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Research paper

High cognitive reserve in bipolar disorders as a moderator of neurocognitive impairment

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ABSTRACT

Background: Cognitive reserve (CR) reflects the capacity of the brain to endure neuropathology, minimize clinical manifestations and successfully complete cognitive tasks. The present study aims to determine whether high CR may constitute a moderator of cognitive functioning in bipolar disorder (BD).
Methods: 102 patients with BD and 32 healthy controls were enrolled. All patients met DSM-IV criteria for I or II BD and were euthymic (YMRS≤6 and HDRS≤8) during a 6-month period. All participants were tested with a comprehensive neuropsychological battery, and a Cerebral Reserve Score (CRS) was estimated. Subjects with a CRS below the group median were classified as having low CR, whereas participants with a CRS above the median value were considered to have high CR.
Results: Participants with BD with high CR displayed a better performance in measures of attention (digits forward: F=4.554, p=0.039); phonemic and semantic verbal fluency (FAS: F=9.328, p=0.004; and Animal Naming: F=8.532, p=0.006); and verbal memory (short cued recall of California Verbal Learning Test: F=4.236, p=0.046), after multivariable adjustment for potential confounders, including number of admissions and prior psychotic symptoms.
Limitations: The cross-sectional design of the study does not allow the establishment of causal inferences. Additionally, the small size of the sample may have limited some results.
Conclusions: High cognitive reserve may therefore be a valuable construct to explore for predicting neurocognitive performance in patients with BD regarding premorbid status.

1. Introduction

The concept of cognitive reserve (CR) provides a possible explanation for the recurrent discrepancy in clinical practice between the evidence of brain damage and the absence of clinical symptoms (Stern, 2002). It reflects the capacity of the brain to endure neuropathology, minimize clinical manifestations and successfully complete cognitive tasks through an active process by which injury is buffered by pre-existing cognitive processes or by the development of alternative processes (Bosch et al., 2010; Stern, 2012). CR, which embraces terms such as levels of educational and occupational attainment, intelligence or leisure activities in later life (Stern, 2012), seems to alter the development and/or expression of brain pathology or damage; high CR may slow down the clinical presentation of neurocognitive decline while low CR may even boost it.

CR has mainly been investigated in dementia (Bartrés-Faz et al., 2009) and traumatic brain injury (Mathias and Wheaton, 2015). Nevertheless, the concept may seem to be pertinent in a broader range of neurological disorders such as epilepsy (Pai and Tsai, 2005) or multiple sclerosis (Sumowski and Leavitt, 2013) and psychiatric conditions (Barnett et al., 2006). In the case of bipolar disorder, premorbid features related to higher CR have been linked to a better cognitive functioning (Anaya et al., 2015). The cognitive mechanisms that might underlie the CR are still unknown (Stern, 2012). The CR has recently begun to be assessed in psychiatric conditions applying the same methodology as that performed in research on Alzheimer based

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on proxies of educational and occupational levels, leisure and social activities and premorbid intelligence quotient (IQ) (Bartrés-Faz et al., 2009; Solé-Padullés et al., 2009). Following this method, de la Serna et al. (2013) evaluated the CR of children and adolescents diagnosed with early onset first-episode schizophrenia at two-year follow-up. The authors determined that CR was a fair predictor of working memory and attention performance in these patients at two year follow-up (R^2=0.403, F=9.438, p=0.001 and R^2=0.260, F=3.874, p=0.036, respectively) in a linear model that included CR and Positive and Negative Syndrome Scale (PANSS) total score. Moreover CR measures correctly classified 79.8% of the sample as psychotic patients or healthy controls. Similar results on CR in adults diagnosed with first psychotic episode using the same methodological approach have been described (Amoretti et al., 2016). Considering bipolar patients, Forcada et al. also reported the relevance of CR in neurocognitive and psychosocial functioning in euthymic bipolar outpatients by the same method according to linear regression models were the variables CR, current age, age at illness onset, duration of illness and period of clinical stabilization were introduced (Forcada et al., 2015). Considering neurocognitive variables, the model of executive functions accounted for a 55% of the variance (R^2=0.552, F=18.5, p < 0.001) and the model of visual memory accounted for 39% of the variance (R^2=0.389, F=14.9, p < 0.0001). CR showed significant predictable value in both models (β=0.62, p < 0.0001; β=0.44, p=0.0004 respectively). Regarding psychosocial functioning, the model explained 54.4% of the variance (R^2=0.544, F=18.7, p < 0.001), CR showing a significant predictable value (β=−0.47, p < 0.0001) (Forcada et al., 2015). Anaya et al. (2015) have recently demonstrated analogous results on the impact of CR in euthymic bipolar patients in all cognitive domains as well as in psychosocial functioning using a proxy based on the levels of education, occupational attainment and intelligence (Pereda et al., 2000; Stern, 2012). CR, age, chronicity and bipolar type were the variables introduced in the multiple linear regression models of attention, working memory, verbal memory, visual memory, executive functioning and processing speed (R^2=0.10, F=6.69, p < 0.001; R^2=0.20, F=15.22, p < 0.001; R^2=0.20, F=14.55, p < 0.001; R^2=0.14, F=10.18, p < 0.001; R^2=0.12, F=8.58, p < 0.001; R^2=0.18, F=13.29, p < 0.001, respectively). Regression models showed a statistically significant relationship between CR and each cognitive domain (β=0.15, p=0.026; β=0.47, p < 0.001; β=0.43, p < 0.001; β=0.32, p < 0.001; β=0.27, p < 0.001; β=0.44, p < 0.001, respectively) assessed (Anaya et al., 2015). Considering psychosocial functioning, CR, age, chronicity and bipolar type, verbal memory, Hamilton Depression Rating Scale (HDRS) score and number of hospitalizations were the variables introduced in the multiple linear regression model (R^2=0.23, F=10.20, p < 0.001) where CR showed a significant relationship (β=0.25, p=0.008). Moreover, these authors also described a positive association between CR and physical quality of life (R^2=0.06, F=3.75, p=0.003, β=0.16, p=0.016) but a negative association between CR and mental quality of life (R^2=0.21, F=11.98, p < 0.001, β=−0.18, p=0.004) proposing that patients with a better or more preserve cognitive functioning might be more aware of their deficits derived from the disorder and may overestimate them. All in all, no agreement has been reached regarding the methodology of how to assess CR in psychiatric disorders, and in particular, in bipolar disorder.

Since the course of cognitive deterioration in BD is significantly heterogeneous, with some patients having retaining cognitive function and others suffering a progressive cognitive decline (Trotta et al., 2015), we aim to study whether having a high CR may be associated with a better neurocognitive performance. In this case, high CR could be a valuable construct to predict neurocognitive performance in patients with BD regarding premorbid status.

2. Methods

Study participants were enrolled from the Bipolar Disorders Program of the Hospital Clinic of Barcelona. All patients met DSM-IV-TR criteria for bipolar I or II disorder and were euthymic. The clinical state of the patients was determined by the psychiatrist responsible for the follow-up of bipolar patients in the Bipolar Disorders Program using DSM-IV-TR criteria, and the Structured Clinical Interview for Diagnostic Symptoms (SCID, DSM-IV) (First et al., 2002), the Spanish version of the HDRS, 17-item (Ramos-Brieva and Cordero-Villafafila, 1988; Williams, 1988) and the Young Mania Rating Scale (YMRS) (Colom et al., 2002; Young et al., 1978). Euthymia was defined as YMRS≤6 and HDRS≤8, during monthly visits over a 6-month period. Exclusion criteria were the following: estimated Intelligence Quotient (IQ) lower than 85, significant physical or neurologic illness that can affect neuropsychological performance, substance abuse or dependence in the last 12 months and electro-convulsive therapy (ECT) in the preceding year or any psychiatric comorbidity.

Healthy controls (HC) without current or past psychiatric history were recruited in the corridors of Hospital Clínic. They had no first-degree relatives with bipolar or psychosis diagnoses. The exclusion criteria for the HC were the same as those of the patients.

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

2.1. Clinical and psychosocial assessment

Clinical and sociodemographic variables were collected as part of the Bipolar Disorders Program protocol of the Hospital Clínic of Barcelona. The clinical variables included in this study were diagnosis of bipolar type I or II, age at onset of the illness, duration of the illness, the number and type of episodes, number of admissions, suicide attempts, history of psychotic symptoms, rapid cycling course, family history of affective disorders and number and type of medications. Functioning was assessed using the Social and Occupational Functioning Assessment Scale (SOFAS), a scale similar to the GAF that assesses social and occupational functioning regardless of symptomatology (Morosini et al., 2000).

2.2. Neuropsychological assessment

Patients were tested with a comprehensive neuropsychological battery. In order to enhance replication, only tests frequently documented by the neuropsychological literature were employed:

1) Premorbid IQ evaluated with the Wechsler Adult Intelligence Scale Vocabulary subtest (WAIS) (Wechlser, 1997);
2) frontal executive functions tested by the Wisconsin Card Sorting Test (Golden, 1978) and the Stroop Color-Word Interference Test (Golden, 1978);
3) attention assessed by WAIS digit forward subtest (Wechlser, 1997) and Trail Making Test (TMT) part-A (Reitan and Wolfson, 1993);
4) working memory evaluated with the WAIS digit backward subtest (Wechlser, 1997) and the Trail Making Test (TMT) part-B (Reitan and Wolfson, 1993);
5) verbal fluency tested by the phonemic (F-A-S) and semantic (Animal naming) components of the Controlled Oral Word Association Test (COWAT) (Benton and Hamsher, 1976) and;
6) verbal learning and memory assessed by the California Verbal Learning Test (CVLT) (Delis et al., 1987).

2.3. The cerebral reserve score

The Cerebral Reserve Score (CRS) was derived from three measures according to Stern et al. procedures (Stern et al., 1996): estimated IQ, educational level and occupational achievement. Leisure-social activ-