Cognitive reserve as a predictor of two year neuropsychological performance in early onset first-episode schizophrenia

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A B S T R A C T

Introduction: The concept of cognitive reserve (CR) has been defined as individual differences in the efficient utilization of brain networks which allow some people to cope better than others with brain pathology. CR has been developed mainly in the field of aging and dementia after it was observed that there appears to be no direct relationship between the degree of brain pathology and the severity of clinical manifestations of this damage. The present study applies the concept of CR to a sample of children and adolescents with a first episode of schizophrenia, aiming to assess the possible influence of CR on neuropsychological performance after two year follow-up, controlling for the influence of clinical psychopathology.

Methods: 35 patients meeting DSM-IV criteria for schizophrenia or schizoaffective disorder (SSD) and 98 healthy controls (HC) matched for age and gender were included. CR was assessed at baseline, taking into account premorbid IQ, educational–occupational level and leisure activities. Clinical and neuropsychological assessments were completed by all patients at two year follow-up.

Results: The CR proxy was able to predict working memory and attention at two year follow-up. Verbal memory and cognitive flexibility were not predicted by any of the variables included in the regression model. The SSD group obtained lower scores than HC on CR. CR measures correctly classified 79.8% of the sample as being SSD or HC.

Conclusions: Lower scores on CR were observed in SSD than in HC and the CR measure correctly classified a high percentage of the sample into the two groups. CR may predict SSD performance on working memory and attention tasks.

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1. Introduction

The concept of cognitive reserve (CR) has developed in the field of aging and dementia after it was observed that people with the same amount of brain damage could show different clinical expressions depending on their compensatory capacity. CR has been defined as “individual differences in how people process tasks which allow some to cope better than others with brain pathology” (Stern, 2009). This concept is focused on the ability to optimize performance based on more efficient brain network utilization, and may vary depending on environment and lifetime exposure to certain environmental factors.

Although it has been used primarily in the fields of dementia and brain injury, this concept could potentially be applicable to a whole range of neurological and psychiatric conditions. For example, CR could play an important role in the expression of symptoms and functional outcome of schizophrenia patients (Barnett et al., 2006). Studies have shown that patients with schizophrenia with better performance on cognitive tests have better social and functional outcomes (Green et al., 2000; Munro et al., 2002). Holthausen et al. (2002) studied a...
sample of 118 first episode of psychosis patients and classified them according to the presence or absence of cognitive deficits. Results showed that patients with normal cognitive functioning had higher scores on IQ measures and higher educational levels than patients with cognitive difficulties. The authors suggested that the observed differences may have been due to the higher compensation capacity or higher CR of the group with normal cognitive functioning.

An important caveat when investigating CR is the absence of any single measure of this concept. Variables such as occupational and educational attainment, leisure activity and IQ have been used as CR proxies (Stern, 2009). Staff et al. (2004) tested three possible CR proxies (head size, education and occupational attainment) and observed that while education and occupational attainment contributed to CR, intracranial volume did not. There is no consensus as to which CR measures (premorbid IQ, education, occupation or leisure activities) could be the most representative. In the present study, CR was measured with the main CR proxies used in previous literature (i.e. Scarmeas and Stern, 2003; Stern et al., 2005), premorbid IQ, which is thought to partially reflect an ‘innate reserve capacity’, and educational–occupational attainment and leisure activity, which more directly reflect lifetime exposure to particular environmental factors that help develop mental capacities.

Studies in child and adolescent samples with a first episode of schizophrenia have observed a broad range of neuropsychological difficulties in cognitive domains such as attention, working memory, executive function, verbal learning and memory (Kenny et al., 1997; Fagerlund et al., 2006; Mayoral et al., 2008; Zabala et al., 2010). Most of these deficits have been associated in young adults with premorbid functioning and educational and occupational levels (Silverstein et al., 2002; Norman et al., 2005; Rund et al., 2007), which are considered part of CR. However, studies in young patients have also observed that clinical manifestations such as negative symptoms play an important role in neuropsychological performance (Bilder et al., 2000; Fitzgerald et al., 2004). Taking this previous research into account, the aim of the present study was, first, to employ the concept of CR with a sample of children and adolescents with a first episode of schizophrenia in order to compare them to control subjects. The second aim was to assess the influence of CR on neuropsychological performance after a two year follow-up of schizophrenia patients while controlling for the influence of clinical psychopathology.

We hypothesized that the schizophrenia spectrum disorder group (SSD) would show lower CR measures than healthy controls (HC). Moreover, we expected that neuropsychological variables after two years could be predicted by baseline CR measures.

2. Methods

This research was part of the Child and Adolescent First-episode Psychosis study (CAFEPS), a multi-center, longitudinal study aimed at evaluating different clinical, neuropsychological and biological factors, as well as treatment and prognostic factors in these patients; the corresponding methodology has been described previously in detail (Castro-Fornieles et al., 2007). The CAFEPS study included 110 patients aged between 9 and 17 years diagnosed with a first episode of psychosis, and 98 matched healthy controls. Patients were recruited from child and adolescent psychiatry units at six university hospitals and assessed by mental health professionals with experience diagnosing and evaluating subjects with semi-structured interviews and clinical scales. Inclusion criteria for patients were: a) onset of psychosis symptoms less than 6 months prior to baseline assessment and b) age between 7 and 17 years. Exclusion criteria included: a) presence of another concomitant Axis I disorder at the time of assessment that could account for the psychotic symptoms, including substance-induced psychotic disorder, post-traumatic stress disorder, or acute stress disorder; b) IQ below 70 with impaired functioning; c) pervasive developmental disorder d) neurological disorders, including history of head trauma with loss of consciousness; and e) pregnancy. Occasional and regular substance use was not an exclusion criterion if positive symptoms persisted for more than two weeks after a negative urine toxicology test and a substance-induced psychotic disorder was not diagnosed. Socioeconomic status of the whole sample was estimated with the Hollingshead Redlich Scale (Hollingshead and Redlich, 1958).

The healthy control group was matched by age and gender to patients. Sample recruitment and description of both patients and healthy controls have been detailed previously (Castro-Fornieles et al., 2007). The study was approved by the Ethical Review Board of each hospital. All patients and controls and their parents or legal guardians provided written informed consent.

2.1. Subjects

Patients were given clinical and CR assessments at baseline and neuropsychological assessments at two year follow-up. To homogenize the sample and guarantee the stability of the diagnosis, only subjects diagnosed with schizophrenia or schizoaffective disorder (SSD) at the two-year follow-up were included in the study. This group comprised only 35 patients from the total CAFEPS sample. A healthy control group (HC) of 98 subjects matched for age and gender was also recruited.

2.2. Clinical assessment

Clinical assessment at baseline consisted of:
- Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL) (Kaufman et al., 1997) using the Spanish validated adaptation; This is a semi-structured interview, which was administered by psychiatrists trained in the use of the instrument and in the assessment of children and adolescents. Parents and children from both the patients group and control group were interviewed separately.
- Positive and Negative Syndrome Scale (PANSS): This is a 30 item rating scale which aims to assess the symptom severity of patients with psychosis. It is subdivided into three subscales-positive, negative and general psychopathology- and a total score (Kay et al., 1987; Peralta and Cuesta, 1994). Each subscale is evaluated from 1 to 7 according to the severity of the symptoms.

2.3. Assessment of cognitive reserve

Our determination of the main proxies of CR was based on recent literature in the field, with special consideration given to the areas most commonly included in cognitive reserve questionnaires (Bartres-Faz et al., 2009; Sole-Padulles et al., 2009; Bosch et al., 2010). As a result, the CR measure was composed of an estimation of premorbid IQ and a measure of education–occupation levels and lifetime leisure-social activities.

- Premorbid IQ was assessed between 4 and 8 weeks after admission when patients had reached clinical stability. Premorbid IQ was estimated using the Vocabulary subtest of the Wechsler Adult Intelligence Scale—III Revised (WAIS III) (Wechsler, 2001) or the Wechsler Intelligence Scale for Children—Revised (WISC-R) (Wechsler, 1974), depending on the subject’s age. Direct scores of the sub-scale were translated to standard scores, which have a mean of 10 and a standard deviation of 3.

- Education–occupation (EO). Education–occupation was assessed taking into account the number of years of obligatory education that subjects had completed, school performance before the beginning of the disorder, parents’ educational level and questions about the children’s development in terms of language, reading, writing and motor functions. EO could have values between 0 (low level of CR) and 33 (high CR).
- Lifetime leisure and social activities (LS) were assessed by asking the parents about the intellectual pursuits, hobbies, peer relationships and sociability of their children. LS could have scores between 0 (low level of CR) and 30 (high level of CR).

A composite CR score which included premorbid IQ, educational-occupational and leisure activities was obtained for each subject using a Confirmatory factor analysis.

2.4. Neuropsychological assessment

Cognitive assessment was performed at two-year follow-up. All direct scores were standardized and transformed into Z scores, which have a mean of 0 and a standard deviation of 1 based on the performance of the control group at baseline. The cognitive domains assessed were working memory, attention, verbal memory and cognitive flexibility, which have been considered as separable cognitive factors in previous studies (Nuechterlein et al., 2004).

- The working memory domain included the scores obtained on digiscs forward, digits backward and Letter–Number Sequencing of the Wechsler Adult Intelligence Scale—III—Revised (WAIS III) (Wechsler, 2001) and the Trail Making Test part B (Reitan and Wolfson, 1985). In Digits forward the subject must repeat a series of numbers in the same order as has been read by the examiner. The second task requires the subject to say in reverse order the digits that have been read by the examiner. In the Letter–number sequencing task, the examiner reads a list of letters and numbers and asks the subject to say first the numbers, lowest to highest, and then the letters, in alphabetical order. In the Trail Making Test part B (TMT-B) subjects have to draw lines connecting, in alternating order, numbers (from low to high) and letters (in alphabetical order) in the shortest possible time. Time required to complete the task was used as a measure of working memory.

- The attention domain included the TMT-A (Reitan and Wolfson, 1985), and the Continuous Performance Test (CPT (Conners, 2000). In the first task the subject is given a sheet of paper with the numbers 1 through 25 on it, and is instructed to draw lines connecting the numbers as quickly as possible. The time taken to complete the task is recorded. In the CPT test, the subject is required to press the space bar every time any letter other than X appears on the computer screen. When an X appears, the subject must inhibit his/her response. Reaction time and correct responses were used in the statistical analysis.

- The verbal memory and learning domain was assessed with the TAVEC (Verbal Learning Test-Complutense Spain), the Spanish adaptation of the California Verbal Learning Test (CVLT), which provides a learning curve and immediate and delayed memory scores (Benedet and Alejandre, 1998).

- Lastly, the cognitive flexibility domain included the number of mistakes, perseverative errors and perseverations on the Wisconsin Card Sorting Test (WCST) (Heaton et al., 1997) and the interference part of the Stroop test (Golden, 1978). The WCST is a measure of executive function that requires planning strategies and cognitive flexibility in order to change the use of learned strategies. The interference part of the Stroop test measures the subject’s ability to inhibit an automatic predominant response.

2.5. Statistical analysis

Categorical socio-demographic variables were analyzed using the Pearson’s chi-square test, whereas continuous variables were compared between the two groups using the Student’s t test.

To test the normality of the sample distribution, the Kolmogorov–Smirnov test was used, together with the Levene test to assess the equality of variances.

Firstly, in order to confirm the factorial structure of CR and the architecture of cognitive domains, two confirmatory factor analysis (CFA) were performed in the control sample. Both analysis were conducted using EQS 6.1 with the asymptotic free distribution method for the analysis of CR and with maximum likelihood estimation with robust estimation for the cognitive domains analysis. Six different goodness-of-fit statistics were used to assess the fit between the hypothesized models and the data, including χ², the χ²/df ratio, the Akaike Information Criterion (AIC), Bentler–Bonett Normed Fit Index (BBNFI) and Root Mean-Square Error of Approximation (RMSEA).

Secondly, we aimed to test the predictive capacity of CR for each diagnostic group (SSD or HC), so a logistic regression analysis (enter-method), was performed.

Finally, to assess the predictive value of CR on cognitive domains at two-year follow-up, a linear regression analysis was performed in the SSD group with CR as a potential predictor. To test whether our CR proxy was a better predictor of cognitive functions than premorbid IQ, a new linear regression was conducted with premorbid IQ as a predictor. Taking into account the influence of clinical variables on cognitive performance (Basso et al., 1998; Bilder et al., 2000; Fitzgerald et al., 2004; Good et al., 2004), total scores of PANSS were also included in both regression models. All analysis were performed using SPSS 18.0 and significance was set at the p<0.05 level.

3. Results

3.1. Socio-demographic characteristics of the sample

No significant differences were found between SSD and healthy controls in age, gender or parental socioeconomic status. Table 1 shows socio-demographic characteristics of the sample.

3.2. Confirmatory factor analysis of CR

The CFA of CR was based on data from 98 healthy controls. We hypothesized the existence of a three factor structure for CR which includes: premorbid IQ (F1), Education–Occupation (F2) and Lifetime leisure activities (F3). The values obtained on the goodness-of-fit statistics indicate a good fit between the model and the observed data. Thus, the CFA confirm the presence of a three factor structure of CR in our sample. The correlation between latent variables showed significant results specifically for rF1F2 = 0.920 (p<0.001) and rF2F3 = 0.592 (p<0.001). No other correlation was significant.

Tables 2 and 3 summarize the goodness-of-fit index and the results of confirmatory factor analysis of CR.

3.3. Confirmatory factor analysis of cognitive domains

As in CR, the CFA of cognitive domains was performed with the results of the cognitive assessment of 98 healthy controls. The CFA showed the presence of four factors, namely: working memory (F1), attention (F2), verbal memory (F3) and cognitive flexibility (F4). The values obtained on the goodness-of-fit statistics indicated a good fit between the model and the observed data. The correlation between

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significant $\chi^2 (1, N = 133) = 29.15, p > 0.001$ indicating that it was able to distinguish between SSD patients and HC. The model as a whole explained between 21.7% (Cox and Snell R square) and 31.8% (Nagelkerke R squared) of the variance and correctly classified 79.8% of the cases ($B = -0.152; p < 0.001$; Exp (B) = 0.859; CI 95% = 0.804–0.917). The specificity (percentage of the group without the characteristic of interest) of the model was 92.1% and the sensitivity (percentage of the group that has the characteristic of interest) was 58.1%. The positive predictive value of the model was 75%.

### 3.5. Predictive value of CR on cognitive domains

The linear regression analysis to test the predictive capacity of CR on cognitive domains was based on results obtained in patients two years after onset of illness. To assess the effects of clinical variables on neuropsychological performance at two year follow-up, total score of PANSS at baseline was included in the regression analysis. CR predicted the performance at two year follow-up of the SSD subjects on working memory and attention. Verbal memory and cognitive flexibility, however, were not predicted by any of the variables included in the regression model.

To test whether premorbid IQ had greater predictive value than global CR, a new linear regression was conducted with premorbid IQ and total score of PANSS at baseline as potential predictors. Only working memory at two-year follow-up was predicted by the premorbid IQ. However, premorbid IQ and total score of PANSS explained 26.7% of the variance of working memory whereas CR and total score of PANSS explained 40.30%. Table 5 shows the results of linear regressions in cognitive domains.

### 4. Discussion

The main finding of the present study is that our proxy of CR based on premorbid IQ, educational–occupational level and leisure and social activities, was able to predict some cognitive domains such as working memory and attention at two year follow-up. Moreover, SSD patients were shown to have lower scores than control subjects in CR and the CR proxy correctly classified 79.8% of the sample as SSD or HC.

The concept of CR has previously been used in dementia research to help explain the compensatory capacity that some individuals exhibit in terms of their ability to minimize the clinical impact of acquired brain pathology. In this regard, environmental and lifetime factors such as educational level, occupation, leisure activities and premorbid IQ have frequently been considered proxies reflecting CR, since these variables are related to a decreased risk of developing dementia symptoms in epidemiological studies (Scarmeas and Stern, 2003; Valenzuela and Sachdev, 2006; Helzner et al., 2007). In schizophrenia, CR has been proposed as a factor related to better prognosis, higher adherence and less psychotic symptoms in schizophrenia (Leeson et al., 2009).

Taking previous literature (Stern, 2009) into account, our CR measure included premorbid IQ, educational–occupational level and leisure activities, all variables which have been independently linked to schizophrenia (Jones et al., 1994; Zammit et al., 2004; Reichenberg et al., 2005; Chong et al., 2009). Based on these studies, we hypothesized that the SSD group would attain lower scores than HC in our CR measure composite and our results supported this hypothesis, with CR correctly classifying 79.8% of the sample as SSD or HC.

Our study also found that performance on working memory was predicted by CR. Because we aimed to test whether our CR proxy (which included premorbid IQ, educational and occupational level and leisure activities) was a better predictor than premorbid IQ (which had been commonly used as CR proxy in previous literature), the analysis was repeated with Premorbid IQ and total PANSS score as predictors. The results showed that premorbid IQ also predicted working memory. However premorbid IQ only explained 26.7% of

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**Table 2**

CFA model fit summary for CR and cognitive domains.

<table>
<thead>
<tr>
<th></th>
<th>$\chi^2$</th>
<th>df</th>
<th>Ratio</th>
<th>AIC</th>
<th>Model</th>
<th>BBNFI</th>
<th>RMSEA (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive reserve</td>
<td>149.344</td>
<td>24</td>
<td>6.22</td>
<td>202.009</td>
<td>−43.942</td>
<td>.909</td>
<td>0.045 (0.027–0.061)</td>
</tr>
<tr>
<td>Cognitive domains</td>
<td>117.75</td>
<td>51</td>
<td>2.30</td>
<td>239.78</td>
<td>−44.24</td>
<td>.921</td>
<td>0.039 (0.02–0.05)</td>
</tr>
</tbody>
</table>

AIC: Akaike Information Criterion; BBNFI: Bentler–Bonett Normed Fit Index; RMSEA: Root Mean-Square Error of Approximation.

**Table 3**

Standardized parameters. Factor loading of CR variables on CR model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Premorbid IQ (F1)</th>
<th>Education/occupation (F2)</th>
<th>Lifetime leisure activities (F3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vocabulary subtest of WAIS-III/WISC-R</td>
<td>0.573***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years of formal education</td>
<td>0.487**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>School performance before the beginning of the disorder</td>
<td>0.346**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parents’ educational level</td>
<td>0.333**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questions about the development of language, motor functions and writing and reading</td>
<td>0.646**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intellectual hobbies</td>
<td>0.229*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family hobbies</td>
<td>0.636**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peer relationships</td>
<td>0.000***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sociality</td>
<td>0.901***</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.001.
** p < 0.01.

All latent variables showed significant results as follows: $r_{F1F2} = 0.559 (p < 0.001)$; $r_{F1F3} = 0.344 (p < 0.001)$; $r_{F1F4} = 0.235 (p < 0.05)$; $r_{F2F3} = 0.496 (p < 0.001)$; $r_{F3F4} = 0.240 (p < 0.05)$; $r_{F1F4} = 0.294 (p < 0.05)$.

Standardized parameters for cognitive domains and the goodness-of-fit index are provided in Tables 2 and 4.

**Table 4**

Standardized parameters. Factor loading of neuropsychological variables on cognitive domains.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Working memory (F1)</th>
<th>Attention (F2)</th>
<th>Verbal memory (F3)</th>
<th>Cognitive flexibility (F4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digits forward</td>
<td>0.943**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digits backward</td>
<td>0.681**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letter-Number Sequencing</td>
<td>0.650**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Making Test part B</td>
<td>0.799**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction time of CPT</td>
<td>0.646**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct responses on CPT</td>
<td>0.211*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAVEC immediate memory score</td>
<td>0.185*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAVEC delayed memory score</td>
<td>0.910**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAVEC</td>
<td>0.780***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIST errors</td>
<td>0.883**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCST perseverative errors</td>
<td>0.833**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCST perseverative responses</td>
<td>0.992**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop Interference score</td>
<td>0.872**</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.001.
** p < 0.05.

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the variance of the cognitive domain compared to 40.3% of the variance explained by the CR proxy. Thus, CR, a concept which joins together different variables such as premorbid IQ, educational–occupational level and leisure activities, was shown to have greater predictive capacity.

Regarding attention, our CR proxy predicted SSD performance on attention tasks. These results are partially supported by previous literature with adult samples (Meguro et al., 2001; Roldan-Tapia et al., 2012). To our knowledge, there are no studies in child and adolescent patients with SSD which assess the influence of CR on neuropsychological performance; however, previous studies have investigated separately the influence of premorbid IQ and educational level on cognitive performance in SSD samples (Silverstein et al., 2002; Norman et al., 2005; Rund et al., 2007). Rund et al. (2007) found that patients with good levels of premorbid academic functioning had better scores in some neuropsychological areas than those with lower levels of premorbid functioning; and Silverstein et al. (2002) suggested that social and academic adjustment could influence the cognitive performance seen in adult schizophrenia. Moreover, childhood IQ has been shown to be a strong predictor of social outcome in schizophrenia patients in a 21 year follow-up study (Munro et al., 2002), while a number of studies show an inverse relationship between schizophrenia and lower IQ, academic–occupational level and leisure activities (Chong et al., 2009; Koenen et al., 2009; Pitkanen et al., 2009). These variables are usually studied separately, but taken together they could reflect the compensation capacity of patients and have a strong influence on clinical and neuropsychological outcomes.

The role of CR on neuropsychiatric disorders has been previously explained by Barnett et al. (2006), who found some difficulties in the application of this concept in psychiatry. CR and clinical symptoms are not independent from each other, above all in neurodevelopmental disorders such as schizophrenia where the accumulation of CR could be impeded by the disease. Differences at baseline between patients’ and

Table 5
Results of linear regression analysis assessing the predictive capacity of CR and premorbid IQ on neuropsychological variables after two years.

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Predictor</th>
<th>B</th>
<th>S.E.</th>
<th>β</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear regression with cognitive reserve and PANSS total score</td>
<td>Working memory</td>
<td>Cognitive reserve</td>
<td>0.255</td>
<td>0.020</td>
<td>0.960</td>
<td>4.143</td>
</tr>
<tr>
<td>R² = 0.403</td>
<td>PANSS total score</td>
<td>0.020</td>
<td>0.061</td>
<td>0.025</td>
<td>0.118</td>
<td>0.804</td>
</tr>
<tr>
<td>p = 0.001</td>
<td>F = 9.438</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td>Cognitive Reserve</td>
<td>0.047</td>
<td>0.009</td>
<td>0.019</td>
<td>0.088</td>
<td>0.443</td>
</tr>
<tr>
<td>R² = 0.260</td>
<td>PANSS total score</td>
<td>0.009</td>
<td>0.019</td>
<td>0.025</td>
<td>0.205</td>
<td>0.043</td>
</tr>
<tr>
<td>p = 0.036</td>
<td>F = 3.874</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Verbal memory</td>
<td>Cognitive reserve</td>
<td>0.186</td>
<td>0.013</td>
<td>0.041</td>
<td>0.326</td>
<td>1.812</td>
</tr>
<tr>
<td>R² = 0.107</td>
<td>PANSS total score</td>
<td>0.013</td>
<td>0.010</td>
<td>0.021</td>
<td>0.002</td>
<td>0.013</td>
</tr>
<tr>
<td>p = 0.207</td>
<td>F = 1.669</td>
<td></td>
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</tr>
<tr>
<td>Cognitive flexibility</td>
<td>Cognitive reserve</td>
<td>0.048</td>
<td>0.036</td>
<td>0.054</td>
<td>0.166</td>
<td>0.921</td>
</tr>
<tr>
<td>R² = 0.107</td>
<td>PANSS total score</td>
<td>0.036</td>
<td>0.021</td>
<td>0.021</td>
<td>0.302</td>
<td>0.921</td>
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<tr>
<td>p = 0.206</td>
<td>F = 1.672</td>
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<tr>
<td>Linear regression with premorbid IQ and PANSS total score</td>
<td>Working memory</td>
<td>Premorbid IQ</td>
<td>0.610</td>
<td>0.030</td>
<td>0.192</td>
<td>0.480</td>
</tr>
<tr>
<td>R² = 0.267</td>
<td>PANSS total score</td>
<td>0.030</td>
<td>0.025</td>
<td>0.025</td>
<td>0.179</td>
<td>0.317</td>
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<tr>
<td>p = 0.007</td>
<td>F = 5.831</td>
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<tr>
<td>Attention</td>
<td>Premorbid IQ</td>
<td>0.091</td>
<td>0.011</td>
<td>0.061</td>
<td>0.285</td>
<td>1.481</td>
</tr>
<tr>
<td>R² = 0.148</td>
<td>PANSS total score</td>
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<td>0.008</td>
<td>0.008</td>
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</tr>
<tr>
<td>p = 0.159</td>
<td>F = 1.996</td>
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<td>Verbal memory</td>
<td>Premorbid IQ</td>
<td>0.711</td>
<td>0.007</td>
<td>0.280</td>
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<tr>
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<tr>
<td>Cognitive flexibility</td>
<td>Premorbid IQ</td>
<td>0.291</td>
<td>0.035</td>
<td>0.145</td>
<td>0.321</td>
<td>2.010</td>
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<tr>
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<td>0.019</td>
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<td>1.815</td>
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</table>

Significant differences (p<0.05) marked in bold.

Please cite this article as: de la Serna, E., et al., Cognitive reserve as a predictor of two year neuropsychological performance in early onset first-episode schizophrenia, Schizophr. Res. (2012), http://dx.doi.org/10.1016/j.schres.2012.10.026
controls’ CR help confirm this. Nevertheless, the concept could be useful to explain some of the differences between schizophrenia patients in clinical and neuropsychological outcomes.

Regarding the limitations of this study, the main one is that no validated instrument for measuring CR was used. However, this was due to the fact that no such instrument has yet been developed for use with children and adolescents. Another limitation is the relatively small sample size. Additionally, the effects of antipsychotic drugs have not been controlled for. Although previous studies have related antipsychotics and cognitive performance (Keefe et al., 1999), the influence of different antipsychotics on different cognitive functions is not clear: some studies have found an improvement (Andersen et al., 2011; Pardo et al., 2011) whereas others have found no differences (Stip, 2006; Robles et al., 2011).

Nevertheless, our study found lower scores on CR in SSD than in HC and the CR measure correctly classified a high percentage of the sample into SSD or HC. Moreover, CR predicted SSD performance on academic domains. Acta Psychiatr. Scand. 112, 30–39.

Conflict of interest

Elena de la Serna, Inmaculada Baeza, Susana Andrés, Olga Puig, Iñigo Bombin, David Bartrés-Faz, Celso Arango, Ana González-Pinto, Mara Parellada, Maria Mayoral, Montserrat Graell and Soraya Otero affirm that they have no conflicts of interest.

Dr. J. Castro has had the following relationships which may represent a conflict of interest.

Consultant: Eli Lilly and Pfizer.

Travel support: Eli Lilly.

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