the clinical tests. Raters were requested to have demonstrable experience performing cognitive testing and a telephonic training was offered in this context, however few investigators used this resource. Although no major findings were observed with regards to quality of registered data, the lack of training on the administration of the tests has compromised the quality of test administration and in turn, the results presented in this paper.

At the time of the study, we found that little attention has been paid to the cognitive state of patients in Spain due to the low percentage of cases that had received cognitive assessments. Although cognitive deficit is recognized in schizophrenia, a recent survey of psychiatrists in Europe, Asia and the US also revealed that only 12% of psychiatrists use appropriate tests for cognitive assessments, and in general, population-normative data are not used to interpret results (Belgaied et al., 2014).

An individualized assessment of cognitive status, using objective and validated cognitive tests that have normative data available from

the reference population to properly interpret the results, would be appropriate in clinical practices with outpatients. This assessment would provide a good estimate of the cognitive state of patients compared to that of the general population and would inform or advise the patients and their families about their potential functional development in daily life. The assessment would also allow for the observation of the evolution and fluctuation of cognitive states throughout the course of the disease based on the different therapeutic interventions and rehabilitation programs.

Monitoring the ability of *working memory* and speed of information processing becomes particularly relevant in our study because of their potential impact on functional capacity and changes in dosage of drugs, adjustments of antipsychotic drugs or simultaneous medication (anticholinergic agents, etc.).

The EPICOG-SCH cognitive battery subtests allowed us to differentiate among patients according to their overall functional status, their employment status and ongoing training activities. For schizophrenia, short batteries of tests have been shown to have a good correlation with the more thorough long batteries of tests (between 0.56 and 0.77) (Wong et al., 2013). This level of efficiency is significant in clinical situations in which available time for assessment is limited. The EPICOG-SCH battery, which includes four domains relevant to functional outcome, may be a good alternative tool for use in routine clinical practice. This methodology would require completing its psychometric study, analyzing the sensitivity to clinical and pharmacological changes and providing alternative versions of each subtest for repeated administrations.

This study proposes a brief cognitive assessment battery that determines patient cognitive status. The EPICOG-SCH battery, in its experimental version, has proven to be related to functional outcome variables, such as overall disability and occupational status; furthermore, it has proven to be sensitive to clinical aspects of the disease that are related to cognition.

This study constitutes the first step toward the construction and validation of a cognitive battery for clinical practice in schizophrenia with specific purposes. The battery will consist of widely known tests with available normative data, which will allow for use in different health care settings in different countries. This battery will be able to be administered in a limited amount of time, will be easy to interpret, and will require only limited resources. The results of the test battery will provide a good estimate of a patient's cognitive state relative to the general population and will be designed to inform or advise patients and their families about potential functional development for performing activities of daily life.

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Portions of this study's results were presented at the Joint Mid-Year Meeting of the International Neuropsychological Society, the Federation of Spanish Societies of Neuropsychology, the Spanish Neuropsychological Society and the Spanish Psychiatry Society held in Bilbao in July 2007. Partial results were also presented in poster form at the 20th European Clinical Neuropsychological Society (ECNP) Congress, (October 13–17, 2007) and at the 14th Biennial Winter Workshop on Schizophrenia Research, held in Montreux (Switzerland) on February 2–7, 2008.

Contributors

Mrs S. Zaragoza Domingo, Dr J. Bobes and Dr P. García-Portilla designed the study and wrote the protocol. Author Mrs C. Morralla managed the literature searches. Statistical analysis was performed by Dr García-Portilla. All authors contributed to and have approved the final manuscript. See Appendix 1 for a complete list of participating investigators.

Conflict of Interest

S. Zaragoza and Dr. J. Bobes have been advisors for Sanofi-Aventis; C. Morralla is an employee of Sanofi-Aventis (Spain); Dr. P. Garcia-Portilla has no declarations of conflict of interest.

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