TITLE: Assessment of cognitive impairment in psychosis spectrum disorders through self-reported and interview-based measures

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ABSTRACT

Background: Self-reported and interview-based measures can be considered coprimary measures of cognitive performance. We aimed to ascertain to what extent cognitive impairment in psychotic disorders, as assessed with a neuropsychological battery, is associated with subjective cognitive complaints (SCCs) compared to difficulties in daily activities caused by cognitive impairment.

Methods: We assessed 114 patients who had a psychotic disorder with a set of neuropsychological tests and two additional measures: the Cognitive Assessment Interview-Spanish version (CAI-Sp) and the Frankfurt Complaint Questionnaire (FCQ). Patients also underwent a clinical assessment.

Results: The CAI-Sp correlated significantly with all the clinical dimensions, while the FCQ correlated only with positive and depressive symptoms. The CAI-Sp correlated significantly with all cognitive domains, except for verbal memory and social cognition. The FCQ was associated with attention, processing speed and working memory. The combination of manic and depressive symptoms and attention, processing speed, working memory and explained 38-46% of the variance in the patients' CAI-Sp. Education and negative symptoms, in combination with attention, processing speed, and executive functions, explained 54-59% of the CAI-Sp rater's variance. Only negative symptoms explained the variance in the CAI-Sp informant scores (37-42%). Depressive symptoms with attention and working memory explained 15% of the FCQ variance.

Conclusions: The ability to detect cognitive impairment with the CAI-Sp and the FCQ opens the possibility to consider these instruments to approximate cognitive impairment in clinical settings due to their ease of application and because they are less time-consuming for clinicians.

Keywords: Psychosis, schizophrenia, cognition, self-assessment, interview-based, subjective cognitive complaints

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1. INTRODUCTION

Cognitive impairment represents a core feature of psychotic disorders. Psychotic disorders show a similar profile of cognitive impairment, presenting differences in the severity of impairment across the disorders [1]. Neuropsychological testing is the gold standard for the assessment of cognitive functioning. Moreover, in recent years, other instruments to measure cognitive deficits and their repercussions on daily functioning have gained interest as coprimary outcome measures [2]. These instruments are easy to administer and link objective testing performance and its real impact on the lives of patients [3]. The Cognitive Assessment Interview (CAI) [4] is one of these instruments. The CAI comes from two interview-based instruments, the Clinical Global Impression of Cognition in Schizophrenia (CGI-CogS) [3] and the Schizophrenia Cognition Rating Scale (SCoRS) [5]. Both instruments were included in the assessment protocols of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative, which intended to provide information about the impact of new treatments for schizophrenia on cognition and functioning [6-8]. The CAI has shown good psychometric properties, excellent internal consistency and test-retest reliability, as well as high item-to-scale correlations [4,9,10].

Subjective cognitive complaints (SCCs), or basic symptoms, are considered subtle subjective disturbances that involve a variety of cognitive complaints involving attention, perception, memory, thinking, language, movement, vegetative functions, stress tolerance and affect. They can occur in every stage of psychotic illness. Although they are rarely observable, they elicit some behaviours that may make them recognizable to others [11,12]. One of their characteristics is that they are perceived with full insight as deviations of normal mental processes.

In recent years, SCCs have gained interest because of their usefulness in the prediction of conversion to psychosis in young people at ultra-high risk (UHR) for psychosis [13,14]. It has been proposed that SCCs even precede the first attenuated psychotic symptoms that characterize the UHR stage [15,16].

There are several scales used to assess SCCs [17,18], which address them from different approaches, focusing on different aspects. However, all of these approaches have two common characteristics: the subjectivity of these experiences and their “deficit” or “anomalous” nature [19]. One of these scales is the Frankfurt Complaint Questionnaire (FCQ) [20,21]. The original scale was designed based on patients with schizophrenia complaints and had a four-factor structure: central cognitive disturbances, perception and motility, depressivity, and internal and external overstimulation. In contrast, other factorial studies have identified a unidimensional solution underlying the SCCs in the FCQ [19,22]. These instruments exhaustively evaluate SCCs and have become the most extensive instruments used to assess SCCs [23].

Our main aim was to ascertain to what extent cognitive impairment in schizophrenia spectrum disorders, as assessed with a neuropsychological battery, is associated with the subjective experiences of cognitive impairment compared to difficulties in daily activities caused by cognitive impairment. We aimed to ascertain whether patients presenting more severe clinical symptoms and cognitive impairment were able to identify subjective cognitive disturbances and the consequences in their daily activities of cognitive impairments.

2. MATERIAL AND METHODS

2.1. Participants

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In total, 114 patients with a DSM-IV psychotic disorder diagnosis were included in the study. Patients participated in two studies developed in the Department of Psychiatry of the Complejo Hospitalario de Navarra in Pamplona (Spain) between 2008 and 2011. Of these, 72 patients were recruited from consecutive admissions to the acute treatment department, and 42 patients were outpatients who were re-contacted to participate in a follow-up study. Fifty healthy controls were also included to obtain cognitive data for standardization purposes in a nonpsychiatric sample. Previous work with these samples has been already published [24-28,10,9,29].

All participants were aged 17 to 51 years, with no history of head trauma or drug dependence (except tobacco) and an IQ of over 70. Controls were also required to have no history (personal or first-degree relative) of major psychiatric illness.

The Clinical Research Ethics Committee of Navarra approved both studies, and all participants provided written informed consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.2. Procedures

Inpatients were assessed once they were clinically stabilized in two 1.5- to 2-hour sessions by a psychiatrist (LM) and a neuropsychologist (RL or AMS). We contacted outpatients by telephone and invited them to participate in the study. The assessments were distributed in two sessions.

2.2.1. Clinical assessments

We used the Comprehensive Assessment of Symptoms and History (CASH) [30] interview to collect demographic and clinical data. Five psychopathological syndrome scores were obtained for positive, disorganization, negative, and two affective (mania and depression) dimensions.

2.2.2. Cognitive Assessment Interview

The CAI [31] was used to assess the impact of cognitive impairment on daily functioning, or how real world activities are influenced by cognitive impairments. The CAI was developed for use in situations where objective cognitive assessments are not practical, to be used as a co-primary measure in clinical trials or when we want to make an assessment more related to the patient's experience [31]. It includes 10 items that assess six of the seven cognitive domains included in the MATRICS battery [32]: working memory, attention, verbal learning, reasoning and problem solving, processing speed, and social cognition. It was administered to the patient and a close relative (one or both parents or a sibling), considering the predominant functioning of the patient during the last year. These interviews resulted in two independent scores (patient and informant) and were combined by the clinician into a composite rater score. The rater score is based in the patients' and relatives' interviews and when available, other sources (e.g., medical records, or other knowledge of the patient). In 21 cases, no informant was available. Thus, the rater's score was based on the patient interview and all information available from medical records.

In the CAI, higher scores reflect poorer cognitive functioning, but we reversed the scores, so that higher scores indicate better functioning. The items are rated on a 7-point Likert-type scale. We used a Spanish version of the CAI (CAI-Sp), which was approved by the original authors [10]. The CAI has demonstrated adaptability to other countries, including Spain [33,34].

2.2.3. Neuropsychological assessments

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We chose a set of neuropsychological tests to assess each of the seven cognitive domains included in the MATRICS initiative [7,32]. Table 1 shows the tests used and the variables that composed each of the cognitive domains.

2.2.4. Frankfurt Complaint Questionnaire

The FCQ [20,19] is a self-rated questionnaire for the assessment of subjective cognitive disturbances. It consists of 98 items, each of which is rated on a 0-1 point scale, considering the presence-absence of each symptom. The total score is the sum of all the items, so higher scores indicate more subjective cognitive complaints. However, we reversed the scores to make the results more understandable, so higher scores indicated better performance.

2.3. Data analysis

We compared the demographic characteristics and cognitive scores of patients and controls with t-test (age), chi-squared test (gender) and Mann-Whitney U (years of education, verbal and visual memory, and executive function), according to their distribution.

Using the means and standard deviations of the control group, we converted all neuropsychological variables to z-scores. These z-scores were averaged to calculate each of the cognitive domains (see Table 1). To explore the reliability of the cognitive domains and the FCQ and CAI-Sp items, we used Cronbach's alpha.

Since most of the variables analysed were not normally distributed, we calculated nonparametric Spearman's correlation coefficients to explore the associations between the CAI-Sp, FCQ, cognitive domains, clinical syndrome scores and antipsychotic treatment in chlorpromazine equivalents. To assess the percentage of variance of the CAI-Sp and the FCQ total score explained by clinical and cognitive variables, we performed hierarchical regression analyses. We performed the relevant transformations to ensure that the requirements for the regression analyses were met. To determine which variables to include in the regression, we performed Spearman correlations between the CAI-Sp (patient, informant and rater) and the FCQ with age, education, clinical syndromes and cognitive domains. The variables with p-values less than 0.05 were included in the regression model.

All data analyses were performed using the statistical package IBM SPSS for Windows (version 25.0) [45]

3. RESULTS

The Cronbach's alpha results indicated moderate to high reliability for all the cognitive domains (see Table 1). CAI-Sp patients, informants and raters showed Cronbach's alpha values of 0.845, 0.916 and 0.919, respectively. Additionally, the FCQ showed high reliability, with an alpha value of 0.974.

The sociodemographic and clinical characteristics of the sample are shown in Table 2. The patient sample had a lower proportion of women than the controls (33.3% vs. 46%). Controls showed significantly higher education than patients. Regarding neuropsychological assessment, patients underperformed healthy controls in all the cognitive domains assessed. Age, verbal memory and social cognition did not show any significant association (Table 3, Supplementary material). To avoid multicollinearity between cognitive variables, we performed one analysis per cognitive function.

We transformed the independent variables (CAI scores with logarithmic transformations, and FCQ with squared root transformations) and explored the residuals of the hierarchical regressions, to ensure that they had a normal distribution. The residuals of the regression between the CAI patients score, education and clinical variables and visual memory did not have a normal distribution. Thus, we performed an ordinal regression, grouping the CAI patient scores according to the quartiles. Regarding CAI informant scores, the residuals of the

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regression analysis including visual memory as independent variable did not have neither a normal distribution, so we applied a logistic regression after dichotomizing the dependent variables by the median.

Table 4 shows the significant models obtained for each of the dependent variables (CAI-Sp patient/informant/rater scores). For CAI-Sp patient scores, the model that explained the higher percentage of variance included manic and depressive symptoms and processing speed (42.6% of the variance). Manic and depressive symptoms were significant with processing speed (46% of the variance) and working memory (43% of the variance)). Attention, in combination with depressive symptoms, explained 41% of the variance of CAI-Sp scores. Executive functions and visual memory did not show statistical significance when included in the analyses.

Regarding CAI-Sp informant scores, only negative symptoms showed significant values in the regression analyses, explaining between 37.4% and 42.2% of the variance. None of the cognitive functions were significant in the regression models.

CAI rater scores were better explained by negative symptoms and processing speed (58.5% of the variance), followed by negative symptoms and working memory (56.5%) and negative symptoms and attention (57.3%). Education entered the model with executive functions, jointly with negative symptoms (54%). Visual memory was not significant when included in the regression model.

The regression analyses with the FCQ total score as the dependent variable showed lower explained variance results than the CAI-Sp analyses. Attention was the only cognitive domain that entered the model, together with depressive symptoms, and explained 15.5% of the variance in the FCQ total score.

4. DISCUSSION

In this work, we aimed to ascertain to what extent cognitive impairment in schizophrenia spectrum disorders, as assessed with a neuropsychological battery, is associated with SCCs compared to real-world disturbances caused by cognitive impairment. SCCs were assessed with the FCQ, a self-report questionnaire, and the presence of real-world disturbances caused by cognitive impairment was assessed with the CAI-Sp, which is an interview-based instrument. Our results showed that both instruments were able to significantly identify cognitive impairment but with quantitative and qualitative differences. Cognitive impairment in combination with depressive and manic symptoms explained 33-57% of the variance in the CAI-Sp scores, whereas only 15% of the variance in the FCQ was explained by the combination of depressive symptoms with attention. Moreover, while the CAI-Sp scores were related to each cognitive function (except for verbal memory and social cognition), the FCQ scores were significantly associated with basic cognitive processes, such as attention, working memory and processing speed.

The CAI-Sp has been shown to be a valid and reliable instrument that can be used to assess cognitive functioning in the context of its impact on daily living [10]. Cognitive functioning assessed with the CAI-Sp was associated with illness severity, since we found a positive association between positive, negative, disorganized and depressive symptoms and CAI-Sp patient, informant and rater scores. Additionally, a higher presence of manic symptoms was associated with lower CAI-Sp patient scores. When clinical symptoms were combined with objective cognitive assessment in the regression analyses, we found that manic and depressive symptoms were significant when including CAI-Sp patient regression models, while mainly negative symptoms were significant in the CAI-Sp informant and rater models. These different associations can be explained considering the subjective perception of the manifestation of symptoms. Depressive and manic symptoms can lead patients to overestimate and underestimate, respectively, their cognitive difficulties [46-48]. Additionally, depressive symptoms have been associated with enhanced neurocognitive insight [49] and with self-reported cognitive performance [50]. However, the repercussion in daily activities of negative

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and positive symptoms may be more visible to caregivers and clinicians, so these symptoms may influence their appreciation of the impact of cognitive functioning in the daily lives of patients. In fact, real-life functional impairment associated with cognitive impairment reported by the informants was not significant in the regression analyses, and negative symptoms explained a high percentage of their ratings. Patient education, in combination with negative symptoms and executive functions, also explained a high percentage of the variance in the CAI-Sp rater scores. Knowledge of patients' educational levels may influence raters' expectations about their cognitive deficits and, as a consequence, about their ability to cope with these difficulties in real life.

The CAI-Sp rater scores obtained higher associations in the correlation and regression analyses than the CAI-Sp patient and informant scores. This was an expected result, since raters completed the CAI-Sp with all the information available, both the interviews of patients and caregivers and those available from medical charts and other sources. Similar results have been obtained in previous works [9,10,51].

The lack of association between the CAI-Sp and verbal memory may be because we employed a verbal learning test to assess the domain "verbal memory". However, the CAI-Sp items that refer to verbal memory consider everyday activities also related to episodic and semantic memory (e.g., memory of recent events). Social cognition, otherwise, is considered a different construct than neurocognition, although they are related [52,53], and social cognition is a mediator between neurocognition and functional outcome [54,55].

Regarding SCCs, higher rates of positive and depressive symptoms and poorer performance in attention, working memory and processing speed were associated with higher scores on the FCQ. The combination of these clinical symptoms and cognitive functions resulted in one significant regression model, including depressive symptoms and attention. Depressive symptoms may contribute to the distress caused by subjective experiences, acting as an enhancer of the effect of attention impairments on subjective cognitive complaints.

The interrelationship between cognitive deficits, SCCs, clinical symptoms and how cognitive deficits impact real-life functioning may be difficult to disentangle. Subtle subjective experiences are sometimes nonspecific but may respond to an underlying information processing deficit, as has been proposed by other authors [17]. Indeed, subjective cognitive complaints and cognitive deficits have in common that they often precede the onset of psychotic illness [56].

SCCs can be present at the early stages of psychotic illness, but they can also appear during a psychotic episode and in remitted patients. They differ from psychotic symptoms in that the latter are experienced as real, while the former are spontaneously recognized by the patient as an abnormal experience [12]. Few studies have explored the associations of SCCs and objective cognitive performance. Our group, for example, found strong associations between FCQ scores and visuospatial, working memory, processing speed and executive function measures in a sample of patients with schizophrenia [57]. Glenthoj et al. [58] reported associations between emotion recognition processing speed and basic cognitive symptoms, concluding that basic cognitive symptoms are associated with different levels of processes. However, their work focused on ultrahigh risk (UHR) patients with psychosis. Additionally, in UHR patients, Schultze-Lutter et al. [59] found modest associations between affective-dynamic disturbances, which is a cognitive basic symptom subdomain, with attention and processing speed measures. Comparelli et al.[60] assessed a sample of remitted (outpatients) and short-term patients with schizophrenia spectrum disorders. They observed associations of subjective disturbances with reasoning and problem solving, executive control and social cognition scores in the whole sample. However, when analysing both groups separately, they only found an association with reasoning and problem solving scores in the remission group. In our work, the FCQ scores were associated with attention, working memory and processing speed, which are key functions that act as resources for carrying out other high-order cognitive processes [61]. These

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associations are not only congruent with the nonspecificity of SCCs but also highlight the utility of a self-reported measure to screen for cognitive impairment in an exploratory way.

Differences between our results and those obtained in previous works could be explained by the characteristics of the samples (UHR patients vs. patients with a psychotic disorder) [12,58] and by the instruments used to measure subjective cognitive complaints and cognitive impairment [60]. As an example, Comparelli et al. used, as a sustained attention test, WCST nonperseverative errors, while we used the CPT-IP test and Digits forward and Spatial span forward subtests.

Patients with schizophrenia and related disorders are considered to underestimate their cognitive impairments and difficulties in real-life functioning, making self-assessment of these areas fallible in those disorders [62,50]. However, there are other possible explanations for the low correlations between self-reported measures and behavioural measures, such as differences in scale reliability and differences in the processes underlying the distinct measures [63,64].

Our results show that the CAI-Sp for the patient and rater are able to detect specific difficulties in daily functioning associated with cognitive deficits, except for verbal memory and social cognition, while the FCQ identifies better basic cognitive processes than those of higher complexity, such as executive functions or memory processes. One possible explanation is the capacity of patients to recognize and report subjective cognitive disturbances and to differentiate them from real cognitive impairment. The combination of depressive symptoms and cognitive performance accounts for a high percentage of the variance of the CAI-Sp reported by patients and, to a lesser extent, of subjective experiences of cognitive deficits. Thus, we may conclude that patients are able to differentiate which of their daily experiences are due to cognitive deficits and which are not.

4.1. Conclusions

In summary, the FCQ in combination with psychopathological assessment may provide the clinician an approach to the difficulties in basic cognitive processes experienced by the patients, with the advantage of being less time-consuming for the clinician, compared to the CAI-Sp, which requires two interviews of approximately 15 minutes each to be completed. Although they are not comparable in terms of the information obtained, these instruments can be added to the tools of the clinician, depending on the aims and available time. Neuropsychological testing is undoubtedly the gold standard for assessing cognitive impairment, but we may consider other instruments to approximate cognitive impairment, such as self-reported measures and interview-based scales, which may have more ecological validity and help in making clinical decisions.

4.2. Limitations

Our sample was heterogeneous regarding diagnoses due to naturalistic recruitment. Thus, our results cannot be generalized to specific diagnoses. Additionally, we mixed outpatients and inpatients, although inpatients were clinically stabilized and close to discharge.

This was a cross-sectional study, which can also be considered a limitation. Longitudinal studies are desirable to assess the stability over time of the associations found.

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Table 1. Tests and measures used to calculate the composite scores for each cognitive domain.

Cognitive domain	Test and measures used to calculate the domain's composite score	Chronbach's alpha
Attention/vigilance	Continuous Performance Test-Identical pairs [35,32]: d' scores (2, 3 and 4 digits). Digits forward (WAIS-III) [36]: direct score Spatial Span forward of the Wechsler Memory Scale-III (WMS-III) [37] : direct score	0.767
Processing speed	Digit Symbol Coding and Symbol Search subtests of the WAIS-III: direct scores Word and Word-colour parts of the Stroop test [38]: direct scores Trail Making Test (form A) [39]: time in seconds	0.851
Verbal memory	España-Complutense Verbal Learning Test (TAVEC) [40] :Short and long-term free recall and recognition scores	0.833
Visual memory	Brief Visual Memory Test-Revised (BVMT-R) [41]: direct score	---
Working memory	Digit and Spatial Span backwards tests (WAIS-III and WMS-III, respectively): direct scores Letter-number Sequencing (WAIS-III):direct score Arithmetics (WAIS-III): direct score	0.807
Executive functions	Wisconsin Card Sorting Test-64 cards computerised version (WCST-64) [42]: total number of categories, total number of errors, number of perseverative errors and number of conceptual-level responses) Hayling Test [43]: total score Semantic and phonological fluency: number of animal names and words starting with "p" produced in 1 minute, respectively	0.811
Social cognition	Managing Emotions section of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) [44]: total section score	---

Table 2. Sociodemographic and clinical characteristics of the sample.

	Patients (n=114)	**Controls (n=50)**	**Students' t / X^2 / z**
Age	35.28 (7.37)	32.72 (8.94)	n.s.
Gender (F/M)	38/76	27/23	**6.21 (p=0.013)**
Education	11.63 (3.48)	13.90 (3.11)	**-4.07 (p<0.001)***
Age at illness onset	24.90 (8.17)	-	
Years since illness onset	11.75 (7.62)	-	
Antipsychotic treatment (CPZ equivalents, mg per day)	412.64 (306.44)		
NEUROPSYCHOLOGICAL ASSESSMENT			
Attention	-0.89 (0.90)	0 (0.73)	**-6.17 (p<0.001)**
Processing speed	-1.37 (0.95)	0 (0.77)	**-8.91 (p<0.001)**
Verbal memory	-0.92 (1.19)	0 (0.86)	**-4.69 (p<0.001)***
Visual memory	-1.26 (1.46)	0 (1)	**-5.37 (p<0.001)***
Working memory	-0.77 (0.78)	0 (0.77)	**-5.82 (p<0.001)**
Executive functioning	-1.23 (1.20)	0 (0.62)	**-6.72 (p<0.001)***
Social cognition	-0.79 (0.92)	0 (1)	**-4.92 (p<0.001)**
DSM-IV DIAGNOSIS			
Schizophrenia Schizoaffective disorder Bipolar disorder Brief psychotic disorder	59 (51.8) 22 (19.3) 29 (25.4) 4 (3.5)		
PSYCHOPATHOLOGICAL DIMENSIONS			
Positive Negative Disorganization Depression Mania	2.21 (1.33) 2.11 (1.50) 1.39 (1.10) 1.79 (1.53) 0.86 (1.16)		
CAI-Sp			
CAI-Sp patient CAI-Sp informant CAI-Sp rater	16.19 (7.57) 18.17 (10.89) 21.65 (11.13)		
Frankfurt Complaint Questionnaire (FCQ)			
FCQ total score	26.56 (22.12)		

*Mann Whitney U

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Table 3. Spearman correlations between CAI-Sp, FCQ and cognitive domains and clinical syndromes.

	CAI-Sp Patient	**CAI-Sp Informant**	**CAI- Sp rater**	**FCQ total score**
SOCIODEMOGRAPHIC AND CLINICAL DATA				
Age	0.03	0.04	-0.03	0.20
Education	0.30**	0.40**	0.49**	0.14
Positive	-0.43**	-0.34**	-0.48**	-0.21*
Negative	-0.57**	-0.60**	-0.64**	-0.11
Disorganised	-0.29**	-0.25*	-0.36**	0.05
Mania	0.24*	0.08	0.18	0.13
Depression	-0.38**	-0.28*	-0.23*	-0.30**
CPZ	0.19	0.07	0.20*	0.04
COGNITIVE DOMAINS				
Attention	0.38**	0.43**	0.53**	0.27**
Processing speed	0.42**	0.34**	0.53**	0.21*
Verbal memory	0.09	0.03	0.17	-0.09
Visual memory	0.29**	0.33**	0.42**	0.09
Working memory	0.39**	0.35**	0.54**	0.22*
Executive functioning	0.28*	0.31**	0.46**	0.04
Social cognition	-0.01	0.09	0.14	-0.11

CPZ: antipsychotic treatment in chlorpromazine equivalents

* $p<0.05$

**$p<0.003$

Table 4. Hierarchical linear regression analyses

Hierarchical regression analyses	Dependent variable	Variables in the model	β (CI 95%)	p-value	Step 1 Adjusted R^2	Step 2 Adjusted R^2
1st step: Education, positive, negative, disorganized, mania and depressive symptoms 2nd step: cognitive functions (1 function per analysis)	CAI-Sp patient[a]	Depressive symptoms Attention	-0.033 (-0.053, -0.013) 0.047 (0.015, 0.079)	<0.001 0.004	0.359	0.407
		Manic symptoms Depressive symptoms Processing speed	0.035 (0.012, 0.057) -0.03 (-0.048, -0.012) 0.057 (0.027, 0.087)	0.003 0.002 <0.001	0.382	0.455
		Manic symptoms Depressive symptoms Working memory	0.032 (0.009, 0.055) -0.031 (-0.05, -0.012) 0.057 (0.017, 0.097)	0.008 0.002 0.006	0.386	0.426
		**Manic symptoms Depressive symptoms Negative symptoms Visual memory	0.427 (0.064, 0.79) -0.39 (-0.677, -0.103) -0.542 (-0.889, -0.195) -	0.021 0.008 0.002 n.s.	0.422*	0.440*
		Manic symptoms Depressive symptoms Executive functions	0.03 (0.005, 0.054) -0.031 (-0.051, -0.011) -	0.017 0.002 n.s.	0.385	0.383
1st step: Education, positive, negative, disorganized, and depressive symptoms 2nd step: cognitive functions (1 function per analysis)	CAI-Sp informant[a]	Negative symptoms Attention	-0.056 (-0.085, 0.027) -	<0.001 n.s.	0.391	0.395
		Negative symptoms Working Memory	-0.059 (-0.088, -0.03) -	<0.001 n.s.	0.413	0.422
		Negative symptoms Processing speed	-0.06 (-0.089, -0.032) -	<0.001 n.s.	0.383	0.383
		Negative symptoms Executive functions	-0.054 (-0.084, -0.025)	0.001 n.s.	0.381	0.374
1st step: Education, positive, negative, disorganized, and depressive symptoms 2nd step: cognitive functions (1 function per analysis)	CAI-Sp rater[a]	Negative symptoms Attention	-0.61 (-0.086, -0.036) 0.059 (0.025, 0.094)	<0.001 0.001	0.524	0.573
		Negative symptoms Working memory	-0.065 (-0.09, -0.04) 0.076 (0.03, 0.122)	<0.001 0.001	0.519	0.565
		Negative symptoms Processing speed	-0.068 (-0.09, -0.044) 0.07 (0.035, 0.104)	<0.001 <0.001	0.519	0.585
		Education Negative symptoms Visual memory	0.014 (0.003, 0.024) -0.069 (-0.095, -0.044) -	0.013 <0.001 n.s.	0.519	0.536
		Education Negative symptoms Executive functions	0.013 (0.003, 0.024) -0.065 (-0.091, -0.039) 0.037 (0.008, 0.067)	0.016 <0.001 0.013	0.513	0.540
1st step: Positive and depressive symptoms 2nd step: Cognitive functions (1 function per analysis)	FCQ[b]	Depressive symptoms Attention	-0.435 (-0.736, -0.134) 0.657 (0.185, 1.128)	0.005 0.007	0.092	0.155
		Depressive symptoms Processing speed	-0.413 (-0.727, -0.100) -	0.010 n.s.	0.091	0.109
		Depressive symptoms Working memory	-0.403 (-0.714, -0.092) -	0.012 n.s.	0.091	0.115

CI: Confidence interval

[a] Bonferroni correction for multiple comparisons: 0.01

[b] Bonferroni correction for multiple comparisons: 0.017

*Nagelkerke R

**Ordinal regression

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