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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.

Table 1
Clinical and demographical characteristics of bipolar patients and healthy controls at baseline (values are expressed as mean, standard deviation is shown in brackets).

	Bipolar Patients (n = 51)	Healthy Controls (n = 39)	Test/p-value
	Mean (SD) / Median (Range)	Mean (SD) / Median (Range)	
Age	44.91 (14.14) / 45 (22–65)	40.44 (12.15) / 37 (19–62)	$Z = -1.45$; p = 0.15
Years of Education	14.32 (2.83) / 15 (3–17)	13.79 (2.75) / 13 (7–18)	$Z = -0.95$; p = 0.34
Premorbid IQ (Z-Score)	0.47 (0.62) / 0.40 (−1.80–1.60)	0.46 (0.58) / 0.30 (−1.5–0–8)	$F = -0.13$; p = 0.90
YMRS Score	0.65 (1.31) / 0 (0–5)	0.74 (0.94) / 0 (0–3)	$Z = -1.55$; p = 0.12
HDRS Score	1.88 (2.14) / 1 (0–8)	1.95 (1.81) / 2 (0–5)	$Z = -0.46$; P = 0.64
Age at onset	30.68 (11.30) / 28 (12–56)		
N° of previous depressive episodes	3.77 (2.35) / 3 (1–12)		
N° of previous hypo/manic episodes	2.51 (1.97) / 2 (1–11)		
	%	%	
Gender (Female)	74.51	71.79	$X^2 = 0.46$; p = 0.50
Clinical Subtype (type I)	41.17		
History of psychosis	37.25		

IQ: Intelligence quotient; YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale.

All patients were receiving psychotropic medication at the time of both neurocognitive assessments. Patients showed no difference between baseline and end of follow-up in terms of subclinical symptoms or exposure to benzodiazepines, antidepressants, mood stabilizers, and antipsychotics (Table 2). Patients improved performance in 2 of the 11 neurocognitive measures considered, while the remaining were stable throughout the follow-up period (Table 2). We also compared changes in neurocognitive performance over the follow-up period between patients with and without clinically significant cognitive deficits at baseline (at least one cognitive domain with a performance of 1.5 SD below the mean). There were no differences among these subgroups of patients in the trajectory of the neurocognitive measures considered (all $p > 0.05$; results available upon request).

The number of hypo/manic episodes during the period of study was related with performance in verbal memory (Serial Learning, $R = -0.30$; $p = 0.035$) and executive functions (Trail Making Test B, $R = -0.35$; $p = 0.023$) at the end of follow-up. Similarly, time spent with hypo/manic symptoms was related with final performance in executive functions (Phonological Fluency, $R = -0.34$, $p = 0.025$; and Trail Making Test B, $R = -0.38$, $p = 0.020$). In contrast, time spent with depressive symptoms, number of depressive episodes, and mood instability during the follow-up were no related with neurocognitive functioning (all $p > 0.05$). On the other hand, none of the clinical measures considered were related to changes in neurocognitive performance over the follow-up period (Table 3). The same analysis was performed including only patients with BD type I and the results remain unchanged. Finally, based on the criteria used in a previous study of our group (Martino et al., 2017), we identified 15.7% of the sample of patients who had a progressive clinical course. There were no differences in the trajectory of cognitive deficits between this subgroup of patients and those without progressive clinical course (all $p > 0.05$; results available upon request).

4. Discussion

First, we conducted some analyzes to ensure that the sample of patients included in this study was representative of BD. Compared with healthy controls, patients had deficits in measures of verbal memory, attention, and executive functions, which agrees with meta-analytic findings (Robinson et al., 2006; Torres et al., 2007; Arts et al., 2007). Likewise, patients showed a relatively stable neurocognitive performance over a mean follow-up period of more than 6 years. We lacked longitudinal assessment of the control group, so we cannot confirm the stability of cognitive deficits with our findings. In fact, the stability in neurocognitive performance seen in our patient sample could indicate a relative deficit if an improvement was observed in the performance of healthy controls during the same period. Notwithstanding, it is important to emphasize that our findings closely reproduce those of the pioneering longitudinal neurocognitive studies in which changes in cognitive performance over time was similar in BD patients and healthy controls (Samamé et al., 2014). Moreover, some recent longitudinal studies reported no differences in neurocognitive trajectories between BD patients and healthy controls using also a follow-up period of 6 years (Santos et al., 2014; Mora et al., 2016).

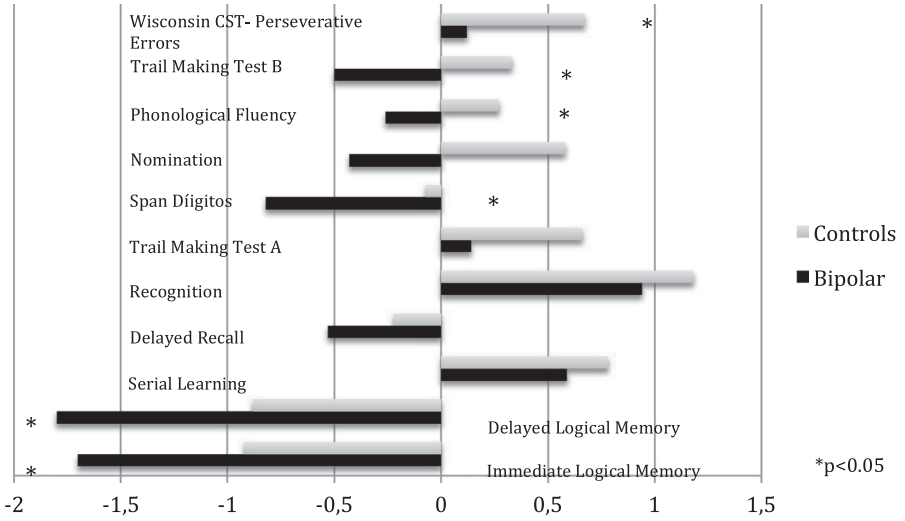

Fig. 1. Neurocognitive performance (Z-Score) of bipolar patients and healthy controls at baseline (Mann-Whitney Test).

Table 2
Differences in clinical and neurocognitive features between baseline and end of follow-up in patients with euthymic bipolar disorder.

	Baseline Mean (SD) / Median (Range)	Follow-up Mean (SD) / Median (Range)	Test/p-value
YMRS score	0.65 (1.31) / 0 (0–5)	0.37 (1.31) / 0 (0–6)	$Z = -1.17$; $p = 0.24$
HDRS score	1.88 (2.14) / 1 (0–8)	1.27 (2.09) / 0 (0–7)	$Z = -1.51$; $p = 0.13$
Benzodiazepines (IFD score)	0.96 (1.13) / 0 (0–4)	0.88 (1.42) / 0 (0–5)	$Z = -0.67$; $p = 0.50$
Antidepressants (IFD score)	1.19 (1.48) / 0 (0–4)	1.02 (1.59) / 0(0–5)	$Z = -0.98$; $p = 0.32$
Mood Stabilizers (IFD score)	3.25 (1.02) / 3 (0–5)	3.10 (1.25) / 3 (0–5)	$Z = -1.01$; $p = 0.31$
Antipsychotics (IFD score)	1.06 (1.10) / 1 (0–4)	1.31 (1.79) / 0 (0–4)	$Z = -0.69$; $p = 0.49$
Neurocognitive Variables			
Immediate Logical Memory	−1.73 (1.33) / −1.34 (−5.58–0.38)	−1.58 (1.36) / −1.36 (−6.01–0.50)	$Z = -0.48$; $p = 0.33$
Delayed Logical Memory	−1.96 (1.52) / −1.78 (−5.65–0.42)	−1.71 (1.46) / −1.48 (−5.12–1.10)	$Z = -0.46$; $p = 0.65$
Serial Learning	0.58 (1.34) 0.52 (−1.84–4.49)	0.72 (1.20) / 0.49 (−1.72–4.33)	$Z = -1.20$; $p = 0.33$
Free Delay Recall	−0.57 (1.43) / −0.53 (−4.26–1.68)	−0.23 (1.36) / 0.01 (−4.54–1.98)	$Z = -1.81$; $p = 0.07$
Recognition	0.85 (0.62) / 1.05 (−1.31–1.95)	1.10 (0.75) / 1.05 (−1.65–2.32)	$Z = -1.06$ $p = 0.42$
Trail Making Test A	0.14 (1.56) / 0.22 (−8.50–1.89)	0.46 (1.00) / 0.59 (−3.21–1.80)	$Z = -1.30$; $p = 0.19$
Forward Digit Span	−0.79 (1.32) / −0.89 (−3.50–2.00)	−0.48 (1.33) / −0.50 (−3.43–2.00)	$Z = -1.24$; $p = 0.21$
Nomination	−0.35 (1.28) / 0.04 (−5.00–1.25)	0.14 (1.03) / 0.58 (−2.20–1.55)	**$Z = -3.77$; $p < 0.001$**
Phonological Fluency	-0.25 (0.90) / −0.33 (−2.06–1.60)	-0.28 (0.92) / −0.18 (−2.37–1.26)	$Z = -0.54$; $p = 0.59$
Trail Making Test B	−0.50 (1.96) / 0.06 (−9.73–1.41)	−0.08 (1.64) / 0.24 (−4.61–2.09)	$Z = -1.39$; $p = 0.16$
Wisconsin CST- Perseverative Errors	0.15 (1.24) / 0.00 (−2.40–3.40)	0.56 (1.30) / 0.40 (−2.00–3.40)	**$Z = -2.71$ $p = 0.007$**

YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale.

Altogether, the sample of patients included in this study is representative of findings reported in BD both in term of the profile of cognitive impairments and the long-term trajectory.

The main aim of this study was to explore the longitudinal relationship between clinical course and neurocognitive impairments. For this purpose, we reassess the neurocognitive performance of a sample of patients after a relatively long period of time, during which the clinical course was precisely documented through the mood-chart technique. This procedure, that implies personal interviews at periods usually between 1 and 2 months, minimizes the risk of recall bias. As expected, the clinical course of the patients was highly variable throughout the follow-up, suffering from 0 to 6 hypo/manic episodes and 0–8 depressive episodes. Similarly, time spent with hypo/manic symptoms ranged from 0% to 21% and time spent with depressive symptoms ranged from 0% to 38%. Both the number of hypo/manic episodes and the time spent with hypo/manic symptoms throughout the period of study were related with verbal memory and executive functions deficits at the end of follow-up. These results are equivalent to those of cross-sectional studies that reported a negative relationship between the number of previous affective episodes, especially the hypo/manic ones, and neurocognitive performance (Robinson and Ferrier, 2006). In contrast, there was no relationship between any of the measures of clinical course used with changes in neurocognitive performance during the follow-up period. These results do not support the hypothesis of neuroprogression according to which cognitive deficits would increase with successive episodes (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). On the contrary, our results may suggest that patients with higher cognitive deficits are also those with more frequency of episodes and vice versa, although cognitive deficits would not be modified with successive episodes.

The proper interpretation of the findings of this study is speculative nowadays since they might be explained by several biologically plausible mechanisms. First, this pattern of association could be observed if cognitive deficits were the cause more than the consequence of the greater number of episodes. For example, patients with higher cognitive impairment would have narrow adherence to medication or would have decreased ability to obtain benefit from psychoeducation programs, which could condition an increased risk of recurrences and a poorer clinical course compared with patients with preserved cognitive functioning. A previous study reported a close relationship between cognitive impairment and poor treatment adherence (Martinez-Arán et al., 2009), while the role of cognitive status regarding the benefit obtained of psychoeducational programs, to our knowledge, was not evaluated up to date. An alternative explanation of the findings of our study, not mutually exclusive with the above, might be derived from the existence of common causes of both cognitive deficits and poor clinical course. Different risk factors, such as comorbidity with anxiety disorders (Wu et al., 2011), alcohol or substance use disorders (van Gorp et al., 1998; Levy et al., 2008; Sanchez-Moreno et al., 2009), hypothyroidism (Martino and Strejilevich, 2015), and exposure to typical antipsychotics (Donaldson et al., 2003; Frangou et al., 2005) among others, were associated with both cognitive deficits and increased risk of recurrences in patients with BD. From this perspective, the presence of these risk factors in some patients could simultaneously condition the existence of a worse clinical course and a greater cognitive impairment regarding

Table 3
Spearman correlation between clinical course measures and changes in neurocognitive performance over the follow-up period.

	Nº Hypo/manic Episodes	Nº Depressive Episodes	Mood Instability	Time spent Hypo/manic	Time spent Deoressive
Immediate Logical Memory	R = −0.17, p = 0.21	R = −0.02, p = 0.87	R = −0.12, p = 0.42	R = −0.28, p = 0.07	R = −0.00, p = 0.98
Delayed Logical Memory	R = 0.19, p = 0.20	R = 0.06, p = 0.65	R = 0.07, p = 0.63	R = −0.15, p = 0.34	R = 0.07, p = 0.64
Serial Learning	R = −0.12, p = 0.43	R = −0.21, p = 0.16	R = −0.01 p = 0.94	R = −0.19, p = 0.21	R = −0.12, p = 0.45
Free Delay Recall	R = 0.09, p = 0.54	R = 0.12, p = 0.42	R = 0.05, p = 0.74	R = −0.02, p = 0.88	R = 0.01, p = 0.93
Recognition	R = 0–0.26, p = 0.06	R = 0.09, p = 0.52	R = −0.00, p = 0.98	R = −0.17, p = 0.28	R = 0.01, p = 0.94
Trail Making Test A	R = −0.08, p = 0.61	R = 0.15, p = 0.33	R = −0.06, p = 0.72	R = −0.10, p = 0.56	R = −0.10, p = 0.53
Forward Digit Span	R = 0.20, p = 0.17	R = −0.41, p = 0.78	R = 0.21, p = 0.17	R = 0.24, p = 0.13	R = 0.00, p = 0.99
Nomination	R = 012, p = 0.42	R = 0.05, p = 0.73	R = −0.01, p = 0.94	R = 0.19, p = 0.22	R = −0.01, p = 0.94
Phonological Fluency	R = −0.09, p = 0.54	R = 0.11, p = 0.44	R = −0.13, p = 0.41	R = −0.10, p = 0.52	R = −0.02, p = 0.90
Trail Making Test B	R = −0.08, p = 0.62	R = 0.06, p = 0.71	R = −0.03, p = 0.86	R = −0.20, p = 0.21	R = 0.06, p = 0.70
Wisconsin CST- Perseverative Errors	R = −0.03, p = 0.85	R = 0.08, p = 0.57	R = 0.09, p = 0.54	R = 0.23, p = 0.15	R = −0.02, p = 0.91

patients without risk factors. Finally, another alternative explanation of our findings is that the common cause of cognitive deficits and poor clinical course were determined by some pathophysiological difference underlying subgroups of patients with BD. For example, based in a low premorbid IQ, poor premorbid adjustment and neurological signs, a recent study suggested the existence of a subgroup of BD patients with neurodevelopmental deviance (Arango et al., 2014). Furthermore, two studies reported that both low and high levels of intelligence and school performance in youth are associated with an increased risk of developing BD, which also supports the view of pathophysiological subgroups (Gale et al., 2013; MacCabe et al., 2010). Therefore, it is possible to hypothesize about the existence of a subgroup of patients in whom some pathophysiological alteration (i.e. neurodevelopmental abnormalities) involving the prefrontal–subcortical pathways that regulate both mood state and cognitive functioning (Pessoa, 2008; Strakowski et al., 2012), could predispose to a greater magnitude of cognitive deficits and frequency of episodes. In contrast, another subgroup of patients without such factor might have relatively preserved cognitive functioning and lower number of affective episodes. Altogether, there are multiple possible explanations about the association between cognitive deficits and affective episodes, and future research is needed to clarify this issue.

Several considerations must be taken into account to interpret the results of this study. The sample size is relatively small limiting especially subgroup analysis, such as changes in neurocognitive performance during follow-up of patients with and without clinically significant cognitive deficits at baseline. Hence, these data should be taken as preliminary findings. Second, this study was conducted in patients from a research database updated over time, and we included only patients with a follow-up period of more than 48 uninterrupted months, which could imply a potential selection bias. However, we compared the sample of patients included in this study with a random sample of patients of our database not included (either because they performed neurocognitive assessment without being monitored in our program, or because they were followed up in our program but for a period shorter than 48 months). There were no differences between these patient groups in any clinical or nueocognitive variables at baseline (all $p > 0.05$, results available upon request). Moreover, our sample had a relatively benign course based on the shortest time spent ill compared with previous studies (Judd et al., 2002, 2003). This might be a consequence of having included patients with strict criteria of euthymia both at baseline and end of follow-up, which was necessary to evaluate core cognitive deficits and not those determined by affective symptoms. In contrast, this study was conducted with a clinical sample (or prevalence sample), which might tend to overestimate the morbidity and cognitive deficits of patients with BD (Cohen and Cohen, 1984). Likewise, we included patients with more than 10 years of length of illness and around 6 previous affective episodes. Therefore, we cannot rule out the possibility that changes in neurocognitive performance secondary to affective episodes may occur earlier in the course of the disorder. Although a recent study reported that neurocognitive impairment showed select improvements in the first year after the initial manic episode (Torres et al., 2014), long-term studies in this population are needed to improve our knowledge about the trajectory of neurocognitive deficits in BD. Finally, all patients were taking psychotropic medications. Hence, drug-related effects cannot be excluded from the interpretation of the findings.

Notwithstanding these limitations, this study contributes to understand the longitudinal relationship between clinical course and cognitive impairments in BD. Our results suggest that the longitudinal trajectory of cognitive deficits in BD is relatively independent of the number of episodes or time spent ill. Future research is needed to clarify the nature of the association between higher cognitive deficits and number of episodes.

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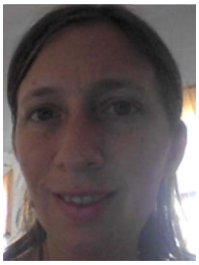

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