Long-Term Outcome of Cognitive Impairment in Bipolar Disorder

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ABSTRACT

Objective: To evaluate the longitudinal course and outcome of cognitive deficits and their clinical correlates in bipolar disorder.

Method: One hundred thirteen participants (68 patients and 45 healthy controls) were assessed by the means of a neuropsychological battery targeting attention, psychomotor speed, verbal memory, and executive functions at baseline: 68 euthymic outpatients with a *DSM-IV* diagnosis of bipolar disorder (53 bipolar I and 15 bipolar II) were enrolled at the Bipolar Disorder Unit of the Hospital Clinic of Barcelona. Forty-five patients completed the follow-up. The assessments started in February 1999 and finished in July 2010. The primary outcome of the study was the change in the neuropsychological performance in the patient group.

Results: Repeated-measures analyses showed significant effects of time in 2 cognitive domains: attention and executive functions. Attention slightly improved ($P = .043$) but executive function worsened ($P = .001$). Regression analyses showed that the duration of illness and baseline subdepressive symptoms were associated with poor performance in executive function. Subdepressive symptoms at endpoint were associated with poor functioning. The best predictor of low functioning was verbal memory dysfunction at baseline.

Conclusions: The cognitive impairment remained stable across the follow-up period in many measures assessed except for a worsening of executive measures, which have been found to be associated with the duration of illness and subdepressive symptoms.

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Bipolar disorder is associated with neurocognitive impairment. Areas of impairment include executive functions, verbal learning and memory, attention, and processing speed.[1–5]

Although the findings do not suggest a global cognitive dysfunction like that seen in schizophrenia,[6–8] this pattern of cognitive deficits is likely to adversely affect psychosocial functioning and insight, increasing the risk of nonadherence and leading to manic relapses, thereby causing more cognitive dysfunction.[9,10]

At present, the exact origin of cognitive deficits is unknown. Multiple factors are thought to play a role such as the presence of psychotic symptoms, higher chronicity, and number of episodes, specially the manic ones.[11,12] Other recognized risk factors include substance abuse, particularly alcohol dependence,[13] and certain medications used to treat bipolar disorder.[14] Biological risk factors may include abnormal neuroendocrine responses, in particular cortisol-related ones.

Some groups demonstrated that newly diagnosed, stable bipolar patients already present core neuropsychological deficits at illness onset,[15] whereas other groups found that recurrence of mania and multiple episodes may have a long-term neuropsychological impact.[16,17] The etiopathogenic mechanisms leading to neurocognitive disability are probably a combination of neurodevelopmental and neurodegenerative processes, suggesting a mixed model.[18]

We do not know much about the course and outcome of cognitive deficits in bipolar disorder. Assessing neurocognitive change over time can give us information about the potential brain changes that take place over the course of the illness.

So far, there is a paucity of studies on neurocognition in bipolar disorder, and most of them had small sample sizes. The longest one is a 15-year follow-up study.[19] Most of these studies indicate that deficits remain stable or slightly worsen over time.[20–24]

The main goal of this study was to examine the pattern of change in neurocognitive performance over a period of nearly 9 years in bipolar patients in euthymia at baseline and at endpoint and determine whether these cognitive changes are related to clinical variables.

METHOD

Participants

Patients participating in this study were enrolled at the Bipolar Disorders Program of the Hospital University Clinic of Barcelona.[25,26] All patients met *DSM-IV* criteria for bipolar I or II disorder and were euthymic. The diagnosis and clinical state of the patients was determined by 2 psychiatrists using *DSM-IV* criteria with the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I),[27] the Spanish version of the Hamilton Depression Rating Scale (HDRS, 17-item),[28,29] and the Young Mania Rating Scale (YMRS).[30,31] Euthymia was defined as YMRS score ≤ 6 and HDRS score ≤ 8 during monthly visits over a 6-month period. Exclusion criteria were (1) history of head injury or loss of consciousness, (2) neurologic illness, (3) substance dependence

Clinical Points

- Neuropsychological impairment in enthymic bipolar disorder patients remains stable across time with the exception of executive measures.
- Illness duration and subdepressive symptoms are associated with poorer performance in executive functions.
- Early intervention strategies in bipolar disorder aiming to ameliorate cognitive dysfunctions and enhance functioning are required.

(in the last year), (4) mental retardation (IQ < 70), (5) significant medical disorder, (6) electroconvulsive therapy in the last year, and (7) subsyndromal fluctuations.

The controls were recruited from the general population in Barcelona and screened for Axis I psychiatric disorders using the SCID-I; those with mental conditions or with affected first-degree relatives were excluded. After being screened for inclusion, 68 bipolar patients and 40 controls were included in the study after signing the informed consent form. Forty-five patients (66.2%) underwent reassessment at 6 to 11 years' follow-up. Twenty-three patients (33.8%) discontinued the study before the end for the following reasons: 11 patients withdrew consent after participating at baseline, 6 patients were not found (change of address or physician), and 6 patients were excluded due to exclusion criteria: older age (n = 1), current comorbidity with alcohol (n = 1), current neurologic disease (n = 2), and the presence of acute depressive symptomatology (n = 2). Figure 1 presents the study sample procedure. Ethical approval for the study was granted by the hospital's Ethics Committee, and patients provided written consent.

Clinical and Psychosocial Assessment

Data on clinical variables were collected as part of the protocol of the Bipolar Disorders Program of the Hospital Clinic of Barcelona. As mentioned above, the clinical state of bipolar patients was established using the SCID-I, the YMRS, and the HDRS. Overall functioning status was assessed at baseline (T1) via SOFAS[32] and at endpoint (T2) via the Functional Assessment Short Test (FAST).[33]

The clinical interview and psychosocial functioning tests were administered by trained psychiatrists, whereas the neuropsychological evaluation was carried out by trained neurophysiologists who were blind to the results of the clinical and psychosocial assessments. Test and retest were performed by different raters.

Neuropsychological Assessment

An extensive review of previous literature guided the choice of neuropsychological tests used in the present study. In order to enhance the possibility of replication, only tests frequently documented by the neuropsychological literature were employed.[34,35] Almost all the cognitive tasks belong to the preliminary summary of cognitive tasks for use in bipolar disorder research proposed by The International Society for Bipolar Disorders (ISBD).[36]

- Estimated premorbid IQ: Vocabulary subtest (Wechsler Adult Intelligence Scale [WAIS])[37]
- Frontal executive functions: Wisconsin Card Sorting Test (WCST)[38]; Stroop Color-Word Interference Test (SCWT)[39]; FAS (phonemic fluency) and animal naming (Controlled Oral Word Association Test)[40]; Trail Making Test B (TMT-B)[41]
- Attention/Concentration and mental tracking: digit subtest (WAIS)[37]; Trail Making Test A (TMT-A)[41]
- Verbal learning and memory: California Verbal Learning Test (CVLT)[42]

The patients were retested at T2 with the same neurocognitive test battery.

Statistical Analyses

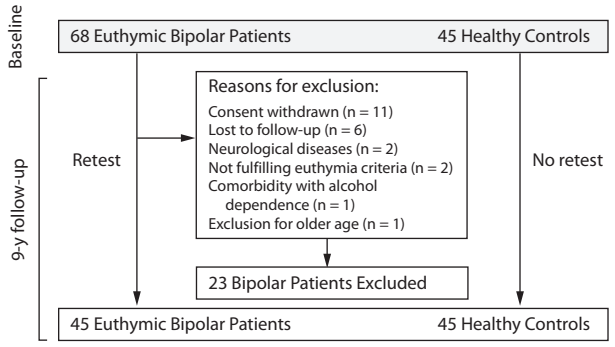
First, we performed the cross-sectional analyses comparing the 2 groups (bipolar patients and controls) regarding clinical and sociodemographic characteristics by means of analysis of variance (ANOVA) and χ^2 tests, as appropriate. Performance on the neuropsychological tests was compared across the 2 groups by means of multivariate ANOVA (MANOVA). Since multiple dependent variables were used, a prior protective multivariate analysis of covariance (MANCOVA) analysis was performed with residual depressive symptoms as measured by the HDRS and IQ as covariates and group as a main factor.

Second, to analyze change in cognitive functioning, repeated-measures ANOVAs were used to compare the clinical and neuropsychological differences at 2 time points: T1 and T2. To examine the categorical variables such as past history of psychotic symptomatology at T1 and T2, the McNemar test was used.

Associations between neurocognitive, clinical, and psychosocial variables were examined with Pearson correlations, taking into account the neuropsychological variables that showed differences across the follow-up (WCST categories, Trail Making Test B, digits forward, and animal naming). The clinical variables introduced were those potentially related to neuropsychological impairment: subclinical symptoms (measured by HDRS and YMRS), total number of episodes (manic, depressive, mixed, and hypomanic), number of hospitalizations, and suicide attempts. As regards psychosocial functioning, we correlated FAST scores at T2 with neuropsychological and clinical variables at T1 and T2.

To identify predictors of neuropsychological and psychosocial functioning, all potentially clinically significant variables were introduced in a lineal regression model as dependent variables. Later, the neuropsychological variables and FAST assessment at T2 were introduced as dependent variables in a stepwise procedure in order to clarify the direction of the association. For the predictive variables, we calculated the interactions between the significant neuropsychological variables and the clinical ones.

Figure 1. Study Sample Procedure



Cognitive functioning scores were transformed into Z-scores using the mean and standard deviation of the control group.

Data analyses were performed using PASW Statistics version 18.0.0 (Predictive Analytics SoftWare, Chicago, Illinois).

RESULTS

Cross-Sectional Impairment

Demographic and clinical characteristics. No differences between groups were found with respect to age, gender, years of education, and subclinical hypomanic symptoms. Most of the patients were taking medication; 8 (7%) were on monotherapy. The majority were on 2 (17%) or 3 drugs (14%). Only 7 (6%) were medication-free.

The patient and the control group differed at T1 regarding subdepressive clinical symptoms, which were higher in the bipolar group ($F_{1,12} = 6.32$; $P = .013$) and the estimated premorbid IQ, which was higher in the control group ($F_{1,12} = 21.32$; $P < .001$). The patients had a mean duration of illness of more than 12 years at baseline. Almost half of the patients were not employed and presented a mean score of 68 on the GAF scale, showing some psychosocial difficulties. Almost 70% of the patients presented a history of psychotic symptomatology, and 60% had positive family history of affective illness.

Neurocognition. With regard to neuropsychological performance, even after controlling for the effect of mild subdepressive symptoms, the bipolar group showed more impairment than the control group in 14 neurocognitive measures (results available upon request). The bipolar group was more impaired on tests related to attention, verbal memory, and executive functions. When we controlled for estimated premorbid IQ, 9 measures continued to show impairment in the bipolar group, especially the domains related to verbal memory and attention, as well as some measures of executive functions, but to a lesser extent (results available upon request).

An additional analysis was performed in order to identify differences between patients who could (n = 45) and those who could not be reassessed (n = 23). Hence, we ran a 1-way ANOVA for continuous variables in order to know if both groups (reassessed vs not reassessed) differed with regard to clinical and/or neuropsychological data. Statistical significance was set at $P < .05$. The results indicate that the patient groups did not differ from each other in any clinical or neuropsychological variable.

Table 1. Baseline Clinical Variables and Repeated-Measures ANOVAs for Bipolar Patients

Demographic and Clinical Variables	Baseline (T1) (n = 68)[a]	Follow-Up (T2) (n = 45)[a]	Statistical Analysis	
			F	*P*
Age, y	39.31 (12.04)	48.47 (11.27)	NA	NA
Educational level, y	12.24 (3.56)	12.24 (3.56)	NA	NA
Estimated premorbid IQ	105.69 (9.14)	107.40 (8.31)	1.54	.22
Age at onset, y	26.16 (10.69)	26.16 (10.69)	NA	NA
Chronicity, y	13.33 (9.50)	22.26 (9.59)	756.76	< .001
No. of episodes				
Total	9.96 (7.94)	14.33 (13.46)	16.96	< .001
Manic	2.60 (3.08)	3.33 (3.59)	15.47	< .001
Hypomanic	2.49 (3.08)	3.53 (4.79)	9.01	.004
Depressed	3.53 (3.37)	5.64 (7.01)	9.36	.004
Mixed	0.96 (2.04)	1.33 (2.44)	6.63	.013
No. of hospitalizations	2.15 (2.41)	2.71 (2.74)	11.89	.001
No. of suicide attempts	0.59 (1.26)	0.95 (1.85)	7.52	.009
HDRS score	2.81 (2.34)	3.96 (3.06)	4.05	.050
YMRS score	1.28 (1.65)	1.89 (1.76)	2.64	.11
SOFAS score	68.08 (14.33)	…[b]	NA	NA
FAST score	…[c]	22.82 (13.91)	NA	NA
Unemployed, n (%)	29 (42.6)	28 (62.2)	NA	NA

[a]Values shown as mean (SD) unless otherwise noted.
[b]SOFAS administered only at T1.
[c]FAST administered only at T2.
Abbreviations: FAST = Functional Assessment Short Test, HDRS = Hamilton Depression Rating Scale, NA = not applicable, SOFAS = Social and Occupational Functioning Assessment Scale, YMRS = Young Mania Rating Scale.

Longitudinal Impairment

Demographic and clinical characteristics. Mean time between the first and second exploration was 8.9 years (range, 6.7–11.1 years). Patients were in the euthymic phase both at T1 and at T2; however, during the almost 9-year follow-up, the patients had a mean of 6 episodes. The work activity was similar after the follow-up; around half of the patients (52%) were unemployed. As regards medication, treatment patterns did not change significantly after follow-up: 2 patients (2%) were drug-free, 6 patients (7%) were on monotherapy, and most of the patients were on treatment with 2 (16%) or 3 drugs (14%). At T2, more patients experienced significatively more psychotic symptoms than at T1 (17 patients; 37%; $P = .001$). The demographic and clinical characteristics of the patients group at T2 are summarized in Table 1.

Neurocognition. Repeated measures revealed some significant effect of time (T1 vs T2) in 2 cognitive domains: attention and executive functions.

Frontal Executive Function

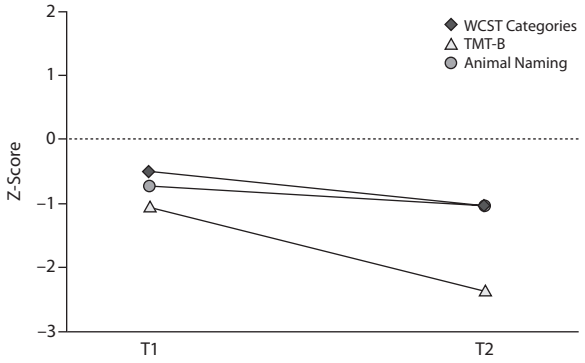
In the WCST, which assesses abstraction, concept formation, mental flexibility, set shifting, and capacity to learn from experience, we found lower scores in T2 compared to T1 in categories ($F_{43.1} = 6.25$; $P = .001$), and a tendency to

Table 2. Repeated-Measures ANOVAs for Each Cognitive Domain[a]

	Bipolar Patients (n = 45)		Healthy Controls (n = 45)		Statistical Analyses		
Cognitive Test[b]	T1	T2	T1	T2[c]	*F*	*df*	*P*
Frontal Executive Function							
WCST							
Categories	5.07 (1.58)	4.40 (2.09)	5.58 (1.17)	…	6.25	43.1	.016
Perseverative errors	13.45 (12.97)	18.07 (15.54)	8.71 (6.19)	…	3.19	43.1	.081
SCWT							
Interference	1.15 (6.58)	0.09 (7.16)	3.93 (8.36)	…	0.20	43.1	.653
TMT							
Trail B	104.10 (69.12)	160.89 (169.51)	76.56 (36.22)	…	6.27	43.1	.016
Attention/Concentration and Mental Tracking							
Subtest Digits (WAIS)							
Digits forward	5.44 (1.45)	5.91 (1.22)	6.36 (1.28)	…	4.34	43.1	.043
Digits backward	4.19 (1.23)	4.20 (1.14)	4.84 (1.14)	…	0.01	43.1	.920
TMT							
Trail A	41.85 (16.43)	44.89 (23.50)	30.71 (11.34)	…	0.24	43.1	.621
Verbal Fluency							
FAS (COWAT)	33.35 (10.85)	30.64 (8.97)	38.09 (11.69)	…	1.74	43.1	.193
Animal naming	18.39 (4.58)	16.16 (4.51)	21.71 (5.62)	…	5.25	43.1	.027
Verbal Learning and Memory							
CVLT							
List A (total)	45.98 (12.35)	43.53 (13.85)	54.16 (9.19)	…	0.04	43.1	.831
Free short-recall	9.42 (3.68)	9.04 (4.12)	11.64 (3.16)	…	0.22	43.1	.636
Cued short-recall	10.66 (2.93)	10.49 (3.56)	13.07 (2.33)	…	0.31	43.1	.581
Free delayed-recall	9.94 (3.70)	9.58 (4.15)	12.78 (2.85)	…	0.18	43.1	.671
Cued delayed-recall	10.87 (3.16)	10.38 (3.67)	13.33 (2.48)	…	0.43	43.1	.514
Recognition	13.95 (2.04)	14.11 (1.95)	15.11 (1.19)	…	0.89	43.1	.349

[a]Raw scores have been included.
[b]Values shown as mean (SD).
[c]The healthy control subjects did not undergo follow-up assessment.
Abbreviations: ANOVA = analysis of variance, COWAT = Controlled Oral Word Association Test, CVLT = California Verbal Learning Test, SCWT = Stroop Color-Word Interference Test, T1 = baseline assessement, T2 = follow-up assessment, TMT = Trail Making Test, WAIS = Wechsler Adult Intelligence Scale, WCST = Wisconsin Card Sorting Test.

Figure 2. Z-Scores of the Executive Domains Variation Over Time



Abbreviations: T1 = baseline assessment, T2 = follow-up assessment, TMT-B = Trail Making Test B, WCST = Wisconsin Card Sorting Test.

more perseverative errors was found at T2 with respect to T1 ($F_{43.1} = 3.19$; $P = .081$). We also calculated the difference between a higher and lower rate of perseverative errors. The cutoff point has been situated at 24 errors. We found significantly higher differences between the perseverative errors found at T2 when compared to T1 (25 patients; 55.5%; $P = .05$). Moreover, we found a worse performance in TMT-B at endpoint compared to baseline ($F_{43.1} = 6.27$; $P = .0016$). In another executive measure, the SCWT, assessing selective attention, response inhibition, and processing speed, no differences were found between baseline and endpoint ($F_{43.1} = 0.20$; $P = .653$).

Attention/concentration. Bipolar patients improved slightly in their performance on the digits forward task ($F_{43.1} = 4.34$; $P = .043$). The performance in the digits backward and TMT-A did not change across the time.

Verbal fluency. No significant differences were found regarding phonetic fluency between T1 and T2 in the bipolar sample; however, patients performed significantly worse across time in the executive measure of semantic fluency (animal naming) ($F_{43.1} = 5.04$; $P = .027$).

Verbal learning and memory. There was no main effect of time in any of the verbal measures. Such deficits found in T1 were maintained over time.

Performances on cognitive tests are provided in Table 2. Figure 2 shows the Z-scores of the neuropsychological domains variation over time.

Relationship Between Clinical and Functional Characteristics and Cognitive Performance

Pearson correlations revealed significant associations between TMT-B performance and duration of the illness and subdepressive symptoms. No additional correlations were found between the neuropsychological variables that exhibit significant differences across the follow-up. For the rest of

neuropsychological variables assessed, we found moderate correlations ($r > 0.40$) between all verbal measures and subdepressive symptoms and with functional outcome except for the recognition task. Some verbal measures (verbal learning and cued-delayed recall task) were correlated with the severity of illness, while number of hospitalizations and free recall (immediate and delayed) were correlated with duration of the illness.

In the bipolar group, psychosocial functioning at T2 was correlated at T1 with an executive measure, namely perseverative errors from WCST ($r = 0.43$, $P = .016$) and verbal learning ($r = -0.36$, $P = .041$) and free ($r = -0.36$; $P = .044$) and cued ($r = -0.38$; $P = .031$) long delay recall measures from the CVLT.

In order to measure the change in cognitive function, we also calculated the difference between the endpoint and baseline scores of cognitive measures. Then, we recalculated Pearson correlations. A positive correlation between the executive measure animal naming and subdepressive symptomatology was found ($r = 0.36$; $P = .015$).

Associations between neuropsychological, clinical, and psychosocial variables are available upon request.

Following findings of previously reported literature,[12,43] the clinical variables introduced in the linear regression models were history of psychotic symptoms, HDRS scores, chronicity, hospitalizations, total episodes, and manic episodes. These variables were entered using a stepwise method. Linear regression analyses showed that the duration of the illness was the variable that best predicted performance on neuropsychological tests such as animal naming, TMT-B, and digits forward ($\beta = -0.18$, $t = -2.59$, $P = .013$). The model reached significance ($F = 6.74$, $P = .013$), explaining 20.3% of the variance. We did not find any other predictive variable of neuropsychological performance. Subsequently, we introduced the same variables while taking the clinical variables as dependent, and no significance was found. As regards functional outcome, the subdepressive clinical symptoms at T2 and verbal memory at T1 were the best predictors for the overall functioning assessed with the FAST ($\beta = 14.5$, $t = 4.21$, $P = .005$; $\beta = 2.14$, $t = 3.13$, $P = .045$).

DISCUSSION

To date, the small number of available follow-up studies suggested that deficits in bipolar disorder were stable or slightly progressive, but did not allow conclusions to be reached regarding the long-term evolution. Our study analyzes the progression of cognitive performance of bipolar euthymic patients during a long period of time (almost 9 years, on average).

The 4 main findings of our study are as follows: (1) euthymic bipolar patients show significantly more cognitive dysfunctions than control subjects in almost all cognitive domains; (2) the impairment remains stable across a period of 6.7–11.1 years in many measures assessed, with the exception of executive measures; (3) the illness duration and subdepressive symptoms are associated with a worse performance in executive functions; (4) subdepressive clinical symptoms and verbal memory dysfunctions are the best predictors of poor functioning.

Regarding the first finding, the results are in agreement with previous literature. In cross-sectional studies, recovered bipolar patients show persistent deficits in attention, verbal memory, and executive functions.

Our second finding indicates that the main cognitive dysfunctions persist over time, which is consistent with previous follow-up studies.[19,20,22,44] Arts et al[24] found an improvement in selective attention after 2 years of follow-up and stability in sustained attention and motor speed. We found a significant improvement only in the attention domain assessed with TMT-A.

Moreover, in the present study, bipolar patients showed significantly greater worsening in the executive domain, especially in verbal fluency and cognitive flexibility.

The presence of executive deficits has been suggested to predate illness onset, as shown in unaffected first-degree relatives.[45–47] Hence, these deficits may worsen with the illness progression. A recent study found differences in executive functions in patients with 1 manic episode compared with those who had 3 or more.[16] This longitudinal course would suggest a combination of the neurodevelopmental hypothesis for the emergence of neuropsychological dysfunction in bipolar disorder, whereas the neuropsychological deterioration would more likely be a consequence of the disorder itself, that is, of the neuroprogression.[18] The concept of allostatic load helps explain the cumulative disruptive health effects of intermittent episodes and stressors. The term *allostatic load* refers to a cumulative multisystemic view of the physiologic toll that is required for adaptation. Cortisol and oxidative stress are major biomarkers of increased allostatic load. The prefrontal cortex is the brain region associated with an overall set of executive functions with many glucocorticoid receptors involved. Hypercortisolemia induced by prolonged exposure to stress during an affective episode may result neurotoxic for this particular region and might serve as model to explain a further decrease in cognition.[48]

Deficits in executive functioning are notably related to functional impairment in patients with bipolar disorder, often resulting in failure to reach optimal levels of psychosocial functioning.[11,49–51]

Which are the factors that can explain the worsening of executive domain? According to the third finding of the study, the duration of the illness and subdepressive symptoms may be responsible for the decline. Several studies have investigated the impact of duration of the illness on neuropsychological function. Our results are consistent with previous reports,[52,53] in which scores on tests of executive function were negatively related to the length of illness.

The negative impact of subdepressive symptomatology on cognitive functioning is well documented. Bonnin et al[10] found the presence of subdepressive symptomatology at baseline as the unique predictor of cognitive functioning.

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Finally, our last finding indicates that subdepressive clinical symptoms and verbal memory dysfunctions are the best predictors of a worse functioning. Different studies have addressed this issue: subclinical depressive symptoms may negatively influence functioning in bipolar disorder.[54–56] These results are highly consistent with other follow-up studies.[19,57] However, in the short term, manic symptoms were reported to be the clinical variable that best predicts functioning.[47]

In our previous studies, features of illness severity such as chronicity and number of episodes have been associated with a worse performance in verbal learning and memory.[58] In the current study, the evolution of initial deficits, especially in executive functioning, showed a marked impairment over time, although one has to bear in mind that those patients are chronically ill and toxic effects of prior affective episodes (before baseline) cannot be excluded either. This factor may limit our findings due to the fact that our sample had a mean chronicity of 13 years at baseline and around 26 years of chronicity at T2. This chronic bipolar sample may represent a more severely ill subgroup of patients and could not be representative of bipolar patients in general.

Another limitation is that, due to lack of follow-up assessment in the control group, we were not able to control for the effect of age upon cognitive performance. However, the time difference between the 2 assessments was long enough to avoid practice effects.

The strengths of the current study are that the patient sample is well characterized and rigorous euthymia was ensured at both baseline and endpoint assessment.

Strategies aiming to ameliorate cognitive dysfunction were recently put forward with the aim of obtaining functional recovery. A cognitive remediation program, focusing on residual depressive symptoms and impairments in cognitive functioning, has been developed for bipolar disorder.[59] The importance of an early intervention is backed up by the studies showing that patients with a high number of previous affective episodes are less likely to respond to psychological treatment,[60,61] due, probably, to the fact that patients in advanced stages of illness may present a progressive impairment of coping mechanism and resilience alongside a more prominent cognitive impairment, rendering restructuring of cognitive functions more complicated.

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Potential conflicts of interest: **Dr Torrent** served as a speaker for Bristol-Myers Squibb. **Dr Martinez-Arán** served as a speaker for Bristol-Myers Squibb, Otsuka, and Pfizer and is a stock shareholder in Pfizer. **Dr Reinares** served as a speaker for AstraZeneca and Pfizer. **Dr Tabarés-Seisdedos** has received grants from Lilly, Pfizer, and AstraZeneca and honoraria from AstraZeneca. **Dr Popovic** has served as a speaker for Bristol-Myers Squibb. **Dr Vieta** has received research grant/research support from Almirall, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Generalitat de Catalunya, GlaxoSmithKline, Janssen-Cilag, Novartis, Pfizer, Sanofi-Aventis, Servier, Seventh European Framework Programme, and Spanish Ministry of Science and Innovation; has served as a consultant to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Research Institute, Gedeon Richter, GlaxoSmithKline, Janssen-Cilag, Jazz, Lundbeck, Merck Sharpe and Dohme, Novartis, Otsuka, Pfizer, Sanofi, Servier, Schering-Plough, Takeda, and United Biosource Corporation; and has served on the speakers or advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Research Institute, Gedeon Richter, GlaxoSmithKline, Janssen-Cilag, Jazz, Lundbeck, Merck Sharpe and Dohme, Novartis, Otsuka, Pfizer, Sanofi, Servier, Schering-Plough, Takeda, and United Biosource Corporation. **Drs Bonnin, Solé, Daban, Rosa**, and **Salamero** have no conflicts of interest.

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