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Research paper

Longitudinal relationship between clinical course and neurocognitive impairments in bipolar disorder

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ABSTRACT

Background: The aim of this study was to estimate the relationship between clinical course and trajectory of neurocognitive functioning during a follow-up period in a sample of euthymic bipolar patients.
Methods: Fifty-one patients with BD performed two-neurocognitive assessment separated by a period of at least 48 months. The clinical course during the follow-up period was documented by: three measures 1) number of affective episodes, 2) time spent ill, and 3) mood instability.
Results: Patients were followed-up for a mean period of 73.21 months. Neurocognitive performance tended to be stable throughout the follow-up. Performance in verbal memory and executive functions at the end of study were related with the number of hypo/manic episodes and time spent with hypo/manic symptoms during the follow-up. None of the clinical measures considered were related to changes in neurocognitive performance over the follow-up period.
Limitations: The relatively small sample size limits the value of subgroup analysis. The study design does not rule out some risk of selection bias.
Conclusions: Although there may be a positive relationship between number of episodes and neurocognitive deficits in patients with bipolar disorder, successive episodes do not seem to modify the trajectory of neurocognitive functioning over time. Theoretical implications of these findings are discussed.

1. Introduction

Nowadays it is well known that a significant proportion of patients with bipolar disorder (BD) exhibit cognitive deficits even during euthymic periods (Burdick et al., 2014; Martino et al., 2014; Cullen et al., 2016). Since the first cross-sectional studies, a positive relationship between the number of affective episodes and the degree of cognitive impairment was reported with some consistency (for a review see Robinson and Ferrier, 2006). More recent studies have confirmed this association. In a study conducted by López-Jaramillo et al. (2010), euthymic BD patients with more than three manic episodes showed worse overall cognitive performance compared with those with only one episode of mania. Similarly, Torres et al. (2010) reported that patients after resolution of their first manic episode showed smaller impairments in verbal memory and executive functions than those reported in meta-analyses of samples of euthymic non-first episode BD patients. These findings tended to be interpreted as that cognitive deficits would increase with successive affective episodes, and subsequently it was included in multiple reviews as evidence supporting the neuroprogression hypothesis and staging models proposed for BD (Berk, 2009; Berk et al., 2007, 2011; Cardoso et al., 2015; Gama et al., 2013; Kapczinski et al., 2009, 2014; Post et al., 2012; Rodrigues et al., 2014; Vieta et al., 2011).

However, although interesting, this view of the progressive nature of the cognitive impairment in BD require some caution. First, cross-sectional studies are based on the retrospective report of previous affective episodes, which have been shown to be rather imprecise in patients with BD (Martino et al., 2016). Additionally, direction of causality of the association between previous episodes and cognitive impairment cannot be established accurately from cross-sectional studies (Martino et al., 2013). In fact, even if cognitive functioning were stable throughout the course of the BD, this association would be observed if patients with greater cognitive impairments were those with the highest number of recurrences over the course of the disorder. Moreover, neuroprogressive hypothesis collides against the results of the first longitudinal studies, which seem to show that cognitive deficits

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are static rather than progressive (Samamé et al., 2014). It could be objected that these longitudinal studies lack the duration that might be necessary to show a progressive cognitive deterioration, since the majority have periods of follow-up of less than 5 years. Likewise, most of the longitudinal studies have not evaluated closely the relationship between the trajectory of cognitive deficits and the clinical course during the follow-up period. Overall, it has been mentioned that more research is required before concluding that there is a progressive deterioration of cognitive functioning with successive episodes throughout the course of the BD (Strejilevich et al., 2015).

In order to clarify this issue, the aim of this study was to evaluate the relationship between the clinical course and the trajectory of cognitive deficits. Taking into account the limitations of previous studies, we documented the clinical course through the mood chart technique during a relatively long follow-up period. Based on the results of previous longitudinal studies, we hypothesized that trajectory of cognitive deficits could be relatively independent of the clinical course during the follow-up period.

2. Methods

Fifty-one subjects were retrospectively selected from the outpatients population of the Bipolar Disorder Program of Favaloro University with the following inclusion criteria: age between 18 and 65 years old; diagnosis of BD type I or type II according to DSM-IV using Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996); a period of follow-up of more than 48 uninterrupted months in our Program during which they performed two neurocognitive assessment separated by a period of at least 48 months; and euthymia (defined by Hamilton Depression Rating Scale ≤8 and Young Mania Rating Scale 6) for at least 8 weeks previous to both neurocognitive assessment. Exclusion criteria were: history of substance abuse/dependence, history of mental retardation, neurological disease, or any unstable clinical condition (as hypothyroidism) that could affect the clinical course or neurocognitive functioning. Additionally, 39 healthy controls were included: these had no antecedent of neurological disease, neither history of psychotic or affective disorders in themselves or a first-degree family member, and they were not taking psychotropic medication. The Hospital Ethics Committee approved the study and all subjects gave written informed consent for their participation after receiving a complete description of the study.

2.1. Clinical assessment

In addition to SCID, all subjects were evaluated with the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), and Young Mania Rating Scale (YMRS) (Young et al., 1978). Additional demographical and clinical information was obtained from clinical charts and direct patients interview (age, gender, years of education, age at illness onset, bipolar subtype, previous manic/hypomanic and depressive episodes, lifetime history of psychosis). When possible, attempts were made to verify these historical data with third- party reports (such as medical records, family interview). Average exposure to antidepressants, mood stabilizers, antipsychotics, and benzodiazepines during follow-up was assessed with the Clinical Scale of Intensity, Frequency, and Duration of Psychopharmacological Treatment (IFD) (Peralta and Cuesta, 2002). This scale provides a quantitative measure of current exposure to different groups of psychotropic medications in a 0–5 points range (0 = no medication, 1 = sporadic low dose, 2 = continued low dose; 3 = middle dose, 4 = high dose, and 5 = very high dose).

Clinical course during the follow-up period was assessed by three measures for each patient: 1) Affective episodes (depressive and hypo/manic) based on DSM-IV criteria; 2) Time spent ill documented at each visit (with intervals usually around 1–2 months) with a modified life charting technique rated by the treating psychiatrist on a weekly basis. This life chart technique was used in previous studies by our group (Strejilevich et al., 2013; Martino et al., 2017) and was developed without the knowledge or purpose of the present work; and 3) Mood instability: based on a previous study of our group (Strejilevich et al., 2013) a Mood Instability Factor was calculated as a ratio between number of mood changes and years of follow-up; considering all mood changes including those from euthymia to subclinical symptoms or full blown episodes and from full blown episodes or subclinical symptoms to euthymia.

2.2. Neurocognitive assessment

Both at baseline and follow-up, patients performed an extensive neuropsychological battery selected to assess the following cognitive domains: 1) Attention: Forward Digit Span (Wechsler, 1950), and Trail Making Test part A (Reitan, 1958); 2) Verbal memory: Memory Battery of Signoret (Signoret and Whiteley, 1979). This test evaluates immediate and delay recall of a short story, and the serial learning of a twelve word list of different semantic categories (3 trials), free delay recall, and recognition with semantic clues and multiple options of them; 3) Language: Boston Naming Test (Kaplan, 1983); and 4) Executive functions: Wisconsin Card Sorting Test (Heaton, 1981), Trail Making Test part B (Reitan, 1958), and Phonological Fluency (Benton, 1983).

Additionally, estimated premorbid IQ was calculated with the WAIS vocabulary subtest at baseline (Wechsler, 1955).

2.3. Data analysis

Raw-score of neurocognitive performance were transformed to z-scores based on normative data of each test. The assumption of normality and homoscedasticity of each variable was analyzed with the Kolmogorov-Smirnov normality test and Levene´s test respectively. Since most continuous variables such as number of episodes during follow-up or time spent ill were skewed, non-parametric tests were used.

Patient and control groups were compared in clinical-demographical and neurocognitive variables using Mann-Whitney or chi squared tests as appropriate.

Differences between baseline and end of follow-up in terms of clinical, pharmacological, and neurocognitive variables for each patient were analyzed as two related samples with the Wilcoxon Signed Rank Test. Changes in neurocognitive functioning were calculated as the difference between performance at end of follow-up and baseline, with negative results indicating deterioration and positive results meaning improved performance. Relationship between trajectory in neurocognitive functioning and the different measures of clinical course during follow-up were assessed with Spearman correlation. Taking into account the preliminary nature of this study, no corrections were applied for multiple comparisons / correlations. Despite the asymmetric distribution of certain variables, results are also expressed as mean and standard deviation to improve understanding.

3. Results

Clinical and demographical features of patients and healthy controls are showed in Table 1. Overall, patients with euthymic BD showed poor performance than healthy controls in measures of verbal memory, attention, and executive functions (Fig. 1).

The period of follow-up was 73.21 (SD = 18.27, median = 72, range = 48–111) months during which patients experienced a mean of 2.04 (SD = 1.98, median = 1.5, range = 0–8) depressive episodes and 0.89 (SD = 1.36, median = 0, range = 0–6) hypo/manic episodes. On average, patients spent 79.98% of the follow-up euthymic, 15.69% (range = 0–38.54) with depressive symptoms, and 4.34% (range = 0–21.00) with hypo/manic symptoms. Likewise, patients had a mean of 2.62 (range = 0–7.32) mood changes for each year of follow-up.