TITLE: PREMORBID ADJUSTMENT AND CLINICAL CORRELATES OF COGNITIVE IMPAIRMENT IN FIRST-EPISODE PSYCHOSIS. THE PEPsCog STUDY.

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ABSTRACT

Background: The extent to which socio-demographic, clinical, and premorbid adjustment variables contribute to cognitive deficits in first-episode schizophrenia spectrum disorders remains to be ascertained.

Aims: To examine the pattern and magnitude of cognitive impairment in first-episode psychosis patients, the profile of impairment across psychosis subtypes and the associations with premorbid adjustment.

Methods: 226 first-episode psychosis patients and 225 healthy controls were assessed in the PEPsCog study, as part of the PEPs study.

Results: Patients showed slight to moderate cognitive impairment, verbal memory being the domain most impaired compared to controls. Broad affective spectrum patients had better premorbid IQ and outperformed the schizophrenia and other psychosis groups in executive function, and had better global cognitive function than the schizophrenia group. Adolescent premorbid adjustment together with age, gender, parental socioeconomic status, and mean daily antipsychotic doses were the factors that best explained patients' cognitive performance. General and adolescent premorbid adjustment, age and parental socioeconomic status were the best predictors of cognitive performance in controls.

Conclusions: Poorer premorbid adjustment together with socio-demographic factors and higher daily antipsychotic doses were related to a generalized cognitive impairment and to a lower premorbid intellectual reserve, suggesting neurodevelopmental impairment was present before illness onset.

KEYWORDS: Schizophrenia spectrum disorders, first episode psychosis, premorbid adjustment, cognition.

1. INTRODUCTION

Cognitive deficits are considered core features of schizophrenia spectrum disorders and, among other reasons, they are considered important for their impact on functional outcome (Green et al., 2004). FEP represents an excellent opportunity for research, because confounding factors such as hospitalization, long-term treatments and chronicity are minimized (Goldberg et al., 2010).

The cognitive profile of schizophrenia patients has been widely detailed in research, presenting a generalized cognitive impairment and specific deficits in attention, memory and learning, executive functions, working memory and processing speed (Flashman and Green, 2004; Heinrichs and Zakzanis, 1998; Reichenberg and Harvey, 2007). Regarding other psychotic disorders, research has focused primarily on the comparison between schizophrenia and psychotic affective disorders, reporting milder deficits in bipolar patients although qualitatively similar to patients with schizophrenia (Aas et al., 2014; Reichenberg et al., 2009; Schretlen et al., 2007). Schizophrenic patients also show greater effect sizes in premorbid and current intelligence quotient (IQ) at illness onset when compared to other psychosis (Zanelli et al., 2010).

Several premorbid factors, such as a lower IQ and poorer adjustment, have been associated with cognitive impairment in the early phases of psychosis. However, there is no agreement on these findings. Otherwise, premorbid IQ (van Winkel et al., 2006) as well as IQ at psychosis onset (Leeson et al., 2010; Leeson et al., 2009) have been shown to be predictors of functional outcome in the long term. These findings support the cognitive reserve theories (Barnett et al., 2006), which propose that patients with higher premorbid intellectual function have more resilience to cope with the neural damage associated with the illness, better brain structure or neural functionality compensating for the deficits.

Premorbid adjustment refers to a subject's social, interpersonal, academic and occupational functioning prior to the onset of psychotic symptoms (Addington and Addington, 2005). Poor premorbid adjustment has been related to higher rates of relapse and poorer clinical outcome (Addington and Addington, 2005; Levy et al., 2012). Neurodevelopmental disturbances are assumed to underlie poor premorbid adjustment, which represents one of the key prognostic indicators of schizophrenia (McGlashan, 2008). The relationship between premorbid adjustment and cognitive functioning has been examined in several studies. In a sample of FEP, Rund et al. (2007) found that a good premorbid level of academic functioning was associated with better verbal learning outcomes 1 year after the episode and better working memory outcomes 2 years later. A strong association has been found between poor

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childhood academic functioning and poor outcomes on working memory tests (Larsen et al., 2004).

The *"Phenotype-genotype and environmental interaction. Application of a predictive model in first psychotic episodes"* or PEPs study is a multicentre, longitudinal, naturalistic, follow-up study designed to evaluate clinical, neuropsychological, neuroimaging, biochemical and genetic variables in a sample of 335 first-episode psychosis (FEP) patients in Spain, matched with healthy controls by age, sex and socio-economic status. Patients were recruited from sixteen centres located across Spain from April 2009 to April 2011. The aim of this project was to assess clinical characteristics, functional prognostic factors, diagnostic specificity of findings, and pathophysiological changes in the brain during the first 2 years after a first psychotic episode (Bernardo et al., 2013).

The aims of the present study were to examine: 1) the pattern and magnitude of cognitive impairment in FEP patients after clinical stabilization of the acute episode; 2) the differences between psychosis subtypes and healthy control groups; 3) the relationship between premorbid adjustment abnormalities with cognitive impairment; and 4) the relative contribution of premorbid adjustment abnormalities to cognitive impairment taking account of the main socio-demographic and clinical variables.

2. METHODS

The PEPs study was composed of four modules: general, pharmacogenetics, neuroimaging and neurocognition. In the current article, we focus on the neurocognition module (hereon referred to as the PEPsCog study), so the data presented concern the participants who were included in this module.

2.1. Participants.

Patients included in the PEPs study met the following inclusion criteria: age between 7 and 35 years old, presence of psychotic symptoms of less than 12 months' duration, being fluent in Spanish and provision of written informed consent. The exclusion criteria were: mental retardation according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (APA, 1994) criteria (including both an IQ below 70 and impaired functioning), history of head trauma with loss of consciousness and organic disease with mental repercussions. The healthy control subjects were matched with the patients according to their age (±10%) and the socio-economic status (SES) of their parents ±1 level (see below). Controls also had to be fluent in Spanish and give written informed consent. The exclusion criteria for controls were the same as for the patients, plus presence of a present or past psychotic

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disorder or major depression. The study was approved by the research ethics committees of all participating clinical centres.

In the PEPs study, patients were assessed on five occasions: at recruitment (baseline), and then at two months, six months, one year and two years. Controls were only assessed at baseline and two years. Patients' cognitive assessments were performed at the two-month visit to ensure their clinical stability. The current report is based on premorbid, clinical and cognitive data gathered at baseline and two months.

Initially, 335 FEP patients and 253 controls were included in the PEPs study. The PEPsCog study included participants who completed more than one neuropsychological test (n=547; 515 adults and 32 under 16 years old participants). For the purposes of the present study, we only included the adult participants who completed seven or more of the ten neuropsychological tests of the study, which represented more than 95% of the sample. The final sample for the PEPsCog study consisted of consisted of 491 subjects: 266 patients and 225 controls.

2.2. Procedures

2.2.1. Clinical assessments

Demographic and premorbid data were collected for all participants, including age, gender, years of education, current occupation and living arrangements. Parental socioeconomic status (SES) was assessed with the Hollingshead-Redlich Index of Social Position (Hollingshead and Redlich, 1958).

Psychopathological assessment was carried out with the Positive and Negative Symptom Scale (PANSS; Kay et al., 1987; Peralta and Cuesta, 1994), the Young Mania Rating Scale (YMRS; Young et al., 1978) and the Montgomery-Asberg Depression Rating Scale (MADRS; Lobo et al., 2002; Montgomery and Asberg, 1979).

Pharmacological treatment was also recollected at each visit. Antipsychotic daily doses were converted to chlorpromazine equivalents (Gardner et al., 2010).

Diagnoses were determined with the SCID-I and II, (First, 1997a; First, 1997b) according to the DSM-IV criteria. Then patients were grouped into three diagnostic categories: 1) broad schizophrenia spectrum (BS) patients, which included schizophrenia, schizophreniform and schizoaffective disorders; 2) broad affective spectrum (BA) patients, which included bipolar disorder I and II, and manic and depressive episodes with psychotic symptoms; and 3) other psychoses (OPs), which included brief psychotic disorders, psychoses not otherwise specified and toxic psychoses.

The Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982) was applied to assess retrospectively premorbid adjustment across childhood (up to 11 years), early

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adolescence (12 to 15 years), late adolescence (16 to 18 years), and adulthood (19 years and above). Each item is rated on a 0 to 6 point scale, with 0 indicating normal adjustment and 6 indicating severe impairment. The PAS was completed based on information of the patients and parents or close relatives.

The Global Assessment of Functioning (GAF; APA, 1994) scale was used to assess the severity of symptoms and the level of functioning, on a scale from 1 to 100.

2.2.2. Cognitive assessments.

Cognitive functioning was assessed using a comprehensive battery of 10 standardized neuropsychological tests, validated in the Spanish population. It was designed to encompass 6 of the 7 cognitive dimensions proposed in the MATRICS battery (Green and Nuechterlein, 2004; Nuechterlein, 2006). Premorbid IQ and handedness were also assessed. Table 1 shows the neuropsychological tests that were administered and the measures selected for computing each domain score.

The tests were administered by experienced psychologists in two sessions of 1-1.5 hours, and were conducted sequentially in the same order from lowest to highest level of difficulty in order to reduce as much as possible the effect of fatigue and to facilitate cooperation. A good to excellent inter-rater reliability among psychologists was indicated by intraclass correlation coefficients > 0.80 in two of the tests of the battery: the WAIS Vocabulary subtest and WCST, in which the final score may partially depend on the judgment of the psychologist administering and correcting the test.

2.2.3. Data analysis

The distribution of the parametric variables (demographic, clinical and neuropsychological measures) was evaluated using measures of skewness and kurtosis. As skewness could not be totally corrected by transforming the data, we decided to use the original data.

All neuropsychological variables were then transformed into standard equivalents (z-scores). Scores for cognitive domains were calculated by averaging the z-scores of the relevant measures, listed in the previous sub-section, and then standardized against the healthy control group. Lastly, an overall cognitive performance (Global Cognitive Index, GCI) score for each group was calculated by averaging scores on the seven cognitive domains. Reliability was assessed by calculating Chronbach's alpha for all subscales scores composed of more than one score, except for the GCI. All cognitive scores were calculated such that higher values indicated better performance.

Missing data of the neurocognitive domains were analyzed with the Missing Values Analysis Module of the SPSS program (IBM Corp., 2011).

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Demographic and clinical characteristics in patients and healthy controls were compared with t-tests and chi-square tests. Correlations between demographic, clinical and cognitive variables were tested using Pearson's rank correlation coefficients. All tests were two-tailed.

Group differences in neuropsychological test performance between patients and healthy controls were explored using between-subject univariate ANOVA with effect sizes (Cohen's *d*) of group differences and Scheffe post-hoc tests. Analysis of covariance (ANCOVAs) was conducted including as covariates those socio-demographic variables in which both groups differed significantly.

Multivariate analysis of variance (MANOVA) was used to compare the profile of cognitive performance among the patient groups (BS, BA, OP), using diagnostic groups and gender as the between-group factor and the cognitive domains as the within-group factors.

A series of hierarchical regression models (using the enter method) of the score of each cognitive domain were then used to examine the association of cognitive impairment with 1) demographic characteristics (age, gender and parental SES), 2) premorbid adjustment, and 3) clinical dimensions (PANSS psychomotor poverty, disorganization and reality distortion, MAD and YMRS scores), and daily antipsychotic doses (AP), entered in that order. For the regression analyses, we only entered variables that were correlated with the cognitive domain scores with a $p \leq 0.05$ in the bivariate analyses, as well as gender if differences in the cognitive domains were found between males and females. As years of education are included in the PAS, we considered it an indicator of premorbid adjustment so we did not include it in the regression analyses. The outcome of primary interest was the incremental proportion of variance explained by each model in the hierarchical series.

All analyses were conducted using IBM SPSS Statistics for Windows (IBM Corp., 2011).

3. RESULTS

3.1. Socio-demographic and clinical characteristics

Socio-demographic and clinical characteristics are summarised in Table 2. Patients had fewer years of education, poorer psychosocial functioning as assessed by the GAF and lower parental SES than controls.

3.2. Neuropsychological results

Supplementary table 1 shows the data concerning the missing values in the neurocognitive domains. Missing values were below the 10% for each cognitive domain. Little's MCAR test (Little, 1998) was applied to analyze whether the missing data were missing completely at random. The result was not significant (Chi-Square = 106.691, DF = 87, Sig. =

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0.075), suggesting that the missing data were completely at random and no further computations should be performed. Therefore, the whole sample of patients and controls with 7 or more tests was included in the subsequent analyses.

3.2.1. Differences between patients and controls.

Years of education and parental SES differed between patients and controls so they were included as covariates in the ANCOVAs. Patients underperformed controls across all measures explored, except for the Trail Making Test B:A ratio (Table 3).

The Cronbach's alpha coefficients for the composite scores of the neuropsychological tests were as follows for patients and controls, respectively: 0.697 and 0.705 for the processing speed score, 0.730 and 0.644 for the verbal memory score, 0.846 and 0.862 for the working memory score, 0.757 and 0.704 for the executive function score and 0.933 and 0.873 for the social cognition score. All scores indicated moderate to high reliability. No significant differences were found between patients and healthy controls in the alpha coefficients of cognitive functions with the Feldt test, except in verbal memory (W=0.758, p=0.016) and social cognition (W=0.527, p=0.001) scores.

3.2.2. Neuropsychological performance of the different diagnostic groups

Comparisons across the different diagnostic groups (BS, BA and OP) in clinical, premorbid and cognitive variables are shown in the Supplementary Table 2.

Table 3 shows the results of the ANOVAs between the groups' scores on the tests, and also their composite scores for each neurocognitive domain compared to the control group. Controls showed better performance than the BS and OP groups in every test and cognitive domain, except for the Trail Making Test B:A ratio. Controls and the BA groups did not differ in CPT, Digit Span forward, the WCST measures or total score of the MSCEIT. Among the patients' groups, the BA group had better premorbid IQ and executive function scores than the BS and OP groups. In addition, the BA group performed better than the BS group in the total and perseverative errors of the WCST and the Global Cognitive Index.

Figure 1 highlights the pattern in cognitive impairment domains for each of the diagnostic groups compared to the control group, as well as the total patient sample.

MANOVA revealed main effects of diagnosis ($F = 12.76$, $p<0.001$, Wilks' $\Lambda = 0.53$) and gender ($F = 3.75$, $p=0.001$, Wilks' $\Lambda = 0.93$) on neurocognitive measures, but the interaction between these two factors was not significant ($F=1.29$, $p=0.171$, Wilks' $\Lambda = 0.93$). The same results were obtained when controlling for years of education and parental SES.

3.2.3. Associations of demographic, clinical and premorbid adjustment variables with neuropsychological performance.

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Supplementary Table 3 lists all the Pearson's correlation coefficients for the demographic variables, clinical assessments, premorbid adjustment and cognitive domains, both for patients and controls.

The results of the hierarchical linear regression analyses are shown in Table 4. In the patients' group, the model which best explained the estimated variance in premorbid IQ (19.4%) was composed of age, gender, parental SES and premorbid adjustment in late adolescence. Higher parental SES made a significant contribution to the variance in all the cognitive domains, except for verbal memory, executive function and social cognition. Being male was associated with a better performance on IQ and working memory tests, while being older was associated with better scores on premorbid IQ, attention and social cognition. Regarding clinical scales, the only significant association found was a positive correlation between scores on the PANSS reality distortion and in the verbal memory domain. In addition, higher doses of antipsychotics were related to poorer performance in processing speed, verbal memory, working memory and executive function domains, as well as a lower GCI score. Poorer premorbid adjustment scores in adolescence had an effect on premorbid IQ and the GCI. The model which explained the most estimated variance involved GCI (32%) and was composed of parental SES, premorbid adjustment in early adolescence and higher doses of antipsychotics. Additionally, we performed Pearson correlations to analyze the association between antipsychotic doses and patients' clinical severity. Total antipsychotic doses at the 2 months visit showed significant correlations with GAF scores ($r = -0.33$, $p < 0.001$), and the PANSS positive ($r = 0.17$, $p = 0.005$), negative ($r = 0.33$, $p < 0.001$) and general scores ($r = 0.19$, $p = 0.002$).

In the control group, higher parental SES was associated with higher premorbid IQ, verbal memory, working memory and the GCI scores, and being older with better attention and GCI. Regarding premorbid adjustment, an association was found between better general premorbid adjustment and higher premorbid IQ, processing speed, verbal memory and executive function scores, while late adolescent premorbid adjustment was positively associated with working memory performance. No significant associations were observed between the demographic and premorbid adjustment variables and the social cognition domain.

4. DISCUSSION

Four main findings can be highlighted from our results.

First, a slight to moderate cognitive impairment was found in the entire patient group compared to controls. Verbal memory, processing speed and premorbid IQ were the most

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impaired domains (around 1-1.5 standard deviations poorer performance than the control group), while attention was the least impaired (less than 0.5 standard deviations poorer than in the controls).

Second, the cognitive impairment profile of the three diagnostic groups revealed similar patterns of impairment compared to controls, with limited differences among them. Only the broad spectrum affective group did not differ from controls in the attention domain. Moreover, they outperformed the schizophrenia and other psychosis groups in executive function, showed higher premorbid IQ than both groups and also less global cognitive impairment than the schizophrenia group. Schizophrenia and other psychosis groups did not differ in cognitive functions or in individual tests.

Third, good premorbid adjustment was strongly related to better cognitive performance in all domains and global cognition, except in the attention domain. Low premorbid IQ was also associated with poor premorbid adjustment, except in the adult stage. In the control group, the general scale of the PAS showed the highest associations with premorbid IQ, verbal memory and global cognition. Regarding specific PAS periods, adjustment during late adolescence was related to verbal memory and global cognitive functioning.

Fourth, hierarchical multiple regression analyses showed that adolescent premorbid adjustment together with age, parental SES, gender and antipsychotic doses were the factors that best explained cognitive performance in patients, while general and adolescent premorbid adjustment, age and parental SES were related to cognitive performance in controls.

FEP patients as a whole group showed the greatest cognitive impairment in verbal memory compared to controls, and also showed slight to moderate impairment in processing speed, attention, working memory, executive function and social cognition. Poor performance in memory function in FEPs is a relatively common finding in other studies (Bilder et al., 2000; Joyce et al., 2005; Mesholam-Gately et al., 2009; O'Connor et al., 2012) and it has been proposed that poor verbal memory may be used as an endophenotypic trait (Owens et al., 2011); as a marker of conversion to psychosis in individuals at high risk (O'Connor et al., 2012; Seidman et al., 2010); and even that it may be an indicator of prefrontal-hippocampal neurodevelopmental abnormalities (Lencz et al., 2006). The magnitude and type of impairments found in this study are generally in agreement with other studies in FEP (Bilder et al., 2000; Galderisi et al., 2009; Heydebrand et al., 2004), the exception being that we found a different pattern regarding attention, the broad spectrum affective group not differing from controls in this domain. However, this result must be interpreted with caution, because we relied on only the CPT detectability score to assess attention.

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The differences found among psychosis subtypes reinforce findings previously reported (Seidman et al., 2002; Zanelli et al., 2010), and are in agreement with population studies (Koenen et al., 2009) reporting higher premorbid IQ in patients with affective psychosis than those with schizophrenia (Gilvarry et al., 2000; Toulopoulou et al., 2006) and with authors proposing that low premorbid IQ should be considered a diagnostic indicator of schizophrenia in the DSM-V (Keefe and Fenton, 2007); a risk factor for developing other neuropsychiatric disorders, such as depression and generalized anxiety disorders (Koenen et al., 2009; Martin et al., 2007; Zammit et al., 2004); and a marker of cognitive reserve (Barnett et al., 2006; Stern, 2002).

Cognitive impairment has been related to either poor psychosocial premorbid adjustment (Silverstein et al., 2002) or to poor premorbid academic functioning (Allen et al., 2005; Chang et al., 2013; Larsen et al., 2004; Norman et al., 2005). Several studies have presented evidence of neuroregressive processes such as excessive pruning or inflammation in late adolescence which may underlie the cognitive deficits seen in FEP (Howes et al., 2012; Meyer, 2013). Adolescence has been described as a high-challenge period in life, in which social and cognitive deficits come to light in subjects at risk of psychosis (Lucas et al., 2008). Thus, the different contribution of premorbid adjustment to cognitive impairment in patients and controls may be due to the neurodevelopmental disturbances associated with psychoses. Poorer premorbid adjustment was associated with a generalized cognitive impairment at illness onset and with a low premorbid intellectual reserve, suggesting neurodevelopmental impairment was present before illness onset.

Certain associations were found between cognitive performance and clinical symptoms; mainly psychomotor poverty was related to verbal memory and global cognitive functioning, while disorganization symptoms were associated with these domains and also with premorbid IQ, working memory and attention. Weaker associations were found of reality distortion with verbal memory and global cognition, on the one hand, and manic symptoms with premorbid IQ, verbal memory, and social and global cognition, on the other. An association of cognition with negative and disorganization dimensions is a common finding in literature (Cuesta and Peralta, 1995; Mohamed et al., 1999), but the results of the hierarchical regression analyses suggest relative independence of clinical and cognitive domains (Cornblatt et al., 1997; Crespo-Facorro et al., 2009; Davidson et al., 2009; Liddle, 1996; Nieuwenstein et al., 2001).

Other variables not usually considered in FEP studies, such as parental SES, age, gender and treatment, were associated with cognitive impairment in patients and controls. Higher levels of SES in the general population are linked to economic resources and environmental

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enrichment, which leads to better brain development (Jefferson et al., 2011). Likewise, higher SES at adolescence has been found to mediate between low cognitive functioning and risk for schizophrenia, suggesting that in enriched environments, cognitive impairment may reflect neurodevelopmental problems, while in low socioeconomic background it may be related to decreased opportunities (Goldberg et al., 2011). Other FEP studies have not found any significant association between parental SES and cognition (Bilder et al., 2000; Galderisi et al., 2009).

We also found better performance in working memory and a higher premorbid IQ in male patients. Research on gender differences in psychosis in recent years has found a poorer course of illness and greater functional impairment in males (Hafner and an der Heiden, 1997), but conclusions relating to cognition are controversial. Previous research concluded that female status predicted higher cognitive functioning in schizophrenia patients (Lewine, 2004) but also that males performed better than female patients in verbal and visual memory and visuospatial processing (Lewine et al., 1996). Bilder et al. (1992) reported higher premorbid IQ among males in a mixed sample of FEP and chronic schizophrenia patients. Other FEP studies have identified few differences between males and females (Hoff et al., 1998), similar to those found in the general population (Albus et al., 1997; Ayesa-Arriola et al., 2014).

Age was related to higher premorbid IQ and better social cognition in patients, and to better global cognition in controls. In our FEP sample, recruitment age was close to the onset of psychosis, so brain maturation may be more consolidated in older patients.

Higher daily doses of antipsychotics were also associated with poorer performance on processing speed, verbal memory, working memory, and executive function tests as well as global cognitive impairment and lower premorbid IQ. As our patients were clinically stable, these results may indicate that patients with more severe symptoms had greater cognitive impairment and received more antipsychotic treatment (Bilder et al., 2000). Indeed, positive association between clinical symptoms severity and higher antipsychotic doses was found. However, in the regression analyses daily doses of antipsychotics remained as an explanatory variable in 4 out of the 8 cognitive domains assessed, while only disorganization and reality distortion scores explained a small amount of the attention and verbal memory variance. Although our study was not a clinical trial, our results suggest that antipsychotic treatment was related to a worse performance in the aforementioned cognitive domains. Recent research has shown that cognitive improvement reported in drug clinical trials may be due to practice or placebo effects rather than a real effect of treatment on cognition (Goldberg et al., 2010).

Summarizing, our findings add evidence to the association of premorbid adjustment and cognition, considering other factors that have also demonstrated to be related to cognitive

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functioning such as age, gender, education, parental SES and treatment. Specifically, adolescence adjustment showed the strongest relationship with cognitive performance, reinforcing the idea that adolescence may be a critical period in the onset of psychosis.

Strengths and limitations

The PEPsCog study has several strengths. First, the sample recruited can be considered representative of Spanish psychiatric admissions for acute psychosis. Second, the sample is large enough to ensure the generalizability of the results. Moreover, we had extensive data on a large sample of healthy controls, matched with the patients by socio-demographic characteristics, an element that has been missing in other studies (Heydebrand et al., 2004; Rund et al., 2004; Townsend et al., 2001). Third, we included a large group of patients with "other psychoses", which represents a pool of patients that are often excluded from first-episode psychosis studies (Addington et al., 2003; Galderisi et al., 2009; Heydebrand et al., 2004; Rund et al., 2004). And fourth, the broad neuropsychological battery used in the assessments enabled us to obtain a comprehensive cognitive profile of patients and controls.

Findings from this study must, however, be viewed within the context of its limitations. First, even though there are studies reporting high FEP diagnosis stability for schizophrenia and bipolar disorders at 24 months or more in research settings (Schimmelmann et al., 2005; Schwartz et al., 2000), diagnoses of other psychoses have been observed to be highly unstable over time (Amini et al., 2005; Komuravelli et al., 2011; Whitty et al., 2005). On the other hand, we will be able to confirm the diagnosis because our patients are being reassessed longitudinally in 2 years as part of the ongoing PEPs study.

Longitudinal assessments may also help to clarify the relationships between cognitive impairment, antipsychotic doses and clinical symptoms.

In addition, while premorbid adjustment is a strong predictor of cognitive impairment and illness course (Ruggero et al., 2010), caution is warranted in attributing causalities since premorbid adjustment is a final common pathway for the interplay between genetic and environmental agents that may be ethiopathogenetically related to psychosis or only act as risk factors for developing psychosis or general impairment in functioning.

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Figure 1. Patterns of cognitive impairment for each of the diagnostic groups and the total patient sample, compared to controls.

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Appendix 1.

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Conflict of interest

None.

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Contributors

The PEPsCog study is part of a broader project, the PEPs study. Miguel Bernardo is the coordinator of the PEPs study. Manuel J. Cuesta is the coordinator of the cognition's module (PEPsCog). Both of them designed the cognition's module. Ana M. Sánchez-Torres, Bibiana Cabrera and Miquel Bioque participated in the development of the cognitive protocols, the recruitment of the sample and the participant's assessment. Iluminada Corripio, Ana González-Pinto, Antonio Lobo, Julio Sanjuan, Mara Parellada, and Jerónimo Saiz-Ruiz are the principal investigators of their research centres. Mara Parellada, Jerónimo Saiz-Ruiz and Miguel Bernardo also are coordinators of other modules of the PEPs study. Jessica Merchán-Naranjo, Igor Bombín and Elena de la Serna participated in the recruitment and assessment of the sample. Ana M. Sánchez-Torres managed the literature searches and data analyses. Manuel J. Cuesta wrote the first draft of the manuscript. All the authors, including the PEPs group authors listed in the Appendix 1, contributed to the final draft of the manuscript.

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Table(s)

Table 1. Neuropsychological tests used in the PEPsCog

Cognitive domain	Type of test	Description of test and measures used for domain summary scores
Laterality	Edinburgh Handedness Inventory (Oldfield, 1971)	Indicate your preferences in the use of hands in a range of activities. Measure: Total score
Premorbid IQ	Wechsler Adult Intelligence Scale-III, Vocabulary Test (Wechsler, 1999)	Give oral definitions for words. Measure: direct score and standardized score. Estimated premorbid IQ is calculated from the standardized score: (SS x 5) + 50
Attention	Continuous Performance Test-II (CPT; Conners, 2000)	Respond to a series of letters on a computer screen by pressing a key when you detect letters other than the letter "X". The assessment contains six blocks that vary in the rate of submission of the letters. Measure: Mean response sensitivity (D-prime).
Processing Speed	Trail Making Test (Form A) (Reitan and Wolfson, 1993)	Connect, by making pencil lines, 25 encircled numbers randomly arranged on a page in proper order. Measure: Time to complete this (form A)
	Stroop Test, Word-Colour (Golden, 1978)	Read the words and the colors of a series of XXXX as quickly as possible in 45 s. Measure: Number of items completed
Executive Function	Wisconsin Card Sorting Test, (WCST-128; Heaton et al., 1993)	Complete a complex task of categorization set shifting, and respond to feedback from the computer. Measure: Number of completed categories and percentage of conceptual responses, total errors and perseverative errors.
	Trail Making Test (Form B)(Reitan and Wolfson, 1993)	Draw lines connecting characters that are sequentially alternating between numbers and letters. Measure: Time to complete this (form B), B/A ratio (time to complete form B divided by time to complete form A).
	Stroop Test, Color-Word Interference effect (Golden, 1978)	Name the colour in which the colour names are printed and disregard their verbal content. Measure: Interference index (WC- WxC/W+C)
	Controlled Oral Word Association Test, FAS-Test (Loonstra et al., 2001)	Generate as many words as possible beginning with F, A and S in three separate trials of 60 s. Measure: The sum of all correct responses
	Test Barcelona, Animal Words (Peña-Casanova, 1990)	Produce as many animal names as possible in a one-minute interval. Measure: Number of correct responses
Working Memory	Wechsler Adult Intelligence Scale-III, Digit Span Test (Wechsler, 1999)	Repeat a number sequence in the same and reverse order as presented. Measure: total number of series correctly repeated forward, backwards and the sum of both.
	Wechsler Adult Intelligence Scale-III, Letter-Number Sequencing (Wechsler, 1999)	Listen to a combination of numbers and letters read aloud by the tester and reorganize the sequence listing first the numbers in ascending order and then the letters in alphabetical order. Measure: number of correct sequences.
Verbal Memory	California Verbal Learning Test, Spanish version (TAVEC)(Benedet and Alejandre, 1998)	Recall as many words as possible from a list of 16 words read aloud by the tester. The procedure is repeated five times, and recall is tested immediately and after a delay. Measure: total number of words recalled after the five trials, immediately and delayed.
Social cognition	Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT; Mayer et al., 2009)	Rate the helpfulness of certain moods and assess the effectiveness of strategies to manage emotions. Measure: Understanding emotions, managing emotions and total emotional intelligence scores.

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Table 2. Demographic and clinical characteristics of the sample

	Adults 16 or over (n=491)		
	Patients (n=266)	**Healthy controls (n=225)**	***t* or X^2 *(p)***
Age (years)	24.22 (5.56)	25.08 (5.92)	-1.66 (0.097)
Gender (male/female)	177/89	142/83	0.63 (0.427)
Years of education	12.57 (3.45)	14.61 (3.21)	**-6.61 (<0.001)***
GAF (baseline)	63.49 (14.28)	92.83 (5.56)	**-30.38 (<0.001)***
Handedness (% right/left/mixed)	87.6/8.6/3.8	86.5/9.4/4	0.12 (0.942)
Marital status			
Single	229 (86.1)	187 (83.1)	
Married	20 (7.5)	20 (8.9)	-1.11 (0.775)
Divorced	4 (1.5)	3 (1.3)	
Cohabitation >6 months	13 (4.9)	15 (6.7)	
Parental socioeconomic status (H-R scale)			
High	53 (19.9)	52 (21.8)	
Medium-high	27 (10.2)	46 (19.2)	
Medium	67 (25.2)	71 (29.7)	**19.69 (0.001)***
Medium-low	84 (31.6)	58 (24.3)	
Low	31 (11.7)	9 (3.8)	
Unknown	4 (1.5)	2 (0.8)	
	PATIENTS' SAMPLE (N=266)		
Clinical Ratings	**Baseline**	**2 months**	
PANSS			
Positive Syndrome	18.15 (7.96)	11.45 (5.05)	
Negative Syndrome	18.48 (8.02)	16.42 (6.63)	
General psychopathology	37.23 (12.46)	29.40 (9.85)	
Total	73.86 (23.94)	57.27 (19.22)	
MADS	12.37 (9.76)	10.07 (7.9)	
YRMS	8.65 (10.11)	2.63 (4.52)	
AP treatment (chlorpromazine equivalents)	547.82 (457.35)	431.23 (350.38)	

GAF: Global Assessment of Functioning Scale; H-R: Hollingshead-Redlich scale; PANSS: Positive and Negative Syndrome Scale; MADS: Montgomery-Asberg Depression Scale; YMRS: Young Rating Mania Scale; AP: Daily doses of antipsychotic treatment

Table 3. Raw scores (means and standard deviations) and ANCOVA results comparing the neuropsychological test scores in patients and controls and ANOVA results comparing the three diagnostic groups and controls.

	Patients (n=266)	Controls (n=225)	†Cohens d'	ANCOVA* F(p)	ANOVA F(p)**	d.f.	
Premorbid IQ	92.46(15.21)	106.7(13.86)	**-0.98**	**74.26(<0.001)**	**42.69(p<0.001)**	3, 489	C > Sch, AffPsy, OP AffPsy>Sch, OP
Processing speed					**47.52(p<0.001)**	3, 481	C > Sch, AffPsy, OP
TMT-A	41.06(19.19)	28.1(10.61)	**-0.87**	**56.78(<0.001)**	**28.05(p<0.001)**	3, 491	C > Sch, AffPsy, OP
Stroop-Word	96.01(20.53)	110.5(17.77)	**-0.76**	**48.86(<0.001)**	**23.28(p<0.001)**	3, 482	C > Sch, AffPsy, OP
Stroop-Color	62.83(14.34)	77.38(14.2)	**-1.02**	**88.18(<0.001)**	**40.43(p<0.001)**	3, 481	C > Sch, AffPsy, OP
CPT-II Detectability /Attention	0.66(0.52)	0.93(0.58)	**-0.49**	**14.38(<0.001)**	**8.53(p<0.001)**	3, 447	C > Sch, OP
Verbal memory					**59.65(p<0.001)**	3, 480	C > Sch, AffPsy, OP
TAVEC-Total recall	46.37 (11.47)	59.66(9.25)	**-1.28**	**140.26(<0.001)**	**58.64(p<0.001)**	3, 483	C > Sch, AffPsy, OP
TAVEC-Short-term recall	9.59(3.55)	13.09(2.64)	**-1.13**	**102.18(<0.001)**	**46.07(p<0.001)**	3, 485	C > Sch, AffPsy, OP
TAVEC-Long-term recall	10.03(3.46)	13.58(2.48)	**-1.20**	**113.04(<0.001)**	**51.88(p<0.001)**	3, 484	C > Sch, AffPsy, OP
Working memory					**33.57(p<0.001)**	3, 490	C > Sch, AffPsy, OP
Digit span forward	8.54(1.83)	9.6(2.18)	**-0.53**	**14.22(<0.001)**	**12.24(p<0.001)**	3, 491	C > Sch, OP
Digit span backward	5.63(1.97)	7.29(2.08)	**-0.82**	**47.98(<0.001)**	**26.82(p<0.001)**	3, 491	C > Sch, AffPsy, OP
Digit span total score	14.15(3.19)	16.89(3.72)	**-0.79**	**40.86(<0.001)**	**25.55(p<0.001)**	3, 491	C > Sch, AffPsy, OP
Letter and number sequencing	8.81(2.81)	11.31(2.63)	**-0.92**	**59.41(<0.001)**	**34.22(p<0.001)**	3, 490	C > Sch, AffPsy, OP
Executive function					**41.91(p<0.001)**	3, 445	C > Sch, AffPsy, OP AffPsy > Sch, OP
FAS	28.09(9.33)	38.71(10.24)	**-1.09**	**91.25(<0.001)**	**46.87(p<0.001)**	3, 477	C > Sch, AffPsy, OP
Semantic ("animals")	16.86(4.69)	22.7 (5.79)	**-1.12**	**103.44(<0.001)**	**52(p<0.001)**	3, 481	C > Sch, AffPsy, OP
TMT-B	93.24(45.33)	58.70(22.98)	**-1.01**	**69.31(<0.001)**	**34.29(p<0.001)**	3, 489	C > Sch, AffPsy, OP
TMT B:A	2.45(1.06)	2.23(0.79)	-0.24	3.59(0.059)	**4.04(p=0.007)**	3, 489	C > AffPsy
WCST-Categories	4.73(1.81)	5.63(1.1)	**-0.62**	**23.47(<0.001)**	**16.66(p<0.001)**	3, 464	C, AffPsy > Sch, OP
WCST-Total errors (%)	31.47(16.64)	19.54(11.78)	**-0.84**	**47.91(<0.001)**	**27.46(p<0.001)**	3, 464	C > Sch, OP AffPsy > Sch
WCST-Perseverative errors (%)	16.89(11.51)	10.57(7.01)	**-0.68**	**29.47(<0.001)**	**17.96(p<0.001)**	3, 465	C > Sch, OP AffPsy > Sch
WCST-Conceptual level responses (%)	58.57(22.74)	73.43(15.93)	**-0.77**	**38.20(<0.001)**	**21.72(p<0.001)**	3, 462	C > Sch, OP
Stroop-Interference	2.18(8.88)	6.19(8.44)	**-0.46**	**15.53(<0.001)**	**10.63(p<0.001)**	3, 481	C > Sch, OP
Social cognition					**25.74(p<0.001)**	3, 453	C > Sch, AffPsy, OP
MSCEIT-Understand	94.71(13.21)	105.48(15.28)	**-0.76**	**48.37(<0.001)**	**21.76(p<0.001)**	3, 453	C > Sch, AffPsy, OP
MSCEIT -Managing	91.82(11.28)	99.33(10.36)	**-0.69**	**39.16(<0.001)**	**19.25(p<0.001)**	3, 453	C > Sch, AffPsy, OP
MSCEIT -Total	92.67(12.44)	99.76(16.73)	**-0.49**	**18.64(<0.001)**	**10.05(p<0.001)**	3, 467	C > Sch, OP
Global cognitive index					**95.04(p<0.001)**	3, 385	C > Sch, OP, AffPsy AffPsy > Sch

* Years of education and parental socioeconomic status as covariates. ** ANOVAs of the three diagnostic groups and healthy controls.
† Effect sizes are calculated such that negative values indicate poorer performance in patients.
C: control; Sch: schizophrenia/schizophreniform/schizoaffective; AffPsy: affective psychoses; OP: other psychoses
TMT: Trail Making Test; CPT: Continuous Performance Test; TAVEC: Test de Aprendizaje Verbal España-Complutense; WCST: Wisconsin Card Sorting Test; MSCEIT: Mayer-Salovey-Caruso Emotional Intelligence Test

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Table 4. Hierarchical regression models of cognitive performance and sociodemographic characteristics, premorbid adjustment, clinical dimensions and daily antipsychotic doses.

		Variables in the model	β	t	R^2 adjusted	p
Estimated premorbid IQ	**Patients**	Age	0.23	3.74	0.194	<0.001
		Gender	0.18	3		0.003
		Parental SES	-0.20	-3.31		0.001
		PAS late adolescence	-0.21	-1.96		0.052
	Controls	Parental SES	-0.21	-3.10	0.086	0.002
		PAS General	-0.21	-3.13		0.002
Processing speed	**Patients**	Parental SES	-0.24	-3.81	0.206	<0.001
		AP	-0.29	-4.5		<0.001
	Controls	PAS General	-0.15	-2.13	0.016	0.034
Attention	**Patients**	Age	0.14	2.11	0.025	0.036
		Parental SES	-0.15	-2.21		0.029
	Controls	Age	0.19	2.74	0.031	0.007
Verbal memory	**Patients**	PANSS Reality distortion	0.19	2	0.166	0.047
		AP	-0.26	-3.82		<0.001
	Controls	Parental SES	-0.16	-2.37	0.062	0.019
		PAS General	-0.15	-2.17		0.032
Working memory	**Patients**	Parental SES	-0.24	-3.94	0.159	<0.001
		Gender	0.21	3.45		0.001
		AP	-0.14	-2.33		0.021
	Controls	Parental SES	-0.14	-2.02	0.082	0.044
		PAS late adolescence	-0.30	-3.36		0.001
Executive functions	**Patients**	AP	-0.19	-2.76	0.116	0.006
	Controls	PAS General	-0.20	-2.59	0.032	0.010
Social cognition	**Patients**	Age	0.24	3.32	0.091	0.001
GCI	**Patients**	Parental SES	-0.23	-3.53	0.320	0.001
		PAS early adolescence	-0.37	-2.58		0.011
		AP	-0.26	-3.76		<0.001
	Controls	Age	0.19	2.55	0.141	0.012
		Parental SES	-0.21	-2.84		0.005

SES: socioeconomic status; PANSS: Positive and Negative Syndrome Scale; AP: Daily doses of antipsychotic treatment; GCI: Global Cognitive Index

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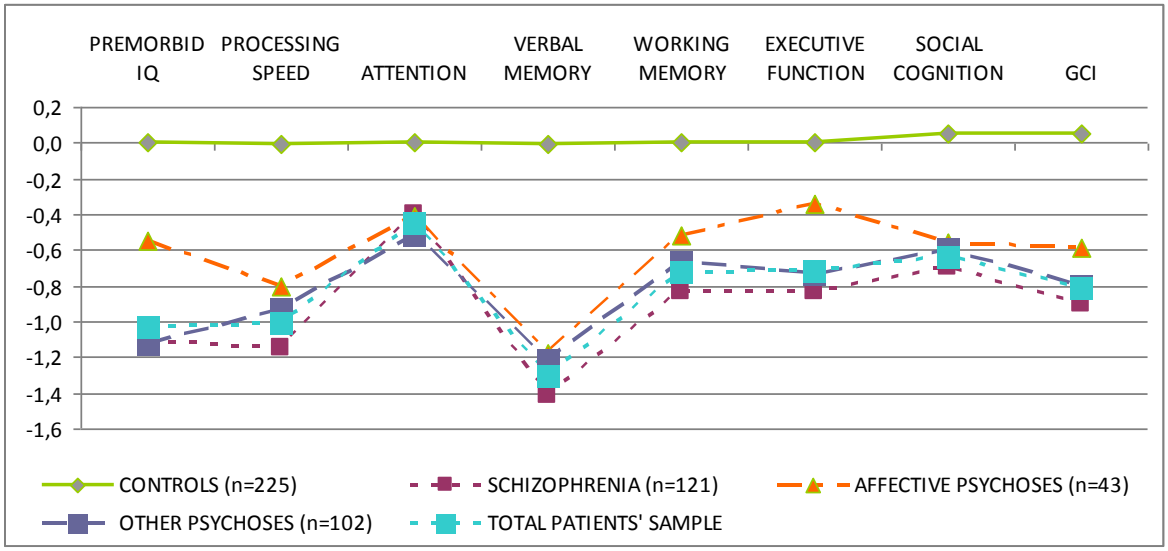
Figure(s)

Figure 1. Patterns of cognitive impairment for each of the diagnostic groups and the total patient sample, compared to controls.



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