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The impact of cognitive reserve in the outcome of first-episode psychoses: 2-year follow-up study

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Abstract
The concept of cognitive reserve (CR) suggests that the premorbid intelligence quotient (IQ), years of education and leisure activities provide more efficient cognitive networks and therefore allow a better management of some conditions associated to cognitive impairment.
Fifty-two DSM-IV diagnosed FEP subjects were matched with 41 healthy controls by age, gender and parental socio-economic status. All subjects were assessed clinically, neuropsychologically and functionally at baseline and after a two-year follow-up. To assess CR at baseline, three proxies have been integrated: premorbid IQ, years of education-occupation and leisure activities. Higher CR was associated with better cognitive, functional and clinical outcomes at baseline. The CR proxy was able to predict working memory, attention, executive functioning, verbal memory and global composite cognitive score accounting for 48.9%, 19.1%, 16.9%, 10.8% and 14.9% respectively of the variance at two-year follow-up. CR was also significantly predictive of PANSS negative scale score (12.5%), FAST global score (13.4%) and GAF (13%) at two-year follow-up. In addition, CR behaved as a mediator of working memory (B=4.123) and executive function (B=3.298) at baseline and of working memory (B=5.034) at 2-year follow-up. An additional analysis was performed, in order to test whether this mediation could be attributed mainly to the premorbid IQ. We obtained that this measure was not enough by itself to explain this mediation.
CR may contribute to neuropsychological and functional outcome. Specific programs addressed to improve cognition and functioning conducted at the early stages of the illness may be helpful in order to prevent cognitive and functional decline.

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1. Introduction

The concept of cognitive reserve (CR) refers to the ability of an adult brain to make flexible and efficient use of cognitive networks when performing tasks in the presence of brain pathology in order to minimize symptoms (Stern, 2002). Therefore, the CR can become a skill set that allows some people to actively offset the effects of the disease which might explain the fact that some individuals with similar brain pathology have a higher functioning than others (Stern, 2013). In the field of dementia it is hypothesized that the CR includes the capacity to withstand damage, ability to compensate for damage through the use of alternate networks, and remodeling and plasticity (Stern, 2006; Esiri and Chance, 2012). However, the concept of CR has not been accurately defined and has been characterized by different variables. The way to conceptualize a measure of CR remains open to debate. The most common proposed proxy indicators of CR includes years of educational attainment, occupation, leisure activities, and premorbid IQ (Barnett et al., 2006; Stern, 2009; de la Serna et al., 2013; Forcada et al., 2014). Among the indicators of CR, educational attainment may be the most widely studied and is most commonly used as definition of CR in previous studies, especially in dementia (Le Carret et al., 2005; Ngandu et al., 2007). The CR is primarily determined by genetic and neurodevelopmental factors, but may vary depending on the environment and exposure to certain factors such as education, lifestyle and mental and physical activities (Bora, 2015).

Different studies have shown that cognition can be considered a predictor of patients' outcome in schizophrenia (Green, 1996), finding a relationship between cognition and functional level (van Winkel et al., 2007). There have been attempts to associate CR with the clinical expression of the disease such as proposed in a study by Barnett et al. (2006) who found that the severity of symptoms for any given level of pathology would be greater for those individuals with low CR. Higher CR, in change, is normally associated with a later onset of psychosis, a positive moderator of the impact of psychosis on clinical outcomes, and having a greater capacity for reasoning and a greater insight (Leeson et al., 2011, 2012). The latter has a significant impact on social functioning in schizophrenia. A recent study revealed that almost 70% of patients had deficits in their insight and more severe positive and negative symptoms at admission, worse functioning and worse adherence which was significantly associated with poorer insight (Schennach et al., 2012). Regarding cognition, in a sample of children and adolescents with FEP, the CR predicted performance in some cognitive domains such as attention and working memory at two-year follow-up (de la Serna et al., 2013).

It has not been shown that CR measures increase the effectiveness of interventions to improve cognitive functioning in schizophrenia (Kontis et al., 2013). However, in that study the cognitive reserve was defined only by premorbid measures such as premorbid IQ and vocabulary knowledge. Considering a broader view of CR including lifetime exposure to certain environmental factors like leisure activity, some authors have suggested that implementing interventions enhancing CR may minimize the decline on cognitive and psychosocial functioning in the future in mental disorders (Forcada et al., 2014; Anaya et al., 2016; Vieta and Torrent, 2015).

So far, studies of CR have focused primarily on patients with evolving chronic neurodegenerative conditions such Alzheimer disease, HIV, or multiple sclerosis (Vance et al., 2013; Boots et al., 2015; Martins Da Silva et al., 2015). The relevance of this paradigm to the clinical expression in psychiatric disorders remains poorly understood (Schneider et al., 2014). The aim of this study was to observe the predictability of CR in functional, clinical and cognitive measures at two years-follow up in an adult sample of subjects with FEP. We hypothesized that CR would predict cognitive, clinical and functional recovery in individuals with a FEP at two-year follow-up. Firstly, we expected to find a lower CR in patients with schizophrenia compared to healthy controls based on the neurodevelopmental hypothesis of schizophrenia, and secondly, we expected to find a more CR in those patients with good functional, clinical and cognitive outcomes.

2. Experimental procedures

2.1. Participants

For the present study we recruited a sample of 52 patients and 41 healthy controls (HC) through the Schizophrenia and the Bipolar Disorder Units at the Hospital Clinic of Barcelona.

The inclusion criteria for patients were: 1) diagnosis of a first psychotic episode; 2) age between 18–35 years old at the time of first evaluation; 3) presence of psychotic symptoms of less than 12 months' duration and 4) speak Spanish correctly. Exclusion criteria were: 1) mental Retardation according to DSM-IV criteria (including not only an Intelligence Quotient lower than 70 but also impaired functioning); 2) history of head trauma with loss of consciousness and organic disease with mental repercussions.

The patients matched with HC by age ($\pm$ 10%), sex and parental socio-economic status (SES) of their parents $\pm$ 1 level (see assessments). HC without evidence of psychiatric or neurological history were recruited from a pool of volunteers. Controls also had to be fluent in Spanish. The exclusion criteria for controls were the same as for the patients, plus the presence of a current or past psychotic disorder or major depression and having a first degree relative with psychotic disorder history.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice and the Hospital Clinic Ethics and Research Board. All participants provided written informed consent prior to be included in the study.

2.2. Assessments

2.2.1. Clinical and sociodemographic assessment

We gathered all the relevant clinical and sociodemographic data including: age, gender, years of education, pharmacological treatment measured by chlorpromazine equivalents based on international consensus (Gardner et al., 2010), Duration of Untreated Psychosis (DUP) calculated as the number of days between the first manifestations of psychotic symptoms until the initiation of adequate treatment and tobacco use. Diagnoses were determined with the SCID-I and II (First et al., 1997a, 1997b) according to DSM-IV criteria. Parental socio economic status (SES) was determined using Hollingshead's Two-Factor Index of Social Position (Hollingshead and Redlich, 1958). The SES score is calculated based on the parent who has reached higher level, with a range from 8 to 72.

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