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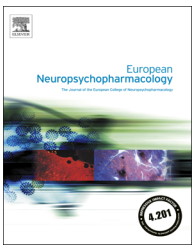

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The influence of cognitive reserve on psychosocial and neuropsychological functioning in bipolar disorder

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Abstract
Cognitive reserve (CR) refers to the hypothesized capacity of an adult brain to cope with brain pathology in order to minimize symptomatology. CR was initially investigated in dementia and acute brain damage, but it is being applied to other neuropsychiatric conditions. The present study aims at examining the fit of this concept to a sample of euthymic bipolar patients compared with healthy controls in order to investigate the role of CR in predicting psychosocial and cognitive outcome in bipolar disorder (BD). The sample included 101 subjects: 52 patients meeting DSM-IV-TR criteria for BD type I or II and 49 healthy controls (HC) matched for age and gender. They were all assessed with a cognitive battery tapping into executive and memory functioning. CR was obtained using three different proxies: education-occupation, leisure activities and premorbid IQ. Psychosocial functioning was evaluated by means of the Functioning Assessment Short Test (FAST). MANCOVAs were performed to determine differences in cognitive and functioning variables. Linear regression analyses were carried out to predict neuropsychological and psychosocial outcomes. Euthymic bipolar patients showed worse neuropsychological performance and psychosocial functioning than HC. The linear regression models revealed that CR was significantly predictive of FAST score ($\beta = -0.47$, $p < 0.0001$),

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Executive Index ($\beta = 0.62$, $p < 0.0001$) and Visual Memory Index ($\beta = 0.44$, $p = 0.0004$), indicating that CR is a significant predictor of cognitive and psychosocial functioning in euthymic bipolar outpatients. Therefore, CR may contribute to functional outcome in BD and may be applied in research and clinical interventions to prevent cognitive and functional impairment.

1. Introduction

The concept of cognitive reserve (CR) refers to the hypothesized capacity of an adult brain to cope with brain pathology in order to minimize symptomatology (Stern, 2002). This concept was proposed after observing that there appeared to be no direct relationship between the severity of brain pathology and the clinical manifestations of the damage. High cognitive reserve is seen as a protective factor against the development and expression of neurological conditions, while low reserve would be a vulnerability factor to decrease the threshold for the onset of symptoms, functional impairment and clinical presentation of disease (Barnett et al., 2006). Because CR may not be easily quantified, proxy measures such as pre-morbid IQ, educational and occupational attainment, and leisure activities have served as surrogates (Stern, 2009).

Initially, CR was investigated in dementia and acute brain trauma, but the concept is being applied to other neurological diseases and, recently to some psychiatric conditions with particularly high burden of disease (Catalá-López et al., 2013). With regard to psychiatric disorders, CR has been scarcely studied, but it is present implicitly in a large number of studies assessing premorbid intelligence as a key role in the development and outcome of psychiatric disorders (Khandaker et al., 2011; Koenen et al., 2009; Payá et al., 2013; Schulz et al., 2014; Zammit et al., 2004). Cognitive reserve appears to be protective against neurological illness in terms of cognitive and functional outcomes; yet it is unclear if CR is similarly protective against psychiatric conditions in the same outcomes (Tucker and Stern, 2011). Although it is well established that low intelligence is a risk factor for schizophrenia, its neurodevelopmental nature complicates the issue of CR as the pathological process can interfere the accumulation of cognitive reserve in the early ages.

In contrast to schizophrenia, a number of longitudinal studies have failed to find differences in childhood intelligence between controls and individuals who will later develop bipolar disorder (BD) (Cannon et al., 2002; Koenen et al., 2009; Reichenberg et al., 2002; Zammit et al., 2004). In fact, a recent study reports not lower, but actually higher intelligence in males developing "pure" BD as compared to the general population (Gale et al., 2013). BD has traditionally been associated with a better outcome than schizophrenia because of a presumed absence of cognitive impairment and seemingly normal functioning between episodes. However growing evidence indicates that residual mood symptoms, neurocognitive impairment and psychosocial dysfunction remain even during remission in BD (Bonnín et al., 2012). The most reported cognitive deficits which persist in euthymic states affect executive-function and verbal learning (Arts et al., 2008; Bora et al., 2009; Mur et al., 2007). These findings may confer a particular role for cognition in BD, and the CR hypothesis would suggest that those individuals with lower cognitive reserve would be more severely ill. Moreover, cognitive impairment has been revealed as a determinant of the functional disability in BD, together with other clinical factors such as disease severity, chronicity and residual symptoms that contribute to poor functional outcome in BD (Gyulai et al., 2008; Martínez-Arán et al., 2007; Mur et al., 2009). Therefore, the aim of this study was to investigate the role of CR in predicting psychosocial and cognitive outcome in euthymic bipolar patients.

2. Experimental procedures

2.1. Subjects

Patients had been enrolled into the study from the Lithium Clinic Program at Hospital Santa Maria, Lleida, Spain. Inclusion criteria for patients required fulfillment of DSM-IV-TR criteria for bipolar I or II disorder and to be in remission for at least 3 months. Patients were characterized as euthymic if they had a total score below 8 in the Hamilton Rating Scale for Depression (HAM-D; 17-item) and a total score below 6 in the Young Mania Rating Scale (YMRS) for at least 3 months at the time of assessment. Exclusion criteria were the following: significant physical or neurologic illness, substance abuse or dependence in the last 12 months and electroconvulsive therapy (ECT) in the preceding year.

Healthy controls, matched in terms of gender and age, were recruited via advertisements and from non-medical hospital staff. They had no current or past psychiatric history, as determined by the Structured Clinical Interview for DSM-IV Axis I Disorders, and had no first-degree relatives with bipolar or psychosis diagnoses. Exclusion criteria were the same as for patients.

The present sample included up to 101 subjects (52 patients with BD and 49 healthy controls) who agreed to participate and who were evaluated at a full clinical interview by a psychiatrist; the evaluation included demographic, clinical and treatment assessment. Patients also had blood and urine tests, including thyroid function, serum lithium levels, and urine drug control. The study was approved by the Local Ethics Committee, and written informed consent was obtained from all participants (patients and healthy controls).

2.2. Demographic and clinical data

Demographics and clinical data were systematically obtained and included the following information: age, gender, years of education, current job status, and family history of mental illness. For bipolar outpatients, the