Long-Term Stability of Cognitive Impairment in Bipolar Disorder: A 2-Year Follow-Up Study of Lithium-Treated Euthymic Bipolar Patients

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Objective: To determine the course of cognitive impairment of bipolar disorder with a 2-year longitudinal study and to investigate whether the neuropsychological profile is related to clinical and psychosocial variables in a sample of lithium-treated euthymic bipolar outpatients.

Method: Thirty-three bipolar disorder patients (all of whom were diagnosed according to DSM-IV-TR criteria and were treated during 2003 at the Lithium Clinic Program at Santa Maria Hospital, Lleida, Spain) and 33 healthy, matched controls were cognitively assessed twice over a 2-year follow-up period. All patients were receiving the same mood-stabilizer pharmacotherapy (lithium) at the first evaluation, and they were euthymic (Hamilton Rating Scale for Depression score lower than 8 and Young Mania Rating Scale score lower than 6) for at least 3 months before both evaluations. Cognitive assessment was performed by means of a neuropsychological test battery tapping into the main cognitive domains (executive function, attention, processing speed, verbal memory, and visual memory).

Results: Repeated-measures multivariate analysis of covariance showed that there were main effects of group in the executive domain ($p < .04$) and in processing speed ($p < .04$). Multiple linear regression analysis showed that none of the variables predicted psychosocial functioning (as measured with the Global Assessment of Functioning scale) ($R^2 = 0.12$, $F = 2.08$, $p = .1$). Multilevel logistic regression analysis showed that processing speed appeared to be significant as an indicator of low work activity (Exp[B] = 1.25, 95% CI = 1.005 to 1.547, $p = .04$).

Conclusions: Executive function and processing speed are the cognitive domains affected in euthymic bipolar outpatients, and such deficits are maintained over time. Our results show that executive dysfunction is the main long-term neuropsychological deficit of bipolar disorder. Slower processing seems to be related to worse work adaptation.

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Neurocognitive impairment has consistently been considered a central feature in bipolar disorder. It is well established that there are persistent neuropsychological deficits even during euthymia in bipolar disorder patients.[1–10] This fact challenges the former idea that impairment is transient and limited to the acute phases of the illness. Previous studies have failed to agree on which cognitive functions are impaired during euthymia: while some studies suggest that mainly verbal memory and executive function are affected (see reference 11 for a review), Savitz et al.[12] suggest that many other cognitive domains are also affected. The meta-analysis presented by Robinson et al.[13] suggests that verbal memory appears to be as impaired as executive functioning. However, as noted in that work, verbal memory measures are based on list-learning tasks that are known to involve executive strategies.[14] Frangou et al.[10] have found that in representative treatment samples of remitted bipolar patients, executive dysfunction seems to be the main deficit. Accordingly, we have recently found,[15] when recruiting typical euthymic outpatients treated in clinical settings (without a bias towards severity or polypharmacy), that executive functioning alone may account for the neuropsychological impairment of bipolar disorder.

Most of the previously published studies have been cross-sectional (see references 12 and 13 for a review), and their conclusions lead to the necessity of longitudinal

TAKE-HOME POINTS

- Cognitive deficits in patients with bipolar disorder do not appear to be transient or state-dependent and may be a long-term trait of the illness.
- The cognitive profile associated with bipolar disorder in remission seems to implicate deficits in executive function and processing speed.
- Clinicians should consider the cognitive dysfunction in patients with bipolar disorder, providing treatments that do not worsen, or that even improve, cognitive functioning and avoiding polypharmacy when possible.
- Cognitive impairment may have consequences for functional outcome.

studies to address the question of whether cognitive impairments worsen with progression of the illness. Only a few studies have thoroughly addressed the impact of neurocognitive functioning on bipolar disorder course using longitudinal designs.[16,17] These studies are not conclusive and have not been replicated. Thus, it is difficult to draw any conclusions about the course of the cognitive impairment in bipolar patients. Furthermore, it is still not possible to ascertain whether the deficits are stable and independent of symptoms. As a consequence, it would be essential to perform within-subjects longitudinal studies examining fluctuations in performance over time. The aim of this study is to find out the longitudinal neurocognitive profile of euthymic bipolar outpatients, compared to healthy matched controls, over a 2-year period.

METHOD

Subjects

All bipolar patients enrolled in the study were recruited from the Lithium Clinic Program at Santa Maria Hospital, Lleida, Spain. This program covers the whole health area, comprising about 140,000 inhabitants. All patients treated at the lithium clinic during 2003 were considered for the study—there were 106 outpatients. Of those, 44 met inclusion criteria and were admitted into the study,[15] and 33 of these (75% of the initial sample) were reevaluated at the 2-year follow-up. Eleven patients discontinued the study, 5 of whom refused to participate at follow-up and 6 of whom no longer met study criteria (2 had clinically significant medical illness and 4 showed clinically significant bipolar disorder symptoms). The final sample included 17 men and 16 women who agreed to participate and to be evaluated twice with the same clinical interview, biochemical tests, and neuropsychological battery.

Inclusion criteria for entry into the study required that patients, aged 18 to 65 years, fulfilled DSM-IV-TR criteria for bipolar I or II disorder, had been in remission for at least 3 months prior to evaluation, and had received the same pharmacotherapy treatment over the same period of time. In addition, following the procedure of previous studies,[13] patients were characterized as euthymic if they had a total 17-item Hamilton Rating Scale for Depression (HAM-D)[18] score below 8 and a total Young Mania Rating Scale (YMRS)[19–20] score below 6 for at least 3 months prior to the time of assessment. Exclusion criteria were the following: clinically significant physical or neurologic illness; substance abuse or dependence in the last 12 months; electroconvulsive therapy in the preceding year; and cotreatment with any mood-stabilizing medication other than lithium. For the second evaluation, patients had to fulfill the same inclusion and exclusion criteria, with the exception that medication could have changed during the 2 years. Therefore, at follow-up, all subjects were retested if they had been euthymic for at least 3 months, as confirmed by the same criteria as at baseline.

Thirty-three healthy controls from the same geographic area, matched in terms of gender, age, and years of education, were recruited via advertisements and from nonmedical hospital staff. Controls had no current or past psychiatric history, as determined by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).[21] They had no first-degree relatives with bipolar or psychotic diagnoses. Controls were subject to the same exclusion criteria and were assessed with the same full study protocol as the patients. They were also evaluated twice (at baseline and 2 years later).

On average, the second evaluation (T2) occurred 24.2 months after baseline (T1) (range, 22.7–25.5 months) and was conducted by the same neuropsychologist and psychiatrist. The local ethics committee approved the study, and written informed consent was obtained from all participants (patients and healthy controls).

Demographic, Clinical, and Pharmacologic Data

All these data were systematically obtained and included in the study. Demographic variables for bipolar outpatients and healthy controls were age, gender, years of education, and relatives' antecedents of mental diseases. Clinical variables were obtained from the sample of bipolar patients: age at onset, number of prior manic

episodes and hospitalizations, period of stabilization (years), duration of illness (years), history of psychotic symptoms, seasonal pattern, suicide attempts, and bipolar subtype (I or II).

All patients were given biochemical tests, including thyroid function, serum lithium levels, and drugs urine control. None of the patients showed significant clinical alterations in relation to any of the variables of the biochemical tests, except for thyroid function: 2 patients had subclinical hypothyroidism at T1, and 3 different patients had subclinical hypothyroidism at T2.

In addition to the variables mentioned above, some psychometric variables were included for the 2 groups (bipolar patients and healthy controls): estimated premorbid IQ (to ensure matching between groups) and YMRS and HAM-D scores (to control for subclinical symptoms). It is known that bipolar disorder impacts social functioning, employment, and work productivity. Thus, in this study we categorized work status as active (including students and housewives and those subjects with a full-time or part-time job), inactive (those unemployed or on temporary sick leave), or retired/disabled (pensioners or those on permanent sick leave). In addition, patients and controls were assessed with the Global Assessment of Functioning (GAF)[22] scale to obtain information about global psychosocial activity. This scale is widely used to measure psychosocial functioning.[23]

With respect to the pharmacologic variables, all outpatients were receiving lithium as the only mood-stabilizing medication at T1 (dose, 400–1600 mg/day; serum lithium levels, 0.43–0.95 mmol/L; treatment duration, 0.5–14.0 years). At T2, 4 patients were drug-free and all the others were receiving lithium as the only mood stabilizer (dose, 400–1600 mg/day; lithium levels, 0.48–1.02 mmol/L; treatment duration, 0.3–16.0 years). At both time points, we found patients receiving only lithium monotherapy and patients receiving drug combinations: lithium plus an antidepressant (selective serotonin reuptake inhibitor), lithium plus an antipsychotic (second-generation antipsychotic), or lithium plus both an antidepressant and an antipsychotic.

Neuropsychological Assessment

For the cognitive evaluation, we chose neuropsychological tests that were frequently documented in previous literature.[11–13] Our battery included neuropsychological tests that tapped into broad cognitive categories in order to provide a more general pattern of cognition (a detailed explanation of this battery can be found in reference 15). The estimated mean IQ of the subjects was obtained from the weighted scores of the vocabulary and block-design subtests of the Wechsler Adult Intelligence Scale-III (WAIS-III)[24] because these 2 scores are the most highly correlated with total IQ. Following are the components of our neuropsychological test battery: (1) the vocabulary, block design, and digits subtests from the WAIS-III[24]; (2) the Wisconsin Card Sorting Test (WCST)[25]; (3) the Stroop Color and Word Test[26]; (4) the FAS verbal fluency task of the Controlled Oral Word Association Test–Categories[26]; (5) the Trail Making Test,[27] parts A (TMT-A) and B (TMT-B); (6) the Conners' Continuous Performance Test II (CPT-II)[28]; (7) the California Verbal Learning Test (CVLT)[29]; and (8) the Rey Complex Figure Test (RCFT).[30]

Statistical Procedures

Data analyses were carried out with the statistical package SPSS for Windows, version 14.0 (SPSS Inc., Chicago, Ill.). Comparison of differences between groups for sociodemographic characteristics was accomplished with a univariate analysis of variance by examining a single factor of group (outpatients vs. healthy controls); the Student t test and nonparametric tests were used when needed. These differences were analyzed at 2 time points, T1 and T2.

Following the guidelines of Lezak et al.,[31] all neuropsychological tasks were sorted by cognitive domain: executive function, attention, processing speed, verbal memory, and visual memory. The majority of the cognitive variables met the criteria of normality; therefore, parametric tests were applied. Separate repeated-measures multivariate analyses of covariance (MANCOVAs) were performed by defining the measurements for each cognitive domain. The 3 following measures were the dependent variables for the executive function MANCOVA: digit span backward, TMT-B, and FAS (total score). The inhibition domain included the number of perseverative errors on the WCST, number of perseverative errors on the CPT-II, and inhibition on the Stroop task. For the attention domain analysis, dependent variables were digit span forward, detectability index of the CPT-II, and Stroop task interference. The processing speed domain incorporated the TMT-A and the hit reaction time in the CPT-II. The verbal memory domain took into account the first trial of the CVLT, the total number of learned words on the CVLT (trials 1–5), short-term and long-term recall, and recognition. Finally, visual memory was delimited by short-term (immediate) and long-term (delayed) recall of the RCFT test. Number of categories on the WCST and number of errors on the WCST did not fit normal distribution and were not included in the analyses of covariance (executive domain and inhibition domain MANCOVA, respectively). Estimated premorbid IQ was included as a covariate since it showed significant difference between groups.

We analyzed cognitive impairment related to clinical, demographic, and pharmacologic variables in the group of bipolar patients. Given that the low-level mood symptoms may impact on cognitive functioning, partial correlations were carried out for quantitative variables (HAM-D and YMRS scores were controlled for). The association

Table 1. Demographic, Clinical, and Pharmacologic Variables at Baseline (T1) and at 2-Year Endpoint (T2)

	Bipolar Patients (N = 33)		Healthy Controls (N = 33)	
Variable	T1	T2	T1	T2
Age, mean (SD), y	40.7 (13.2)	42.5 (13.4)	41.7 (11.7)	43.8 (11.7)
Years of education, mean (SD)	11.0 (3.2)	11.0 (3.2)	12.3 (3.3)	12.5 (3.5)
Estimated premorbid IQ, mean (SD)	97.6 (11.7)	99.8 (10.8)	105.3 (7.9)	106.3 (9.8)
YMRS score, mean (SD)	1.9 (2.4)	1.4 (1.8)	0.5 (0.8)	0.4 (0.8)
HAM-D score, mean (SD)	2.0 (2.0)	1.8 (1.6)	1.3 (1.4)	1.1 (0.9)
GAF score, mean (SD)	71.4 (9.5)	70.3 (8.0)	92.3 (4.4)	91.2 (5.6)
Age at onset, mean (SD), y	22.9 (10.5)	22.9 (10.5)		
No. of hospitalizations, mean (SD)	3.0 (3.4)	3.3 (3.9)		
Total no. of manic episodes, mean (SD)	2.8 (2.7)	2.9 (2.8)		
Years of stabilization, mean (SD)	2.8 (3.0)	3.3 (3.0)		
Duration of illness, mean (SD), y	17.6 (12.8)	19.5 (12.7)		
Years of lithium treatment, mean (SD)	4.7 (3.5)	6.5 (4.2)		
Serum lithium level, mean (SD), mmol/L	0.69 (0.17)	0.69 (0.18)		
Lithium doses, mean (SD), mg/d	1091 (245)	988 (436)		
Gender, N (%)				
Male	17 (51.5)		17 (51.5)	
Female	16 (48.5)		16 (48.5)	
Current work status, N (%)				
Active	18 (54.5)	14 (42.4)	30 (90.9)	32 (97.0)
Inactive	6 (18.2)	8 (24.2)	2 (6.1)	0 (0)
Retired/disabled	9 (27.3)	11 (33.3)	1 (3.0)	1 (3.0)
Positive family history of mental illness, N (%)	27 (81.8)	27 (81.8)	9 (27.3)	9 (27.3)
Lifetime history of psychotic symptoms, N (%)	26 (78.8)	26 (78.8)		
Lifetime history of seasonal pattern, N (%)	22 (66.7)	22 (66.7)		
Personal history of suicide attempts, N (%)	18 (54.5)	18 (54.5)		
Diagnosis, N (%)				
Bipolar I disorder	24 (72.7)	24 (72.7)		
Bipolar II disorder	9 (27.3)	9 (27.3)		
Type of current medication, N (%)				
Lithium	15 (45.5)	12 (36.4)		
Lithium + antidepressant	9 (27.3)	8 (24.2)		
Lithium + antipsychotic	8 (24.2)	9 (27.3)		
Lithium + antidepressant + antipsychotic	1 (3.0)	0 (0)		
None	0 (0)	4 (12.1)	33 (100)	33 (100)

Abbreviations: GAF = Global Assessment of Functioning, HAM-D = Hamilton Rating Scale for Depression, YMRS = Young Mania Rating Scale.

analyses between qualitative variables were performed using the Spearman correlation.

In the bipolar patient group, we used a multiple linear regression model to identify the variables that could be good predictors of psychosocial functioning at T2. The clinical and neuropsychological variables that correlated with the GAF at T1 were introduced into the model using a hierarchical stepwise method. In addition, a multilevel logistic regression test was performed to identify predictive variables of work status at T2, as defined above. The variables included in the analysis were selected using the same criterion as in the multiple linear regression model.

RESULTS

Demographic, Clinical, and Pharmacologic Results

The demographic, clinical, and pharmacologic characteristics of the euthymic bipolar group and control group at the 2 time points (T1 and T2) are shown in Table 1. At T1, the 2 groups (patients and healthy controls) did not differ with respect to gender, age, and years of education. There was a significant difference in YMRS scores ($F = 9.8$, $df = 1,65$; $p = .003$), but no difference in HAM-D scores was found. Estimated premorbid IQ showed a significant difference between the 2 groups ($F = 9.9$, $df = 1,65$; $p = .002$), although such a difference was not clinically significant (mean IQ scores were within ± 1 SD from the average). With regard to work activity, both groups displayed significant differences ($\chi^2 = 11.4$, $df = 2$, $p = .003$). The group of bipolar patients showed worse psychosocial adaptation, as measured by the GAF scale ($F = 131.2$, $df = 1,65$; $p < .001$).

At T2, bipolar patients and healthy controls were similar in gender ratio, education, and age, as at T1; the 2 groups differed, however, in YMRS score, estimated IQ, work activity, and GAF score ($p < .05$). At T2, the HAM-D score also showed a significant difference between the 2 groups ($F = 4.2$, $df = 1,65$; $p = .04$). At 2-year follow-up, the group of bipolar patients exhibited no significant change in their clinical or psychosocial characteristics ($p > .4$) except work status ($\chi^2 = 65.9$, $df = 4$, $p < .001$). There were also differences in medication between T1 and T2 ($\chi^2 = 61.6$, $df = 9$, $p < .001$).

Thirteen (39%) of the 33 patients relapsed once during the study period (4 suffered a manic episode, and 9, a depressive episode). There were no differences in any of the

Table 2. Neurocognitive Results at Baseline (T1) and at 2-Year Endpoint (T2) for All Participants[a]

	Bipolar Patients (N = 33)		Healthy Controls (N = 33)		Statistical Analysis		
Test	T1	T2	T1	T2	F	df	p Value
Executive tests					0.8[b]	3,61	…
TMT part B[c]	89.2 (35.3)	96.9 (58.8)	64.6 (23.2)	63.8 (23.4)	4.7[d]	1,63	.035
FAS	38.2 (11.5)	36.5 (13.9)	44.9 (9.6)	42.3 (10.2)	1.5[d]	1,63	…
WAIS-III digit span backward	4.8 (1.7)	4.9 (1.8)	5.9 (1.8)	6.3 (1.5)	4.6[d]	1,63	.036
Inhibition					0.3[b]	3,61	…
Stroop inhibition	36.9 (10.6)	36.8 (10.5)	44.3 (6.9)	46.6 (9.9)	9.5[d]	1,63	.003
No. of perseverative errors WCST[c]	25.4 (19.8)	20.2 (11.8)	15.6 (10.3)	11.1 (8.6)	4.6[d]	1,63	.037
No. of perseverative errors CPT-II[c]	1.9 (3.2)	1.8 (3.3)	0.2 (0.4)	0.3 (0.8)	5.0[d]	1,63	.029
Attention					1.7[b]	3,61	…
Stroop interference	0.1 (6.5)	–0.2 (8.7)	1.4 (5.7)	4.5 (8.1)	0.9[d]	1,63	…
WAIS-III digit span forward	7.7 (1.9)	7.6 (1.9)	8.7 (1.9)	8.4 (1.9)	0.7[d]	1,63	…
CPT-II detectability (d')	0.9 (0.5)	0.9 (0.4)	0.9 (0.4)	1.1 (0.4)	1.4[d]	1,63	…
Processing speed					1.2[b]	2,62	…
TMT part A[c]	44.6 (20.4)	44.5 (22.1)	32.7 (15.4)	30.2 (11.3)	5.3[d]	1,63	.024
CPT-II hit reaction time	462.1 (80.3)	457.2 (58.5)	418.5 (55.5)	429.2 (62.1)	4.6[d]	1,63	.035
Verbal memory					2.6[b]	5,59	.033
CVLT first trial	6.7 (1.8)	6.8 (2.0)	6.7 (1.6)	6.9 (1.9)	0.2[d]	1,63	…
CVLT total words	51.6 (10.9)	50.1 (11.5)	54.2 (8.1)	55.9 (9.5)	1.2[d]	1,63	…
CVLT immediate recall	11.0 (3.1)	11.1 (3.8)	11.4 (2.4)	13.0 (2.1)	0.5[d]	1,63	…
CVLT delayed recall	11.3 (2.9)	11.8 (3.3)	12.4 (2.2)	13.1 (2.5)	1.1[d]	1,63	…
CVLT recognition	14.4 (1.6)	14.9 (1.3)	14.9 (1.4)	14.9 (1.2)	0.0[d]	1,63	…
Visual memory					1.9[b]	2,62	…
RCFT immediate recall	18.9 (6.5)	19.9 (6.3)	22.4 (5.2)	23.4 (5.4)	2.2[d]	1,63	…
RCFT delayed recall	17.9 (5.9)	20.3 (6.3)	22.1 (5.9)	22.7 (5.6)	1.6[d]	1,63	…

[a]Results are shown as mean (SD).
[b]Repeated-measures multivariate analysis of covariance (MANCOVA) multivariate effects for each cognitive domain (group × time interactions with IQ).
[c]In this test, a higher score means a worse performance.
[d]Repeated-measures MANCOVA main effects of group (tests of between-subjects effects).
Abbreviations: CPT-II = Continuous Performance Test II, CVLT = California Verbal Learning Test, FAS = verbal fluency task of the Controlled Oral Word Association Test, RCFT = Rey Complex Figure Test, TMT = Trail Making Test, WAIS-III = Wechsler Adult Intelligence Scale-III, WCST = Wisconsin Card Sorting Test.
Symbol: … = not significant.

demographic or clinical variables between relapsed and nonrelapsed patients ($p > .1$), not even in the number of manic episodes. Neurocognitively, relapsers did not show worse performance than nonrelapsers when compared at T2.

Five (15%) of the 33 patients had subclinical hypothyroidism. There were no significant differences in any of the pharmacologic variables (duration of lithium treatment, doses, or current lithium level) or psychometric variables (which measured subclinical symptoms) between patients with and without subclinical hypothyroidism.

Neuropsychological Results

We analyzed the results of 33 remitted bipolar outpatients versus 33 healthy controls by T1 versus T2. After controlling for the covariate (estimated premorbid IQ), repeated-measures MANCOVA revealed no significant interactions of time (T1 vs. T2) by group (patients vs. controls) except in verbal memory (all neuropsychological results are displayed in Table 2). There were main effects of group (see Table 2 and Figure 1) in the executive domain (TMT-B and digit span backward), in the inhibition domain (all the tasks included in the repeated-measures MANCOVA), and in processing speed (the 2 tasks included). There was no main effect of time in any of the cognitive domains.

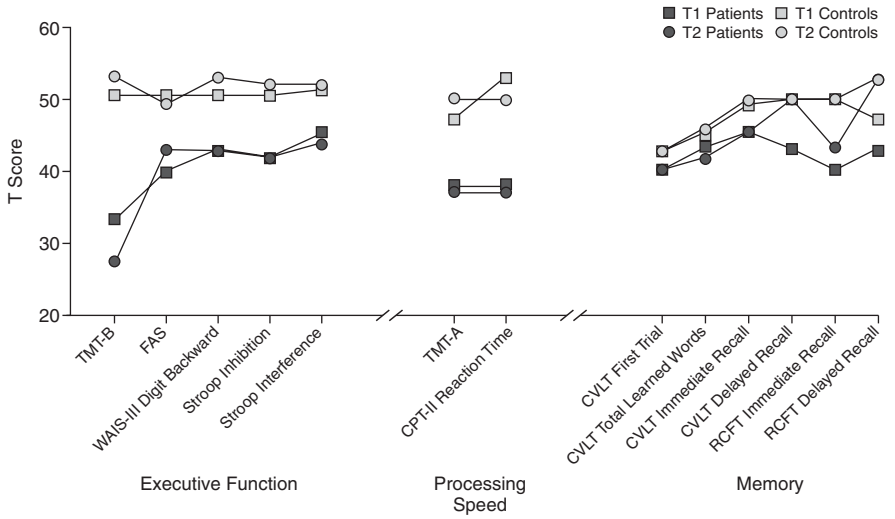
In terms of univariate effects, detectability on the CPT-II from the attention domain showed a time by group effect ($F = 4.9$, $df = 1,63$; $p = .03$). Additionally, the CVLT immediate recall showed a univariate effect of time by group ($F = 6.3$, $df = 1,63$; $p = .01$). To rule out the implication of hypothyroidism's effects on the results, the analyses were rerun, excluding the 5 patients who had subclinical hypothyroidism. The neuropsychological results did not change, and statistical differences were observed on the same neurocognitive measures.

Association Results

Partial correlations (controlling for HAM-D and YMRS scores) were used in order to establish which clinical and neuropsychological variables correlated with the GAF scale. In the bipolar group, we found a correlation between GAF scores and number of manic episodes ($r = –0.41$, $p = .02$) and number of hospitalizations ($r = –0.49$, $p = .006$). None of the neuropsychological variables correlated with the GAF.

Spearman correlations were used to determine the clinical and neuropsychological variables that correlated with work status. We found that bipolar outpatients

Figure 1. Neuropsychological Performance of the 2 Groups (patients and healthy controls) by 2 Time Points (baseline [T1] and 2-year endpoint [T2]) for Those Tests That Showed Group Effects in the Multivariate Repeated-Measures Analyses[a]



[a]Raw scores were transformed into t scores from normative data for adult subjects.[26] Transformation makes the comparison among tests more easily understandable.
Abbreviations: CPT-II = Continuous Performance Test II, CVLT = California Verbal Learning Test, FAS = verbal fluency task of the Controlled Oral Word Association Test, RCFT = Rey Complex Figure Test, TMT = Trail Making Test, WAIS-III = Wechsler Adult Intelligence Scale-III.

showed a relation between work status and TMT-A scores ($r = 0.5$, $p = .003$) and Stroop inhibition scores ($r = –0.4$, $p = .03$).

In the bipolar group, after selecting all the variables that were correlated with the GAF, multiple linear regression analysis showed that none of the variables predicted psychosocial functioning, as measured by the GAF ($R^2 = 0.12$, $F = 2.08$, $p = .1$). On the other hand, the multilevel logistic regression analysis accounted for 73% of the variance (Nagelkerke pseudo $R^2 = 0.730$, $\chi^2 = 34.2$, $p < .001$). Only the TMT-A scores appeared to be significant as an indicator of poor work status, i.e., not actively working (Exp[B] = 1.25, 95% CI = 1.005 to 1.547, $p = .04$).

DISCUSSION

In order to determine the course of neuropsychological deficits in bipolar disorder, a cognitive follow-up study controlling for practice effects is required. Here, we present a 2-year follow-up study including a control group at the 2 time points. Our results suggest that executive functioning and processing speed are the cognitive domains truly affected in euthymic bipolar outpatients. Remarkably, we find that such deficits are maintained over time. Furthermore, these deficits do not seem to be influenced by any relapse during this 2-year period since most of the patients had no relapse or relapsed in a depressive episode (as described in reference 8, the effect of depressive episodes on cognitive functioning is less than that of manic episodes). Additionally, it is probable that relapses within a given period may occur randomly. The results on verbal memory and detectability on CPT-II show that bipolar patients exhibited similar performance over time, whereas healthy controls improved their performance at T2. Thus, the learning ability might be affected in bipolar patients. It must be noted, however, that the performance on these tasks was very similar in both groups (patients and controls), indicating no clinical relevance of such results.

At the present time, the profile of neuropsychological deficits in euthymic bipolar patients is still a matter of debate. Previous findings suggested that although bipolar patients did not display global cognitive impairments, they did have specific deficits in some domains, which mainly include verbal memory and, to a lesser extent, executive functioning. In this regard, previous reviews[11,12] highlighted both executive and verbal memory impairments as the neuropsychological profile of euthymic bipolar patients. Robinson et al.,[13] in a recent meta-analysis, quantified these deficits and reported larger effect sizes in these 2 aspects. These authors[13] suggest that not all the executive functions are equally impaired, while memory deficits may be related to the lack of executive strategies. Our results show that the most affected domain seems to be executive function and that the deficit is stable over time, providing new clues about the underlying disease process involved. A possibility is that verbal memory problems might be more closely related to polypharmacy and poor outcome.[32] Thus, the hypothesis that executive dysfunctions may appear earlier as part of neurodevelopmental abnormalities,[33,34] whereas verbal memory dysfunctions may

represent a consequence of the illness process itself[8] (for a review, see reference 35), should be investigated.

The importance of our results is clear given the few prospective studies available and the little information obtained about the stability and long-term course of cognitive impairments in bipolar disorder. Mainly 2 other studies have addressed the question of the course of cognitive functioning with a design similar to ours. Engelsmann et al.[16] failed to detect evidence of memory decline over a 6-year interval in 18 lithium-treated patients. Balanzá-Martínez et al.[17] assessed schizophrenic and bipolar patients twice over a 3-year follow-up period, reporting persistent cognitive impairments. However, healthy controls were assessed only at baseline in that study, which might represent a methodological problem. Our patients and matched controls were all assessed at the 2 time points, which provides methodological strength and might be more informative about the long-term neurocognitive functioning of these patients as compared to those in previous studies. Although the lengthy follow-up would rule out the practice effects, many methodological issues have been overcome by assessing the healthy controls twice within the same period. We have adopted a multivariate repeated-measures approach to simultaneously model all the cognitive domains as a function of group (patients vs. healthy controls). This procedure is advantageous because simultaneous modeling boosts statistical efficiency by allowing for correlations among the neuropsychological variables. Additionally, it avoids multiple comparisons. On the other hand, all subjects completed a comprehensive neuropsychological battery that evaluated broad cognitive categories in order to provide a more general pattern of cognitive functioning. We believe that this battery is more informative than focusing on 1 single task or cognitive domain.

Regarding the association results, none of the demographic, clinical, or pharmacologic variables showed a statistically significant relationship with the neuropsychological variables except for work status. A work status of active, inactive, or retired showed a relation with processing speed and inhibition; also, the slower processing of information was predictive of worse work adaptation. Impaired processing speed may represent a limitation for competitive jobs, in which a good performance involves a balance between quantitative and qualitative parameters. Bipolar patients are often afraid of returning to their jobs after sick leave because they feel they will not be able to reach their previous level of work. Given that the work status was worse at T2, it is feasible that maintained executive deficits could account for such difficulties in work-related adaptation. Unexpectedly, none of the neuropsychological variables were related to GAF, while 2 clinical variables (number of manic episodes and number of hospitalizations) were related to poorer psychosocial adaptation, although these variables were not predictive of worse functioning.

The fact that we find no association between cognitive and other clinical variables, such as number of episodes or chronicity, differs from previous findings. Cognitive deficits may be more persistent the longer the duration of illness or the higher the number of manic episodes,[4,7] although these relationships have not always been confirmed.[2,15] Our cognitive results seem to be independent of the clinical course. However, given that we find that cognitive impairment is related to worse employment activity, we conclude that work status represents a more ecological variable than the score obtained with the GAF. Malhi et al.,[36] however, suggest that the assumption that cognitive testing relates to "real world" functioning may be erroneous. Nevertheless, even the suspicion that patients with worse cognitive function may display poorer psychosocial outcomes should warrant the effort to get more insight on this issue and to develop appropriate interventions.

The bipolar sample in this study may be representative of patients who attend a lithium clinic in a given area and shows some clinical features that are worth mentioning. First, the patients received a unified treatment (lithium), and, therefore, they were not excessively medicated (less than 3 drug classes), which possibly may have reduced the effect on cognition (attributable to side effects or interactions associated with polypharmacy).[5,6,37] However, in the present study, it is not possible to determine whether lithium treatment affected cognition, as this study had an observational, nonrandomized design, and 1 group (patients) was treated, while the other (healthy controls) was not.

Second, the sample allowed a careful follow-up, given that the patients displayed adherence to therapeutic programs, which might explain the low attrition rate after 2 years. As a potential limitation, these patients may also represent a self-selected population in which, at the very least, patients at high risk of poor outcome are underrepresented.[38,39] Furthermore, due to the limited sample size, some potential statistical differences were not found in some relevant subgroups (such as subclinical hypothyroidism or subtypes of treatments). It is known that hypothyroidism has been caused by lithium at rates between 2% and 15% and that this disorder is often associated with cognitive impairment.[40] Nevertheless, the degree to which mild or subclinical hypothyroidism impacts mood and cognitive functioning and whether these symptoms respond to treatment remain controversial.[41]

In summary, our study suggests that bipolar patients are impaired in executive function and processing speed, and this impairment is maintained over a 2-year period in euthymic patients. This cognitive impairment seems to be persistent but stable over time. Our study adds new clues on the longitudinal neuropsychological profile of bipolar disorder by establishing executive dysfunction as the core deficit. Longitudinal neuropsychological studies are an important contribution to psychiatry given that they

can help achieve better understanding of the course of mental illnesses. This contribution is important since the data might facilitate more effective treatments for patients (e.g., treatments that do not worsen, or that even improve, cognitive functioning and that avoid polypharmacy when possible). Likewise, when taking patients' cognitive course into account, improvements in psychosocial outcome can be attained by means of rational medication, psychoeducation, enhanced health care, and, perhaps, cognitive remediation.[42]

Drug name: lithium (Eskalith, Lithobid, and others).

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